Women's brain health: disentangling the role of menopause and ageing

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Declaration

I, Ananthan Ambikairajah, hereby declare that, except where acknowledged, this work is my own and has not been submitted for a higher degree at any other university or institution. I analysed all data independently and drafted all chapters of this thesis.

Ananthan Ambikairajah

"Principles for the Development of a Complete Mind:

Study the science of art. Study the art of science. Develop your senses - especially learn how to see. Realise that everything connects to everything else."

— *Leonardo da Vinci*

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To my son, Oliver. I dedicate this to you.

Publications arising from the thesis

Chapters 2, 3, 4, 5, and 6 have been published in the following articles:

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Abstract

Maintaining a healthy brain has been recognised as an important health challenge facing women, given global estimates indicate almost twice as many women die of dementia than men. In part, this is due to their increased longevity, however, this does not explain all of the difference. Other contributors include different exposure to risk factors as well as sex-related physiological differences. This thesis focused on the latter, specifically in relation to possible impacts of menopause, as this stage of life has been suggested to involve particular risks to brain health. To address this question, five studies were conducted to precisely characterise and quantify (1) changes in fat mass during menopause; (2) lipid profile differences during menopause; (3) heterogeneity of menopause nomenclature used in peer-reviewed literature; (4) changes in fat mass and the brain; and (5) menstruation history (including menopausal status and age at menopause) and the brain. Moreover, an important conceptual and theoretical question embedded throughout this thesis has been to determine how much of the observed effects were attributable to ageing, rather than a possible effect of menopause. This has been a significant challenge, given menopause and ageing co-occur.

The first two studies revealed that fat mass was higher in postmenopausal compared to premenopausal women across most measures, with the exception of leg fat which decreased, indicative of a potential change in fat mass distribution after menopause. However, the change in fat mass quantity was predominantly attributable to increasing age with menopause having no detectable additional influence. Furthermore, lipoproteins were significantly higher in postmenopausal women than premenopausal women, with the exception of high-density lipoprotein, which was not significantly different between groups. Measures of ageing explained some, but not all of the differences in lipid levels.

The third study found a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*.

The fourth study demonstrated that those who suffered from overweight or obesity had smaller hippocampal volumes than those who maintained a normal weight. Furthermore, those who suffered from overweight or obesity in the past, but currently had a normal level of fat mass also had a smaller hippocampus than those who had always maintained a normal weight.

The fifth study revealed an association between menopause and the brain, beyond typical ageing effects. Notably, postmenopausal women had larger brain volumes than premenopausal women but also experience greater decreases in total brain volume, but not hippocampal volume, over time. In addition, delayed age of menopause was negatively associated with brain volume.

The findings from this thesis have demonstrated an association between menopause and the brain, which cannot be uniquely explained by ageing. Specifically, although menopause alone was not found to be negatively associated brain health, it was associated with somewhat poorer brain health when considered concurrently with other changes around menopause. Moreover, when considering that women tend to gain abdominal fat around menopause, as well as develop an unfavourable lipid profile, and given extensive evidence in the literature that higher abdominal fat and lipid levels are associated with a greater risk of cerebro-vascular disease and dementia, hypothesising a link between menopause and poorer brain health seems warranted but will require further confirmation in future research.

As a whole, the findings from this thesis paint an optimistic picture for women's health, since the risk factors identified and linked with deleterious brain health outcomes are modifiable. If adequate support is available at a health policy, clinical and community level, these specific risks to brain health may be reduced or prevented.

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1 Introduction

1.1 General introduction

The average age at menopause is between 46 and 52 years of age (Schoenaker et al., 2014). Given the average life expectancy of women in developed countries is approximately 82 years (Murray et al., 2015), women will, on average, spend almost 40% of their lives in a postmenopausal state. An important health challenge facing postmenopausal women involves maintaining a healthy brain, given dementia is one of the leading causes of death for women globally (GBD 2019 Collaborators, 2021). Moreover, global health statistics from 2019 indicate almost twice as many women died from dementia than men (GBD 2019 Collaborators, 2021). In part, this is due to the increased life expectancy of women, however, more research is required to determine what role menopause may play in maintaining brain health.

The aim of this thesis is to investigate possible direct and indirect associations between menopause and measures of brain health. Moreover, an important focus of this thesis is to determine how much of the observed effects are attributable to ageing compared with a possible effect of menopause. This has been a significant challenge in this area of research because menopause and ageing co-occur. Consequently, the use of a large dataset, such as the UK Biobank study (Sudlow et al., 2015), in conjunction with careful methodological and statistical considerations are necessary, to reliably establish whether a possible effect of menopause on brain health exists, beyond the effect of ageing.

This chapter critically evaluates and discusses evidence relating to the direct and indirect associations between menopause and measures of brain health. Specific **Thesis aims** are introduced, followed by the **Thesis outline**, which provides a summary of key findings from the research reported in Chapters 2-6. Chapters **2** and **3** present results from meta-analyses, which precisely quantify the differences in total fat mass and lipid profiles between premenopausal and postmenopausal women. **Chapter 4** explores the degree of heterogeneity in menopause nomenclature in the literature. **Chapter 5** investigates how longitudinal changes in fat mass, particularly central fat, are associated with brain health. **Chapter 6** investigates the association between measures of menstruation history (including menopause and age at menopause) and brain health. Finally, **Chapter 7** summarises and discusses the implications of these findings in the context of the existing literature; proposes a number of robust insights/recommendations that have emerged from the findings of this thesis (see **Summary of recommendations**); and explores **Future research directions**.

1.2 Menopause

The word *menopause* comes from the Greek words *meno*, which means month, and *pause*, which means stop, thus indicating the end of monthly cycles or menstruation. Menopause is defined as the permanent cessation of menstruation (Harlow et al., 2012). Natural menopause is recognised to have occurred after 12 consecutive months of amenorrhea (i.e. absence of menstruation), for which no other obvious pathological or physiological cause could be determined (World Health Organization, 1980, 1996). Induced menopause, however, is defined as the cessation of menstruation which follows either surgical removal of both ovaries such as an oophorectomy, or iatrogenic ablation of ovarian function including chemotherapy or radiation (World Health Organization, 1980, 1996).

Menopause is associated with diverse social/cultural perspectives and psychological, biological and physiological changes. This thesis will primarily focus on some key biological/physiological changes associated with menopause that are related to brain health.

1.2.1 Biology of menopause

Menopause is a stage of female reproductive ageing that forms a critical part of reproductive senescence (i.e. a decline in reproductive success with increasing age) (Harlow et al., 2012; Lemaitre & Gaillard, 2017). Therefore, to better understand the biological/physiological changes that occur around menopause, it is important to consider menopause within the context of female reproductive ageing.

At a biological level, reproductive ageing in women is characterised by the progressive decline in quality and quantity of the oocytes (i.e. immature ovum or egg cell) residing within the follicles present in the ovarian cortex (Broekmans et al., 2009; Wallace & Kelsey, 2010). The reproductive period begins with menarche, which typically occurs between 11 and 16 years (mean age = 13.53 years and standard deviation [SD] = 0.98 years) (F. Thomas et al., 2001) and is defined by the onset of menstruation (Harlow et al., 2012). However, follicular loss begins in utero and proceeds after birth at a rapid rate (Markstrom et al., 2002). More than 99.9% of ovarian follicles present at birth never reach ovulation, primarily due to apoptosis (i.e. programmed cell death) (Markstrom et al., 2002). After birth, the high rate of follicle loss progressively slows down so that at menarche, approximately 300,000 to 400,000 follicles remain and at menopause, less than 1000 follicles remain (Markstrom et al., 2002). The primary processes that drive follicular loss after birth include ovulation and atresia (i.e. an apoptotic process that occurs throughout the life-course until menopause and results in the progressive degeneration of ovarian follicles) (B. L. Harlow & Signorello, 2000). Approximately 300 to 400 follicles will be lost through ovulation over the life-course, with the remainder lost

via atresia (B. L. Harlow & Signorello, 2000).

Hormonally, the menstrual cycle is regulated by the hypothalamic-pituitary-gonadal (HPG) axis (Silberstein & Merriam, 2000). The KNDy hypothesis suggests a group of colocalised neurons in the hypothalamus, including kisspeptin, neurokinin B (NKB) and dynorphin (collectively called KNDy neurons), form a critical component of gonadotropin-releasing hormone (GnRH) pulse regulation (Moore et al., 2018). Specifically, GnRH pulse onset is initiated by NKB, which acts upon reciprocally connected KNDy neurons to stimulate kisspeptin release (Moore et al., 2018). Conversely, GnRH pulse termination is regulated by the release of dynorphin from KNDy neurons, which inhibit NKB and kisspeptin secretion (Moore et al., 2018). Kisspeptin contributes to the onset of puberty by increasing the secretion of GnRH, which stimulates the anterior pituitary gland to release luteinising hormone (LH) and follicle-stimulating hormone (FSH) (Cortés et al., 2015; Silberstein & Merriam, 2000; Skorupskaite et al., 2014). LH stimulates the theca cells of ovarian follicles to produce progesterone and androstenedione (Silberstein & Merriam, 2000). FSH stimulates the aromatase enzyme in granulosa cells of ovarian follicles to convert androstenedione to testosterone and then to 17-β-estradiol (E2; the most active and prevalent form of estrogen) (Silberstein & Merriam, 2000). In the early to mid-follicular and luteal phases of the menstrual cycle, increasing levels of 17-β-estradiol and progesterone, respectively, act on the hypothalamus and anterior pituitary gland to form a negative feedback loop, thereby suppressing FSH and LH secretion (Silberstein & Merriam, 2000). The granulosa cells also produce inhibins, which contribute to the negative feedback loop by further lowering FSH levels (Silberstein & Merriam, 2000). However, in the late follicular phase, rising levels of 17-β-estradiol act on the hypothalamus and anterior pituitary gland to form a positive feedback loop, causing a surge in LH (Silberstein & Merriam, 2000). FSH levels also increase, however, not to the same degree due to the negative feedback from inhibin (Silberstein & Merriam, 2000).

As reproductive ageing progresses, the depletion of ovarian follicles is associated with a decline in ovarian estrogen, progesterone and inhibin production causing increased FSH and LH levels (Al-Azzawi & Palacios, 2009; Burger, 2002; Harlow et al., 2012). Moreover, primate studies have indicated secondary to ovarian failure, KNDy neurons undergo hypertrophy, resulting in the increased expression of kisspeptin (Rance, 2009; Rometo et al., 2007). Notably, the secretion of androgens, such as testosterone, do not vary as a consequence of menopause (Burger, 2006; Davison et al., 2005). After menopause, the most prevalent form of estrogen is estrone (E1), which is primarily derived from the conversion of adrenally secreted androstenedione via aromatase found in adipose tissue (Burger, 2006; Simpson & Davis, 2001).

Clinically, the hormonal profile for postmenopausal women can result in symptoms such as hot flushes, night sweats and vaginal atrophy (Hickey et al., 2005). The vasomotor symptoms, such as hot flushes, are likely due to KNDy neurons projecting to thermoregulatory regions of the brain (Rance et al., 2013). The severity of symptoms in some women may require the use of treatment for management (Hickey et al., 2005), which are discussed in further detail below.

1.2.2 Hormone replacement therapy

It is important to discuss hormone replacement therapy (HRT, also known as hormone therapy; HT and menopausal hormone therapy; MHT) because of its close relationship with menopause and the brain. Therefore, the following sections provide an overview of the evolution of HRT treatment including the production and composition of HRT (and their associated risks) and current guidelines and trends for HRT use. The links between HRT use and the brain, including the differences in effects and recommended treatment associated with the timing of HRT use (i.e. the 'timing hypothesis') are discussed in **Hormone replacement therapy use and brain health**.

1.2.2.1 Evolution of treatment HRT is defined as therapy containing estrogen or an estrogenic-like compound, such as tibolone, often used to treat symptoms associated with menopause (Pinkerton, 2020). HRT was introduced in the 1940s to help ameliorate some of the short-to-intermediate consequences of menopause, including hot flushes, night sweats, vaginal atrophy and bone loss (Wentzensen & Trabert, 2015). Despite still being used for these purposes, the composition of commercially available HRT has changed substantially over the years due to their associated risks (Davis et al., 2005; Kohn et al., 2019). Initially, HRT was composed solely of estrogen derived from the urine of pregnant women (Davis et al., 2005; Kohn et al., 2019). However, the high cost and low yield of production led to the development of conjugated equine estrogens (CEE; derived from pregnant mare urine) and synthetic forms of estrogen (such as diethylstilbestrol) (Davis et al., 2005; Kohn et al., 2019). By the 1970s, research indicated that women who used estrogen therapy had a 350% to 660% increased risk of endometrial cancer compared with non-users (Smith et al., 1975; Ziel & Finkle, 1975). Since then, available estimates from a meta-analysis suggest estrogen users have 130% increased risk of endometrial cancer compared with non-users (95% confidence interval [CI]: 110% to 150%) (Grady et al., 1995). Importantly, this risk increased with increasing dosage and duration of estrogen use (Grady et al., 1995). Although, for reasons currently unknown, the risks of endometrial cancer were significantly lower with the use of synthetic estrogen (women who have ever used HRT have a 30% increased risk compared with women

who have never used HRT, 95% CI: 10 to 60%) (Grady et al., 1995). Notably, the addition of progestin for 10 or more days per month mitigates any risk of endometrial cancer associated with estrogen use (M. C. Pike et al., 1997). However, epidemiological studies have since indicated that estrogen and progestogen use is associated with other health risks, including a 14% increased risk of breast cancer (compared with women who have never used HRT) which increased with increasing duration of use ($\geq$ 5 years use of HRT vs women who have never used HRT; 35%, 95% CI: 21% to 49%) (Cancer, 1997). Importantly, this effect reduces after cessation of HRT and disappears after 5 years ($\geq$ 5 years cessation of HRT vs women who have never used HRT; 7%, 95% CI: -3% to 18%) (Cancer, 1997).

In the 1990s, several cohort studies suggested HRT use in postmenopausal women could be beneficial for the prevention of osteoporosis, coronary heart disease and dementia (Grodstein et al., 1997; Stampfer & Colditz, 1991; Yaffe et al., 1998). These early results led to the development of the Women's Health Initiative (WHI) double blinded randomised controlled trial, which supported the use of HRT (comprising CEE and medroxyprogesterone acetate [MPA]) for the reduction of osteoporotic fractures by 24% (95% CI: 15% to 31%) (Rossouw et al., 2002). Surprisingly, HRT use increased coronary heart disease risk by 29% (95% CI: 2% to 63%) and indicated a possible 26% increased risk of breast cancer (95% CI: 0% to 59%), which raised concerns given the evidence of potential harm to participants involved (Rossouw et al., 2002). Furthermore, a subgroup of 7510 women in the WHI, aged 65 and older participated in the Women's Health Initiative Memory Study (WHIMS), which found HRT use increased the risk for probable dementia (i.e. dementia diagnosis established by clinical and neuropsychological examination) by 105% (95% CI: 21% to 248%) (Shumaker et al., 2003). The health risks from the WHI were deemed to exceed the benefits and the trial was stopped early (average follow-up, 5.2 years; planned duration, 8.5 years) (Rossouw et al., 2002). Notably, follow up studies revealed that CEE alone had no benefit nor harm on coronary heart disease (Hsia et al., 2006), nor probable dementia risk (Shumaker et al., 2004) and lowered the risk of breast cancer by 45% (95% CI: 66% to 11%) (Chlebowski et al., 2015). Despite these more recent findings, the aforementioned endometrial cancer concerns do not support the use of unopposed estrogen in women with a uterus and require other forms of HRT to be further investigated.

The generalisability of findings from the WHI to early postmenopausal women (i.e. within 5 years since the final menstrual period (Harlow et al., 2012)) warrants caution, given 67% of women in the WHI study were $\geq$ 60 years and 100% of women in the WHIMS study were $\geq$ 65 years (Rossouw et al., 2002; Shumaker et al., 2003). Moreover, majority of women in the WHI had never used HRT before and were predominantly asymptomatic, which is

not representative of the majority of early postmenopausal women who seek HRT for the treatment of symptoms associated with menopause (Ettinger et al., 1999). However, the findings from the WHI were instrumental in shaping the current guidelines for HRT use.

1.2.2.2 Guidelines and trends for hormone replacement therapy use The current guidelines suggest HRT use is not recommended without a clear indication, such as the treatment of menopausal symptoms, and should not be used for the prevention of cardio-metabolic diseases (de Villiers et al., 2016; Moyer & U.S. Preventive Services Task Force, 2013). Furthermore, women who choose to use HRT must be informed of the risks and the dosage should be titrated to the lowest most appropriate and effective dose (de Villiers et al., 2016). Currently, women who have previously had breast cancer should not use HRT (de Villiers et al., 2016).

The lack of careful, considered and critical media coverage of the initial findings from the WHI study (Brown, 2012) likely contributed to the decline in the prescription and use of HRT in western countries after 2001 (Collaborative Group on Epidemiological Studies of Ovarian Cancer, 2015; Ettinger et al., 2012; Steinkellner et al., 2012). Interestingly, an 18 year follow up study of the WHI participants found no association between the use of HRT (CEE + MPA or CEE alone) and risk of cardiovascular disease (CVD), cancer or all-cause mortality (Manson et al., 2017), which further support current practice guidelines for HRT use (de Villiers et al., 2016). The forthcoming decades will determine whether more recent findings and guidelines will influence future trajectories for the prescription and use of HRT.

Notably, HRT use for the treatment of menopausal symptoms is closely tied to age at menopause onset (Ettinger et al., 1999; Harlow et al., 2012), which is discussed in detail below.

1.2.3 Age at menopause

Aristotle (384 to 322 B.C.) noted "fifty marks the limit of the capacity of reproduction in women" (Amundsen & Diers, 1970). Current research indicates that menopause typically occurs between 46 to 52 years (mean age at natural menopause [ANM] = 48.78 years, SD = 1.45 years) (Schoenaker et al., 2014), with a 61% chance of having experienced menopause by age 52 years (Cramer & Xu, 1996).

Changes in sex hormones have been investigated as possible predictors of age at menopause. For example, Anti-Mullerian hormone (AMH) is a peptide growth factor produced by granulosa cells of ovarian follicles in women (Vigier et al., 1984). The decrease in the number of ovarian follicles with age has been associated with decreased AMH levels (de Vet et al., 2002; van

Rooij, 2002). Since AMH is detectable in peripheral circulation (Kevenaar et al., 2006) and does not change in response to an acute endogenous rise in FSH, unlike estrogen and inhibins, it has emerged as a possible biomarker for measures of ovarian ageing (de Vet et al., 2002; Feyereisen et al., 2006; van Rooij, 2002). Although, evidence suggests that the combination of AMH and age does not provide a statistically significant improvement to predictions of time to menopause than age alone (Age C-statistic = 84%, 95% CI = 83 to 86%; Age + AMH C-statistic = 86%, 95% CI = 85 to 87%) (Depmann et al., 2018).

The reasons why predicting age at menopause is important are discussed in **Health outcomes associated with menopause**. However, it is important to note that age and AMH levels do not completely predict age at menopause (Depmann et al., 2018; Freeman et al., 2012). This is likely because other genetic and environmental/lifestyle factors are associated with the onset of menopause and are discussed next.

1.2.3.1 Factors that may influence age at menopause As highlighted in **Biology of menopause**, age at natural menopause is determined by the non-renewable ovarian reserve, which is established during fetal development and continuously depleted until reproductive senescence (Broekmans et al., 2009; Ruth et al., 2021; Wallace & Kelsey, 2010). A meta-analysis of 22 genome-wide association studies (GWAS), consisting of 38,968 women of European descent has identified 17 loci associated with age at natural menopause (Stolk et al., 2012). Genes within these areas that were significantly associated with age at natural menopause were related to DNA damage, repair and replication (discussed in more detail in **Genomic instability**), thus highlighting the importance of this pathway in determining age at menopause via ovarian reserve and its rate of depletion (Ruth et al., 2021). Notably, all 17 loci accounted for 2.5% - 4.1% of the observed variance in age at natural menopause (Stolk et al., 2012). Given available scientific evidence suggests that approximately 31% to 74% of the variation in age at menopause can be explained by genetic factors (Murabito et al., 2005; Snieder et al., 1998; Treloar et al., 1998; van Asselt et al., 2004), it is likely that many more genetic loci predicting age at natural menopause remain to be found.

1.2.3.1.1 Mother's and sister's age at menopause Studies of twins have found that five years after their co-twins had undergone menopause, 86% of monozygotic twins (single egg fertilised to form one zygote and then divides into two separate embryos) whereas 55% of dizygotic twins (two eggs fertilised by two sperms to form two zygotes) had reached menopause themselves (Snieder et al., 1998). Notably, the average age at menopause for monozygotic and dizygotic twins was 49 and 48 years respectively and the standard deviation for age at menopause was less than 5 years for both monozygotic and dizygotic twins (monozygotic

twins SD = 4.5; dizygotic twins SD = 4.8) (Snieder et al., 1998). Given that approximately 68% of monozygotic and dizygotic twins would have undergone menopause between 43 and 54 years, these findings indicate that a strong genetic component likely underlies age at menopause. This is consistent with research on mother-daughter pairs, which has indicated the heritability of menopausal age to be 44% (95% CI: 36% to 50%) (van Asselt et al., 2004). However, heritability estimates, particularly from twin registries, tend to overestimate genetic contributions, as heritability estimates cannot effectively distinguish between genetic factors and early shared environmental influences or household exposures that are similar among family members. Since many of the environmental factors are unmeasured or unknown, adjustments are not possible.

Women are 5-6 times more likely to have early menopause (i.e. age at menopause < 45 years) if their mother has also experienced early menopause (Cramer et al., 1995; Torgerson et al., 1997). However, conclusions may be limited by a reliance on self-reported data and consequently recall bias, given the low to moderate proportion of women who know their mother's menopausal age. For example, one study reported as low as 51% of their sample were able to provide their mother's age at menopause (Torgerson et al., 1997). Similarly, further bias may arise from women who have experienced early menopause, as they may be more likely to remember if their mothers and sisters also had similar experiences (Torgerson et al., 1997).

In summary, there is likely a strong genetic component to age at menopause, however, reported estimates may be larger than the true effect and also susceptible to recall bias. These factors may, in part, help explain the heterogeneity in reported effects despite the consistency in the direction of the association. Given reported genetic estimates, it is likely that 30 to 50% of variation in age at menopause may be related to environmental factors. As a result, teasing apart the genetic and environmental/lifestyle factors remains an important area for future research.

1.2.3.1.2 Age at menarche Age at menarche represents a measure of ovarian follicular reserve and may be an important determinant of age at menopause (Wallace & Kelsey, 2010). A key consideration when examining the association between age at menarche and age at menopause is the accuracy of self-reported age at menarche in middle age, given the extended interval between age at menarche and data collection (Cooper et al., 2006). A longitudinal study of 1000 women self-reported age at menarche at 48 years of age, which was compared with medical records during their adolescence (Cooper et al., 2006). Less than half (43.6%) accurately recalled their age at menarche onset (Cooper et al., 2006). Moreover, the

correlation between self-reporting in later adulthood and adolescent medical records was only moderate (r = 0.59) (Cooper et al., 2006). However, correlations are not very good indices of accuracy of reporting. This is because most women experience menarche between 11 and 16 years and this event is not normally distributed around a mean in the population of 13.53 years and a standard deviation of 0.98 years (F. Thomas et al., 2001). Using Chebyshev's inequality (which states that at least 75% of data values of any distribution must be within two standard deviations from the mean), 75% of the sample of 1,000 women (i.e. 750 women) would fall between 11.57 and 15.49 years (a period of 1,431 days). On average, these women will experience menarche approximately 2 days apart from one another (1,431 days/750 women = 1.91 days/women). Regression dilution means that if each woman makes an error in their estimation of age at menarche from 0 to 180 days in a random direction, the correlation between age at menarche reported at adolescence and age at menarche reported at 48 years could be dramatically reduced, despite excellent recollection (i.e. within 6 months of accuracy, given age at menarche is typically abstracted up to a year in most datasets). In contrast, the mean error for reporting/recall (i.e. recalled age at menarche - original age at menarche) is a more useful measure when assessing accuracy. Previous studies have revealed the mean recall error is less than .08 years (Must et al., 2002). This suggests that long term recall of age at menarche is a relatively accurate measure.

The association between age at menarche and age at menopause appears inconsistent (Roman Lay et al., 2020). Some studies have found women who reach menarche at younger ages are also more likely to reach menopause at younger ages (Brand et al., 2015; Henderson et al., 2008; Mishra et al., 2017; Ruth et al., 2016), whereas others report no association (Nagel et al., 2005; Yasui et al., 2012). Mendelian randomisation studies have indicated potential causal relationship between later age at menarche leading to a later age at menopause (C. Prince et al., 2022). One possible explanation is that the size of the effect is small and therefore requires a large sample size to detect the effect. A large cohort study of 273,474 women indicated that every 1 year earlier age at menarche below 11 years was associated with a 3% increased odds (99.995% CI: 1% to 6%) of earlier age at menopause (Ruth et al., 2016). Another large cohort study of almost 340,000 women found that age at menopause was almost independent of age at menarche (Bjelland et al., 2018). However, women who were 16 years or older at menarche reached menopause 1 year later than the reference group (menarche at 13 years) (Bjelland et al., 2018). Taken together, these findings indicate a weak and possibly non-linear relationship between age at menarche and age at menopause. A recent meta-analysis revealed no significant linear relationship between age at menarche and age at menopause, although, possible non-linear relationships were not explored (Roman Lay et al., 2020).

1.2.3.1.3 Smoking Previous reviews of the literature indicate smoking is a prominent determinant of earlier age at menopause (Parente et al., 2008; Schoenaker et al., 2014; Sun et al., 2012). Meta-analyses have revealed that the onset of menopause in women who smoke regularly occurred up to one year earlier compared to their non-smoking counterparts (Schoenaker et al., 2014; Sun et al., 2012). One possible biological mechanism proposed to explain these findings is the cumulative exposure to polycyclic aromatic hydrocarbons, which is found in tobacco smoke and leads to irreversible damage to ovarian follicles (Essenberg et al., 1951; Mattison & Thorgeirsson, 1978). Contrary to this hypothesis, smoking has been shown to be associated with hormonal production, including decreased serum estrogen (Meek & Finch, 1999) and increased androgen levels (Bancroft & Cawood, 1996), which may contribute to earlier natural age at menopause. Thus, it is likely multiple mechanisms are involved, however, evidence suggests smoking may influence hormone levels in a way that is reversible upon cessation of smoking (Tziomalos & Charsoulis, 2004) and is consistent with a meta-analysis that reported no significant differences in age at natural menopause between ex-smokers and non-smokers (Schoenaker et al., 2014).

An important limitation to this area of research has been the diverse criteria used to classify/define cigarette smoking and menopause, which may have also influenced the precision of estimates. Notably, the degree of heterogeneity of menopause nomenclature in the literature is discussed in greater detail in **Chapter 4** of this thesis.

1.2.3.1.4 Geographical location and socioeconomic factors Age of menopausal onset has been reported to vary by geographical region (Palacios et al., 2010; Schoenaker et al., 2014). In particular, age at natural menopause is lowest among African, Latin American, Asian and Middle Eastern countries (approximately 48 years of age) and highest in Europe and Australia (approximately 51 years of age), followed by America (approximately 49 years of age) (Schoenaker et al., 2014). Meta-regression analyses have revealed that 68.5% of the variability in age at menopause was accounted for by geographic region (Schoenaker et al., 2014). Beyond genetic and racial factors (Murabito et al., 2005; F. Thomas et al., 2001), these findings suggest that age at menopause may be associated with socioeconomic factors and/or other lifestyle differences that vary between regions. However, there is little consensus in the literature regarding the association between factors related to socioeconomic status and age at menopause. This is likely because factors related to socioeconomic status interact in multiple ways to produce different outcomes. Therefore, the following section explores the relationships between key socioeconomic variables related to age at menopause, including education, access and use of oral contraceptives, age at primiparity (i.e. a woman giving birth for the first time), gravidity (i.e. number of times a woman has been pregnant) and

professional occupation, and further discusses ways in which these factors may interact.

Results from a systematic review with meta-analysis of 9 cross-sectional studies concluded both middle and high education levels were associated with four and eight month later age at natural menopause, respectively, compared with low education (Schoenaker et al., 2014). Although, it is possible that these results are confounded or mediated by other unmeasured socioeconomic factors related to age at menopause. For example, women who have a university level education, a higher income and higher job stability, all of which are indices of higher socioeconomic status, tend to have their first child later (Molina-García et al., 2019). Research has revealed that the increasing age at first full term pregnancy is associated with later age at natural menopause (Nagel et al., 2005). Although, medical reasons were also cited as a key explanation for advanced maternal age (Molina-García et al., 2019). Taken together, these factors likely suggest that a later age at menopause may be related to factors indicative of better socioeconomic circumstances.

In 2012, most global pregnancies took place in regions where age at menopause was lowest, including 56% in Asia and 25% in Africa (Sedgh et al., 2014). These statistics likely reflect regional population size and age differences, however, they may also represent socioeconomic status, which has been acknowledged as both a cause and consequence of the number of pregnancies, particularly unintended pregnancies (Bearak et al., 2018). Additional possible explanations include differing access to quality health care, nutrition and education (Canavez et al., 2011; Moslehi et al., 2017). Moreover, these results may, in part, reflect regional access and use of oral contraceptives (Global prevalence: 8%; Asia: 5.3%; Africa: 5.8%; Developed regions: 16.5%) (Christin-Maitre, 2013; United Nations, 2019), which may help explain why oral contraceptive use is associated with a later age at menopause (Roman Lay et al., 2020). Other socioeconomic dimensions, including professional occupation, revealed age at natural menopause was later in women with a middle or high occupation level compared with low occupation level (Schoenaker et al., 2014). The mechanisms underlying these associations remains unclear. This highlights that teasing apart the underlying socioeconomic factors that may mediate the relationship between socioeconomic status and age at menopause has proven difficult and requires further investigation.

1.2.3.1.5 Fat mass A systematic review with meta-analysis of six cross-sectional published studies and unpublished data from the Longitudinal Study on Women's Health indicated that there was no clear association between overweight or obesity and age at natural menopause (Schoenaker et al., 2014). However, when compared with those who had a normal body mass index (BMI; $18.5 kg/m^2$ to $24.9 kg/m^2$), those who suffered from overweight or obesity had a

later age in menopause (Schoenaker et al., 2014). One possible biological mechanism that may help explain these findings is the elevated circulating levels of estrogen in women who suffer from overweight and obesity, which may result in delayed age at natural menopause (Leidy, 1996). This is because adipose tissue has a major endocrine function (Trayhurn, 2005) whereby it synthesises estrogens from androgens (L. R. Nelson & Bulun, 2001). Therefore, increased adiposity is likely to promote higher levels of circulating estrogen, which may result in delayed age at natural menopause. However, another possibility is that the accumulation of fat mass during midlife is confounded by ageing (Kuk et al., 2009), which closely covaries with age at natural menopause (see **Age at menopause**). Therefore, future research will need to delineate precisely how fat mass changes around menopause, and how much of this change is attributable to ageing. This will allow future researchers to partition out the effect of age when assessing the association between changes in fat mass and age at menopause by comparing typical fat mass trajectories attributable to ageing compared with a possible effect of menopause. These questions are addressed in **Chapter 3** of this thesis.

1.2.4 Health outcomes associated with menopause

There are health benefits and costs to having early or late menopause, depending on which measures of health are assessed. Earlier menopause has been associated with greater risk of osteoporosis ($<$ 47 vs $\geq$ 47 years; 83%, 95% CI: 22% to 174%) (Svejme et al., 2012), cardiovascular disease (CVD; <50 vs 50 years; 25%, 95% CI: 15% to 35%) (Atsma et al., 2006), all-cause mortality ($<$ 45 vs $\geq$ 45 years; 12%, 95% CI: 3% to 21%) (Muka et al., 2016), and increased odds of type II diabetes ($<$ 45 vs 45-55 years; 15%, 95% CI: 4% to 26%) (Anagnostis et al., 2019). Furthermore, early age at menopause has been associated with indices of accelerated ageing, such as the GrimAge index which is a composite measure for age and surrogate biomarkers of physiological risk factors and stress factors (A. T. Lu et al., 2019). In contrast, late menopause has been associated with increased incidence of breast ($\geq$ 55 vs 50-54 years; 12%, 95% CI: 7 to 17%) ("Menarche, Menopause, and Breast Cancer Risk," 2012), ovarian ($>$ 52 vs $\leq$ 45 years; 46%, 95% CI: 6% to 99%), (Tsilidis et al., 2011) and endometrial cancer ($\geq$ 55 vs 45 to 49 years; 53%, 95% CI: 13% to 106%) (Karageorgi et al., 2010).

Given these findings, it is important to explore the possible evolutionary origins of menopause to better understand the raison d'être for menopause and its association with health outcomes.

1.2.5 Evolutionary origins

Reproduction is a key component of the theory of evolution and the survival of a species (Darwin & Bynum, 2009). One reason for this is because reproduction enables favourable characteristics to be passed on through genetic material from parents to offspring (Darwin & Bynum, 2009). In most species, reproductive senescence and somatic senescence occur at similar rates (Kirkwood & Shanley, 2010). However, in some circumstances, reproductive senescence is accelerated relative to somatic senescence, leading to a prolonged post-reproductive lifespan (Croft et al., 2015). The question of why some species experience reproductive senescence before the end of their natural lifespan remains an unsolved problem in biology (Medawar, 1952; G. C. Williams, 1957).

Initially, it was proposed that prolonged post-reproductive lifespans were reflective of improvements in medicine and living standards (Croft et al., 2015). However, prolonged post-reproductive lifespans have been reported in some species other than homosapiens, including resident killer whales, short-finned pilot whales, narwhals and beluga whales (Croft et al., 2015; Ellis et al., 2018). The existence of menopause and prolonged post-reproductive lifespans in animals living in the wild highlights that it is unlikely to be solely due to improvements in health care and mortality rates. Another possibility is the grandmother hypothesis (Hawkes et al., 1998; Hawkes et al., 1997), which postulates that post-reproductive females increase the survival or reproductive success of their offspring by enabling their children to breed earlier, more frequently and successfully (Lahdenperä et al., 2004). This contribution likely confers a survival advantage through enhanced parental support and protection. It also ensures that women are not subjected to the increased mortality risks associated with late-life pregnancy, which is linked to lower offspring survival (Penn & Smith, 2007). Furthermore, menopause reduces intergenerational conflict over resources associated with reproduction, known as the reproductive conflict hypothesis (Cant & Johnstone, 2008). However, there is mixed support for the grandmother hypothesis, which is partly related to assumptions used in statistical models (Croft et al., 2015).

These hypotheses are grounded within the theory of evolution by means of natural selection, which suggests that there is likely a selective advantage, or at least a comparatively smaller disadvantage of menopause, given it has remained, despite possible selective pressures (e.g. competition for resources associated with reproduction) (Darwin & Bynum, 2009). However, the possible social and evolutionary benefits of menopause outlined above, may not necessarily extend to positive health outcomes. Therefore, it is important to explore the physiological changes associated with menopause, which can influence health outcomes.

1.2.6 Physiological changes associated with menopause

To better understand the health outcomes associated with menopause, we need to determine precisely what physiological changes occur around menopause. This thesis will primarily focus on changes in fat mass and cholesterol/lipid levels around menopause. This is because overweight and obesity are major societal problems associated with a number of deleterious health and wellbeing outcomes including type II diabetes (Guh et al., 2009), dementia (Anstey et al., 2011) and cardiovascular disease (CVD) (Wilson et al., 2002) resulting in a significant global disease burden (Withrow & Alter, 2011) and poorer quality of life (Larsson et al., 2002). Available evidence suggests obesity accounts for between 0.7 to 6% of total health care costs in many developed countries (Withrow & Alter, 2011; World Health Organization, 2007). When costs associated with being overweight are included, estimates increase to 9.1% (standard error [SE] = 4.6%) (Finkelstein et al., 2003). These costs will likely rise over time, given current trends indicate that by 2030 approximately 60% of the world's adult population could be either overweight or obese; almost double the prevalence reported in 2005 (33%) (Kelly et al., 2008). The obesity epidemic has important implications for middle-aged women since they are disproportionately affected by obesity, compared with men (global obesity prevalence in adults (from 2005): Men = 7.7%, 95% CI: 7.4% to 7.9% and Women = 11.9%, 95% CI: 11.6% to 12.2%) (Kelly et al., 2008; Swinburn et al., 2011).

Dyslipidemia is also a significant risk factor for CVD (Liu & Li, 2015) and dementia (Anstey et al., 2017). For example, a meta-analysis revealed a low-density lipoprotein (LDL) level > 4 mmol/L was associated with a more than six-fold risk of CVD relative to a LDL level < 2.5 mmol/L (OR: 6.32, 95% CI: 3.00 to 13.32) (Akioyamen et al., 2019). High total cholesterol in midlife (> 6.5mmol/L) was associated with a 114% increased dementia risk (95% CI: 33% to 244%), compared to those who did not have high total cholesterol in midlife (Anstey et al., 2017). Taken together, these findings are of particular importance for women as CVD is one the leading causes of death in women worldwide, closely followed by dementia (H. Ritchie & Roser, 2018; World Health Organization, 2013). Although, in some countries such as the UK and Australia, dementia is the leading cause of death in women, followed by CVD (H. Ritchie & Roser, 2018; World Health Organization, 2013). Many potential mechanisms have been implicated. Those directly related to menopause are discussed below. Less specific biological mechanisms related to ageing, are discussed in the **Physiological changes associated with midlife** section of this thesis.

1.2.6.1 Fat mass changes associated with menopause Animal studies have found ovariectomised (OVX) mice, used as models for human menopause, gained 25% more weight

than mice undergoing a sham operation, despite consuming equal amounts of food (Rogers et al., 2009). Furthermore, OVX mice had decreased energy expenditure, without any changes in energy intake, resulting in adipocyte hypertrophy, adipose tissue inflammation and hepatic steatosis (i.e. fatty liver) (Rogers et al., 2009). Notably, the use of estrogen has been shown to protect female mice from adipocyte hypertrophy, adipose tissue oxidative stress, inflammation and fatty liver disease (Stubbins et al., 2012). These findings suggest that hormonal changes, particularly the reduction in estrogen levels, may in part be associated with the observed increases in fat mass around menopause. However, one limitation of using OVX animal models for menopause is that they more closely reflect surgically induced menopause than natural menopause. The abrupt removal of ovaries in the OVX animal models means gradual changes in hormones around menopause are not accurately represented. This can be problematic, since distinct differences in health outcomes exist between women who undergo surgical menopause compared with natural menopause, particularly for neurological health. For example, women who underwent either unilateral or bilateral oophorectomy before the onset of menopause had a 46% (95% CI: 13% to 90%) increased risk of cognitive impairment or dementia compared with women who had not had an oophorectomy (Rocca et al., 2007). As a result, the limitations of the OVX animal model led to the development of an accelerated ovarian failure model of menopause, which used 4-vinylcyclohexene diepoxide (VCD) to selectively accelerate the natural loss of primordial follicles (Van Kempen et al., 2011). When administered at low doses, VCD causes apoptotic cell death of primordial follicles, but it does not affect peripheral tissues, including that of the liver, nor does it affect brain inflammation markers (Van Kempen et al., 2011). Moreover, VCD-treated mice more accurately model the biology of menopause than OCV mice as demonstrated by increased levels of FSH, declining estrogen levels and irregular menstrual cycles as they become follicle-depleted. (Romero-Aleshire et al., 2009). Importantly, VCD-treated mice increased their weight more rapidly than premenopausal controls (Romero-Aleshire et al., 2009). These findings indicate that hormonal changes around menopause may be particularly relevant in modulating increases in body fat.

Other possible contributions to fat mass include kisspeptin (Dudek et al., 2018; Hudson & Kauffman, 2022; Hussain et al., 2015; Tolson et al., 2014). Thus far, kisspeptin has been discussed in the context of its role within KNDy neurons to contribute to the HPG axis and thermoregulation (Moore et al., 2018; Rance, 2009; Rance et al., 2013). However, kisspeptin signalling appears to regulate a wide variety of metabolic parameters including body weight and energy expenditure, adiposity and adipose tissue function, food intake, glucose metabolism, respiratory rates and locomotor activity (Dudek et al., 2018; Hudson & Kauffman, 2022; Hussain et al., 2015; Tolson et al., 2014). Notably, kisspeptin receptor knockout (KO) mice have indicated a sexually dimorphic role for kisspeptin in body composition (Hudson &

Kauffman, 2022; Tolson et al., 2014). Specifically, female kisspeptin receptor KO mice are 30% heavier than wild type controls, which was not observed in the male kisspeptin receptor KO mice (Hudson & Kauffman, 2022; Tolson et al., 2014). Body composition analyses revealed that the overall increase in bodyweight in female kisspeptin KO mice was primarily due to fat mass changes, with decreasing lean mass having a small but significant effect (Tolson et al., 2014). Notably, male kisspeptin receptor KO mice showed a 19% greater decrease in lean mass compared with KO females, which may explain the lack of detectable overall increase in body weight (Tolson et al., 2014). Analyses of metabolic rates and energy expenditure revealed that increased weight gain in female kisspeptin receptor KO mice results from reduced locomotor activity in the face of slightly reduced food intake and reduced energy expenditure, whereas thyroid hormone production is not disturbed (Tolson et al., 2014). These findings are seemingly incongruent with the increased expression of kisspeptin observed after ovariectomy, due to the hypertrophy of KDNy neurons (Rance, 2009; Rometo et al., 2007). Evidently, further research is required to evaluate the cause of body weight sex differences in kisspeptin receptor KO animals and the broader contributions of changes in KDNy neurons around menopause.

Most longitudinal studies in women have also revealed a significant increase in fat mass around menopause, however, the magnitude of reported effects varies substantially (Abdulnour et al., 2012; Akahoshi et al., 2001; Ford et al., 2005; Franklin et al., 2009; Janssen et al., 2008; Lee et al., 2009; Liu-Ambrose et al., 2006; Lovejoy et al., 2005; Macdonald et al., 2005; Razmjou et al., 2018; Soreca et al., 2009). For example, the average change in body weight between premenopausal and postmenopausal women ranges from 0.70kg to 6.69kg (Franklin et al., 2009; Lee et al., 2009; Liu-Ambrose et al., 2006; Lovejoy et al., 2005; Macdonald et al., 2005; Razmjou et al., 2018; Soreca et al., 2009), whereas mean change in body fat percentage ranged from 0.64% to 5.10% (Franklin et al., 2009; Lee et al., 2009; Lovejoy et al., 2005; Razmjou et al., 2018). The reasons for this are likely related to the hetereogeneity of measures used between studies when investigating fat mass changes in quantity and distribution. Moreover, factors such as varying sample sizes and length of follow up likely contribute to the observed variation in magnitude of reported change in fat mass. It is also possible that unmeasured and/or unreported genetic and environmental factors (e.g. ethnicity, dietary changes, physical activity levels, metabolic activity, and variation in sleep length and quality (Davis et al., 2012; Demerath et al., 2011; Patel et al., 2006; Sternfeld et al., 2004)) that varied between studies account for some of the observed differences in estimates. Furthermore, the heterogeneity in criteria used between studies when defining premenopausal and postmenopausal women may be particularly relevant. This is addressed in **Chapter 4** of this thesis.

The observed changes in fat mass in women may be related to hormonal shifts around menopause. As noted above, available evidence indicates that the decrease in endogenous estrogen levels associated with menopause may modulate body fat quantity and distribution (J. K. Park et al., 2013; Razmjou et al., 2018; Sowers et al., 2007; Tremollieres et al., 1996). Moreover, for women, hormonal shifts during midlife include having a higher androgen (i.e. testosterone) to estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition (Janssen et al., 2015). The accumulation of central fat, particularly visceral fat, has significant clinical implications since the best available estimates suggest a 1cm increase in waist circumference is associated with a 2% (95% CI: 1 to 3%) increased risk of CVD (De Koning et al., 2007). Indeed, some longitudinal studies have indicated postmenopausal women have higher waist circumference than premenopausal women (Janssen et al., 2008; Razmjou et al., 2018). One very small study (sample size = 8 women) reported a similar direction of effect, however, did not find any significant associations between menopausal status and waist circumference (Franklin et al., 2009), most likely due to inadequate statistical power. In addition, HRT use may also moderate possible changes in fat mass around menopause, although the evidence is currently unclear. Results from a Cochrane review reported no statistically significant differences in mean weight or BMI gain between women who either used or did not use HRT (Kongnyuy et al., 1999). However, this review was published more than 20 years ago and at a time when there were insufficient studies to examine the effect of HRT on other measures of fat mass including waist to hip ratio and body fat percentage. This prevented the authors from assessing whether a redistribution of body fat from the hips and thighs to the abdomen was associated with HRT use. Although, for abdominal obesity, a meta-analysis of 8 randomised controlled trials found postmenopausal women who used HRT had lower waist circumference and trunk fat than the placebo or no treatment groups (Salpeter et al., 2006). Taken together, these findings highlight that hormonal changes around menopause may be particularly relevant in modulating changes in fat mass and distribution. However, there is a need for a systematic review and meta-analysis that investigates multiple measures of fat mass, including measures of total, central and focal fat mass (i.e. leg fat), to more effectively detect possible redistribution effects, if they exist. This is addressed in **Chapter 2** of this thesis.

1.2.6.2 Cholesterol/lipid changes associated with menopause Lipid profiles are highly related to fat mass, particularly central obesity, however, the underlying pathophysiology is unclear (Hodson et al., 2015). Available evidence indicates that increased abdominal fat is associated with increased free fatty acid levels, increased insulin resistance and a pro-inflammatory state (Carr, 2003). These factors have been associated with increased low

density lipoproteins, increased triglycerides (TG) and decreased high density lipoprotein (HDL) (Carr, 2003; Vekic et al., 2019). Therefore, the observed increases in central fat across menopause may, in part, account for changes in lipid profiles.

Sex differences in lipid profiles have been observed across the lifespan. In men, after the age of 20, the total plasma cholesterol level concentration increases progressively from an average of 3.89 mmol/l at 20 years of age to 5.81 mmol/l at 50 years (Kreisberg & Kasim, 1987). Thereafter, cholesterol levels often remain stable until 70, prior to declining (Kreisberg & Kasim, 1987). In women, plasma cholesterol concentration is slightly higher than in men prior to 20 to 25 years of age, and increases more slowly with age until 55 to 60 years, when it becomes equal to men (Kreisberg & Kasim, 1987). Unlike in men, after 60 years plasma cholesterol concentration continues to increase in women and is approximately 0.65 mmol/l higher than men (Kreisberg & Kasim, 1987). Given an unfavourable lipid profile has been identified as an independent risk factor for cardiovascular disease, these results may help explain why premenopausal women have been found to have lower CVD incidence and mortality rates compared with men of the same age (Mikkola et al., 2013). In contrast, postmenopausal women experience higher mortality rates due to CVD compared to men of the same age (McAloon et al., 2016). Thus, these findings provide some support for the hypothesis that menopause related changes around midlife predispose women to sub-optimal lipid profiles and poorer health outcomes. However, it is also possible that these results reflect the selective survival of men with a healthier cardiovascular risk profile, since men have significantly higher cardiovascular mortality rates than women between the ages of 45 and 65 (Chêne et al., 2015). This survival bias suggests that men who live beyond 65 are typically healthier, which may partly account for the observed differences in lipid profiles between men and women.

One possible change around menopause that may influence lipid profiles includes a change in hormone levels, particularly estrogen. A longitudinal study revealed a 6% increase in total cholesterol (TC), an 11% increase in triglycerides and a 10% increase in low density lipoprotein levels within 3-6 months of menopause (Jensen et al., 1990). Furthermore, there is evidence that lipid profiles fluctuate at different stages of the menstrual cycle in premenopausal women, with the follicular phase (indicative of high endogenous estrogen levels) being associated with decreased TC, LDL and TG (Gaskins et al., 2010). Additionally, the use of hormone therapy has been linked with raised HDL and lowered LDL and TC levels (Godsland, 2001). These findings are supported by results of randomised controlled trials. For example, a randomised controlled trial found that women who used HRT had increased HDL and decreased LDL levels, compared with placebo, independent of age at menopause onset, baseline lipid values

and measures of fat mass (Binder et al., 2001). Taken together, these findings suggest that the decline in estrogen levels that accompanies menopause may have an adverse impact on the overall lipid profile of postmenopausal women.

Interestingly, while some studies report that HDL levels decrease after menopause onset (Jensen et al., 1990; Matthews et al., 1989), others suggest HDL levels remain unchanged (Fukami et al., 1995; J.-L. Zhou et al., 2010). The reasons for these differences remain to be elucidated but may be related to differences in study design and sampling. There is, therefore, a need for a precise synthesis of the existing literature to derive a pooled estimate that may better reflect the real effect. Moreover, a meta-analysis would better clarify typical lipid profile trajectories around midlife. Meta-regression analysis could partition out effects attributable to ageing, compared with a possible effect of menopause. This is addressed in **Chapter 3** of this thesis.

The changes in fat mass and cholesterol/lipid levels observed around menopause, while potentially caused by hormonal changes, could also be attributable to ageing changes. Consequently, the following section discusses ageing and its contributions to physiological changes around menopause and brain health.

1.3 Ageing

Ageing is defined as any change in an organism over time (Bowen & Atwood, 2004). The physiological and neurological changes associated with ageing are the components most related to the focus of this thesis and are discussed in detail below.

1.3.1 Biology of ageing

Ageing is a multifactorial process characterised by the progressive accumulation of damage caused in part by mitochondrial dysfunctions (Trifunovic & Larsson, 2008), Deoxyribonucleic acid (DNA) damage and failure of DNA repair mechanisms (J.-H. Chen et al., 2007; T. Lu et al., 2004), loss of proteostasis causing increased production of misfolded proteins (Hipkiss, 2006) and telomere shortening (Blasco, 2007). The accumulation of damage due to these processes increasingly leads to further cellular dysfunction, greater inflammation and oxidative stress, which progressively leads to cellular senescence and organ failure (Finkel & Holbrook, 2000; Herbig et al., 2006; Jurk et al., 2014). These mechanisms begin from conception (Aitken et al., 2009; Lane et al., 2014; Metcalfe & Alonso-Alvarez, 2010), however, the accumulated burden of pathology accumulates slowly over time (Currais, 2015). The ageing processes observed throughout the body is discussed in more detail in the following sections, given the

important implications for brain health, which is subsequently discussed (see **Brain ageing**).

1.3.1.1 Mitochondrial dysfunction Mitochondria generates cellular energy (adenosine triphosphate; ATP, via oxidative phosphorylation), which produces free radicals as a byproduct (Raha & Robinson, 2000). These free radicals can cause damage to mitochondrial DNA (see **Genomic instability**), which can form a positive feedback loop resulting in the overproduction of free radicals, leading to oxidative stress and inflammation, thereby causing cellular damage and senescence (Currais, 2015; Harman, 1972; Ziegler et al., 2015).

1.3.1.2 Genomic instability The accumulation of genetic damage throughout life is a key hallmark of ageing (López-Otín et al., 2013). Deoxyribonucleic acid (DNA) carries the genetic information for an organism to survive, develop and reproduce (López-Otín et al., 2013). DNA damage refers to alterations in the structure of DNA (Freitas & de Magalhães, 2011). A major cause of DNA damage includes free radicals, such as those produced by the mitochondria (De Bont & van Larebeke, 2004). There are a number of DNA repair mechanisms that are responsible for addressing DNA damage (C. J. Lord & Ashworth, 2012). However, excessive DNA damage or insufficient DNA repair can dysregulate gene expression (Oktay et al., 2015), trigger apoptosis (Norbury & Zhivotovsky, 2004) and cellular senescence (J.-H. Chen et al., 2007).

1.3.1.3 Loss of proteostasis Another hallmark feature of ageing includes dysfunctions in proteostasis (i.e. a network of biological pathways that maintain protein homeostasis by controlling protein synthesis, folding, trafficking, aggregation, disaggregation and degradation (Powers et al., 2009)), which is essential for the stabilisation of correctly folded proteins (Hipp et al., 2019; López-Otín et al., 2013). A source of proteostasis dysfunction include free radicals, which can cause protein misfolding/unfolding (Hipp et al., 2019). If protein degradation is not sufficient, misfolded proteins accumulate, forming protein aggregates, which can become cytotoxic (Hipp et al., 2019).

1.3.1.4 Telomere shortening Telomeres are protein-DNA structures located at the end of chromosomes that protect DNA as it breaks (i.e. during DNA replication) (Rhodes et al., 2002). Telomere length progressively shortens with each mitotic cell division and are therefore commonly used as an index for ageing (Blackburn et al., 2015; Blasco, 2007; Cawthon et al., 2003). The rate of telomere shortening is influenced by mechanisms/factors considered to accelerate ageing, including oxidative stress, obesity and smoking (Epel et al., 2004; Valdes et al., 2005; von Zglinicki, 2002). As a result, telomere exhaustion helps explain replicative senescence (Hayflick & Moorhead, 1961).

1.3.2 Brain ageing

The ageing processes observed throughout the body also occur in the brain and can lead to microstructural changes, which is discussed next.

1.3.2.1 Microstructural changes Microstructural changes in the brain include loss of dendrites and dendritic spines, shrinkage of dendritic trees and neural cell loss. For example, a 46% reduction in spine number and density has been reported in humans over 50 years of age, compared with those less than 50 years of age (B. Jacobs et al., 1997). The biological processes driving the microscopic changes in the brain are analogous to the processes observed throughout the body and are discussed below.

Mitochondrial dysfunction is a major source of oxidative stress, which can lead to the loss of proteostasis and cause misfolded proteins to accumulate, forming protein aggregates (Hipp et al., 2019; Manczak et al., 2006). In the brain, the aggregation of misfolded amyloid-β protein results in amyloid plaques, and misfolded tau protein into neurofibrillary tangles (Braak & Braak, 1991). These misfolded proteins are neurotoxic and cause synapse loss, decreased neural connections and ultimately, neural death (Bloom, 2014).

Mitochondrial dysfunction can also be the cause and consequence of inflammatory processes (Currais, 2015). Both of these processes can increase mitochondrial oxidative stress (López-Armada et al., 2013), thereby causing increased DNA damage, which can lead to neuronal cell dysfunction or loss (via apoptosis) (Gackowski et al., 2008; Kryston et al., 2011). Inflammation has also been shown to impair neurogenesis (i.e. the formation of new neurons) (Ekdahl et al., 2003). This has important implications for the ageing brain as neurogenesis occurs throughout the course of life, initially broadly as the brain develops, and then locally in adulthood in two neural regions (the dentate gyrus subgranular zone of the hippocampus and the subventricular zone) (Gage, 2002; Ming & Song, 2011).

These findings indicate that the underlying mechanisms associated with ageing cause progressive microstructural changes in the brain. They also lead to macrostructural changes in the brain, which are discussed next.

1.3.2.2 Macrostructural changes Microscopic changes in the brain, typified by a loss of dendrites and dendritic spines, shrinkage of dendritic trees and neural cell loss, can lead to macroscopic changes, such as a loss of brain volume. Evidence suggests that brain volume peaks at age 27 for men and age 29 for women (Riddle et al., 2010). When taking into account body/head size, there is no major brain volume difference between males (1.45 kg) and females (1.32 kg) (Riddle et al., 2010). Beyond this, the average rate of decline for total

brain volume is 0.32% per year (Scahill et al., 2003), which increases to 0.64% per year from 73 years onwards (S. J. Ritchie et al., 2015). As a result, the accumulated burden of pathology associated with microstructural changes causes macrostructural changes in brain volume. Certain structures within the brain, such as the hippocampus, appear to be particularly vulnerable to the ageing process (Raz et al., 2010). For example, after the age of 55, the hippocampus decreases in size by 0.38% per year, which accelerates to 1.12% loss per year after the age of 70 (Fraser et al., 2015). These structural changes have functional impacts, including cognitive decline and dementia, which is discussed next.

1.3.2.3 Functional changes The macrostructural changes in the brain, typified by a loss of brain volume, can cause functional changes, such as cognitive decline and dementia. The hippocampus has an important role in learning and memory (Deng et al., 2010; Jarrard, 1993). It is one of the first brain regions to be impacted by Alzheimer's disease pathology and experiences the greatest shrinkage over the course of the disease (Braak & Braak, 1991; Tabatabaei-Jafari et al., 2015). For those who suffer from Alzheimer's disease (AD), the rate of hippocampal decline is greater than typical ageing trajectories (reported in **Macrostructural changes**), with a meta-analysis indicating a 3.33% difference in atrophy rate between AD and controls (J. Barnes et al., 2009). As a result, brain volume loss within the hippocampus has been reliably associated with the early stages of AD (Zakzanis et al., 2003) and is also predictive of conversion to AD from mild cognitive impairment (MCI) (Tabatabaei-Jafari et al., 2020; Tabatabaei-Jafari et al., 2018, 2019), a prodromal stage of AD (Jack Jr. et al., 2018). For these reasons, hippocampal volume is an appropriate marker of brain health and is a key region of focus in this thesis.

There are sex differences in brain ageing, which may be explained by different vulnerability to brain ageing and dementia (genetics or sex-specific physiology) as well as different exposure to risk factors, which is discussed next.

1.3.2.4 Sex differences in brain ageing Global health statistics from 2019 indicate almost twice as many women died from dementia than men (GBD 2019 Collaborators, 2021). The disproportionate death rate in women may be associated with the greater global prevalence of dementia in women, with 14 million more women suffering from dementia than men (GBD 2019 Collaborators, 2021). That is close to the total population of Ireland, New-Zealand and Singapore combined (as of 2017) (Vollset et al., 2020). In part, this is due to women living longer than men (on average) and therefore being more susceptible to developing dementia, since age is one of the biggest risk factors (M. T. Lin & Beal, 2006; Livingston et al., 2020, 2017). However, the observed trend remained after standardising for age, indicating that the

higher death rate and prevalence in women may not be solely due to their longer lifespan (GBD 2019 Collaborators, 2021). Furthermore, results from the Framingham study revealed the remaining lifetime risk of AD was almost twice as high for a 65 year old woman (12%, 95% CI: 9.2% to 14.8%) than a 65 year old man (6.3%, 95% CI: 3.9% to 8.7%) (Seshadri et al., 1997). Therefore, the longer life span observed in women does not fully explain the sex bias for AD but increases the overall prevalence of all-cause dementia in women among the oldest old (Podcasy & Epperson, 2016). For example, the prevalence for AD increases with age and is approximately two-fold higher in women (7.13%, 95% CI: 6.56% to 7.72%) than men (3.31%, 95% CI: 2.6% to 3.80%) living in Europe (Niu et al., 2017). Moreover, current global life expectancy estimates indicate that the number of individuals older than 80 is projected to increase six-fold, from 141 million (in 2017) to 866 million (in 2100) (Vollset et al., 2020). Taken together, this expected growth in the ageing population may have a compounding effect on sex differences for AD and further perpetuate the sex gap.

Sex differences have also been reported for AD related functional and structural brain changes. Evidence suggests that AD related cognitive impairment may progress faster in women than men (Tschanz et al., 2011), which has also been observed in subjects with MCI (K. A. Lin et al., 2015). Moreover, studies of the hippocampus have shown that women diagnosed with AD experience a faster progression of hippocampal atrophy than men (Ardekani et al., 2016). Similar trends were found in those with MCI, with current estimates suggesting atrophy rates were 1 to 1.5% faster in women than men (Hua et al., 2010). Interestingly, the rate of hippocampal atrophy between men and women may also depend on the existing degree of AD pathological burden (Koran et al., 2017). For example, one study revealed that women who presented with cerebrospinal fluid levels of AD biomarkers, such as amyloid-β and tau, showed more rapid hippocampal atrophy and cognitive decline than men (Koran et al., 2017). Additionally, a study with postmortem data demonstrated that each additional unit increase in AD pathological burden was associated with nearly a three-fold increased odds of developing AD in men compared with more than twenty-two-fold increased odds in women (L. L. Barnes et al., 2005).

1.3.2.4.1 Possible reasons for sex differences Many possible explanations for these sex differences have been proposed. For example, complex social and historical reasons, such as disproportionate access to education and occupational opportunities, have been hypothesised to be linked to possible biological explanations for observed sex differences, such as brain reserve (Meng & D'Arcy, 2012; Valenzuela & Sachdev, 2006). However, evidence seems to suggest that whilst lower educational attainment is associated with a higher risk of AD, the increased risk of AD in women cannot be explained by a confounding or moderating effect

of education (Letenneur et al., 1999). One alternative explanation for the sex differences in AD prevalence is the selective survival of men with a healthier cardiovascular risk profile (Chêne et al., 2015). As noted earlier, between the ages of 45 and 65, men have significantly higher cardiovascular mortality rates than women (Chêne et al., 2015). This survival bias suggests that men who live beyond 65 are typically the healthiest selection of men, which may account for, at least in part, the lower risk of developing AD compared to women. Other possible explanations involve interactive effects between sex and genes, such as the $\epsilon 4$ allele of the apolipoprotein E gene (*APOE* $\epsilon 4$). Previous research has demonstrated that women who are positive for the *APOE* $\epsilon 4$ allele were at greater risk of developing AD than men with the allele (Altmann et al., 2014). Although, a meta-analysis indicated that this effect may be limited between the ages of 65 and 75 (Neu et al., 2017). Similarly, *APOE* $\epsilon 4$ was negatively associated with cognition between the ages of 70 and 80 in women only (Mortensen & Høgh, 2001). The reasons for this are unclear, however, possible physiological changes after menopause, including decreased endogenous estrogen production, have been hypothesised to underlie the sex differences (Neu et al., 2017; Riedel et al., 2016). Furthermore, since AD pathology begins decades prior to the presentation of clinical symptoms (Braak & Braak, 1991; Ohm et al., 1995; Zakzanis et al., 2003), it is possible that physiological changes during midlife, including menopause, contributed to observed sex differences in brain health in late life.

Given the average age at menopause is between 46 to 52 years (Schoenaker et al., 2014) and the average life expectancy of women in developed countries lies around 82 years (Murray et al., 2015), women will, on average, spend almost 40% of their lives in a postmenopausal state. It is therefore necessary to better understand whether and how menopause may predispose to poor brain health outcomes, in order to better target interventions and health policy responses. To better understand the health outcomes associated with menopause, we need to determine precisely what physiological changes occur around menopause. Biological mechanisms related to menopause that may underlie fat mass and lipid changes were discussed earlier in **Physiological changes associated with menopause**. Since menopause and ageing co-occur, the following section discusses biological mechanisms associated with ageing that may underlie fat mass and lipid changes around midlife, to better delineate the possible effects attributable to menopause and/or ageing.

1.3.3 Physiological changes associated with midlife

Research that has focused on physiological changes around menopause has often encountered difficulties in determining whether any observed differences are due to ageing or menopause.

This is because menopause is part of the ageing process. Therefore, changes associated with menopause are difficult to disentangle from ageing effects, since ageing and menopause co-occur. Because several age-related changes co-occur at the time of menopause it is important to have a good understanding of the effect of other factors to ensure we do not attribute to menopause effects due to other causes. These other age-related factors and their relative contributions to changes in fat mass are discussed in more detail below.

1.3.3.1 Fat mass changes associated with midlife Fat mass changes during midlife are primarily thought to be driven by changes in metabolism, energy expenditure (i.e. physical activity levels), energy intake (i.e. diet), sleep quality and quantity (Chaput & Tremblay, 2012; Roberts & Rosenberg, 2006). These factors covary with ageing and are therefore important to explore when discussing changes in fat mass during midlife.

Ageing has widely been thought to be accompanied by a progressive decline in resting metabolic rate of approximately 1 to 2% per decade after 20 years of age (Elia et al., 2000; Manini, 2010). However, the observed decrease in metabolic rate with age is closely tied to changes to body composition, including decreases in fat-free mass, which consists of metabolically active tissues, and organs (Piers et al., 1998). Recent evidence demonstrates that after adjusting for fat free mass, metabolic rate remains stable in adulthood (20 to 60 years) and begins to decline slowly (0.7%/year) in older adults ($>$ 60 years) (Pontzer et al., 2021). Overall, decreases in fat-free mass appear to be most influential in predicting fat mass changes in midlife (Pontzer et al., 2021). Although, it is difficult to delineate the contribution of decreasing physical activity to decreases in fat-free mass, as both decline with ageing (Pontzer et al., 2021; Sallis, 2000). Moreover, physical activity has been linked to preserving, and in some cases, improving body composition (Amaro-Gahete et al., 2019) and therefore has an important role for mediating the age-related changes in fat mass. Notably, food intake declines with ageing in healthy individuals (Rolls et al., 1995), despite the fact that the prevalence of overweight and obesity has accelerated in recent decades, with current global estimates indicating that the proportion of adults with a body mass index (BMI) greater than 25 kg/m^2 (i.e. overweight) is one in three (M. Ng et al., 2014; Stevens et al., 2012). These findings may be explained by the aforementioned decreases in the primary drivers of fat mass accumulation (i.e. decreases in fat-free mass and physical activity) that occur with ageing. Therefore, age-related changes in fat mass likely reflect a combined effect of changes in fat-free mass, physical activity and food intake.

Whilst fat-free mass appears to be most influential for changes in fat mass with age, sleep is also likely to substantially impact fat mass changes during midlife. A meta-analysis found

total sleep time and several measures of sleep quality significantly decreased with ageing (Ohayon et al., 2004). This may also be linked to declining physical activity levels with ageing, given exercise can improve sleep quality (Banno et al., 2018). These findings have important implications for changes in fat mass, given a meta-analysis of 14 longitudinal studies found short ($\leq$ 5–6 hours) sleep duration was associated with an increased incidence of obesity compared with those who slept 7-8 hours (Odds Ratio [OR] = 1.45, 95% CI: 1.25 to 1.67) (Wu et al., 2014). There are many possible mechanisms that may help explain these findings. For example, short sleep duration has been associated with elevated ghrelin (responsible for increasing hunger) and reduced leptin (responsible for inhibiting hunger), which can result in increased appetite and possibly explain the association with obesity incidence (Taheri et al., 2004). Another possibility is those who are awake for more of the day have more opportunities to eat (Knutson, 2012). Other hormones that change with ageing, including melatonin, may help account for the observed associations between sleep and fat mass. For example, levels of melatonin, which regulate the sleep wake cycle, fall gradually over the lifespan (Karasek & Reiter, 2002). Furthermore, animal studies have found that melatonin treatment decreases weight gain in response to high-fat diet (Terrón et al., 2013). Therefore, changes in melatonin levels with ageing, may also mediate changes in sleep and fat mass. Without a clear understanding of the primary mechanism underlying the link between sleep and fat mass, it is difficult to determine the relative contribution of sleep to changes in fat mass, compared with other driving factors, such as decreases in fat-free mass and physical activity. Despite this, current evidence indicates that sleep is likely to substantially impact fat mass changes during midlife.

1.3.3.2 Cholesterol/lipid changes associated with midlife As noted previously, lipid profiles are highly related to fat mass, particularly central obesity (Hodson et al., 2015). Therefore, factors that covary with ageing and influence changes in fat mass, including changes in fat-free mass, energy expenditure (i.e. physical activity levels), energy intake (i.e. diet), sleep quality and quantity, are likely to also have a similar magnitude of effect on lipid profiles.

Interestingly, a randomised controlled trial found a diet low in fats, particularly saturated fats, was insufficient in lowering LDL levels (Stefanick et al., 1998). However, changes to diet combined with aerobic exercise resulted in significant reductions in LDL levels (Stefanick et al., 1998). These findings highlight the importance of aerobic exercise in promoting positive health outcomes for lipid levels. Moreover, a systematic review with meta-analysis of 41 randomised controlled trials revealed that women who engage in aerobic exercise can expect improvements in lipid profiles ranging from 2 to 5% (Kelley et al., 2004). Men experienced comparable improvements, however, TG improved by 9% and changes in LDL were non-significant (Kelley

& Kelley, 2005). The reasons for these differences remain to be elucidated, however, one possibility is that the underlying differences in body composition between men and women at baseline may have influenced results.

A meta-analysis of progressive resistance training and lipid profiles found that resistance training was associated with lower TC, LDL and TG in adults (Kelley & Kelley, 2009). However, in these studies it is possible that the observed effects are related to decreases in BMI as a result of progressive resistance training, rather than progressive resistance training itself. These findings further reinforce the close relationship body fat and lipids have with one another. Research has demonstrated that weight loss is associated with favourable changes in lipids (Wood et al., 1988). This is, in part, why weight loss through lifestyle modification is a primary clinical recommendation for individuals who present with an unfavourable lipid profile (Nordestgaard & Varbo, 2014). Furthermore, since physical activity levels tend to decline with ageing in healthy individuals (Sallis, 2000), this may help account for why total cholesterol levels tend to increase with ageing (Kreisberg & Kasim, 1987).

1.4 Menopause, ageing and brain health

Thus far, this thesis has highlighted that women are at a higher risk of cognitive decline and dementia than men. One possible reason for this is, at least in part, due to an effect of menopause. It is not practical and imprecise, due to other exposures, time lag and attrition, to use dementia as an outcome to investigate the effect of menopause, however, cerebral health can be measured at midlife through brain markers such as brain volume. Therefore, the following sections will discuss the possible direct and indirect relationships between menopause and brain health.

1.4.1 Direct associations

1.4.1.1 Menopause and brain health There are many possible underlying mechanisms that may help account for an association between menopause and brain health. One key endocrinological feature of menopause is the decreased endogenous production of estrogen (Harlow et al., 2012). Animal studies have found that low levels of estradiol were associated with decreased density of dendritic spines and synapses in subregions of the hippocampus (Gould et al., 1990; C. Woolley et al., 1990; C. S. Woolley & McEwen, 1992). As noted earlier, the hippocampus is particularly vulnerable to the impact of ageing in healthy individuals (Burke & Barnes, 2006). Moreover, brain volume loss within the hippocampus has been reliably associated with the early stages of AD (Zakzanis et al., 2003) and is also predictive of conversion to AD from mild cognitive impairment (Tabatabaei-Jafari et al., 2020; Tabatabaei-

Jafari et al., 2018, 2019). Studies have also shown that women with low levels of estradiol (5 to 11.9 pg/ml) were four times more likely to have AD compared to women with high amounts of estradiol (19.9 mg/ml to 77 pg/ml), after adjusting for age, education, ethnicity, body mass index and presence of *APOE* $\epsilon 4$ allele (Manly et al., 2000). However, an alternative explanation for these findings is that estradiol levels were lowered in women as a result of having AD. As the ovaries cease to produce estrogens after menopause, it is then primarily produced in a number of extragonadal sites including adipose tissue, bone, smooth muscle cells and the brain (Hemsell et al., 1974; Simpson & Davis, 2001). Individuals suffering from AD experience a loss of fat mass decades prior to AD onset (E. Albanese et al., 2017; Floud et al., 2020). Therefore, the decrease in adipose tissue may account for the lower estradiol levels found in those with AD. Additionally, menopause is associated with changes in other hormones, including lower progesterone levels, which has been associated with AD pathogenesis (C. J. Pike et al., 2009). Another possible explanation is that estrogen depletion, as seen in menopause, is linked to low grade systemic inflammation (Abu-Taha et al., 2009) and the accumulation of pro-inflammatory cytokines (Christensen & Pike, 2015; Pfeilschifter et al., 2002). Previous research has demonstrated that postmenopausal women have higher levels of tumour necrosis factor-α (a pro-inflammatory cytokine) than premenopausal women, which persists after adjustments for age and measures of fat mass (Sites et al., 2002). Furthermore, increases in inflammation around midlife has been associated with smaller hippocampal volumes (Walker et al., 2017), which may in part, account for menopause predisposing women to experience poorer brain health outcomes.

The association between menopausal status and the hippocampus has been inconsistent. Some research has demonstrated that postmenopausal women experience greater decreases in hippocampal volume compared to premenopausal women (Goto et al., 2011; Mosconi et al., 2018), whereas others report no significant differences (G.-W. Kim et al., 2018; Sullivan et al., 2005). This may be because previous studies did not precisely match premenopausal and postmenopausal women for age, which may have confounded a possible effect of menopause with that of typical ageing. Furthermore, the association between other measures of menstruation history (including age at menopause, menarche and duration of reproductive stage) and brain volume remains unclear. Therefore, more research is required to determine the direct association between menopause and measure of brain health, which adequately deals with the confound of ageing. These questions are addressed in **Chapter 6** of this thesis.

The association between measures of menstruation history (including menopausal status, age at menopause, age at menarche and duration of menstruation) and functional brain health outcomes is currently unclear. Some evidence indicates that younger age at menopause,

later age at menarche and shorter reproductive spans are associated with elevated risk of developing dementia (Gilsanz et al., 2019). For example, women with reproductive spans less than 20 years and between 21 to 34 years had a 55% and 26% increased risk of dementia, respectively, compared to those with a reproductive span of 34 years or higher (Gilsanz et al., 2019). However, there is considerable heterogeneity in findings which do not support a consistent association between early menopause and increased dementia risk (Georgakis et al., 2016). This is likely, in part, due to the limited number of large prospective studies that focus on relatively homogeneous samples (Georgakis et al., 2016). Delineating the association between measures of menstruation history and structural brain health outcomes first, may better inform possible links to functional brain health outcomes.

1.4.2 Indirect associations

1.4.2.1 Fat mass changes and brain health Physiological changes after menopause, including weight gain (Davis et al., 2012) may also help explain the association between menopause and brain health. Experimental data in animals has shown that obesity in mice can lead to decreased neurogenesis and accelerated neurodegeneration (Cai, 2013; Julien et al., 2010). Notably, the accumulation of fat tissue, particularly visceral fat, which is often prevalent in individuals with overweight/obesity, elevates levels of pro-inflammatory cytokines (Fontana et al., 2007; Gregor & Hotamisligil, 2011; A. A. Miller & Spencer, 2014), which have been associated with smaller hippocampal volumes (Sudheimer et al., 2014). In animal models, obesity in ageing is associated with a heightened state of systemic inflammation, which exacerbates neuroinflammation and oxidative stress in the hippocampus (Tucsek et al., 2014). These pathophysiological consequences of overweight/obesity have been closely linked with impaired hippocampal integrity in humans (Montagne et al., 2015; Sudheimer et al., 2014). Moreover, inflammation can disrupt feeding pathways in the hypothalamus, which can impact hormones such as insulin and leptin (Thaler et al., 2012). This hormonal change can impair the suppression of hunger and feeding, thereby contributing to obesity (Thaler et al., 2012). These mechanisms are interconnected, given chronic obesity is also associated with a cascade of potentially harmful physiological processes (including oxidative stress and inflammation), which are implicated in the deterioration of metabolic homeostasis (Monteiro & Azevedo, 2010) and has been linked with accelerated neurodegeneration (Glass et al., 2010).

Neuroimaging studies have revealed that the association between fat mass and hippocampal volume in middle to early old-aged adults has been inconsistent with studies reporting negative (Bruehl et al., 2009; Cherbuin et al., 2015; Jagust et al., 2005; Raji et al., 2010), positive (Widya et al., 2011) or no association (Bobb et al., 2014; Driscoll et al., 2012; Hamer & Batty,

2019). The heterogeneous results may be explained by the typical use of BMI as the sole measure of fat mass, which does not precisely index changes in visceral fat and is inherently biased by the ageing process (Romero-Corral et al., 2008). Therefore, other cost-effective, feasible and useful clinical measures, including waist circumference and/or waist-to-hip ratio may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in waist circumference and waist-to-hip ratio have not been adequately investigated in previous studies that have examined the relationship between fat mass and hippocampal volume (Bobb et al., 2014; Cherbuin et al., 2015; Croll et al., 2019; Driscoll et al., 2012). This is addressed in **Chapter 5** of this thesis.

Previous evidence has demonstrated that women with overweight BMI in midlife have an 83% increased risk of developing AD, compared with normal BMI, which was not observed for men with overweight BMI (Anstey et al., 2011). Furthermore, obese BMI in midlife is associated with 3.08 times increased risk of AD for women (95% CI: 2.16 to 4.37) and 2.45 times increased risk for men (95% CI: 1.51 to 3.95), suggesting possible stronger effects for women than men (Anstey et al., 2011). The reasons for this potential sex difference remains unclear, however, one possibility is the hormonal changes around menopause may predispose women to poorer health outcomes. Alternatively, these results may reflect differences in body composition between men and women, as BMI is a relatively imprecise measure of fat mass (Romero-Corral et al., 2008). Furthermore, changes in fat mass, as represented by BMI, are likely confounded by the multifactorial changes in body composition that occur in midlife, including decreases in bone mineral density (Douchi et al., 2003; Steiger et al., 1992) and muscle mass (Shafiee et al., 2017), which may help account for these findings. Interestingly, a post-mortem study of elderly individuals without dementia revealed those with obesity had neuropathological hallmarks of AD, such as higher levels of hippocampal amyloid-beta peptides, amyloid precursor protein and hyperphosphorylated tau protein, compared with those without obesity (Mrak, 2009). Taken together, these findings suggest that fat mass changes in both men and women may be associated with unfavourable brain health outcomes, although women may be disproportionately negatively affected.

1.4.2.2 Cholesterol/lipids changes and brain health Other physiological changes after menopause, including increased levels of LDL, TC and TG (Carr, 2003; Derby et al., 2009; Gaspard et al., 1995; Jensen et al., 1990; Kolovou & Bilianou, 2008) may also help explain the associations between menopause and brain health. Many mechanisms have been proposed that link lipids to brain health. One possibility is that an overload of cholesterol in the plasma membrane of neurons may increase the amyloid-β (a hallmark feature of AD pathology) production in neurons (Marquer et al., 2011). This is also likely, in part, due

to the positive association between elevated cholesterol levels and oxidative stress (Prasad & Kalra, 1993), which can induce membrane damage to neurons (Pappolla et al., 2002). These associations are unlikely to be unidirectional, as amyloid-β induced oxidative stress has been associated with disrupted cholesterol metabolism which, in turn, can trigger a neurodegenerative cascade that leads to AD (Cutler et al., 2004).

The association between cholesterol and brain volume, specifically the hippocampus, is less clear. One study found a positive association between HDL cholesterol and hippocampal and total brain volume in adults (aged 75 to 85), whereby low levels of HDL were associated with smaller hippocampal volumes (Wolf et al., 2004). However, these results could not be replicated in two other studies (Heijer et al., 2005; Ward et al., 2010). One possibility for this discrepancy is low HDL levels being reflective of poor health status, as the initial study that reported an association between HDL and the hippocampus included those who suffer from mild cognitive impairment (Wolf et al., 2004). Furthermore, the effect of diet and exercise was not accounted for, which may have influenced the observed findings. These results highlight the need for longitudinal data that investigates the association between changes in cholesterol levels in midlife with measures of brain health.

For functional outcomes, a meta-analysis revealed that high midlife TC (>6.5 mmol/l) was associated with an increased risk of AD, although insufficient data was available to examine sex differences (Anstey et al., 2017; Anstey et al., 2008). More research is needed to address how changes in cholesterol/lipid profiles in women are associated with brain health. In part, there is limited evidence on this topic because it is currently unclear how much change occurs in cholesterol/lipid profiles in women and how much of this is attributable to ageing, compared with a possible effect of menopause. Therefore, a better understanding of the precise amounts of lipid changes across menopause may better help delineate the links between menopause and brain health. This is addressed in **Chapter 3** of this thesis.

1.4.2.3 Hormone replacement therapy use and brain health The observed fluctuations in global HRT use, as noted in **Guidelines and trends for hormone replacement therapy use**, may also have important implications for womens' brain health. Previous research has demonstrated that the association between HRT use and the brain can depend on the time of initiation and duration of treatment (Boccardi et al., 2006; Erickson et al., 2005; Erickson et al., 2010; C. Lord et al., 2008; Resnick et al., 2009; Wnuk et al., 2012). For example, the initiation of HRT at the time of (or immediately after) menopause has been associated with larger hippocampal volume when compared with women starting HRT 1 to 18 years after menopause (Erickson et al., 2010). However, HRT use had no effect on

hippocampal volume in women between the ages of 60 and 64 (Low et al., 2006) and was associated with hippocampal atrophy when initiated in women 65 years or older (Resnick et al., 2009). Furthermore, the duration of HRT use can negatively impact hippocampal density, whereby prolonged use can result in decreased posterior hippocampal and parahippocampal grey matter density (C. Lord et al., 2010). Similarly, previous studies have found that HRT treatment up to 10 years in duration can preserve brain volume, whereas treatment beyond 10 years increased the degree of brain atrophy and can amplify decline on measures of executive functioning (Erickson et al., 2007). For dementia, a similar trend has been reported whereby women who used HRT in midlife (but not late life) had a 26% reduced risk of developing a dementia diagnosis (Whitmer et al., 2011). Comparatively, women using HRT only in late life had a 48% elevated risk compared to women not using HRT at either time point (midlife/late life) (Whitmer et al., 2011). However, this estimate may be conservative, given an ancillary study to the WHI trial (the WHIMS trial) found that the initiation of HRT in postmenopausal women aged 65 and over was associated with a two-fold increased risk of developing dementia (Shumaker et al., 2003). The differences in the magnitude of the estimates between studies may be explained by the well documented differences that emerge from the less robust design of observational cohort studies, compared with double blinded randomised controlled trials. However, the difference in the follow up period between both studies was 4 years, which may also contribute to the observed results. Taken together, these findings align with the 'timing hypothesis', which has indicated that HRT may provide benefits to younger women, if treatment is initiated soon after menopause (Hodis et al., 2016). Additionally, the beneficial effects of HRT may extend beyond the duration of its use. For example, one study found no significant difference in grey matter volumes between current and past users of HRT (no HRT for 1 year), however, both of these groups showed significantly greater amounts of grey matter than non-users (Erickson et al., 2005). These findings highlight the importance of considering HRT use when examining possible direct and indirect associations between menopause and brain health.

Beyond the use of HRT, other challenges exist when considering the effect of HRT on menopause, ageing and brain health. For example, one longitudinal randomised study found that postmenopausal *APOE* ϵ4 carriers (aged 49 to 69) had greater telomere shortening, a measure of biological ageing, than non-*APOE* ϵ4 carriers (E. G. Jacobs et al., 2013). However, *APOE* ϵ4 carriers who suspended HRT use over a two-year period had greater telomere attrition than those who continued HRT use, who showed no evidence of telomere decline (E. G. Jacobs et al., 2013). Furthermore, the opposite pattern was found in non-carriers, whereby non-*APOE* ϵ4 carriers who discontinued HRT use exhibited telomere maintenance and growth. Therefore, for non-*APOE* ϵ4 carriers, there was no evidence that HRT conferred a protective

effect on cell ageing (E. G. Jacobs et al., 2013). These findings emphasise the complex role HRT has in modulating the effects of ageing in women. Another important consideration for interpreting these results includes the underlying differences between women who have either previously used or never used HRT. For example, research has indicated that women who use HRT tend to be more affluent, educated, leaner and have a better cardiovascular risk profile than non-HRT users. (Matthews et al., 1996; H. D. Nelson et al., 2002). Women who use HRT are also, by definition of their HRT use, more likely to have access to health care and have a greater likelihood of being treated for other comorbid conditions (H. D. Nelson et al., 2002). Furthermore, HRT use may confound the accurate classification of women, particularly between premenopausal and postmenopausal stages. Therefore, careful methodological and statistical consideration for HRT use is required when examining the direct and indirect links between menopause and the brain.

1.5 Current gaps and challenges

1.5.1 Broad gaps and challenges

A number of broad systemic research challenges have made it difficult to determine the association between female specific factors, such as menopause, and brain health. For example, women's health has been historically understudied when compared with men's health (Taylor et al., 2019). Furthermore, whilst animal models have helped further our understanding of underlying genetic, environmental and pathological mechanisms associated with brain health, these studies have predominantly focused on male rodents (Wald & Wu, 2010). This may be because male rodents are more economical than female rodents and do not have an ovarian cycle that could introduce more variability and potentially confound observed results, if not adequately accounted for (Wald & Wu, 2010). The broader implication of this sex crisis in animal research is that, unless sex differences are a key component of the research question, findings from animal models may lead to systematic biases in our understanding of brain health. Notably, this issue is not limited to animal research (Beery & Zucker, 2011; McCarthy et al., 2012). Human research often statistically controls for sex, rather than conducting sensitivity analyses that stratifies results by sex or investigate potential sex interactions (Beery & Zucker, 2011). This can result in similar systematic biases as those observed in animal studies, particularly when sex differences are not explored in meta-analyses. Therefore, it is important for studies to anticipate the need for sex-stratification and have sufficient power to detect sex-specific differences. An additional issue includes the 'file drawer problem' in science, whereby studies that find no effect of sex may not report or publish these findings (Collaboration, 2015; Ioannidis et al., 2014; Ioannidis, 2005; Rosenthal, 1979). These issues

demonstrate an urgent need for research that not only considers sex differences, but also further investigates the association between female specific factors, such as menopause, and brain health. However, investigating the direct and indirect links between menopause and brain health has its own unique set of specific challenges.

1.5.2 Specific gaps and challenges

Thus far, several gaps in our understanding of the association between menopause and brain health have been outlined. Importantly, a key challenge is that changes associated with menopause can be difficult to disentangle from ageing effects, given both co-occur. Consequently, careful methodological and statistical considerations are necessary to reliably establish whether a possible effect of menopause on brain health exists, beyond the effect of ageing.

Another critical challenge is that previous narrative reviews that have described changes in fat mass (Davis et al., 2012) and cholesterol/lipids (Carr, 2003; Gaspard et al., 1995; Kolovou & Bilianou, 2008) around menopause have been limited by a paucity of quantitative estimates, which are typically made available through systematic reviews of the literature with meta-analyses. For fat mass changes during menopause, current studies also vary substantially in the magnitude of their effect sizes. This may, in part, be due to the heterogeneity of measures used between studies when investigating fat mass changes in quantity and distribution. Furthermore, it is unclear precisely how much of this change is attributable to ageing. These are significant issues because without a clear understanding of exactly what changes occur around menopause and by how much, it is difficult to assess the contribution of physiological changes around menopause to brain health.

Another challenge is that the meaning of 'menopause' is widely understood, but often imprecisely defined in research. The standards for defining menopause nomenclature, such as 'premenopause' and 'postmenopause' vary substantially across publications. Although, the precise extent of this heterogeneity remains to be established, perhaps because the extant literature on this topic may be too large to systematically review, it is clear that such variability across studies makes the synthesis and comparison of findings difficult. In recognition of this issue, there have been a number of attempts by international experts to collaboratively develop a comprehensive standardised set of criteria to describe terminology associated with menopause (Harlow et al., 2007; Harlow et al., 2012; Soules et al., 2001; Utian, 1999; World Health Organization, 1980, 1996). Whilst promising developments have been made in recent decades, a follow up investigation regarding the frequency and consistency of uptake and use of the proposed criterion has not been adequately investigated. Therefore, the degree to

which standardised criterion has been successfully implemented for publications relating to menopause research remains unknown.

Neuroimaging studies have revealed that the association between fat mass and hippocampal volume in middle to early old-aged adults have also been inconsistent, with studies reporting negative (Bruehl et al., 2009; Cherbuin et al., 2015; Jagust et al., 2005; Raji et al., 2010), positive (Widya et al., 2011) or no association (Bobb et al., 2014; Driscoll et al., 2012; Hamer & Batty, 2019). The heterogeneous results may be explained, in part, by the typical use of BMI as the sole measure of fat mass, which does not precisely index changes in visceral fat and is inherently biased by the ageing process (Romero-Corral et al., 2008). Therefore, other cost-effective, feasible and useful clinical measures, including waist circumference and/or waist-to-hip ratio may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in waist circumference and waist-to-hip ratio have not been adequately investigated in previous studies that have examined the relationship between fat mass and hippocampal volume (Bobb et al., 2014; Cherbuin et al., 2015; Croll et al., 2019; Driscoll et al., 2012).

Similar inconsistencies have been noted when examining the association between menopause and the brain. Specifically, some research has demonstrated that postmenopausal women experience greater decreases in hippocampal volume compared to premenopausal women (Goto et al., 2011; Mosconi et al., 2018) whereas others report no significant differences (G.-W. Kim et al., 2018; Sullivan et al., 2005). This may be because previous studies did not precisely match premenopausal and postmenopausal women for age, which may have confounded a possible effect of menopause with that of typical ageing. Furthermore, the association between other measures of menstruation history (including age at menopause) and brain volume remains unclear.

Ultimately, these gaps and challenges lead to considerable difficulty in quantifying possible direct and indirect associations between menopause and brain health, which is the core focus of this thesis. Investigating female specific factors, such as menopause, a possible contributor to sex differences for AD, and brain health is essential to progress our understanding of future treatment and prevention advice that directly targets womens' health.

1.6 Thesis aims

The overarching aim of this thesis is to investigate the direct and indirect associations between menopause and measures of brain health. To explore this question, five specific aims were developed.

1.6.1 Aim 1

To investigate fat mass differences between premenopausal and postmenopausal women (**Chapter 2**).

1.6.2 Aim 2

To investigate lipid profile differences between premenopausal and postmenopausal women (**Chapter 3**).

1.6.3 Aim 3

To investigate the degree of heterogeneity in menopause nomenclature from the literature (**Chapter 4**).

1.6.4 Aim 4

To investigate the association between longitudinal changes in fat mass and the brain (**Chapter 5**).

1.6.5 Aim 5

To investigate the association between measures of menstruation history (including menopausal status and age at menopause) and the brain (**Chapter 6**).

1.7 Thesis outline

Five studies were conducted to address the aims of the thesis.

The first study is a review with meta-analysis of differences in fat mass between premenopausal and postmenopausal women. The review revealed that total and central fat mass significantly increased between premenopausal and postmenopausal women, with the exception of leg fat, which decreased. Notably, the change in total fat mass was predominantly attributable to increasing age. Menopause had no significant additional influence. However, the decrease in leg fat and increase in central fat were indicative of possible changes in fat mass distribution after menopause, which were likely to, in part, be due to hormonal shifts that occur during midlife.

The second study is a review with meta-analysis of differences in lipid profiles between premenopausal and postmenopausal women. The review revealed that lipoproteins were significantly higher in postmenopausal women than premenopausal women, with the exception

of high-density lipoprotein, which was not significantly different between groups. Notably, measures of ageing explained some, but not all of the differences in lipid levels between premenopausal and postmenopausal women.

The third study reviewed and discussed critical developments in menopause nomenclature, determined the level of heterogeneity amongst menopause nomenclature and compared the definitions used in the literature with the Stages of Reproductive Aging Workshop criteria. The study found a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. The use of consistent terminology in research will enhance our capacity to compare results from different studies that investigate issues related to women's health and ageing.

The fourth study investigated the associations between changes in fat mass and the brain. The study demonstrated that those who suffered from overweight or obesity had smaller hippocampal volumes than those who maintained a normal weight. Furthermore, those who suffered from overweight or obesity in the past, but currently had a normal level of fat mass also had a smaller hippocampus than those who had always maintained a normal weight. These findings emphasise the importance of maintaining normal weight for brain health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

The fifth study investigated the association between measures of menstruation history (including menopausal status, age at menopause, age at menarche and duration of reproductive stage) and brain health. The study revealed an association between menopause and the brain, beyond typical ageing effects. Notably, postmenopausal women had larger brain volumes than premenopausal women but also experience greater decreases in total brain volume, but not hippocampal volume, over time. Furthermore, early age at menarche, delayed age at menopause and increasing duration of menstruation were not protective for brain health.

2 Fat mass changes during menopause: a meta-analysis

2.1 Abstract

Objective: Fat mass has been shown to increase in ageing women; however, the extent to which menopausal status mediates these changes remains unclear. The purpose of this review was to determine (1) how fat mass differs in quantity and distribution between premenopausal and postmenopausal women, (2) whether and how age and/or menopausal status moderates any observed differences, and (3) which type of fat mass measure is best suited to detecting differences in fat mass between groups.

Study: This review with meta-analysis is reported according to Metaanalysis of Observational Studies in Epidemiology guidelines.

Study Appraisal and Synthesis Methods: Studies (published up to May 2018) were identified via PubMed to provide fat mass measures in premenopausal and postmenopausal women. 201 cross-sectional studies in the meta-analysis, which provided a combined sample size of 1,049,919 individuals and consisted of 478,734 premenopausal women and 571,185 postmenopausal women. 11 longitudinal studies were included in the meta-analyses, which provided a combined sample size of 2,472 women who were premenopausal at baseline and postmenopausal at follow up.

Results: The main findings of this review were that fat mass significantly increased between premenopausal and postmenopausal women across most measures, which included body mass index (1.14 kg/m^2, 95% confidence interval 0.95 to 1.32), body weight (1 kg, 0.44 to 1.57), body fat percentage (2.88%, 2.13 to 3.63), waist circumference (4.63 cm, 3.90 to 5.35), hip circumference (2.01 cm, 1.36 to 2.65), waist to hip ratio (0.04, 0.03 to 0.05), visceral fat (26.90 cm^2, 13.12 to 40.68) and trunk fat percentage (5.49%, 3.91 to 7.06), with the exception of total leg fat percentage, which significantly decreased (-3.19%, -5.98 to -0.41). No interactive effects were observed between menopausal status and age across all fat mass measures.

Conclusions: The change in fat mass quantity between premenopausal and postmenopausal women was predominantly attributable to increasing age; menopause had no significant additional influence. However, the decrease in total leg fat percentage and increase in measures of central fat are indicative of a possible change in fat mass distribution after menopause. These changes are likely to, at least in part, be due to hormonal shifts that occur during midlife with women having a higher androgen (i.e. testosterone) to estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition. Evidently, these findings suggest attention should be paid to the accumulation of central fat after menopause,

whereas increases in total fat mass should be monitored consistently across the lifespan.

2.2 Introduction

Overweight and obesity are major societal problems that are associated with a number of deleterious health and wellbeing outcomes including type II diabetes (Guh et al., 2009), dementia (Anstey et al., 2011) and cardiovascular disease (CVD) (Wilson et al., 2002) resulting in a significant global economic burden (Withrow & Alter, 2011) and poorer quality of life (Larsson et al., 2002). This is of particular importance for women as CVD is the leading cause of death in women worldwide (World Health Organization, 2013). Many potential factors/mechanisms have been implicated in the accumulation of fat mass at midlife, including ageing (Kuk et al., 2009), decreased physical activity levels (Sternfeld et al., 2004) and sarcopenia (i.e. loss of lean muscle mass), which can decrease the resting metabolic rate (Karakelides & Nair, 2005). However, hormonal changes in middle aged women may also be particularly relevant in moderating increases in body fat (Karvonen-Gutierrez & Kim, 2016; Razmjou et al., 2018). Given that the average age of menopause lies between 46 to 52 years (Schoenaker et al., 2014) and the average life expectancy of women in developed countries lies around 81 years (Murray et al., 2015), women will on average spend almost 40% of their lives in a postmenopausal state. It is therefore necessary to better understand whether and how menopause might predispose to increasing body fat to better target interventions and health policy responses.

Menopause is defined as the final menstrual period and is characterized by the progressive decline of endogenous estrogen levels (Harlow et al., 2012). Some studies have proposed that the decrease in endogenous estrogen levels may modulate body fat quantity and distribution resulting in greater overall body fat and an increased amount of central fat in postmenopausal women (J. K. Park et al., 2013; Razmjou et al., 2018; Sowers et al., 2007; Tremollieres et al., 1996). However, there is a divide in the literature with some researchers suggesting that any observed differences in fat mass quantity or distribution in women at midlife are primarily due to ageing, with menopausal status having little to no effect (Douchi et al., 2007; Soriguer et al., 2009; Trikudanathan et al., 2013). The contradictory findings could be due to a number of factors including (i) the intertwined relationship between menopause and ageing, (ii) the heterogeneity in criteria used between studies when defining premenopausal and postmenopausal women and (iii) the heterogeneity of measures used between studies when investigating fat mass changes in quantity and distribution.

Due to the inconsistent evidence, it is important to pool data from available studies to determine the differences in fat mass quantity and distribution between premenopausal and

postmenopausal women. Moreover, confounding factors that may explain effects currently attributed to an altered hormonal profile in women, such as ageing, have not been adequately investigated. As far as we are aware, no study to date has comprehensively reviewed the evidence and precisely estimated the results through meta-analyses. Therefore, the current study aimed to determine (i) how fat mass differs in quantity and distribution between premenopausal and postmenopausal women, (ii) whether and how age and/or menopausal status moderates any observed differences and (iii) which type of fat mass measure is best suited to detecting differences in fat mass between groups.

2.3 Methods

2.3.1 Reporting guidelines

This review with meta-analysis was reported according to MOOSE guidelines (Stroup et al., 2000) and was prospectively registered in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643).

2.3.2 Search string

A search was conducted, limited to the PubMed database, to retrieve both cross-sectional and longitudinal studies that reported fat mass differences in quantity or distribution between premenopausal and postmenopausal women. The following search string was used: ("adipose tissue" OR "adiposity" OR "subcutaneous fat" OR "obesity" OR "overweight" OR "body weight" OR "body fat distribution" OR "body mass index" OR "BMI" OR "DEXA" OR "DXA" OR "dual energy x-ray absorptiometry" OR "waist to hip ratio" OR "waist-hip ratio" OR "waist circumference" OR "x-ray computed tomography" OR "computed tomography" OR "CT scan" OR "caliper" OR "skinfold" OR "skin fold" OR "abdominal MRI" OR "abdominal magnetic resonance imaging" OR "intra-abdominal fat") AND ("menarche" OR "pre-menopause" OR "premenopause" OR "pre-menopausal" OR "premenopausal" OR "reproductive" OR "menopausal transition") AND ("post-menopause" OR "postmenopause" OR "post-menopausal" OR "postmenopausal" OR "non-reproductive").

PubMed filters were used to exclude non-human and non-English studies. No time restrictions were applied to the literature search, which was conducted in May 2018.

2.3.3 Inclusion and exclusion criteria

The eligibility criteria for all included and excluded studies were predefined. Inclusion criteria were specified as follows: (i) peer-reviewed manuscripts written in English or translated from their original language of publication to English; (ii) studies which assessed human participants and (iii) studies that utilised continuous unadjusted measures that provide an estimate of fat mass for both healthy premenopausal and healthy postmenopausal women.

Exclusion criteria were specified as follows: (i) studies that exclusively investigated clinical/pathophysiological populations; (ii) studies that selectively recruited women based on specific fat mass ranges or reported differences in fat mass within a narrow predetermined fat mass range (i.e. only obese women); (iii) studies that matched participants on a measure of fat mass; (iv) cross-sectional studies with fewer than 40 participants to avoid extreme sampling bias and ensure that small studies, which are more likely to be methodologically less robust, are not included; (v) review articles, systematic reviews and meta-analyses; (vi) conference abstracts and (vii) animal studies.

2.3.4 Screening

Duplicate citations were removed from search results and the remaining entries were title screened by a single author (AA). All abstracts were then subdivided and independently double-screened by four authors (AA, NC, HT-J and EW) using the predetermined inclusion/exclusion criteria with any discrepancies resolved through consensus. Finally, full-text and supplementary materials of the remaining articles were double-screened against inclusion/exclusion criteria by three authors (AA, HT-J and EW), with data extracted from relevant articles. Where data was missing, authors were contacted via email to obtain relevant information required for inclusion in the review. A bibliographic search of available articles and reviews was also used to identify further studies that fit the inclusion criteria.

2.3.5 Data extraction

All data from included articles was double extracted by two authors (AA and EW) to avoid transcription errors with any disagreement resolved by consensus. Data extracted from each study included (i) sample size; (ii) age; (iii) relevant measures that provide an estimate of fat mass (Table 2.4) including body mass index (BMI), waist circumference (WC), hip circumference (HC), bodyweight (BW), total body fat (BF%;), trunk fat (TF%), waist to hip ratio (WTHR), total leg fat (LF%), abdominal (ASF) and suprailliac skinfold thickness (SISF), abdominal subcutaneous fat (AF) and visceral fat (VF); (iv) whether information such as menopausal status, WC and/or BMI was measured or self-reported; (v) definitions used for

WC, HC, premenopausal women and postmenopausal women; (vi) whether follicle stimulating hormone (FSH) criteria were used; (vii) whether women were age matched and (viii) whether the following criteria were used in sample selection including smoking, surgical menopause, hormone replacement therapy (HRT), CVD and history of drug and alcohol abuse.

2.3.6 Definition of premenopause and postmenopause

The precise definition for 'premenopause' and 'postmenopause' are known to vary substantially within the literature, which has motivated a series of attempts by international experts to collaboratively develop a comprehensive standardised set of criteria to describe the terminology associated with menopause (Harlow et al., 2012; Soules et al., 2001; Utian, 1999; World Health Organization, 1980, 1996). The current gold standard for defining menopause nomenclature is the Stages of Reproductive Ageing (STRAW) + 10 criteria, which was established in 2012 (Harlow et al., 2012). The requirement for papers to adhere to the STRAW + 10 criteria would have limited the scope of the current review and prevented the inclusion of relevant studies, particular those published prior to 2012. Therefore, all studies, which included premenopausal and postmenopausal women (as defined by the authors of those studies), were considered. Furthermore, women classified as perimenopausal were not included in the current meta-analysis, so that a clear comparison could be made between groups, with premenopausal women acting as controls for any effect observed after menopause.

2.3.7 Quality assessment

The quality of included studies was independently assessed by two authors (AA and EW), using an adapted version of the Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). In short, the NOS for cohort studies utilised three categories to evaluate individual study quality including (1) the selection of participants, (2) the comparability of groups and (3) the assessment/ascertainment of the outcome of interest. Notably, an item was removed from the selection and outcome sections of the NOS, which did not address the particular quality requirements of the present review (Supplementary Materials). Furthermore, given that all studies, which included premenopausal and postmenopausal women, were considered, two additional items were added to the comparability section to ensure that studies with better suited designs for comparing these groups were scored accordingly. Any discrepancy in quality assessment was resolved by consensus. If consensus decisions were not possible a third rater was used.

2.3.8 Multiple reports

In the cases where multiple studies had used the same cohort and reported on the same fat mass measures, only one publication was used in any single analysis. Which study to include was based on the following criteria in order of importance: (i) availability of effect sizes in study (or effect sizes provided by authors after contact), (ii) sample size, (iii) methodology quality rating and (iv) publication date of the study (with more recent studies being prioritised). When multiple studies used the same cohort but reported on different fat mass measures, estimates from the same cohort but with different studies were used in separate analyses.

2.3.9 Statistical analysis

All statistical analyses were conducted using the open source software, R (version 3.3.3) (R. C. Team, 2016), running in RStudio (version 1.0.143) (Rs. Team, 2012), using the metafor package (version 2.0.0) (Viechtbauer, 2010) for the meta-analysis.

2.3.10 Summary measures

For both cross-sectional and longitudinal analyses, effect sizes were calculated using the raw (unstandardised) mean difference (D) for fat mass between postmenopausal and premenopausal women i.e.

$$D = \bar{X}_1 - \bar{X}_2$$

The use of raw mean differences was most appropriate, given that the outcome measure of interest (fat mass) was reported on meaningful scales that were consistently used across studies (Borenstein et al., 2009). For cross-sectional studies, the variance of the effect sizes was calculated using the following formula:

$$V_{Dcross-sectional} = \frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}$$

where S_1 and S_2 is the standard deviation for independent groups (i.e. premenopausal and postmenopausal women) and n represents the number of women in each group.

For longitudinal studies, the variance of the effect sizes was calculated using the following formulas:

$$V_{Dlongitudinal} = \frac{S_{diff}^2}{n}$$

$$S_{diff} = \sqrt{S_1^2 + S_2^2 - 2 \times r \times S_1 \times S_2}$$

where r is the correlation between premenopausal and postmenopausal fat mass means.

Where standard errors of the mean (SEM) or 95% confidence intervals (CI) were reported, authors were first contacted and requested to provide the unstandardized means and standard deviations. If the requested information was not provided, the SEM and CI were converted to SD using the method outlined in J. Higgins & Green (2011). Furthermore, volume measurements (cm^3) for computed tomography (CT) scans were converted to surface area (cm^2) by dividing by the following: thickness of slices number of slices.

2.3.11 Meta-analysis

Heterogeneity was assumed because sampling and methodology varied across studies resulting in a distribution of effect sizes (Borenstein et al., 2010). Therefore, a Random Effects (RE) Model using the restricted maximum likelihood estimator was utilised in all analyses to estimate the mean of the distribution of these effect sizes.

Heterogeneity across studies was assessed with Cochran's Q statistic (with $p < 0.01$ indicative of significant heterogeneity) and the I^2 statistic (values 25%, 50% and 75% suggestive of low, moderate and high heterogeneity respectively) (J. P. Higgins et al., 2003). To identify studies that excessively contributed to heterogeneity, sensitivity analyses were conducted using the leave-one-out-method. Meta-regression analyses using a mixed effect model were conducted to determine the influence of moderators, such as ageing. For cross-sectional studies comparisons of fat mass differences between premenopausal and postmenopausal women were made with a test of interaction.

2.3.12 Reporting bias

The possible impact of publication bias was assessed by visually inspecting funnel plots and with the Egger regression test (Egger et al., 1997). The trim and fill method was also used to estimate the number of studies that may be missing from the meta-analysis and to estimate adjusted effect sizes (Bhagat et al., 2010; Duval & Tweedie, 2000a).

2.4 Results

The search strategy identified 2,994 unique citations, while bibliography searches identified an additional 11 records. After initial screening based on titles and abstracts, 586 publications remained for full-text assessment. After the application of inclusion and exclusion criteria, a further 300 publications were excluded (Figure 2.1). Of the remaining 286 studies, 210 were eligible for inclusion in the quantitative analysis with 201 studies reporting cross-sectional

data (Abate et al., 2014; Abdulnour et al., 2012; Abildgaard et al., 2013; Adams-Campbell et al., 1996; Agrinier et al., 2010; Aguado et al., 1996; C. V. Albanese et al., 2009; Allali et al., 2009; Aloia et al., 1995; Amankwah et al., 2013; Amarante et al., 2011; Amiri et al., 2014; Angsuwathana et al., 2007; Armellini et al., 1996; Arthur et al., 2013; Aydin, 2010; Ayub et al., 2006; Bancroft & Cawood, 1996; Bednarek-Tupikowska et al., 2006; Bell et al., 2007; Ben Ali et al., 2011, 2014; Ben Ali et al., 2016; Berg et al., 2004; Berge et al., 1994; Berger et al., 1995; Berstad et al., 2010; Bhagat et al., 2010; Bhurosy & Jeewon, 2013; Blumenthal et al., 1991; Bonithon-Kopp et al., 1990; Caire-Juvera et al., 2008; Campesi et al., 2016; Carr et al., 2000; Castracane et al., 1998; Catsburg et al., 2014; Cecchini et al., 2012; Cervellati et al., 2009; Chain et al., 2017; Chang et al., 2000; Cho et al., 2008; Cifkova et al., 2008; Copeland et al., 2006; Cremonini et al., 2013; Cui et al., 2007; D'Haeseleer et al., 2011; da Câmara et al., 2015; Dallongeville et al., 1995; Dancey et al., 2001; C. E. Davis et al., 1994; De Kat et al., 2017; den Tonkelaar et al., 1990; Dmitruk et al., 2018; Donato et al., 2006; Douchi et al., 1997; Douchi et al., 2002; Douchi et al., 2007; Dubois et al., 2001; Engmann et al., 2017; Ertungealp et al., 1999; Feng et al., 2008; Formica et al., 1995; C. Friedenreich et al., 2007; C. M. Friedenreich et al., 2002; Fu et al., 2011; Fuh et al., 2003; Gambacciani et al., 1999; Genazzani & Gambacciani, 2006; Ghosh, 2008; Ghosh & Bhagat, 2010; Gram et al., 1997; Guerrero et al., 2017; Guo et al., 2015; Gurka et al., 2016; Hadji et al., 2000; Hagner et al., 2009; Han et al., 2006; Harting et al., 1984; He et al., 2012; Hirose et al., 2003; Hjartaker et al., 2005; Ho et al., 2010; Hsu et al., 2006; Hu et al., 2005; Hunter et al., 1996; Iida et al., 2011; Ilich-Ernst et al., 2002; Ito et al., 1994; Jaff et al., 2015; Jasienska et al., 2005; Jeenduang et al., 2014; Jeon et al., 2011; Jurimae & Jurimae, 2007; Kadam et al., 2010; Kang et al., 2016; Kaufer-Horwitz et al., 2005; H. M. Kim et al., 2007; J. H. Kim et al., 2012; S. Kim et al., 2013; Y. M. Kim et al., 2016; Kirchengast et al., 1996, 1998; Knapp et al., 2001; Koh et al., 2008; Konrad et al., 2011; Kontogianni et al., 2004; Konukoglu et al., 2000; Koskova et al., 2007; Kotani et al., 2011; Kraemer et al., 2001; Kuk et al., 2005; Laitinen et al., 1991; Lejskova et al., 2012; Ley et al., 1992; W. Y. Lin et al., 2005; Lindquist & Bengtsson, 1980; Lindsay et al., 1992; Lovejoy et al., 2005; Lyu et al., 2001; Maharlouei et al., 2013; Malacara et al., 2002; Manabe et al., 1999; Manjer et al., 2001; Mannisto et al., 1996; Martini et al., 1997; Marwaha et al., 2013; Matsushita et al., 2003; Matsuzaki et al., 2017; Matthews et al., 1989; Mesch et al., 2006; Meza-Munoz et al., 2006; Minatoya et al., 2014; Mo et al., 2017; Muchanga Sifa et al., 2014; Muti et al., 2000; Nitta et al., 2016; Noh et al., 2013; Nordin et al., 1992; Ohta et al., 2010; Oldroyd et al., 1998; Pacholczak et al., 2016; J.-H. Park et al., 2012; Y. M. Park et al., 2017; Pavlica et al., 2013; Phillips et al., 2008; Polesel et al., 2015; Pollan et al., 2012; Portaluppi et al., 1997; Priya et al., 2013; Rantalainen et al., 2010; Reina et al., 2015; Revilla, Villa, Hernandez, et al., 1997, 1997; Rice et al., 2015;

Rico et al., 2001, 2002; Roelfsema & Veldhuis, 2016; Rosenbaum et al., 1996; Salomaa et al., 1995; Sarrafzadegan et al., 2013; Schaberg-Lorei et al., 1990; Schwarz et al., 2007; Shakir et al., 2004; Sherk et al., 2011; Shibata et al., 1979; Sieminska et al., 2006; Skrzypczak et al., 2007; Skrzypczak & Szwed, 2005; Soderberg et al., 2002; Son et al., 2015; Soriguer et al., 2009; Staessen et al., 1989; Suarez-Ortegon et al., 2012; Suliga et al., 2016; Sumner et al., 1998; Tanaka et al., 2015; T. Thomas et al., 2000; Torng et al., 2000; Toth et al., 2000; Tremollieres et al., 1996; Trikudanathan et al., 2013; Van Pelt et al., 1998; Veldhuis et al., 2016; F. Wang et al., 2012; W. Wang et al., 2005; W. S. Wang et al., 2012; Wee et al., 2013; P. T. Williams & Krauss, 1997; Wing et al., 1991; Xu et al., 2010; Yamatani et al., 2013; Yannakoulia et al., 2007; Yoldemir & Erenus, 2012; H. J. Yoo et al., 2012; K. Y. Yoo et al., 1998; Yoshimoto et al., 2011; Žeželj et al., 2010; Zhong et al., 2005; J.-L. Zhou et al., 2010; Y. Zhou et al., 2015; Zivkovic et al., 2011) and 11 studies reporting longitudinal data (Abdulnour et al., 2012; Akahoshi et al., 2001; Ford et al., 2005; Franklin et al., 2009; Janssen et al., 2008; Lee et al., 2009; Liu-Ambrose et al., 2006; Lovejoy et al., 2005; Macdonald et al., 2005; Razmjou et al., 2018; Soreca et al., 2009).

Some studies included multiple sub-cohorts of premenopausal and postmenopausal women based on factors such as age (Akahoshi et al., 2001), ethnicity (Aloia et al., 1995; Gurka et al., 2016), physical activity level (Harting et al., 1984; Van Pelt et al., 1998) and geographic location (Formica et al., 1995; Malacara et al., 2002; Mo et al., 2017). In these cases, the sub-cohorts were extracted separately and treated as discrete samples. Therefore, 217 cross-sectional (Table 2.5) and 13 longitudinal samples (Table 2.6) were included in the analyses.

2.4.1 Study quality rating

For cross-sectional studies, 101 studies were of high quality as demonstrated by their scores ranging from 7 to 9 stars on the adapted version of the Newcastle Ottawa Scale (maximum 9 stars), 78 studies were of moderate quality (4 to 6 stars) and 22 studies were of poor quality (0 to 3 stars; Table 2.7). Almost all longitudinal studies were of high quality, with the exception of one study (Franklin et al., 2009), which was of moderate quality with a score of 4 (Table 2.8).

2.4.2 Summary estimates

The unstandardised mean differences (i.e. estimate) of each fat mass measure for both cross-sectional and longitudinal studies are presented in Table 2.1 and Table 2.2 respectively. Standardised estimates for cross-sectional and longitudinal studies are presented in Table 2.9

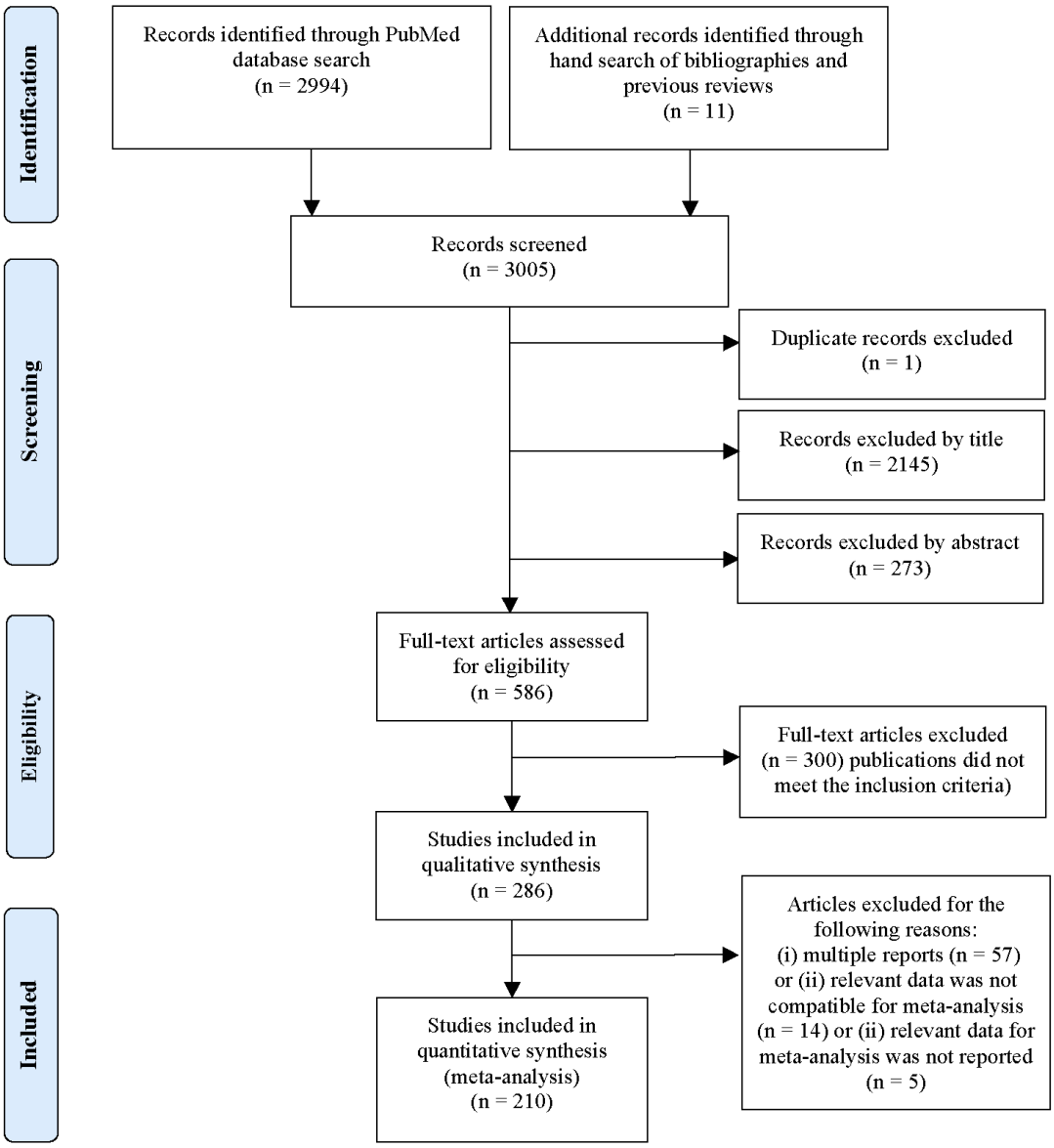

Figure 2.1: Flow chart of search, screening and selection process for studies included in the systematic review and meta-analyses.

and Table 2.10, respectively. Cross-sectional studies compared separate premenopausal and postmenopausal groups, whereas for longitudinal studies, all women were premenopausal at baseline and postmenopausal at follow up.

2.4.3 Cross-sectional meta-analysis

2.4.3.1 Cross-sectional Body Mass Index 171 cross-sectional studies investigated the relationship between BMI and menopausal status. The analyses revealed that the mean BMI difference was 1.14 kg/m^2 (SE = 0.09), with a yearly mean age difference of 0.07 $kg/m^2/year$ (Table 2.1).

2.4.3.2 Cross-sectional Body Weight 109 cross-sectional studies investigated the relationship between BW and menopausal status. The analyses revealed that the mean BW difference was 1.00 kg (SE = 0.29), with a yearly mean age difference of 0.07 kg/year (Table 2.1).

2.4.3.3 Cross-sectional Waist Circumference 70 cross-sectional studies investigated the relationship between WC and menopausal status. The analyses revealed that the mean WC difference was 4.63 cm (SE = 0.37), with a yearly mean age difference of 0.30 cm/year (Table 2.1).

2.4.3.4 Cross-sectional Waist to Hip Ratio 48 cross-sectional studies investigated the relationship between WTHR and menopausal status. The analyses revealed that the mean WTHR difference was 0.0421 (SE = 0.0045), with a yearly mean age difference of 0.0026/year (Table 2.1).

2.4.3.5 Cross-sectional Body Fat Percentage 46 cross-sectional studies investigated the relationship between BF% and menopausal status. The analyses revealed that the mean BF% difference was 2.88% (SE = 0.38), with a yearly mean age difference of 0.21%/year (Table 2.1).

2.4.3.6 Cross-sectional Hip Circumference 25 cross-sectional studies investigated the relationship between HC and menopausal status. The analyses revealed that the mean HC difference was 2.01 cm (SE = 0.33), with a yearly mean age difference of 0.13 cm/year (Table 2.1).

2.4.3.7 Cross-sectional Abdominal Fat and Visceral Fat 10 cross-sectional studies investigated the relationship between AF/VF and menopausal status using CT scans. The analyses revealed that the mean AF difference was 28.73 cm^2 (SE = 10.29), with a yearly mean age difference of 1.92 $cm^2/year$, however, the mean VF difference was 26.90 cm^2 (SE = 7.03), with a yearly mean age difference of 1.81 $cm^2/year$ (Table 2.1).

2.4.3.8 Cross-sectional Suprailliac Skinfold Thickness 9 cross-sectional studies investigated the relationship between SISF and menopausal status. The analyses revealed that the mean SISF difference was 2.65 mm (SE = 1.12), with a yearly mean age difference of 0.13 mm/year (Table 2.1).

2.4.3.9 Cross-sectional Trunk Fat Percentage 7 cross-sectional studies investigated the relationship between TF% and menopausal status. The analyses revealed that the mean TF% difference was 5.49% (SE = 0.80), with a yearly mean age difference of 0.40%/year (Table 2.1).

2.4.3.10 Cross-sectional Abdominal Skinfold Thickness 4 cross-sectional studies investigated the relationship between ASF and menopausal status. The analyses revealed that the mean ASF difference was 6.46 mm (SE = 3.04), with a yearly mean age difference of 0.35 mm/year (Table 2.1).

2.4.3.11 Cross-sectional Total Leg Fat Percentage 3 cross-sectional studies investigated the relationship between LF% and menopausal status. The analyses revealed that the mean LF% difference was -3.19% (SE = 1.42), with a yearly mean age difference of -0.17%/year (Table 2.1).

Table 2.1: Output for cross-sectional studies.

		Total sample size		Mean age (SD)		Mean (SD)	Mean fat mass (SD)		Unstandardised	
Fat mass measure	**k (Samples)**	**PreM**	**PostM**	**PreM**	**PostM**	**Age difference**	**PreM**	**PostM**	**Estimate (95% CI)**	**p-value**
Body mass index	171 (181)	453 036	523 796	41.96 (3.69)	59.42 (3.06)	14.82 (5.36)	24.75 (1.60)	26.64 (1.25)	1.14 (0.95 - 1.32)	<0.0001
Bodyweight	109 (122)	113 603	204 845	43.36 (4.71)	59.55 (3.27)	15.00 (5.37)	64.82 (7.91)	66.12 (9.17)	1.00 (0.44 – 1.57)	0.0005
Waist circumference	70 (72)	214 712	326 639	42.28 (3.65)	59.07 (1.91)	16.23 (4.24)	78.58 (4.24)	83.61 (3.19)	4.63 (3.90 - 5.35)	<0.0001
Waist-to-hip ratio	47 (50)	199 140	309 797	42.39 (3.44)	59.09 (1.42)	16.17 (3.20)	0.78 (0.03)	0.81 (0.03)	0.04 (0.03 - 0.05)	<0.0001
Body fat percentage	46 (52)	58 605	113 226	43.81 (4.67)	59.55 (3.81)	14.83 (6.56)	32.44 (3.47)	35.69 (3.84)	2.88 (2.13 - 3.63)	<0.0001
Hip circumference	25 (25)	185 885	297 189	42.48 (3.08)	59.15 (0.95)	16.22 (2.61)	100.30 (2.66)	102.73 (2.25)	2.01 (1.36 - 2.65)	<0.0001
Subcutaneous abdominal fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	194.05 (23.65)	221.21 (32.09)	28.73 (8.56 - 48.91)	0.0053
Visceral fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	69.22 (15.75)	104.36 (13.92)	26.90 (13.12 - 40.68)	0.0001
Suprailiac skinfold thickness	9 (10)	1103	745	39.76 (4.41)	61.89 (4.77)	21.46 (6.49)	22.16 (7.04)	24.55 (9.90)	2.65 (0.45 - 4.85)	0.0181
Trunk fat percentage	7 (7)	39 335	95 756	45.28 (6.61)	59.68 (3.41)	14.32 (6.21)	31.27 (4.78)	33.74 (5.36)	5.49 (3.91 - 7.06)	<0.0001
Abdominal skinfold thickness	4 (5)	199	359	40.64 (6.32)	62.99 (5.16)	21.04 (5.00)	26.65 (8.14)	29.43 (9.82)	6.46 (0.51 - 12.42)	0.0335
Total leg fat percentage	3(3)	991	524	36.96 (1.13)	55.18 (5.17)	19.41 (5.87)	36.33 (5.47)	36.00 (2.62)	-3.19 (-5.98 - -0.41)	0.0246

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; k = number of studies; SD, Standard Deviation; CI, Confidence Interval. Note: Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. $p < 0.05$ considered significant.

2.4.4 Longitudinal meta-analysis

2.4.4.1 Longitudinal Body Mass Index 8 longitudinal studies investigated the relationship between BMI and menopausal status. The analyses revealed that the mean BMI change was 0.93 kg/m^2 (SE = 0.34), with an annual change of 0.14 $kg/m^2/year$ (Table 2.2).

2.4.4.2 Longitudinal Body Weight 7 longitudinal studies investigated the relationship between BW and menopausal status. The analyses revealed that the mean BW change was 2.99 kg (SE = 0.83), with an annual change of 0.37 kg/year (Table 2.2).

2.4.4.3 Longitudinal Total Body Fat Percentage 4 longitudinal studies investigated the relationship between BF% and menopausal status. The analyses revealed that the mean BF% change was 2.18% (SE = 1.01), with an annual change of 0.41%/year (Table 2.2).

2.4.4.4 Longitudinal Waist Circumference 3 longitudinal studies investigated the relationship between WC and menopausal status. The analyses revealed that the mean WC change was 3.82 cm (SE = 1.51), with an annual change of 0.51 cm/year (Table 2.2).

2.4.4.5 Longitudinal Abdominal Fat and Visceral Fat 3 longitudinal studies investigated the relationship between AF/VF and menopausal status using CT scans. The analyses revealed that there was no significant mean AF difference, however a significant difference in VF of 12.95 cm^2 (SE = 2.20) was detected, with an annual change of 3.43 $cm^2/year$ (Table 2.2).

Table 2.2: Output for longitudinal studies.

			Mean age (SD)		Mean (SD)	Mean fat mass (SD)		Unstandardised	
Fat mass measure	**k (Samples)**	**Total sample size**	**PreM**	**PostM**	**Follow up period**	**PreM**	**PostM**	**Estimate (95% CI)**	**p-value**
Body mass index	8 (10)	2 355	46.67 (2.53)	52.80 (3.71)	6.68 (2.38)	24.30 (1.97)	25.03 (2.37)	0.93 (0.26 - 1.59)	0.0061
Bodyweight	7 (7)	525	47.64 (3.06)	55.76 (5.08)	7.82 (5.35)	66.11 (3.89)	69.19 (3.71)	2.99 (1.36 - 4.63)	0.0003
Body fat percentage	4 (4)	176	49.59 (1.24)	55.49 (3.65)	5.82 (3.25)	36.29 (4.88)	37.84 (3.33)	2.18 (0.21 - 4.16)	0.0299
Waist circumference	3 (3)	915	46.99 (2.04)	52.73 (5.17)	7.17 (1.98)	80.79 (3.62)	84.06 (2.61)	3.82 (0.87 - 6.77)	0.0111
Subcutaneous abdominal fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	3.90 (0.39)	215.14 (66.15)	242.28 (77.34)	18.53 (-3.64 - 40.69)	0.1014
Visceral fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	3.90 (0.39)	78.63 (14.45)	92.23 (12.77)	12.95 (8.65 – 17.25)	<0.0001

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; k = number of studies; SD, Standard Deviation; CI, Confidence Interval. Note: Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. $p < 0.05$ considered significant.

2.4.5 Sensitivity analyses

Significant heterogeneity was found in all meta-analyses performed and the proportion of real observed variance (not related to random error) between studies (I^2) was high across all analyses (Figures 2.3 - 2.19). The influence of single studies was investigated further wherever possible (i.e. k > 3) through leave-one-out analyses. The analyses predominantly demonstrated no particularly influential study and showed relative consistency in reported estimates, with a few notable exceptions. For TF% analyses, Guo et al. (2015) was found to be influential, which could be due to the large sample size reported (see Figure 2.2) or because bioelectrical impedance analysis (BIA) was utilised in comparison to the other 6 studies that used dual-energy x-ray absorptiometry (DEXA) scans. When excluded from the analyses, the mean TF% difference between premenopausal and postmenopausal women increased from 5.49% to 6.05% (95% CI 4.94 to 7.15), with I^2 decreasing from 89.90% to 54.44%.

For BF% analyses (cross-sectional), Sherk et al. (2011) was identified as influential whereas for BMI and BW analyses (longitudinal), Soreca et al. (2009) was identified as influential, which could be due to the relatively large mean age difference/follow-up period (41.2 years and 20 years respectively). When removed from analyses, all estimates decreased (BF%: 2.71, 95% CI 2.02 to 3.40; BMI: 0.63, 95% CI 0.32 to 0.94; BW: 2.39, 95% CI 1.22 to 3.55), with I^2 remaining high. For AF analyses (cross-sectional), Hunter et al. (1996) was found to be influential. Despite being a relatively older study (published over 20 years ago), meta-regression analyses revealed that year of publication had no effect on the overall estimate. When excluded from the analyses, the mean AF difference decreased from 28.73 cm^2 to 18.81 cm^2 (95% CI 3.38 to 34.25) with I^2 remaining high.

One study, Franklin et al. (2009), was found to be influential for BF% analyses (longitudinal), which could in part be because of (i) the relatively lower quality of the study (4 stars) when compared with other studies included in the analyses (8 stars); or (ii) BF% was measured using two different methods i.e hydrostatic weighing (at baseline) and air displacement plethysmograph (at follow up) compared with other studies that all used DEXA at baseline and follow up assessment or (iii) the very small sample size of the study (8 participants), comparatively to other studies which have a mean of 56 participants (range 48 – 69). When Franklin et al. (2009) was excluded from the analyses, there was no significant difference in mean BF%.

2.4.6 Publication bias

Funnel plot asymmetry diagnostics and the trim and fill test revealed some evidence of publication bias. Eggers regression test was significant for, ASF, TF% and LF% (cross-

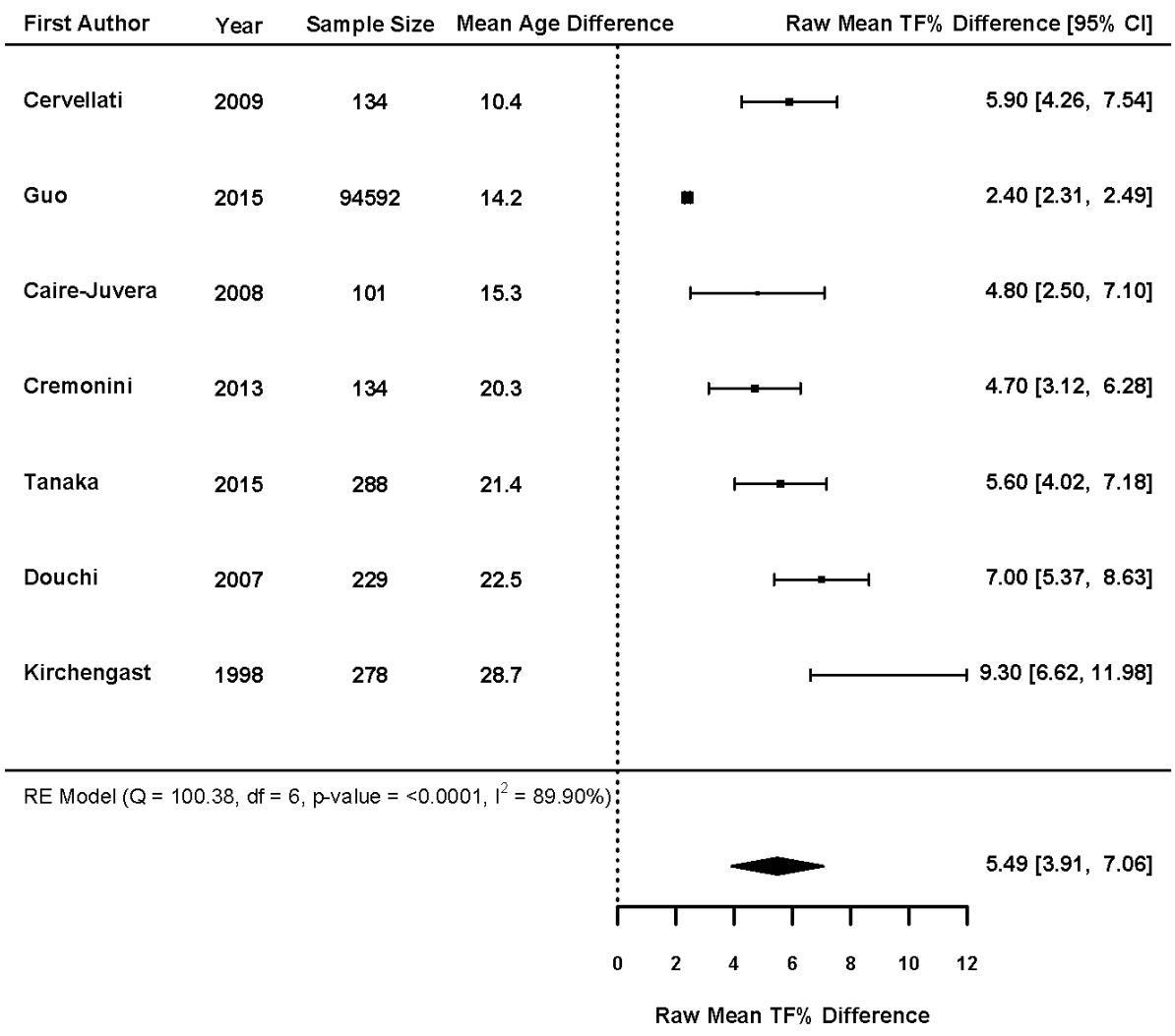

Figure 2.2: Forest plot of the raw mean trunk fat percentage difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TF%, Trunk Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.

sectional analyses), BF% (both cross-sectional and longitudinal analyses) and VF (longitudinal analyses), indicating some degree of asymmetry for these groups. For cross-sectional studies the trim and fill analyses identified 30 missing studies for BMI and 2 for AF, producing larger estimates for both (Figures 2.20 and 2.22). For longitudinal studies, however, 2 missing studies were identified for VF, producing a smaller estimate (Figure 2.24).

2.4.7 Subgroup and meta-regression analyses

The influence of moderators such as ageing (represented as the mean age difference for cross-sectional analyses or length of follow up for longitudinal analyses) and study quality on pooled estimates was investigated by meta-regression analyses using a mixed effects model, where a sufficient number of studies were available to assess the effect of a single predictor (i.e. samples 10) (Field et al., 2012; J. Higgins & Green, 2011). Where meta-regression was possible (i.e. longitudinal BMI and cross-sectional BMI, BW, WC, WTHR, BF%, HC, AF, VF and SSIF), ageing significantly predicted the unexplained variance (9.99 – 73.90%) in fat mass estimates except for HC, AF and SSIF (Table 2.3). No interactive effects were observed between menopausal status and age across all fat mass measures. Furthermore, study quality had no significant effect on the overall estimate.

Table 2.3: Metaregression analyses after removal of the effect that is attributable to normal aging.

				Unstandardised	
Analyses	**Samples**	**Fat mass measure**	R^2	**Estimate (95% CI)**	**p-value**
Longitudinal	10	Body mass index	73.88	0.20 (0.12 - 0.29)	<0.0001
Cross-sectional	176	Body mass index	21.61	0.06 (0.04 - 0.08)	<0.0001
	119	Bodyweight	9.99	0.10 (0.04 - 0.16)	0.0008
	71	Waist circumference	40.13	0.24 (0.16 - 0.32)	<0.0001
	51	Waist-to-hip ratio	24.87	0.0025 (0.0013 - 0.0037)	<0.0001
	50	Body fat percentage	24.75	0.15 (0.07 - 0.24)	0.0005
	25	Hip circumference	15.74	0.09 (-0.02 - 0.21)	0.1201
	10	Subcutaneous abdominal fat	9.03	1.29 (-0.70 - 3.28)	0.2035
	10	Visceral fat	73.90	1.85 (1.04 - 2.67)	<0.0001
	10	Suprailiac skinfold thickness	0.00	0.21 (-0.19 - 0.60)	0.3033

Abbreviations: CI, Confidence Interval; R^2, proportion of observed variance explained by the model; Studies that did not report age were omitted from model fitting. $p < 0.05$ considered significant.

To examine whether the type of measure could influence the results, we performed subgroup analyses on cross-sectional studies that examined BF% to investigate the impact of DEXA scans versus other methods, such as BIA and hydrodensitometry, on quantifying total and regional body fat percentage. Interestingly BIA significantly underestimated the quantity of total body fat compared to DEXA (β = -2.64%, 95% CI -4.23 to -1.04, p-value = 0.0012), which supports previous findings Bolanowski & Nilsson (2001). Similarly, when investigating the effects of measured versus self-reported BMI in cross-sectional studies, self-report significantly underestimated BMI (β= -0.72 kg/m^2, 95% CI -1.34 to -0.09, p-value = 0.0240) compared to direct measurement, which aligns with previous findings (S. P. Ng et al., 2011). After adjusting for the effect of age however, self-report had no significant effect on the overall estimate for BMI. All longitudinal studies computed BMI based on objectively measured height and weight. For VF and AF analyses, the use of surface area estimates that were converted from volumes (which was conducted for one particular study (Trikudanathan et al., 2013)) had no significant effect on the overall estimate. Notably, almost all subgroup analyses that included women using HRT had no significant effect on estimates, except for BF% (significantly increased; = 2.46%, CI 0.16 to 4.76, p-value = 0.0358) and TF% (significantly decreased; = -3.65%, CI -5.91 to -1.38, p-value = 0.0016).

2.5 Discussion

This large scale, comprehensive review with meta-analyses investigated the differences in fat mass between healthy premenopausal and postmenopausal women in both cross-sectional and longitudinal studies. The main findings were that (1) there was an increase in fat mass between premenopausal and postmenopausal women across most measures, specifically BMI, BW, WC, WTHR, BF%, HC, ASF, SISF, VF and TF%, with the exception of LF%, which decreased; and (2) the change in fat mass quantity is largely attributable to increasing age with menopause having no detectable additional influence. These findings are important as they suggest attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan.

The relationship between menopause and ageing can be difficult to disentangle, since both progress concurrently. Previous research indicates that for women aged 18-45 years the typical trends for BMI and BF% is an increase of 0.16 $kg/m^2/year$ and 0.41%/year respectively (Siervogel et al., 1998). Interestingly, the longitudinal analyses presented in this paper reflect similar annual estimates for BMI (0.14 $kg/m^2/year$) and BF% (0.41%/year), which indicates that the rates of change remain the same throughout early adulthood and middle age, with menopause having no detectable additional influence above and beyond the effect

of ageing. Furthermore, the meta-regression analyses revealed consistent but comparatively lower estimates for cross-sectional BMI (0.06 $kg/m^2/year$) and BF% (0.15%/year). The reason for the relatively smaller estimates remains to be elucidated, however, it is possible that unmeasured and/or unreported genetic and environmental factors (e.g. ethnicity, dietary changes, mood disorders and medications used in their treatment, physical activity levels, metabolic activity, and variation in sleep length and quality (Davis et al., 2012; Demerath et al., 2011; Patel et al., 2006; Sternfeld et al., 2004)) that varied between groups in cross-sectional studies account for this. Alternatively, this may also be explained by the well-documented differences emerging from the less robust design of cross-sectional compared to longitudinal studies. As a result, the longitudinal study design is better suited to providing yearly rates of change in fat mass, which are more precise than cross-sectional estimates.

Too few longitudinal studies produced precise estimates of fat mass changes across multiple regions, however, the analysis of cross-sectional studies revealed that LF% decreased by 0.17%/year, whereas fat mass increased in abdominal indexes, such as TF% by 0.40%/year and WC (longitudinal) by 0.51 cm/year, indicative of a potential change in fat mass distribution after menopause. These changes are likely to, at least in part, be due to hormonal shifts that occur during midlife with women having a higher androgen (i.e. testosterone) to estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition (Janssen et al., 2015). Importantly, the increased central deposition of fat has significant clinical implications given that a 1 cm increase in WC has been associated with a 2% increase in risk of CVD (De Koning et al., 2007). Furthermore, a higher testosterone/estradiol ratio has also been associated with deleterious health consequences in women, such as CVD (Zhao et al., 2018). Taken together, these results may help explain the fact that premenopausal women have been found to have lower CVD incidence and mortality rates compared with men of the same age (Mikkola et al., 2013), whereas postmenopausal women experience higher mortality rates due to CVD compared to men of the same age (McAloon et al., 2016). The current analyses suggests that measures sensitive to detecting the central deposition of adiposity, such as TF% and WC would be preferable to BW and BMI, which are commonly used indicators of overweight and obesity. This is of particular importance because of the multifactorial changes in body composition that occur in ageing women which can influence BW and/or BMI estimates, such as (i) a decrease in bone density (Douchi et al., 2003; Steiger et al., 1992), (ii) sarcopenia (Shafiee et al., 2017) and (iii) shrinking (Perissinotto et al., 2002), which indicate that measures less influenced by these changes, such as TF% and WC, would be preferable. Furthermore, when measures of fat mass were standardised (Tables 2.9 and 2.10) cross-sectional analyses revealed that BF% had the largest magnitude of effect across estimates. However, when comparing the precision of confidence intervals, WTHR, WC and

TF% produced comparatively more reliable estimates. These results should be interpreted with caution given that variability across measures, including different samples, sample sizes and measurement error, could not be accounted for.

2.5.1 Hormone replacement therapy and fat mass

Subgroup analyses revealed that the inclusion of women using HRT resulted in a significant increase in BF% (β = 2.46%, CI 0.16 to 4.76, p-value = 0.0358) and a significant decrease in TF% (β = -3.65%, CI -5.91 to -1.38, p-value = 0.0016), suggestive of a potential protective role of HRT in preventing/reducing trunk fat deposition although not in preventing overall fat mass gain. These results align with a previous meta-analysis of 8 randomized control trials, which found that postmenopausal women using HRT had less WC and TF% compared to placebo (Salpeter et al., 2006). Taken together, these findings provide useful estimates for the potential protective effect of HRT on central adiposity given that, to our knowledge, the most recent systematic review on this topic was published almost 20 years ago (Kongnyuy et al., 1999) and had insufficient studies at the time to evaluate the effect of HRT on fat mass distribution. Moreover, since HRT use has complex interactions with the body and brain, with varying benefits and disadvantages depending on the time of initiation, type and duration of treatment (H. D. Nelson et al., 2002), it is important for this topic to be investigated systematically in future, using longitudinal studies.

2.5.2 Strengths and limitations

A key strength of the present study was that a large number of individuals were assessed for cross-sectional analyses, across a wide range of measures that estimated fat mass changes in quantity and distribution between premenopausal and postmenopausal women, resulting in a holistic understanding of body fat changes in women at midlife. Specifically, 201 cross-sectional studies were included in the meta-analysis, which provided a combined sample size of 1,049,919 individuals consisting of 478,734 premenopausal women and 571,185 postmenopausal women.

Notable limitations included the fact that only 11 longitudinal studies were available for inclusion in the meta-analysis, which provided a combined sample size of 2,472 women who were premenopausal at baseline and postmenopausal at follow up. Furthermore, it is possible that relevant studies may have been missed, given that our search was limited to the PubMed database. However, these relative weaknesses were somewhat counterbalanced by the large number of cross-sectional results, which facilitated richer and comprehensive analyses that led to very consistent findings. In addition, women classified as perimenopausal were not included in the current meta-analysis. This was done to ensure that a clear comparison could be made

between groups, with premenopausal women acting as controls for any effect observed after menopause. Moreover, the criteria used to identify premenopausal and postmenopausal women varied substantially between studies and may have reduced the accuracy of the reported effects.

2.6 Conclusion

To our knowledge, this is the first comprehensive review with meta-analysis of both longitudinal and cross-sectional studies investigating changes in fat mass between premenopausal and postmenopausal women. The analyses revealed that fat mass was higher in postmenopausal compared to premenopausal women across most measures, with the exception of LF% which decreased, indicative of a potential change in fat mass distribution after menopause. However, the change in fat mass quantity was predominantly attributable to increasing age with menopause having no significant additional influence. Given that central fat accumulation is associated with an increase in CVD risk, these results may help explain the fact that premenopausal women have been found to have lower CVD incidence and mortality rates compared with men of the same age, whereas postmenopausal women experience higher mortality rates due to CVD compared to men of the same age. An important implication of these findings is that attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan. Further investigation regarding the role of other potential moderators (e.g. genetics, ethnicity, dietary changes, physical activity levels, metabolic activity, mood disorders and medications used in their treatment, age of menopause onset and variation in sleep length and quality) is required to facilitate the development of targeted and effective intervention programs and heath policies aimed at mitigating the risk posed by increased central adiposity in women at midlife.

2.7 Supplementary materials

The supplementary materials for Chapter 2 include:

- **Adapted Newcastle-Ottawa Quality Assessment Form for Cohort Studies**
- **Figure 2.3** Forest plot of the cross-sectional raw mean body mass index difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.4** Forest plot of the cross-sectional raw mean body weight difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BW, Body Weight; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.5** Forest plot of the cross-sectional raw mean waist circumference difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: WC, Waist Circumference; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.6** Forest plot of the cross-sectional standardised mean waist to hip ratio difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: WTHR, Waist to Hip Ratio; Std, Standardised; CI, Confidence Interval; RE Model, Random Effects Model. Note: Standardised units have been used, due to the amount of (residual) heterogeneity with non-positive sampling variances.
- **Figure 2.7** Forest plot of the cross-sectional raw mean body fat percentage difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BF %, Total Body Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.8** Forest plot of the cross-sectional raw mean hip circumference difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: HC, Hip Circumference; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.9** Forest plot of the cross-sectional raw mean abdominal fat difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: AF, Abdominal Fat; CI, Confidence Interval; RE Model, Random Effects

Model.

- **Figure 2.10** Forest plot of the cross-sectional raw mean visceral fat difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: VF, Visceral Fat; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.11** Forest plot of the cross-sectional raw mean suprailliac skinfold thickness difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: SISF, Suprailliac Skinfold Thickness; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.12** Forest plot of the cross-sectional raw mean abdominal skinfold thickness difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: ASF, Abdominal Skinfold Thickness; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.13** Forest plot of the cross-sectional raw mean leg fat percentage difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: LF %, Total Leg Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.14** Forest plot of the longitudinal body mass index change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.15** Forest plot of the longitudinal body weight change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BW, Body Weight; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.16** Forest plot of the longitudinal body fat percentage change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BF %, Total Body Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.17** Forest plot of the longitudinal waist circumference change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: WC, Waist Circumference; CI, Confidence Interval; RE Model, Random Effects Model.

- **Figure 2.18** Forest plot of the longitudinal abdominal fat change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: AF, Abdominal Fat; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.19** Forest plot of the longitudinal visceral fat change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: VF, Visceral Fat; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 2.20** Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; WC, Waist Circumference; WTHR, Waist to Hip Ratio; BF %, Total Body Fat Percentage; T&F, trim and fill.
- **Figure 2.21** Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. HC, Hip Circumference; AF, Abdominal Fat; VF, Visceral Fat; SISF, Suprailliac Skinfold Thickness; TF %, Trunk Fat Percentage; T&F, trim and fill.
- **Figure 2.22** Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. ASF, Abdominal Skinfold Thickness; LF %, Total Leg Fat Percentage; T&F, trim and fill.
- **Figure 2.23** Funnel plots for longitudinal studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; BF %, Total Body Fat Percentage; WC, Waist Circumference; AF, Abdominal Fat; T&F, trim and fill.
- **Figure 2.24** Funnel plots for longitudinal studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; BF %, Total Body Fat Percentage; WC, Waist Circumference; AF, Abdominal Fat; T&F, trim and fill.
- **Table 2.4** Definition of data elements.

- **Table 2.5** Table of study characteristics for cross-sectional studies.
- **Table 2.6** Table of study characteristics for longitudinal studies.
- **Table 2.7** Quality assessment of individual cross-sectional studies.
- **Table 2.8** Quality assessment of individual longitudinal studies.
- **Table 2.9** Output for cross-sectional studies.
- **Table 2.10** Output for longitudinal studies.

Adapted Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Note: A study can be given a maximum of one star for each numbered item within the Selection and Outcome categories. The exception to this is for the Comparability section.

Selection of premenopausal and postmenopausal women

1. Representativeness of the postmenopausal cohort

- Truly representative of the average postmenopausal woman in the community ∗
- Somewhat representative of the average postmenopausal woman in the community ∗
- Selected group of users eg nurses, volunteers
- No description of the derivation of the cohort

2. Selection of the premenopausal cohort

- Drawn from the same or similar community as the postmenopausal cohort ∗
- Drawn from a different source
- No description of the derivation of the premenopausal cohort

3. Ascertainment of menopausal status

- Secure record (e.g. surgical records) ∗
- Structured interview ∗
- Written self report
- No description
- Other

Comparability of Premenopausal and Postmenopausal women

4. Comparability of premenopausal and postmenopausal women on the basis of the study design

- Lifestyle/demographic characteristics of premenopausal and postmenopausal women recorded and reported, with age as a minimum. ∗
- The mean difference in age between premenopausal and postmenopausal women enables a reasonable comparison which is not highly confounded by age (i.e. approximately 10 years or less for cross-sectional studies). Note: For longitudinal studies, an appropriate

Selection	/3
Comparability	/4
Outcome	/2
Total	/9
Rater #1 Initials	
Selection	/3
Comparability	/4
Outcome	/2
Total	/9
Rater #2 Initials	

follow up period is required (i.e. premenopausal at baseline and postmenopausal at follow up). ∗

5. Was a clear definition used to describe premenopausal women

- Yes ∗
- No

6. Was a clear definition used to describe postmenopausal women

- Yes ∗
- No

Outcome

7. Assessment of fat mass

- Measured ∗
- Self report
- No description

8. Was the same method of measuring fat mass conducted for both premenopausal and postmenopausal women

- Yes ∗
- No
- No description

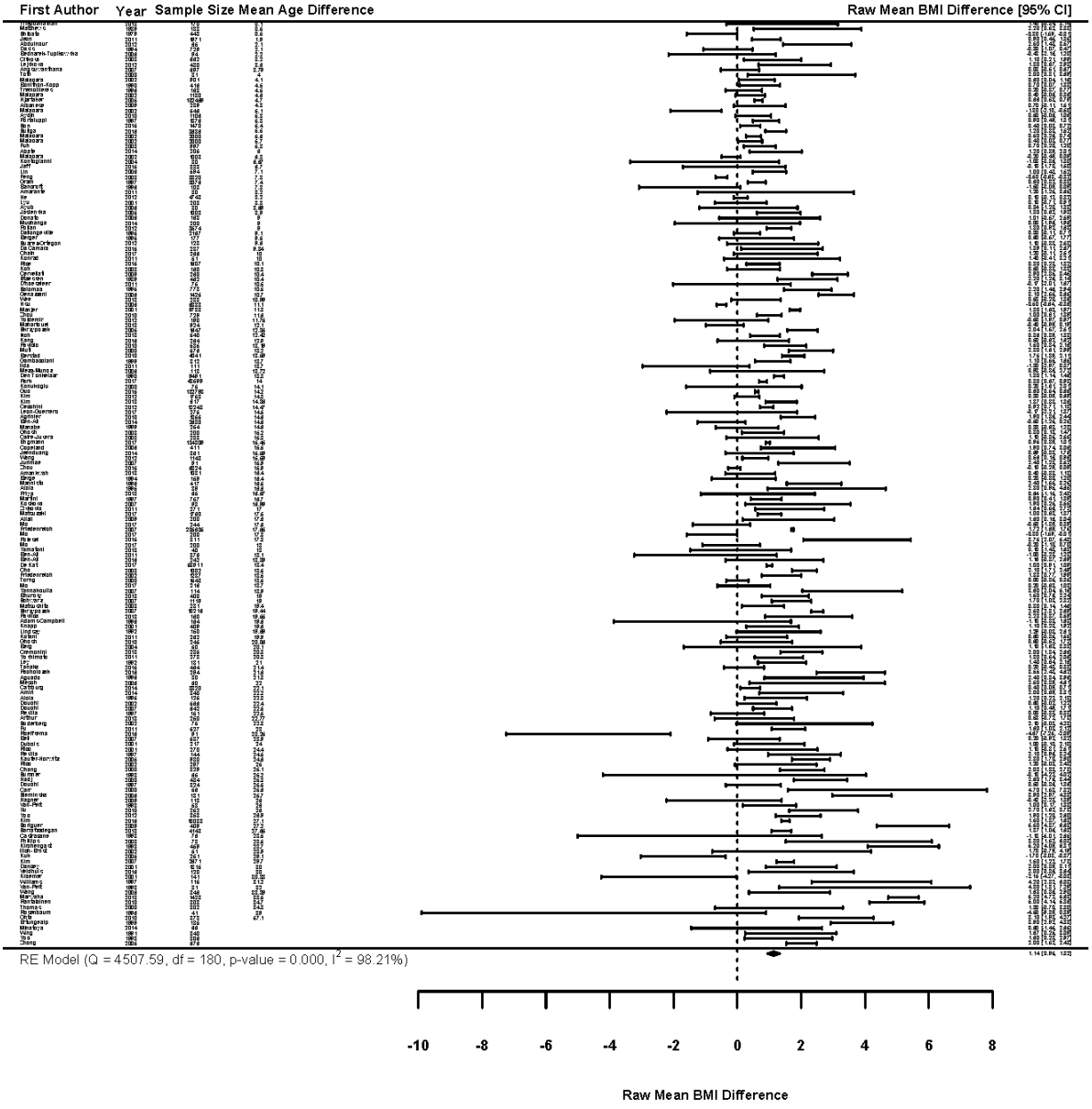

Figure 2.3: Forest plot of the cross-sectional raw mean body mass index difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; RE Model, Random Effects Model.

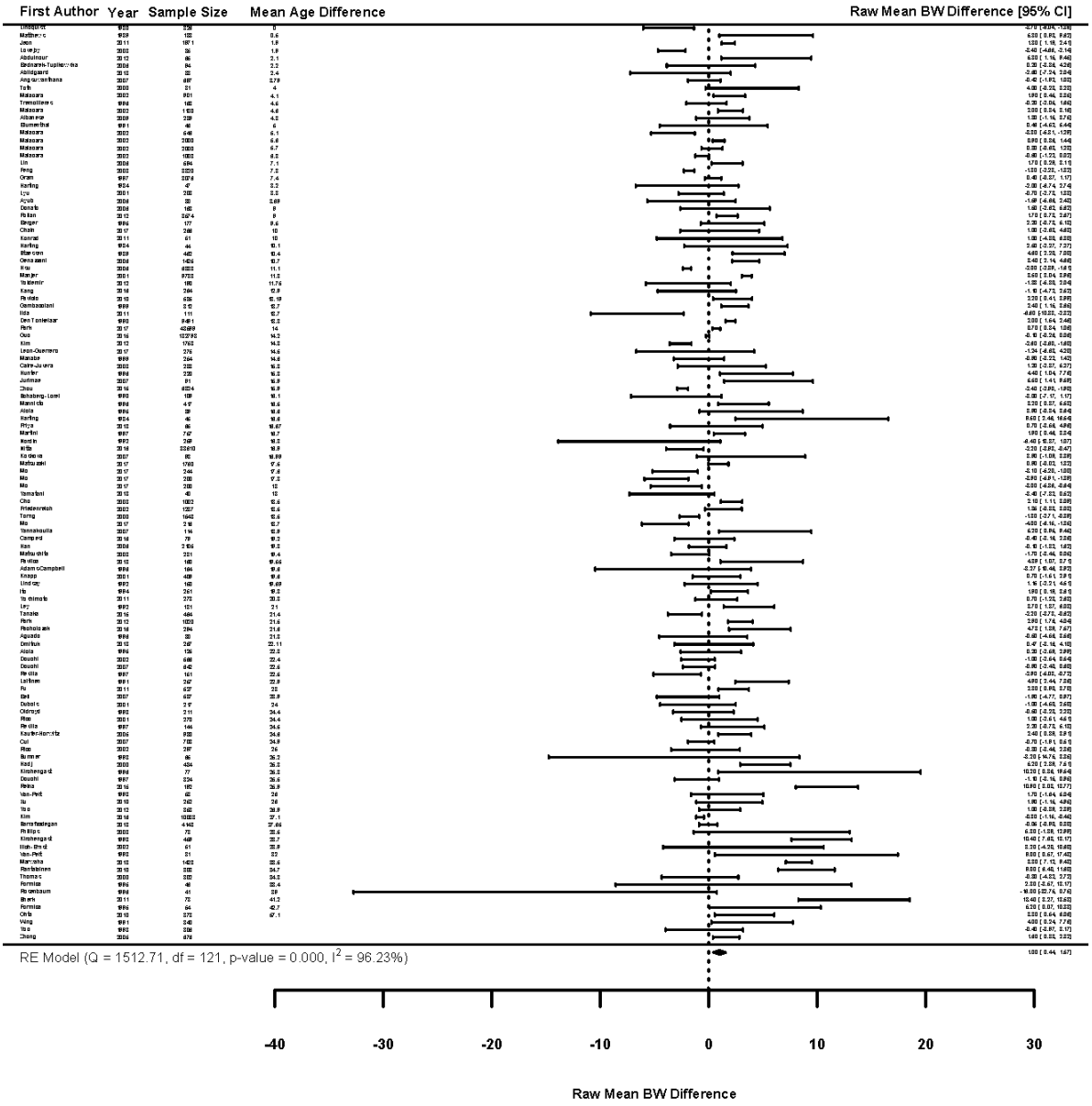

Figure 2.4: Forest plot of the cross-sectional raw mean body weight difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BW, Body Weight; CI, Confidence Interval; RE Model, Random Effects Model.

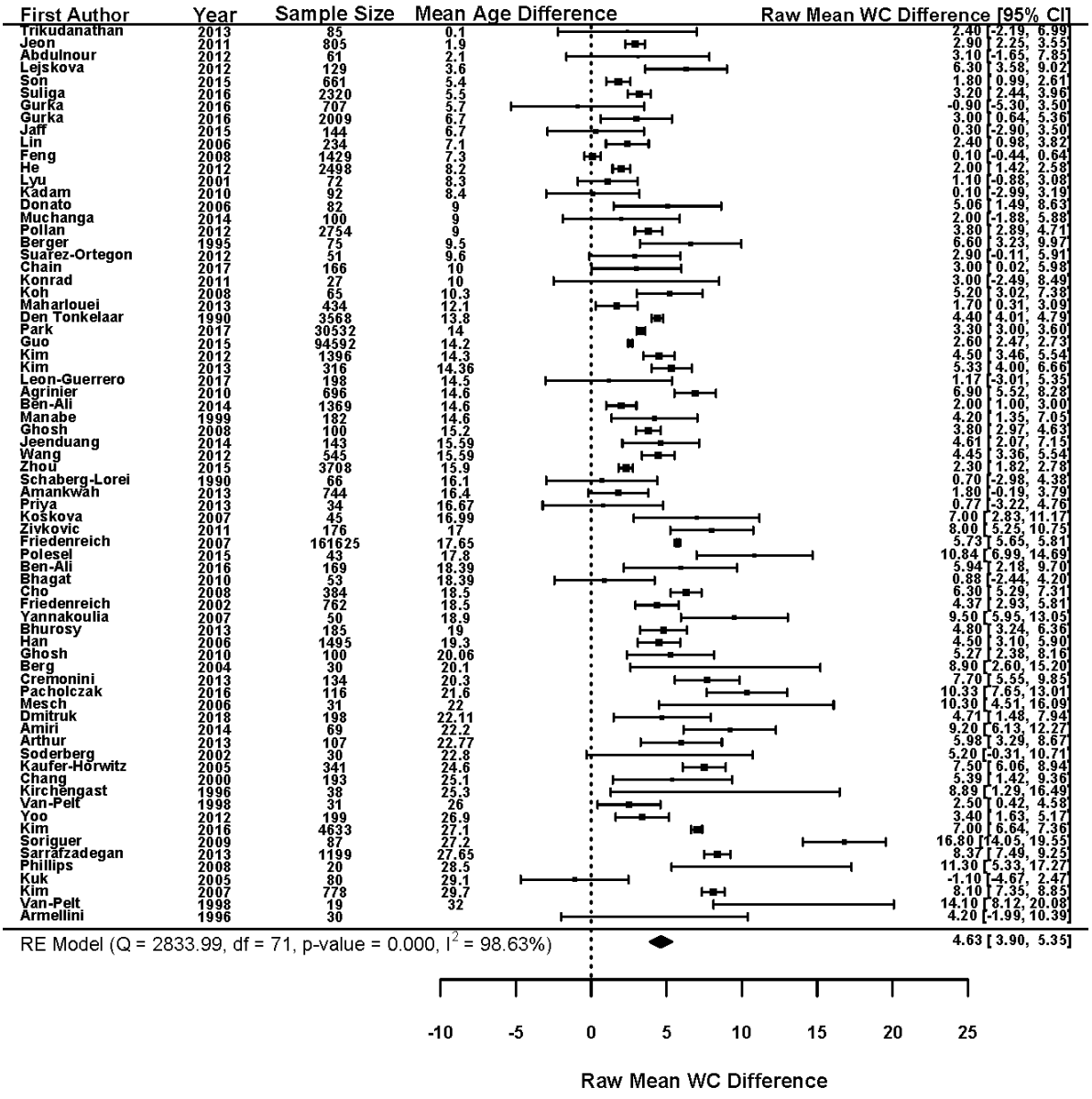

Figure 2.5: Forest plot of the cross-sectional raw mean waist circumference difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: WC, Waist Circumference; CI, Confidence Interval; RE Model, Random Effects Model.

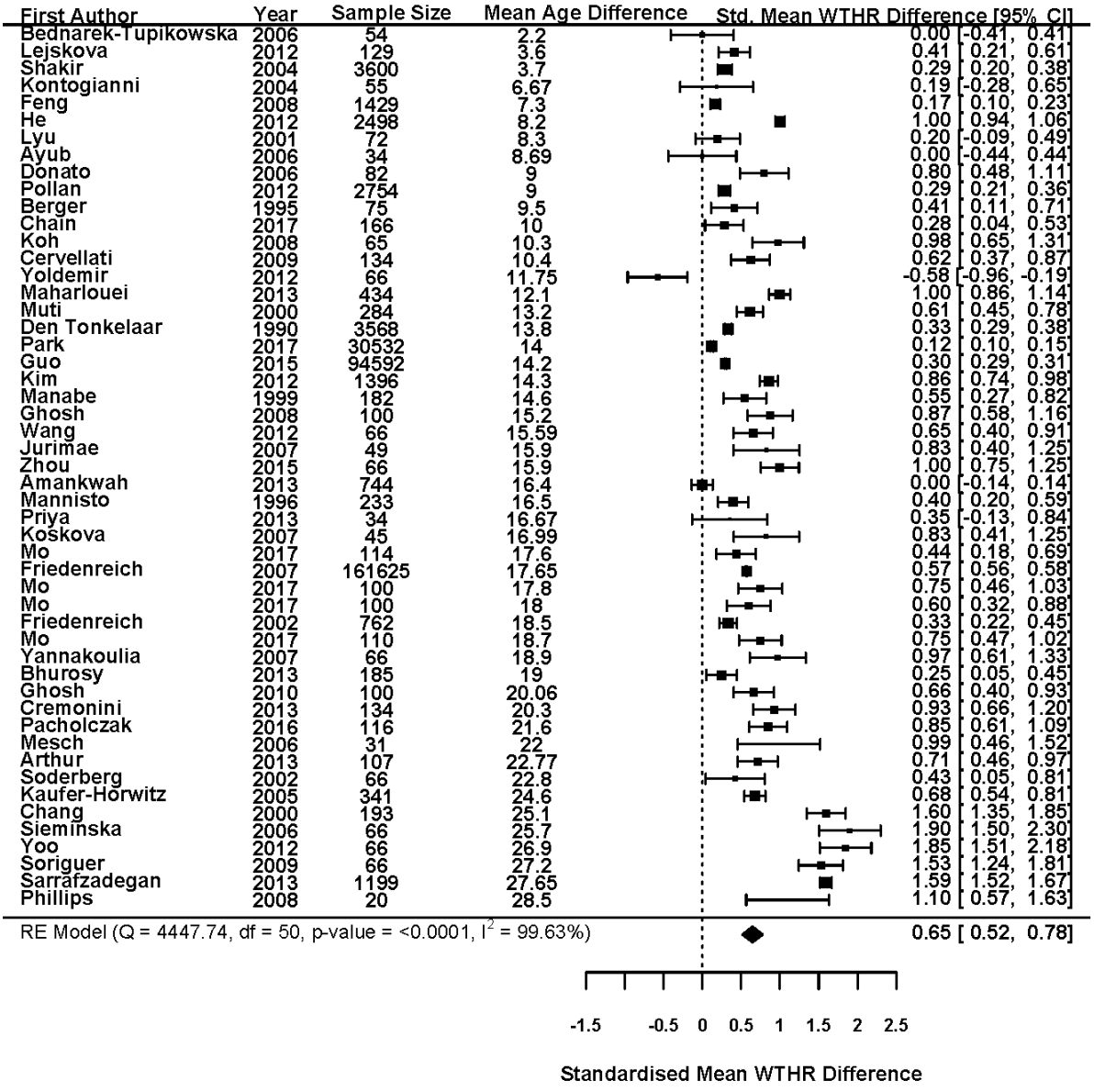

Figure 2.6: Forest plot of the cross-sectional standardised mean waist to hip ratio difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: WTHR, Waist to Hip Ratio; Std, Standardised; CI, Confidence Interval; RE Model, Random Effects Model. Note: Standardised units have been used, due to the amount of (residual) heterogeneity with non-positive sampling variances.

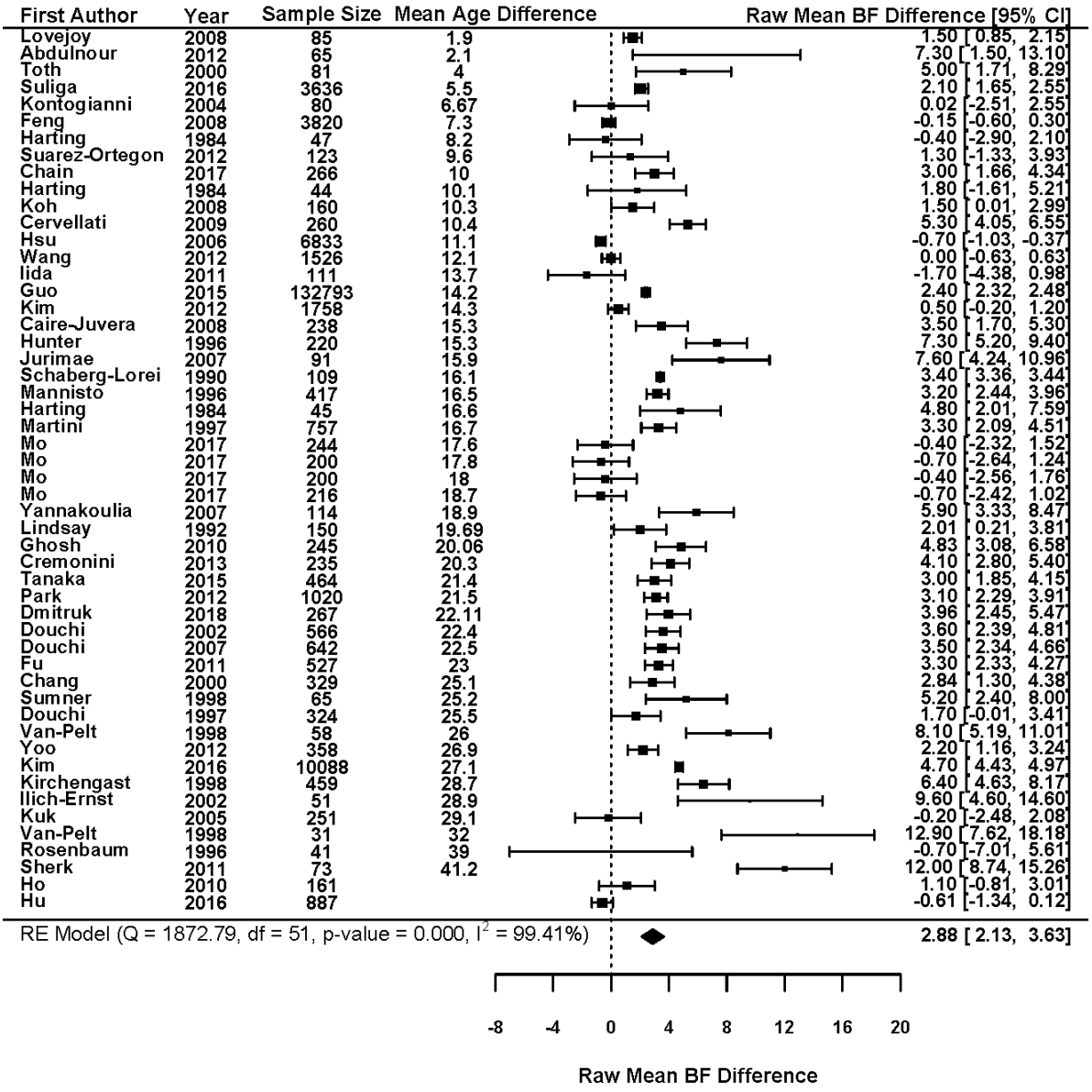

Figure 2.7: Forest plot of the cross-sectional raw mean body fat percentage difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: BF %, Total Body Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.

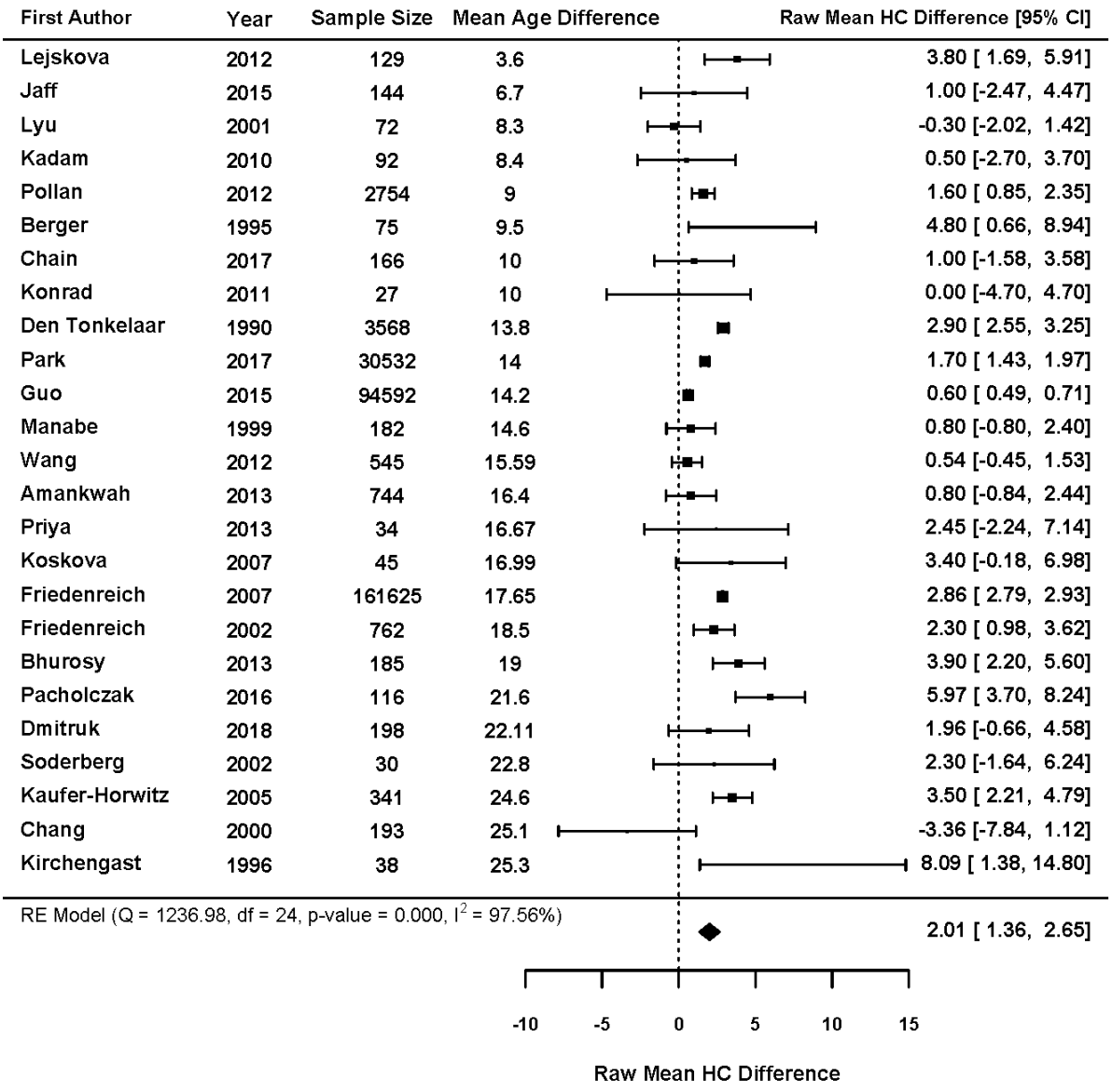

Figure 2.8: Forest plot of the cross-sectional raw mean hip circumference difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: HC, Hip Circumference; CI, Confidence Interval; RE Model, Random Effects Model.

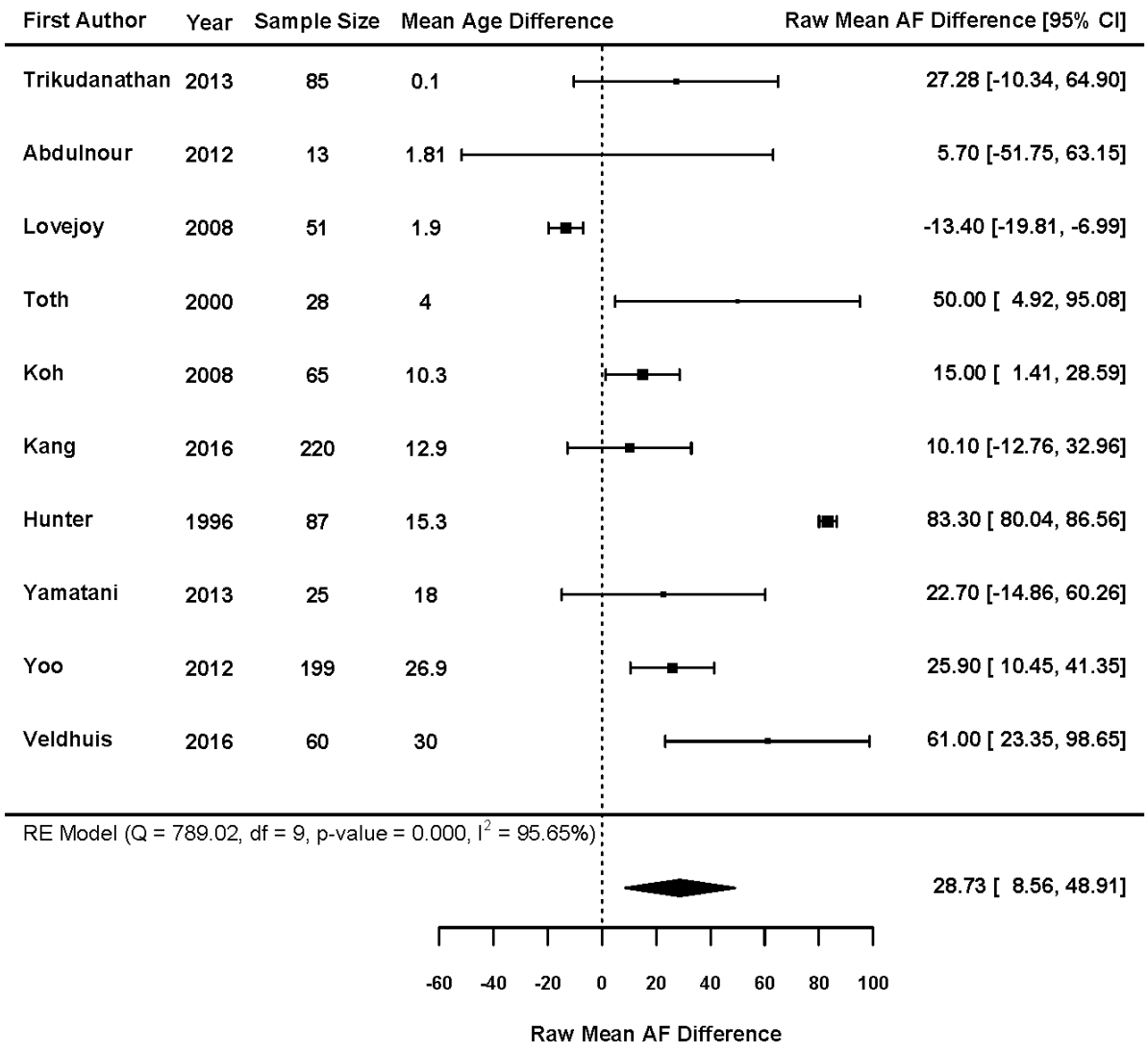

Figure 2.9: Forest plot of the cross-sectional raw mean abdominal fat difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: AF, Abdominal Fat; CI, Confidence Interval; RE Model, Random Effects Model.

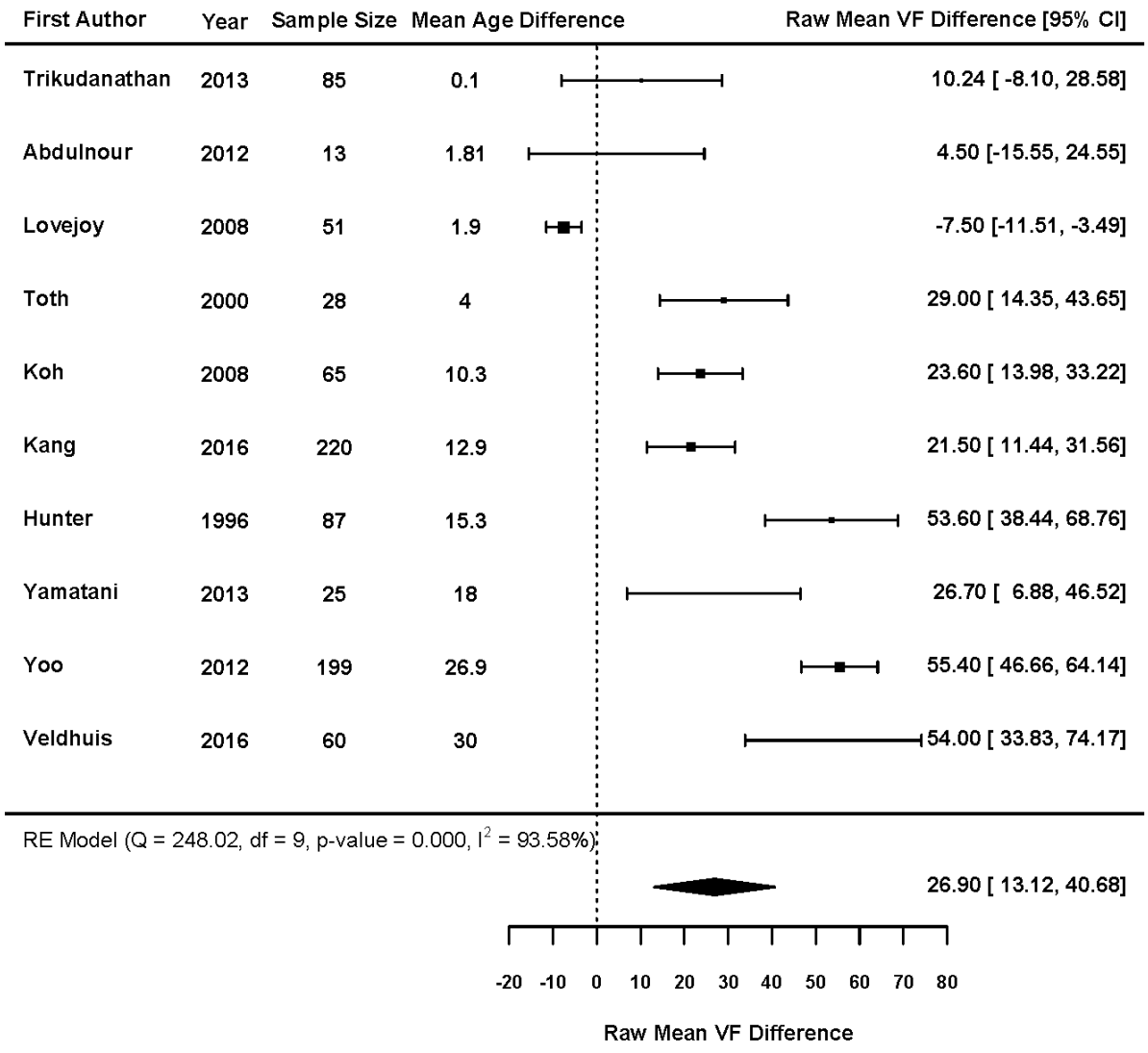

Figure 2.10: Forest plot of the cross-sectional raw mean visceral fat difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: VF, Visceral Fat; CI, Confidence Interval; RE Model, Random Effects Model.

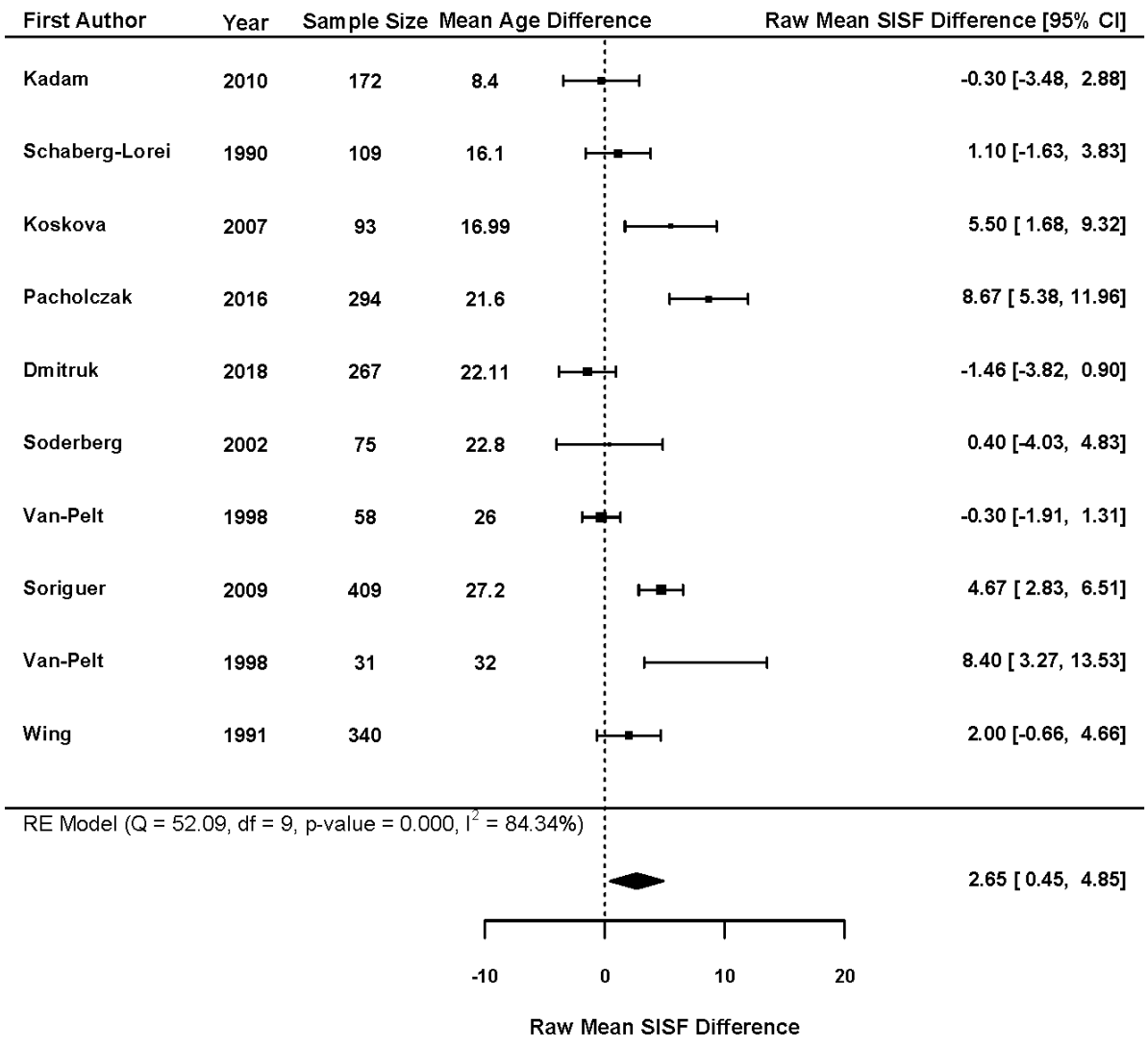

Figure 2.11: Forest plot of the cross-sectional raw mean suprailliac skinfold thickness difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: SISF, Suprailliac Skinfold Thickness; CI, Confidence Interval; RE Model, Random Effects Model.

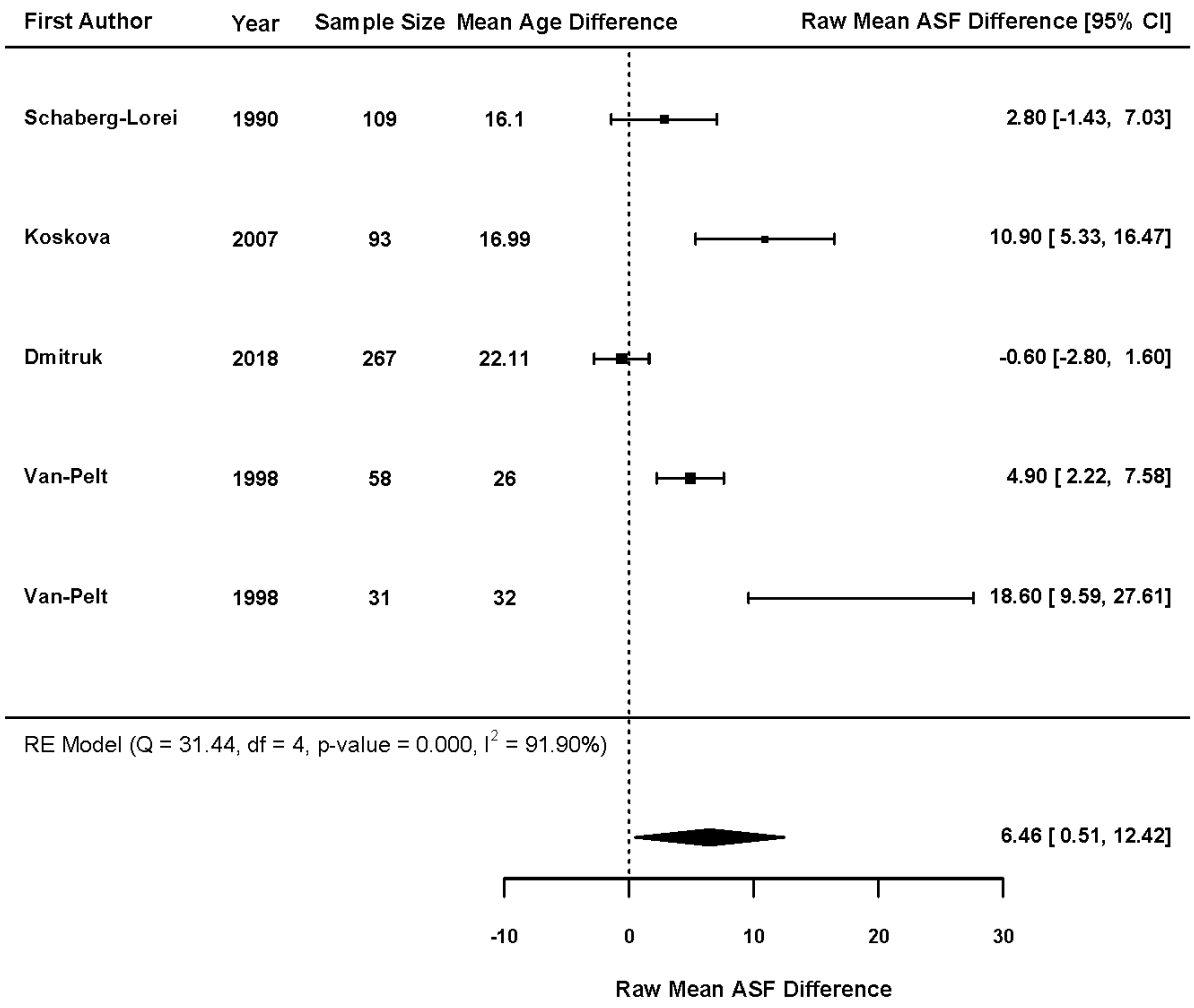

Figure 2.12: Forest plot of the cross-sectional raw mean abdominal skinfold thickness difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: ASF, Abdominal Skinfold Thickness; CI, Confidence Interval; RE Model, Random Effects Model.

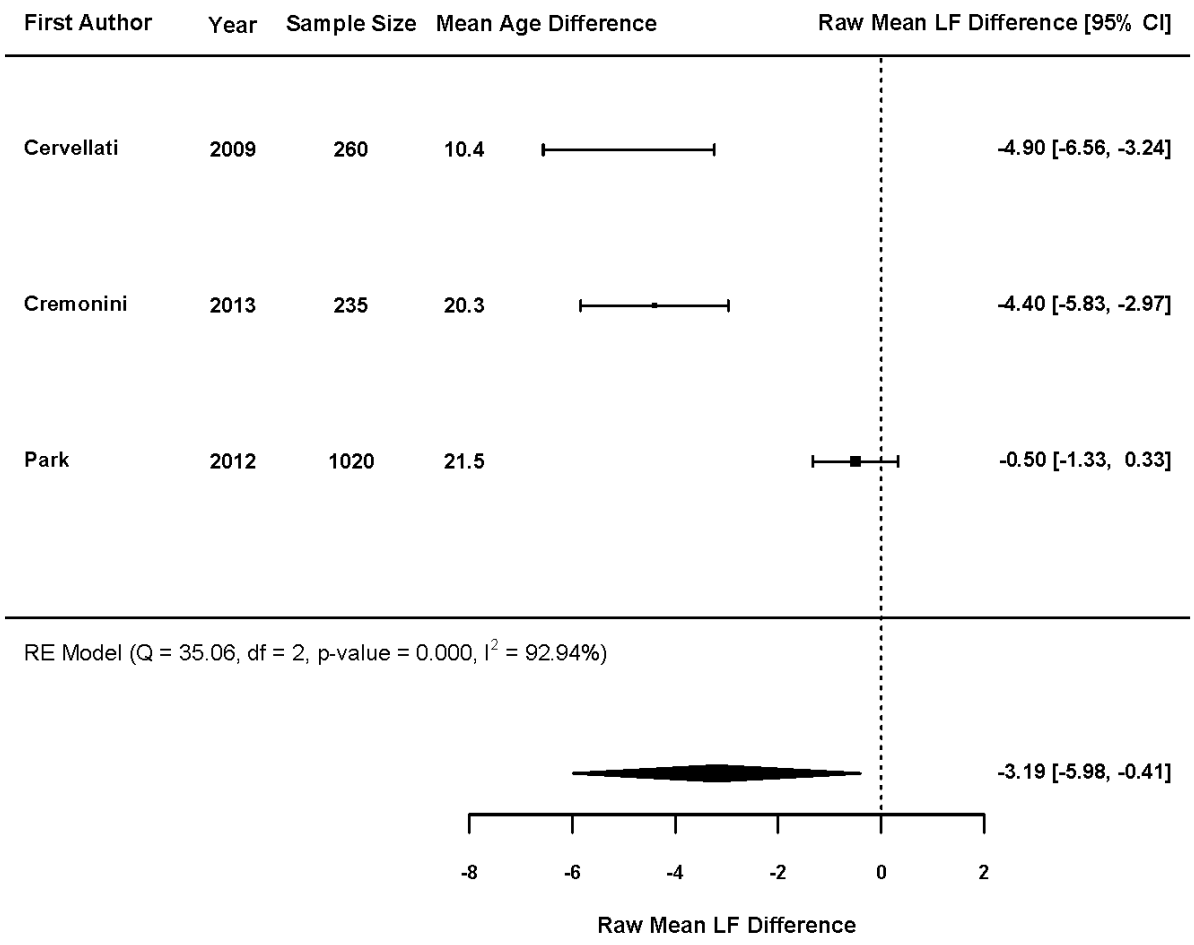

Figure 2.13: Forest plot of the cross-sectional raw mean leg fat percentage difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: LF %, Total Leg Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.

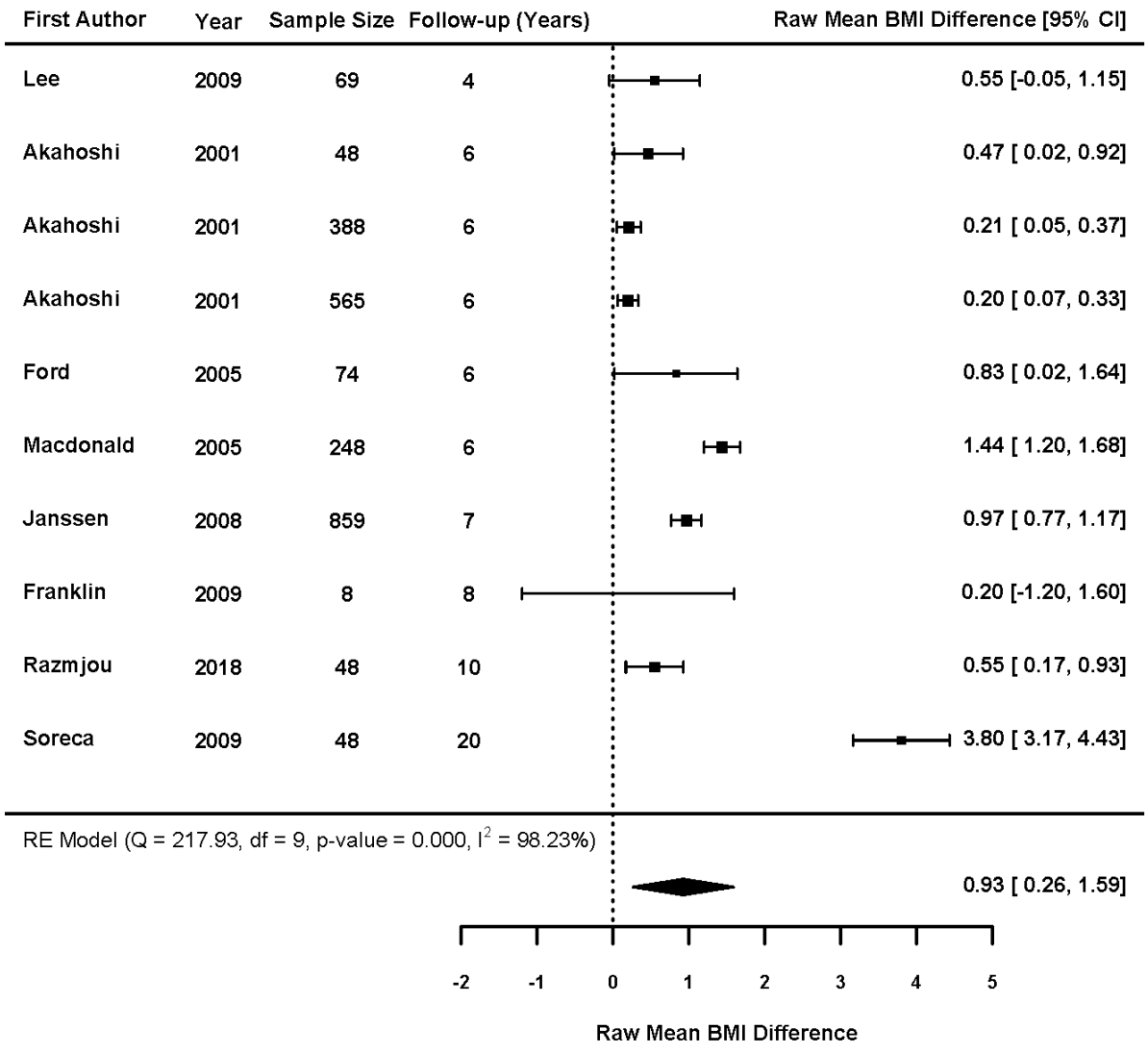

Figure 2.14: Forest plot of the longitudinal body mass index change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; RE Model, Random Effects Model.

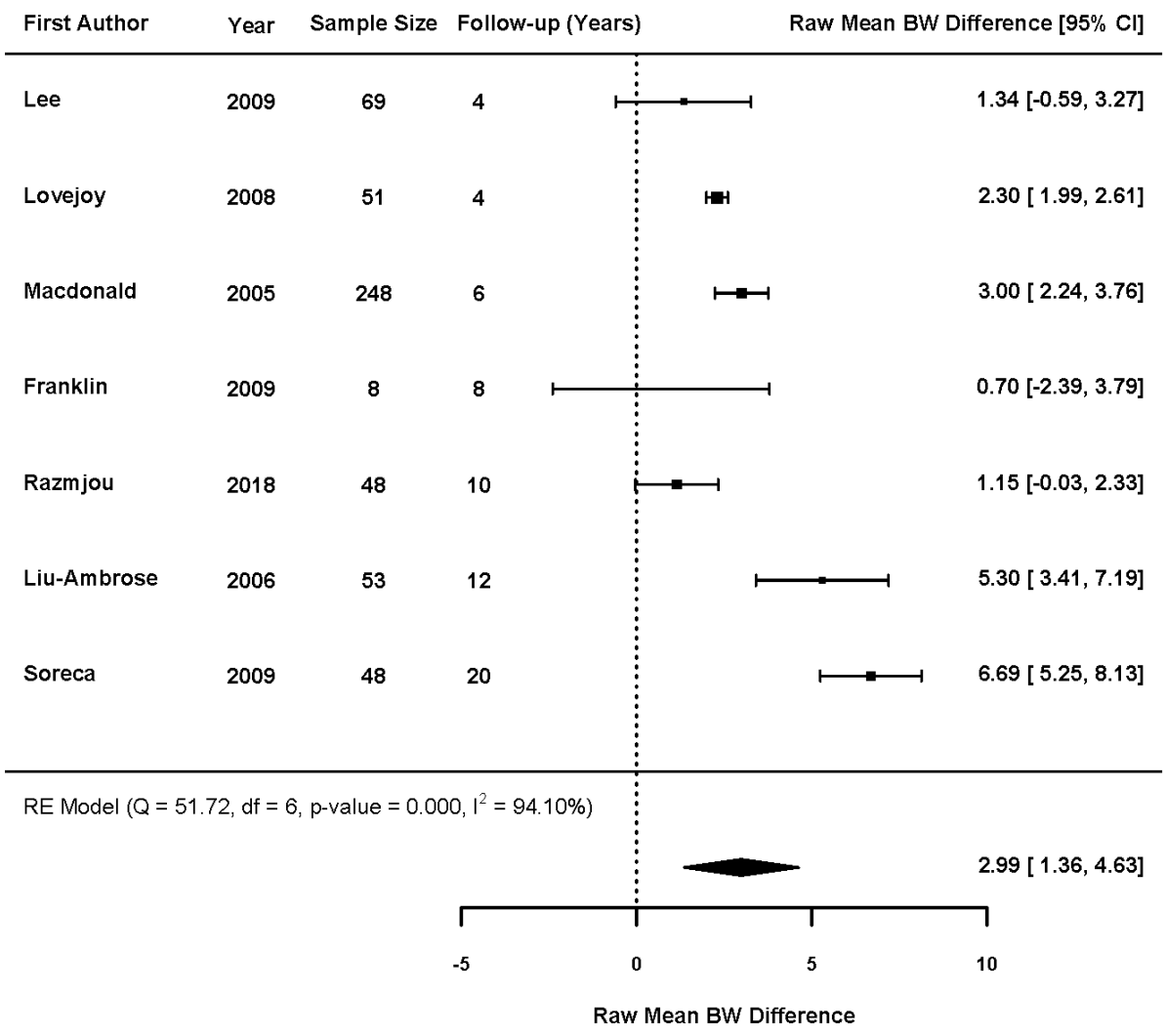

Figure 2.15: Forest plot of the longitudinal body weight change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BW, Body Weight; CI, Confidence Interval; RE Model, Random Effects Model.

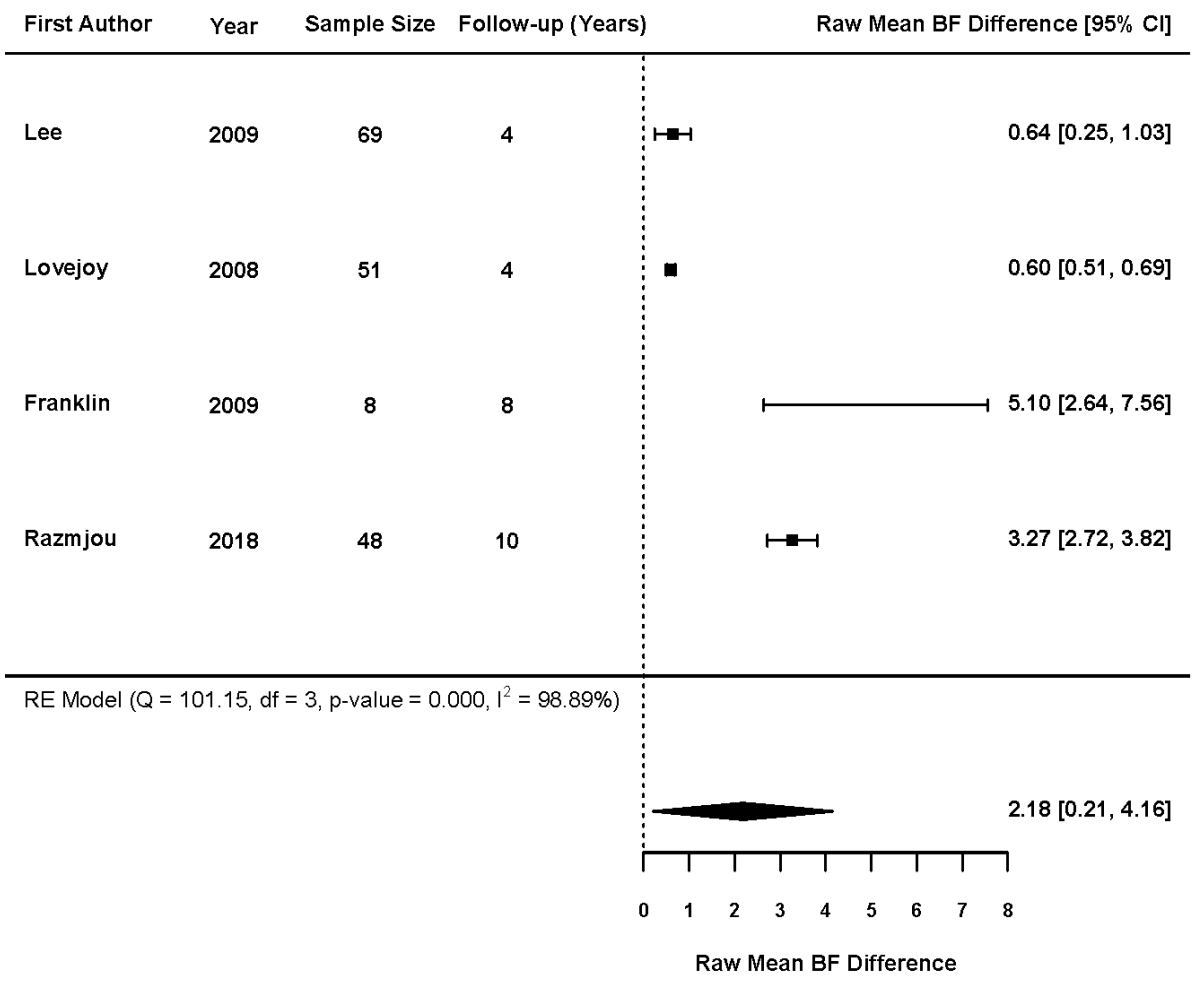

Figure 2.16: Forest plot of the longitudinal body fat percentage change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: BF %, Total Body Fat Percentage; CI, Confidence Interval; RE Model, Random Effects Model.

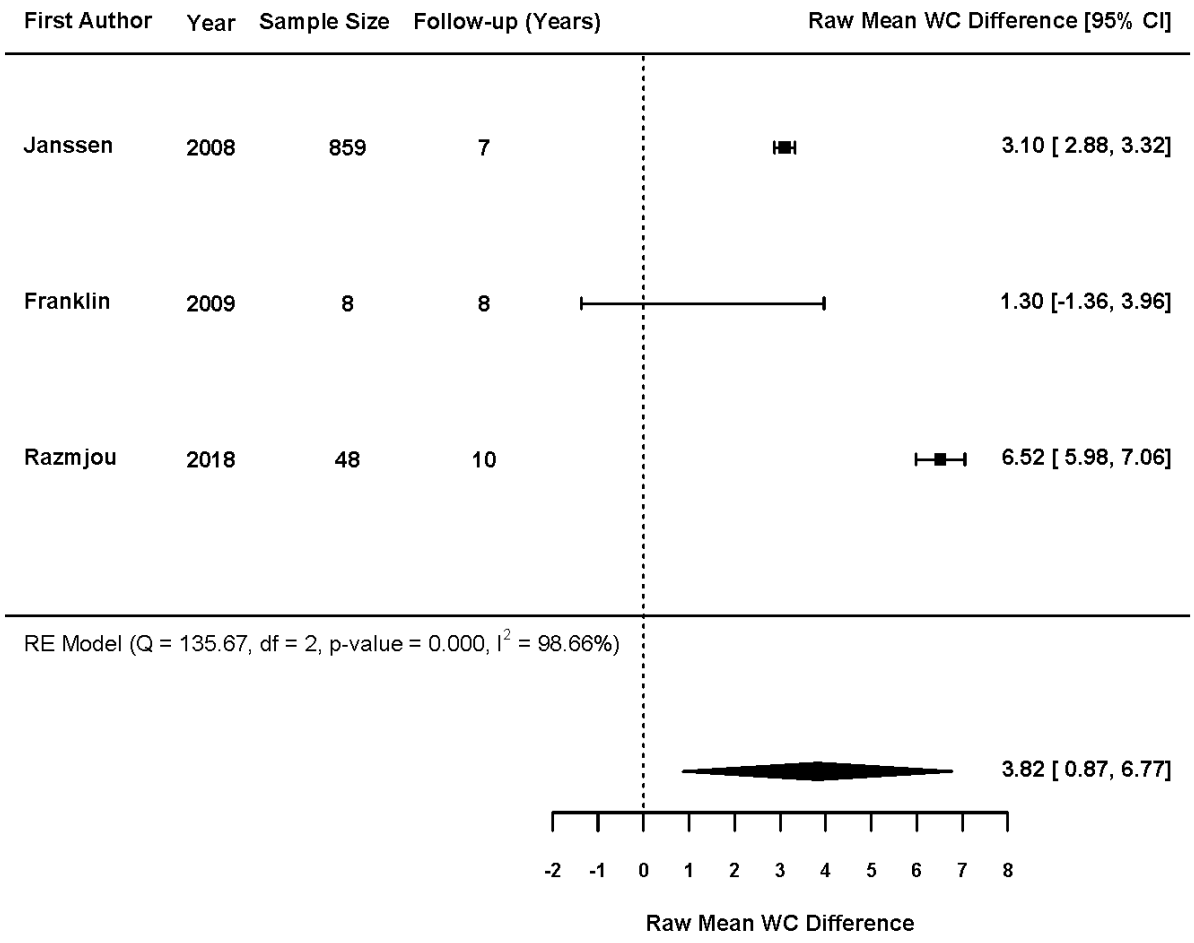

Figure 2.17: Forest plot of the longitudinal waist circumference change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: WC, Waist Circumference; CI, Confidence Interval; RE Model, Random Effects Model.

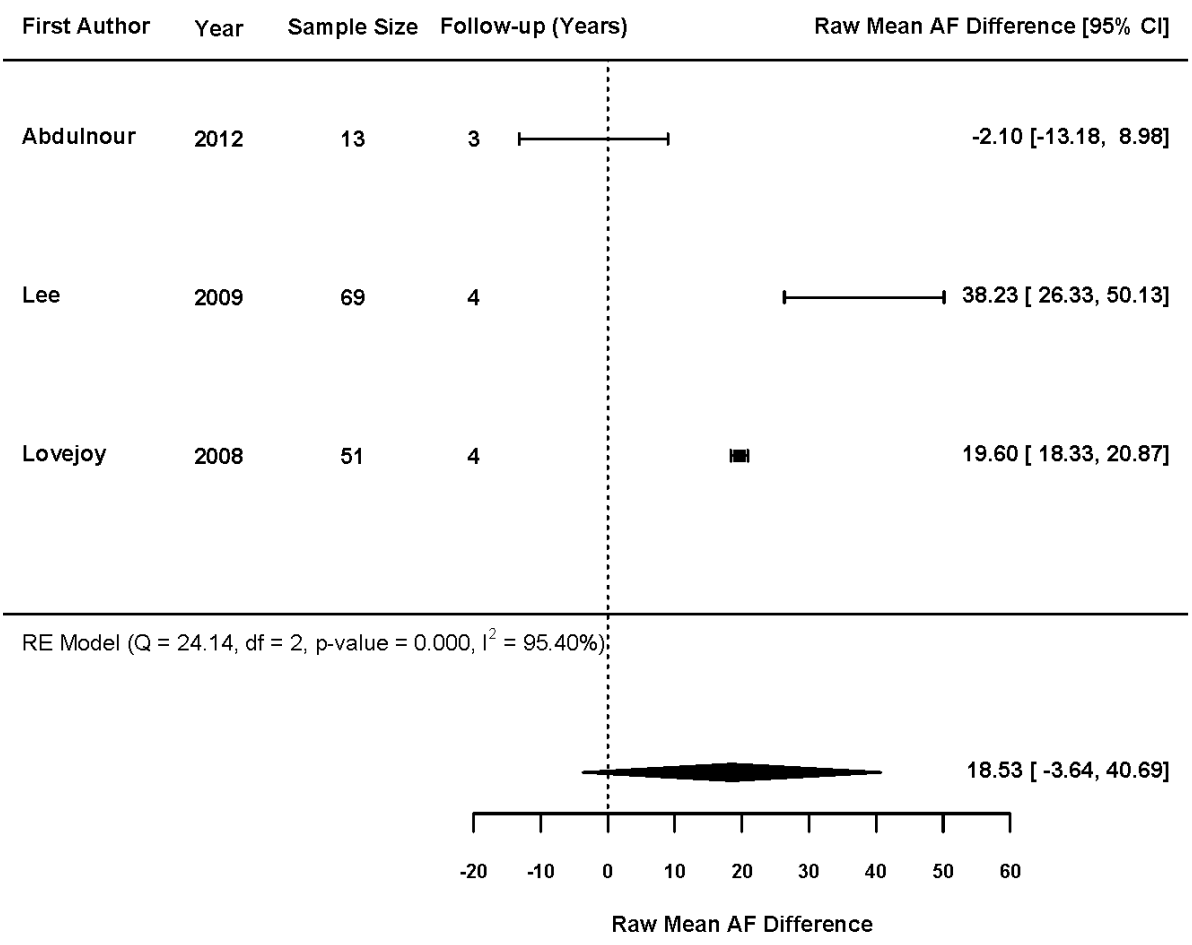

Figure 2.18: Forest plot of the longitudinal abdominal fat change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: AF, Abdominal Fat; CI, Confidence Interval; RE Model, Random Effects Model.

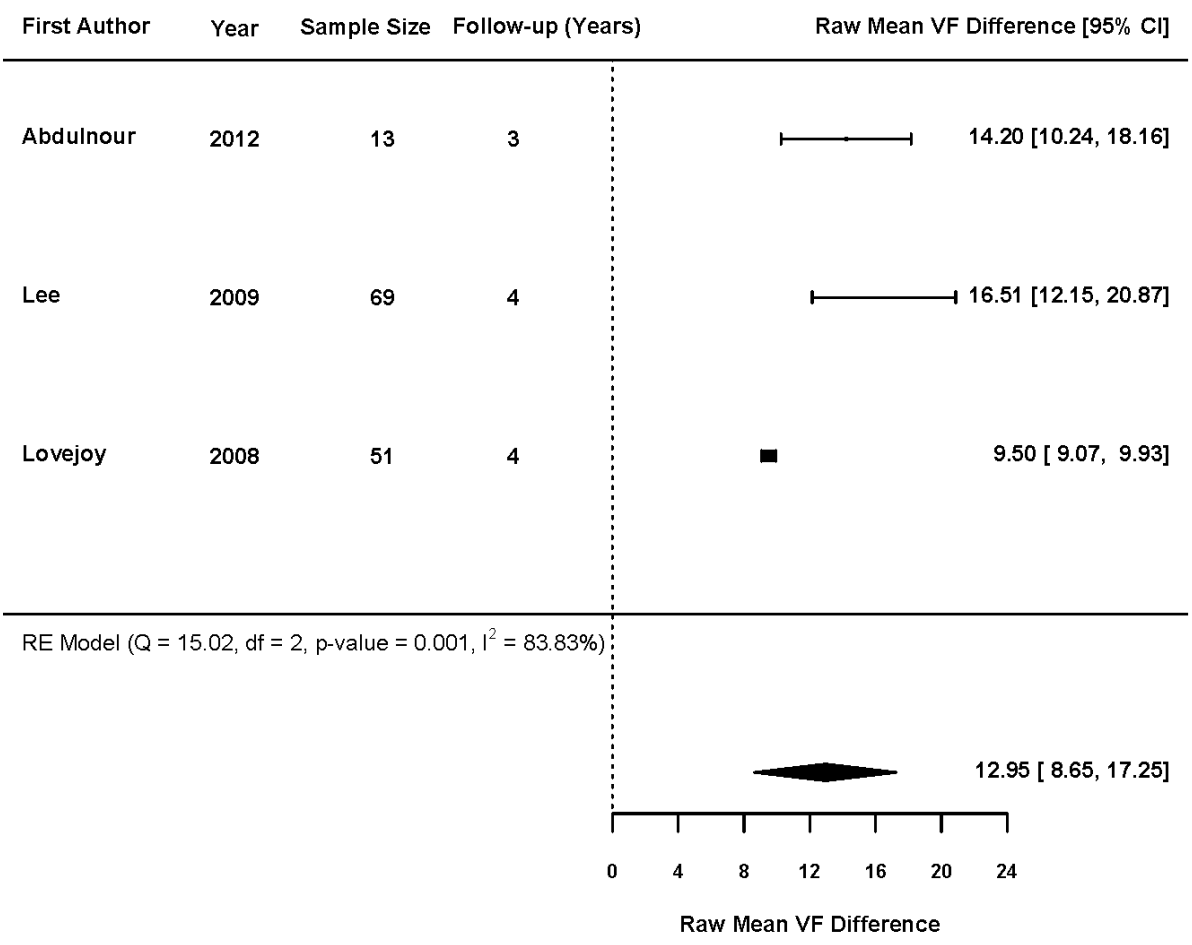

Figure 2.19: Forest plot of the longitudinal visceral fat change for postmenopausal women who were premenopausal at baseline. Studies are ordered by follow up period. Abbreviations: VF, Visceral Fat; CI, Confidence Interval; RE Model, Random Effects Model.

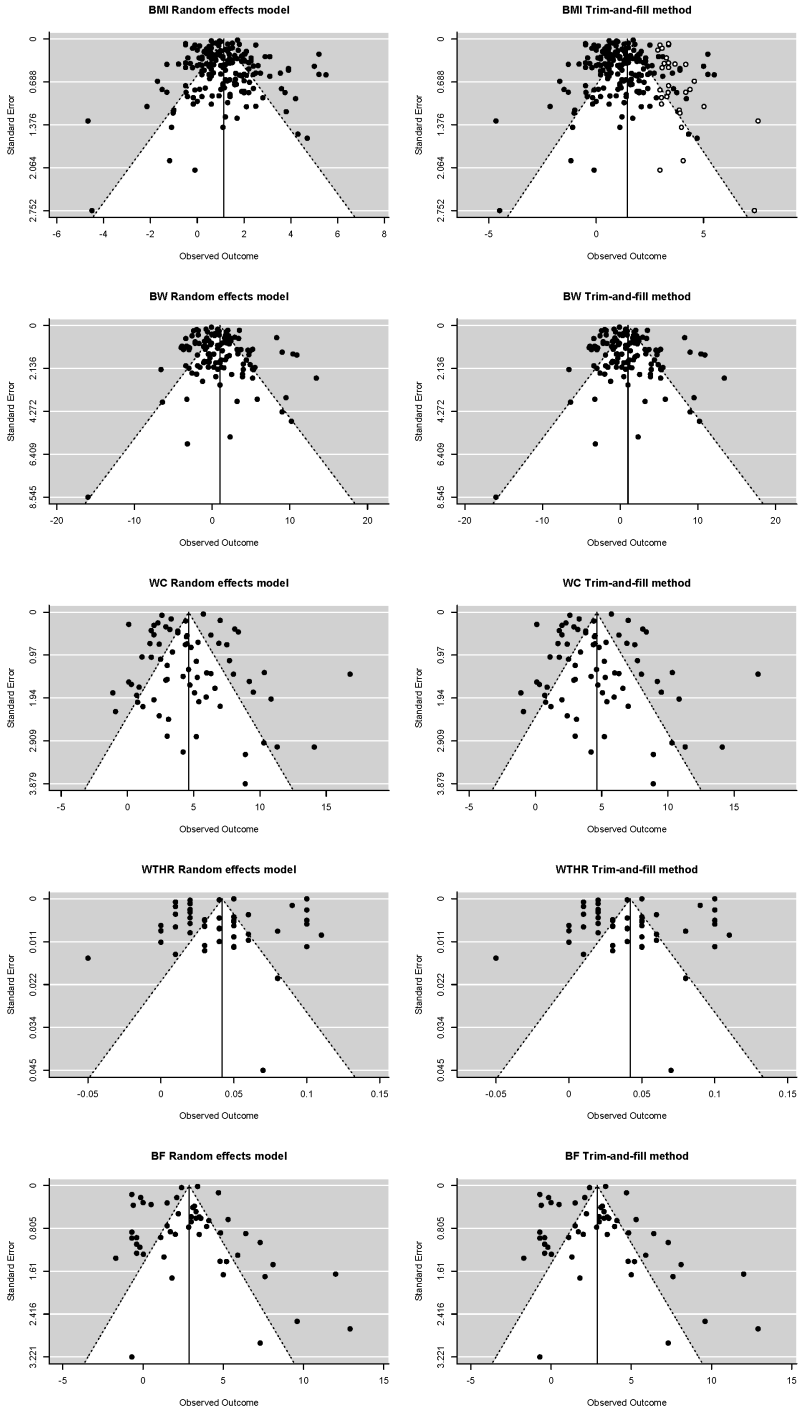

Figure 2.20: Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; WC, Waist Circumference; WTHR, Waist to Hip Ratio; BF %, Total Body Fat Percentage; T&F, trim and fill.

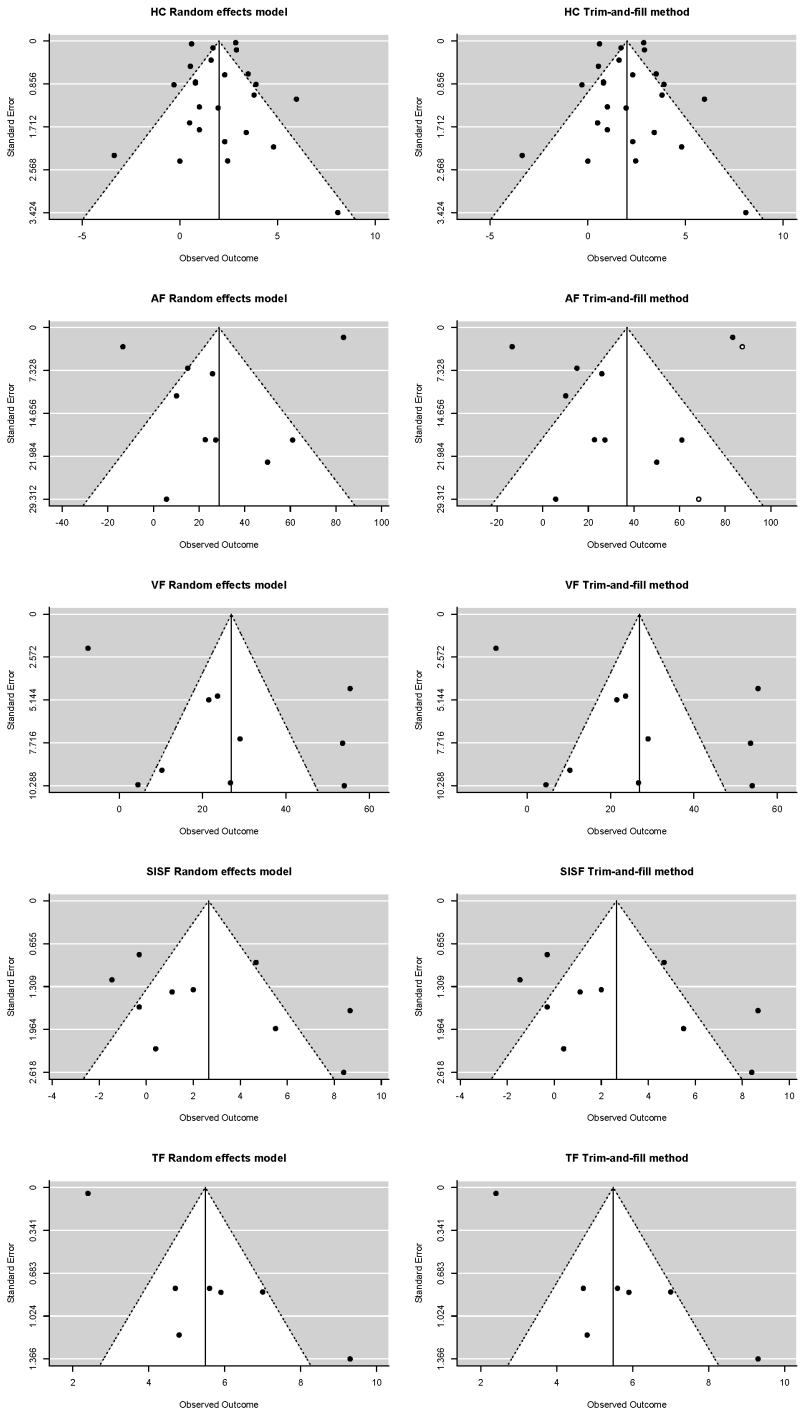

Figure 2.21: Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. HC, Hip Circumference; AF, Abdominal Fat; VF, Visceral Fat; SISF, Suprailliac Skinfold Thickness; TF %, Trunk Fat Percentage; T&F, trim and fill.

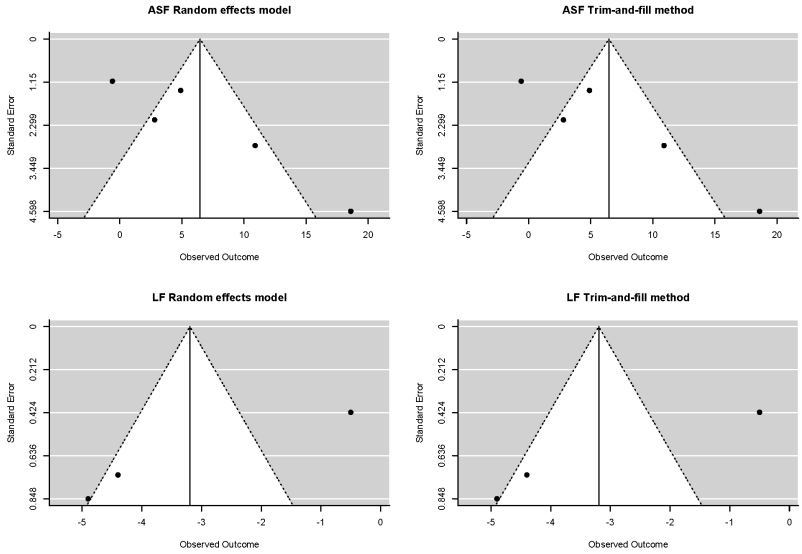

Figure 2.22: Funnel plots for cross-sectional studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. ASF, Abdominal Skinfold Thickness; LF %, Total Leg Fat Percentage; T&F, trim and fill.

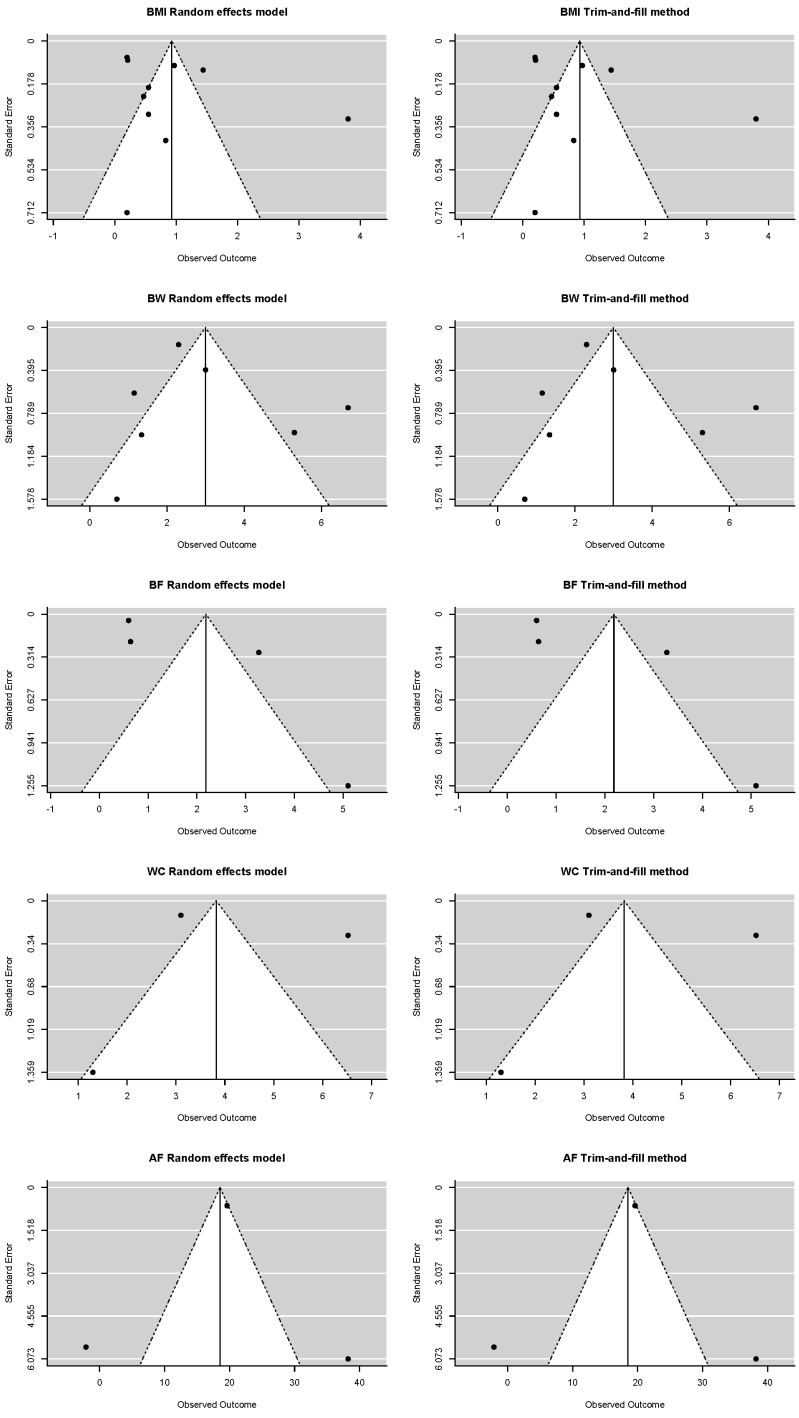

Figure 2.23: Funnel plots for longitudinal studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; BF %, Total Body Fat Percentage; WC, Waist Circumference; AF, Abdominal Fat; T&F, trim and fill.

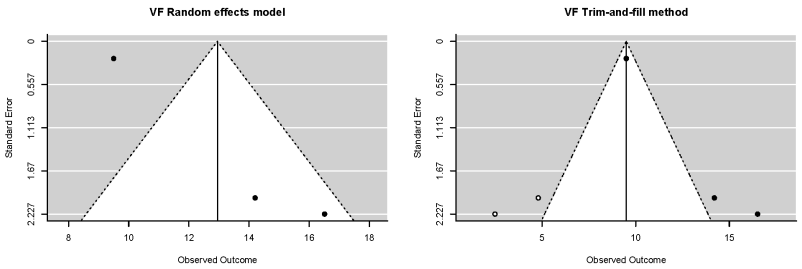

Figure 2.24: Funnel plots for longitudinal studies using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. BMI, Body Mass Index; BW, Body Weight; BF %, Total Body Fat Percentage; WC, Waist Circumference; AF, Abdominal Fat; T&F, trim and fill.

Table 2.4: Definition of data elements.

Data element name	**Abbreviation**	**Unit of measurement**	**Type or method of measurement**
Body Mass Index	BMI	Weight in kilograms divided by height in meters squared (kg/m^2)	Measured directly, or using self-reported weight and height
Body Weight	BW	Weight in kilograms (kg)	Measured directly, or using self-report weight
Waist Circumference	WC	Centimeters (cm)	According to the World Health Organisation, measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest.
Hip Circumference	HC	Centimeters (cm)	According to the World Health Organisation, measured around the widest portion of the buttocks.
Waist to Hip Ratio	WTHR	A ratio of waist circumference to hip circumference	Divide waist circumference by hip circumference
Body Fat Percentage	BF	Percentage (%)	Dual Energy X-ray Absorptiometry (DEXA) or Bioelectrical Impedance Analysis (BIA) or hydrodensiometry or near infrared interactance or skinfold estimates
Trunk Fat Percentage	TF	Percentage (%)	Dual Energy X-ray Absorptiometry (DEXA) or Bioelectrical Impedance Analysis (BIA)
Total Leg Fat Percentage	LF	Percentage (%)	Dual Energy X-ray Absorptiometry (DEXA) or Bioelectrical Impedance Analysis (BIA)
Subcutaneous Abdominal Fat	AF	Centimeters cubed (cm^3)	Computed Tomography (CT) scan
Visceral Fat	VF	Centimeters cubed (cm^3)	Computed Tomography (CT) scan
Suprailliac Skinfold Thickness	SISF	Millimeters (mm)	Measure the thickness of skin at the suprailliac, using calipers
Abdominal Skinfold Thickness	ASF	Millimeters (mm)	Measure the thickness of skin at the suprailliac, using calipers

Table 2.5: Table of study characteristics for cross-sectional studies.

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Abate et al.	2014	205	46.70	-1.90	52.70	-3.40	*	-	-	-	-	-	-	-	-	-	-	-
Abdulnour et al.	2012	65	52.30	-0.50	54.40	-2.00	*	*	*	-	*	-	-	-	-	-	-	-
Abdulnour et al.	2012	31	50.95	-1.31	52.76	-2.16	*	*	*	-	*	-	*	*	-	-	-	-
Abildgaard et al.	2013	33	49.60	-1.80	52.00	-2.00	-	*	-	-	-	-	-	-	-	-	-	-
Adams-Campbell et al.	1996	164	39.30	-6.90	58.90	-10.10	*	*	-	-	-	-	-	-	-	-	-	-
Agrinier et al.	2010	1355	42.80	-4.40	57.40	-5.40	*	-	*	-	-	-	-	-	-	-	-	-
Aguado et al.	1996	80	38.80	-8.40	60.60	-9.60	*	*	-	-	-	-	-	-	-	-	-	-
Albanese et al.	2009	289	48.80	-3.80	53.60	-3.70	*	*	-	-	-	-	-	-	-	-	-	-
Allali et al.	2009	200	43.90	-6.30	61.50	-8.80	*	-	-	-	-	-	-	-	-	-	-	-
Aloia et al.	1995	39	37.50	-5.82	54.10	-7.96	*	*	-	-	-	-	-	-	-	-	-	-
Aloia et al.	1995	125	40.20	-7.20	62.50	-7.81	*	*	-	-	-	-	-	-	-	-	-	-
Amankwah et al.	2013	1031	46.30	-6.50	62.70	-7.20	*	-	*	*	-	*	-	-	-	-	-	-
Amarante et al.	2011	80	43.96	-7.08	52.16	-3.65	*	-	-	-	-	-	-	-	-	-	-	-
Amiri et al.	2014	340	36.80	-11.52	59.00	-7.48	*	-	*	-	-	-	-	-	-	-	-	-
Angsuwanthana et al.	2007	697	49.40	-3.39	53.19	-5.94	*	*	-	-	-	-	-	-	-	-	-	-
Armellini et al.	1996	72	NA	NA	NA	NA	-	-	*	-	-	-	-	-	-	-	-	-
Arthur et al.	2013	250	34.48	-8.85	57.25	-8.28	*	-	*	*	-	-	-	-	-	-	-	-
Aydin et al.	2010	1106	48.70	-2.60	54.00	-3.40	*	-	-	-	-	-	-	-	-	-	-	-
Ayub et al.	2006	80	42.46	-7.30	51.15	-7.71	*	*	-	*	-	-	-	-	-	-	-	-
Bancroft et al.	1996	103	47.60	-3.70	55.40	-3.05	*	-	-	-	-	-	-	-	-	-	-	-
Bednarek-Tupikowska et al.	2006	94	48.30	-2.30	50.50	-3.00	*	*	-	*	-	-	-	-	-	-	-	-
Bell et al.	2007	587	38.90	-7.90	62.80	-8.30	*	*	-	-	-	-	-	-	-	-	-	-
Ben-Ali et al.	2016	242	39.48	-7.79	57.87	-7.65	*	-	*	-	-	-	-	-	-	-	-	-
Ben-Ali et al.	2014	2680	42.90	-5.00	57.50	-7.30	*	-	*	-	-	-	-	-	-	-	-	-
Ben-Ali et al.	2011	376	35.30	-7.60	53.40	-6.20	*	-	-	-	-	-	-	-	-	-	-	-
Berg et al.	2004	50	36.90	-4.10	57.00	-5.30	*	-	*	-	-	-	-	-	-	-	-	-
Berge et al.	1994	159	38.90	-7.20	55.30	-6.10	*	-	-	-	-	-	-	-	-	-	-	-
Berger et al.	1995	177	38.20	-5.00	47.70	-3.80	*	*	*	*	-	*	-	-	-	-	-	-
Berstad et al.	2010	4041	42.83	-5.10	56.42	-5.46	*	-	-	-	-	-	-	-	-	-	-	-
Bhagat et al.	2010	214	33.77	-6.57	52.16	-6.27	-	-	*	-	-	-	-	-	-	-	-	-
Bhurosy et al.	2013	400	34.00	NA	53.00	NA	*	-	*	*	-	*	-	-	-	-	-	-
Blumenthal et al.	1991	46	47.00	-2.00	52.00	-3.00	-	*	-	-	-	-	-	-	-	-	-	-
Bonithon-Kopp et al.	1990	416	47.80	-2.20	52.30	-1.80	*	-	-	-	-	-	-	-	-	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Caire-Juvera et al.	2008	238	44.80	-2.39	60.10	-3.59	*	*	-	-	*	-	-	-	-	*	-	-
Campesi et al.	2016	79	36.20	-7.60	55.40	-5.10	-	*	-	-	-	-	-	-	-	-	-	-
Carr et al.	2000	56	35.40	-8.60	61.00	-4.10	*	-	-	-	-	-	-	-	-	-	-	-
Castracane et al.	1998	76	27.30	-0.63	55.80	-0.85	*	-	-	-	-	-	-	-	-	-	-	-
Catsburg et al.	2014	3320	45.80	-8.90	67.90	-11.20	*	-	-	-	-	-	-	-	-	-	-	-
Cecchini et al.	2012	12243	46.34	-4.28	60.81	-7.51	*	-	-	-	-	-	-	-	-	-	-	-
Cervellati et al.	2009	260	38.10	-6.73	48.50	-6.95	*	-	-	*	*	-	-	-	-	*	-	*
Chain et al.	2017	266	47.00	-5.00	57.00	-7.00	*	*	*	*	*	*	-	-	-	-	-	-
Chang et al.	2000	329	36.10	-6.50	61.20	-6.20	*	-	*	*	*	*	-	-	-	-	-	-
Cho et al.	2008	1002	40.50	-7.80	59.00	-6.60	*	*	*	-	-	-	-	-	-	-	-	-
Cifkova et al.	2008	662	48.90	-2.39	52.10	-1.92	*	-	-	-	-	-	-	-	-	-	-	-
Copeland et al.	2006	411	36.00	-8.50	51.50	-7.70	*	-	-	-	-	-	-	-	-	-	-	-
Cremonini et al.	2013	235	35.20	-10.70	55.50	-4.80	*	-	*	*	*	-	-	-	-	*	-	*
Cui et al.	2007	703	38.40	-8.60	63.30	-6.50	-	*	-	-	-	-	-	-	-	-	-	-
D'haeseleer et al.	2011	75	48.30	-2.30	58.80	-5.40	*	-	-	-	-	-	-	-	-	-	-	-
Da Camara et al.	2015	237	44.63	-3.36	54.47	-5.24	*	-	-	-	-	-	-	-	-	-	-	-
Dallongeville et al.	1995	2167	48.30	-3.40	57.40	-3.90	*	-	-	-	-	-	-	-	-	-	-	-
Dancey et al.	2001	1315	35.00	-5.65	65.00	-6.83	*	-	-	-	-	-	-	-	-	-	-	-
Davis et al.	1994	729	48.10	-1.70	50.20	-1.70	*	-	-	-	-	-	-	-	-	-	-	-
De Kat et al.	2017	53911	36.90	-8.10	55.30	-7.40	*	-	-	-	-	-	-	-	-	-	-	-
Den Tonkelaar et al.	1990	9491	44.00	-3.60	57.80	-7.40	*	*	*	*	-	*	-	-	-	-	-	-
Dmitruk et al.	2018	267	44.48	-2.22	66.59	-6.69	-	*	*	-	*	*	-	-	*	-	*	-
Donato et al.	2006	168	44.30	-3.60	53.30	-3.80	*	*	*	*	-	-	-	-	-	-	-	-
Douchi et al.	1997	324	36.60	-9.40	62.10	-7.70	*	*	-	-	*	-	-	-	-	-	-	-
Douchi et al.	2002	566	39.10	-9.10	61.50	-7.20	*	*	-	-	*	-	-	-	-	-	-	-
Douchi et al.	2007	642	39.00	-9.00	61.50	-7.40	*	*	-	-	*	-	-	-	-	*	-	-
Dubois et al.	2001	217	39.00	-9.00	63.00	-8.00	*	*	-	-	-	-	-	-	-	-	-	-
Engmann et al.	2017	184309	46.27	-3.75	61.72	-7.20	*	-	-	-	-	-	-	-	-	-	-	-
Ertungealp et al.	1999	185	NA	NA	NA	NA	*	-	-	-	-	-	-	-	-	-	-	-
Feng et al.	2008	3820	43.70	-3.00	51.00	-2.60	*	*	*	*	*	-	-	-	-	-	-	-
Formica et al.	1995	54	26.30	-3.64	69.00	-4.68	-	*	-	-	-	-	-	-	-	-	-	-
Formica et al.	1995	46	26.50	-3.82	64.90	-4.23	-	*	-	-	-	-	-	-	-	-	-	-
Friedenreich et al.	2007	285685	41.11	-6.90	58.76	-6.25	*	-	*	*	-	*	-	-	-	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Friedenreich et al.	2002	1237	44.30	-5.90	62.80	-9.00	*	*	*	*	-	*	-	-	-	-	-	-
Fu et al.	2011	527	38.00	-8.60	61.00	-7.20	*	*	-	-	*	-	-	-	-	-	-	-
Fuh et al.	2003	997	43.60	-2.90	49.40	-3.80	*	-	-	-	-	-	-	-	-	-	-	-
Gambacciani et al.	1999	812	41.30	-7.80	55.00	-4.16	*	*	-	-	-	-	-	-	-	-	-	-
Genazzani et al.	2006	1425	42.30	-9.30	53.00	-5.95	*	*	-	-	-	-	-	-	-	-	-	-
Ghosh et al.	2008	200	40.20	-6.50	55.40	-5.20	*	-	*	*	-	-	-	-	-	-	-	-
Ghosh et al.	2010	245	32.66	-5.75	52.72	-5.62	*	-	*	*	*	-	-	-	-	-	-	-
Gram et al.	1997	3076	44.30	-3.50	51.70	-3.60	*	*	-	-	-	-	-	-	-	-	-	-
Guo et al.	2015	132793	45.50	-3.40	59.70	-5.50	*	*	*	*	*	*	-	-	-	*	-	-
Gurka et al.	2016	2177	47.60	-3.40	54.30	-3.60	-	-	*	-	-	-	-	-	-	-	-	-
Gurka et al.	2016	779	47.40	-2.10	53.10	-4.10	-	-	*	-	-	-	-	-	-	-	-	-
Hadji et al.	2000	434	36.50	-10.40	61.80	-8.90	*	*	-	-	-	-	-	-	-	-	-	-
Hagner et al.	2009	118	36.50	-5.17	62.50	-5.43	*	-	-	-	-	-	-	-	-	-	-	-
Han et al.	2006	2105	44.10	-4.60	63.40	-8.90	-	*	*	-	-	-	-	-	-	-	-	-
Harting et al.	1984	45	33.80	-8.20	50.40	-3.80	-	*	-	-	*	-	-	-	-	-	-	-
Harting et al.	1984	47	37.90	-8.20	46.10	-8.20	-	*	-	-	*	-	-	-	-	-	-	-
Harting et al.	1984	44	36.90	-8.10	47.00	-7.30	-	*	-	-	*	-	-	-	-	-	-	-
He et al.	2012	4743	45.80	-3.60	54.00	-3.60	*	-	*	*	-	-	-	-	-	-	-	-
Hirose et al.	2003	16132	42.20	NA	60.00	NA	*	*	-	-	-	-	-	-	-	-	-	-
Hirose et al.	2003	1716	38.00	NA	61.40	NA	*	*	-	-	-	-	-	-	-	-	-	-
Hjartaker et al.	2005	102469	40.70	-5.00	45.40	-4.10	*	-	-	-	-	-	-	-	-	-	-	-
Ho et al.	2010	161	NA	NA	NA	NA	-	-	-	-	*	-	-	-	-	-	-	-
Hsu et al.	2006	6833	41.50	-5.30	52.60	-4.70	*	*	-	-	*	-	-	-	-	-	-	-
Hu et al.	2016	887	NA	NA	NA	NA	-	-	-	-	*	-	-	-	-	-	-	-
Hunter et al.	1996	220	36.20	-9.00	51.50	-10.20	-	*	-	-	*	-	*	*	-	-	-	-
Iida et al.	2011	111	47.60	-3.80	61.30	-6.60	*	*	-	-	*	-	-	-	-	-	-	-
Ilich-Ernst et al.	2002	51	33.00	-9.20	61.90	-3.30	*	*	-	-	*	-	-	-	-	-	-	-
Ito et al.	1994	251	38.80	-10.00	58.60	-5.80	-	*	-	-	-	-	-	-	-	-	-	-
Jaff et al.	2015	338	45.10	-3.30	51.80	-3.86	*	-	*	-	-	*	-	-	-	-	-	-
Jasienska et al.	2005	1003	48.50	-2.81	57.40	-4.41	*	-	-	-	-	-	-	-	-	-	-	-
Jeenduang et al.	2014	361	42.58	-6.62	58.17	-9.65	*	-	*	-	-	-	-	-	-	-	-	-
Jeon et al.	2011	1971	49.30	-8.50	51.20	-9.00	*	*	*	-	-	-	-	-	-	-	-	-
Jurimae et al.	2007	91	40.80	-5.70	56.70	-3.60	*	*	-	*	*	-	-	-	-	-	-	-
Kadam et al.	2010	172	45.60	-4.80	54.00	-7.10	-	-	*	-	-	*	-	-	*	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Kang et al.	2016	264	47.90	-3.30	60.80	-6.00	*	*	-	-	-	-	*	*	-	-	-	-
Kaufer-Horwitz et al.	2005	980	33.70	-8.40	58.30	-6.90	*	*	*	*	-	*	-	-	-	-	-	-
Kim et al.	2007	2671	35.40	-8.10	65.10	-9.30	*	-	*	-	-	-	-	-	-	-	-	-
Kim et al.	2012	1758	50.70	-2.80	65.00	-7.40	*	*	*	*	*	-	-	-	-	-	-	-
Kim et al.	2013	617	42.12	-6.22	56.48	-6.55	*	-	*	-	-	-	-	-	-	-	-	-
Kim et al.	2016	10088	36.90	-8.70	64.00	-9.70	*	*	*	-	*	-	-	-	-	-	-	-
Kirchengast et al.	1998	77	27.10	NA	55.80	NA	*	*	-	-	*	-	-	-	-	*	-	-
Kirchengast et al.	1996	459	26.80	NA	52.10	NA	-	*	*	-	-	*	-	-	-	-	-	-
Knapp et al.	2001	409	40.30	-9.50	59.90	-7.50	*	*	-	-	-	-	-	-	-	-	-	-
Koh et al.	2008	160	44.20	-2.92	54.50	-4.35	*	-	*	*	*	-	*	*	-	-	-	-
Konrad et al.	2011	51	43.00	-5.00	53.00	-4.00	*	*	*	-	-	*	-	-	-	-	-	-
Kontogianni et al.	2004	80	47.80	-3.14	54.47	-5.36	*	-	-	*	*	-	-	-	-	-	-	-
Konukoglu et al.	2000	75	35.40	-8.30	49.50	-4.70	*	-	-	-	-	-	-	-	-	-	-	-
Koskova et al.	2007	93	42.54	-2.50	59.53	-2.71	*	*	*	*	-	*	-	-	*	-	*	-
Kotani et al.	2011	262	44.70	-4.90	64.60	-4.40	*	-	-	-	-	-	-	-	-	-	-	-
Kraemer et al.	2001	141	26.80	-4.90	57.63	-7.47	*	-	-	-	-	-	-	-	-	-	-	-
Kuk et al.	2005	251	37.60	-8.60	66.70	-8.00	*	-	*	-	*	-	-	-	-	-	-	-
Laitinen et al.	1991	257	36.70	-9.00	59.60	-6.40	-	*	-	-	-	-	-	-	-	-	-	-
Lejskova et al.	2012	480	48.60	-2.40	52.20	-2.00	*	-	*	*	-	*	-	-	-	-	-	-
Leon-Guerrero et al.	2017	275	43.94	-6.63	58.44	-8.69	*	*	*	-	-	-	-	-	-	-	-	-
Ley et al.	1992	131	32.00	-6.00	53.00	-5.00	*	*	-	-	-	-	-	-	-	-	-	-
Lin et al.	2006	594	46.00	-3.60	53.10	-4.40	*	*	*	-	-	-	-	-	-	-	-	-
Lindquist et al.	1980	326	50.00	NA	50.00	NA	-	*	-	-	-	-	-	-	-	-	-	-
Lindsay et al.	1992	150	39.65	-9.98	59.34	-8.37	*	*	-	-	*	-	-	-	-	-	-	-
Lovejoy et al.	2008	85	50.20	-0.30	52.10	-0.30	-	*	-	-	*	-	*	*	-	-	-	-
Lyu et al.	2001	203	45.10	-3.40	53.40	-5.00	*	*	*	*	-	*	-	-	-	-	-	-
Maharlouei et al.	2013	924	46.50	-5.00	58.60	-6.70	*	-	*	*	-	-	-	-	-	-	-	-
Malacara et al.	2002	901	46.80	-3.10	50.90	-4.40	*	*	-	-	-	-	-	-	-	-	-	-
Malacara et al.	2002	1180	45.20	-2.90	49.80	-3.28	*	*	-	-	-	-	-	-	-	-	-	-
Malacara et al.	2002	546	44.80	-3.60	49.90	-4.20	*	*	-	-	-	-	-	-	-	-	-	-
Malacara et al.	2002	2000	45.10	-3.40	50.80	-3.40	*	*	-	-	-	-	-	-	-	-	-	-
Malacara et al.	2002	1008	44.30	-2.40	50.60	-2.60	*	*	-	-	-	-	-	-	-	-	-	-
Malacara et al.	2002	2000	45.40	-2.60	51.00	-2.40	*	*	-	-	-	-	-	-	-	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Manabe et al.	1999	254	45.70	-4.20	60.30	-5.50	*	*	*	*	-	*	-	-	-	-	-	-
Manjer et al.	2001	9738	42.80	-7.90	54.10	-3.00	*	*	-	-	-	-	-	-	-	-	-	-
Mannisto et al.	1996	417	43.30	-6.00	59.80	-7.70	*	*	-	*	*	-	-	-	-	-	-	-
Martini et al.	1997	757	43.20	-6.70	59.90	-8.10	*	*	-	-	*	-	-	-	-	-	-	-
Marwaha et al.	2013	1423	31.00	-8.60	64.50	-7.40	*	*	-	-	-	-	-	-	-	-	-	-
Matsushita et al.	2003	281	43.00	-6.30	62.40	-7.90	*	*	-	-	-	-	-	-	-	-	-	-
Matsuzaki et al.	2017	1760	29.30	-9.90	46.80	-6.90	*	*	-	-	-	-	-	-	-	-	-	-
Matthews et al.	1989	138	47.30	-1.50	47.80	-1.60	*	*	-	-	-	-	-	-	-	-	-	-
Mesch et al.	2006	60	33.00	-5.60	55.00	-5.60	*	-	*	*	-	-	-	-	-	-	-	-
Meza-Munoz et al.	2006	113	40.03	-7.16	53.75	-4.28	*	-	-	-	-	-	-	-	-	-	-	-
Minatoya et al.	2014	66	NA	NA	NA	NA	*	-	-	-	-	-	-	-	-	-	-	-
Mo et al.	2017	200	41.70	-6.30	59.70	-6.80	*	*	-	*	*	-	-	-	-	-	-	-
Mo et al.	2017	200	42.00	-5.40	59.80	-7.00	*	*	-	*	*	-	-	-	-	-	-	-
Mo et al.	2017	216	42.10	-6.40	60.80	-8.10	*	*	-	*	*	-	-	-	-	-	-	-
Mo et al.	2017	244	43.20	-7.00	60.80	-7.60	*	*	-	*	*	-	-	-	-	-	-	-
Muchanga et al.	2014	200	44.00	-3.00	53.00	-4.00	*	-	*	-	-	-	-	-	-	-	-	-
Muti et al.	2000	576	44.50	-4.80	57.70	-5.10	*	-	-	*	-	-	-	-	-	-	-	-
Nitta et al.	2016	38610	45.50	-3.80	62.40	-7.80	-	*	-	-	-	-	-	-	-	-	-	-
Noh et al.	2013	540	46.92	-4.70	59.34	-5.82	*	-	-	-	-	-	-	-	-	-	-	-
Nordin et al.	1992	259	43.10	-7.50	59.90	-8.50	-	*	-	-	-	-	-	-	-	-	-	-
Ohta et al.	2010	373	14.80	-1.70	71.90	-4.50	*	*	-	-	-	-	-	-	-	-	-	-
Oldroyd et al.	1998	211	37.20	-8.80	61.60	-7.90	-	*	-	-	-	-	-	-	-	-	-	-
Pacholczak et al.	2016	294	41.80	-6.10	63.40	-10.20	*	*	*	*	-	*	-	-	*	-	-	-
Park et al.	2012	1020	37.00	-7.25	58.50	-7.70	-	*	-	-	*	-	-	-	-	-	-	*
Park et al.	2017	43599	45.60	-5.00	59.60	-6.80	*	*	*	*	-	*	-	-	-	-	-	-
Pavicic et al.	2010	535	45.60	-6.00	58.79	-8.20	*	*	-	-	-	-	-	-	-	-	-	-
Pavlica et al.	2013	160	38.87	-9.81	58.42	-1.01	*	*	-	-	-	-	-	-	-	-	-	-
Phillips et al.	2008	78	32.90	-9.14	61.40	-10.73	*	*	*	*	-	-	-	-	-	-	-	-
Polesel et al.	2015	311	34.83	-8.40	52.63	-5.72	*	-	*	-	-	-	-	-	-	-	-	-
Pollan et al.	2012	3574	49.00	-2.90	58.00	-4.50	*	*	*	*	-	*	-	-	-	-	-	-
Portaluppi et al.	1997	1376	48.00	-3.10	53.30	-4.20	*	-	-	-	-	-	-	-	-	-	-	-
Priya et al.	2013	65	38.65	-6.21	55.32	-6.32	*	*	*	*	-	*	-	-	-	-	-	-
Rantalainen et al.	2010	303	23.00	-4.70	57.70	-4.20	*	*	-	-	-	-	-	-	-	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Reina et al.	2015	192	33.00	-11.00	58.90	-8.90	-	*	-	-	-	-	-	-	-	-	-	-
Revilla et al.	1997	151	37.40	-7.20	59.90	-9.70	*	*	-	-	-	-	-	-	-	-	-	-
Revilla et al.	1997	144	36.10	-6.90	60.60	-10.50	*	*	-	-	-	-	-	-	-	-	-	-
Rice et al.	2015	1607	43.30	-4.10	53.40	-5.30	*	-	-	-	-	-	-	-	-	-	-	-
Rico et al.	2001	270	35.10	-7.70	59.50	-9.80	*	*	-	-	-	-	-	-	-	-	-	-
Rico et al.	2002	297	34.00	-7.00	59.00	-9.00	*	*	-	-	-	-	-	-	-	-	-	-
Roelfsema et al.	2016	91	35.83	-6.84	59.08	-6.81	*	-	-	-	-	-	-	-	-	-	-	-
Rosenbaum et al.	1996	41	27.00	-8.94	66.00	-9.17	*	*	-	-	*	-	-	-	-	-	-	-
Salomaa et al.	1995	778	47.40	-2.40	57.90	-4.90	*	-	-	-	-	-	-	-	-	-	-	-
Sarrafzadegan et al.	2013	4143	32.15	-9.22	59.80	-10.39	*	*	*	*	-	-	-	-	-	-	-	-
Schaberg-Lorei et al.	1990	109	42.30	-4.80	58.40	-5.10	-	*	*	-	*	-	-	-	*	-	*	-
Schwarz et al.	2007	1119	45.60	-4.20	64.60	-8.00	*	-	-	-	-	-	-	-	-	-	-	-
Shakir et al.	2004	4092	53.20	-1.60	56.90	-2.90	-	-	-	*	-	-	-	-	-	-	-	-
Sherk et al.	2011	73	22.80	-2.74	64.00	-3.93	-	*	-	-	*	-	-	-	-	-	-	-
Shibata et al.	1979	448	46.90	-1.40	47.40	-1.40	*	-	-	-	-	-	-	-	-	-	-	-
Sieminska et al.	2006	131	28.20	-4.10	53.90	-3.20	*	-	-	*	-	-	-	-	-	-	-	-
Skrzypczak et al.	2005	1647	43.66	-4.07	56.01	-7.08	*	-	-	-	-	-	-	-	-	-	-	-
Skrzypczak et al.	2007	10216	43.43	-4.93	62.87	-8.53	*	-	-	-	-	-	-	-	-	-	-	-
Soderberg et al.	2002	75	37.90	-7.90	60.70	-6.10	*	-	*	*	-	*	-	-	*	-	-	-
Son et al.	2015	1470	46.80	-2.50	52.20	-3.10	*	-	*	-	-	-	-	-	-	-	-	-
Soriguer et al.	2009	409	36.90	-7.50	64.10	-5.20	*	-	*	*	-	-	-	-	*	-	-	-
Staessen et al.	1989	462	42.60	-5.10	53.00	-5.00	*	*	-	-	*	-	-	-	-	-	-	-
Suarez-Ortegon et al.	2012	123	42.20	-5.60	51.80	-6.80	*	-	*	-	*	-	-	-	-	-	-	-
Suliga et al.	2016	3636	49.70	-3.10	55.20	-3.00	*	-	*	-	*	-	-	-	-	-	-	-
Sumner et al.	1998	65	32.60	-3.70	57.80	-5.90	*	*	-	-	*	-	-	-	-	-	-	-
Tanaka et al.	2015	464	41.40	-6.50	62.80	-6.80	*	*	-	-	*	-	-	-	-	*	-	-
Thomas et al.	2000	302	35.00	-8.60	69.80	-13.10	*	*	-	-	-	-	-	-	-	-	-	-
Torng et al.	2000	1543	42.70	-5.80	61.20	-9.50	*	*	-	-	-	-	-	-	-	-	-	-
Toth et al.	2000	81	47.00	-3.00	51.00	-4.00	*	*	-	-	*	-	*	*	-	-	-	-
Tremollieres et al.	1996	168	49.30	-3.20	53.80	-3.10	*	*	-	-	-	-	-	-	-	-	-	-
Trikudanathan et al.	2013	170	49.30	-3.00	49.40	-3.00	*	-	*	-	-	-	*	*	-	-	-	-
Van-Pelt et al.	1998	31	29.00	-4.12	61.00	-4.36	*	*	*	-	*	-	-	-	*	-	*	-
Van-Pelt et al.	1998	58	30.00	-5.48	56.00	-5.57	*	*	*	-	*	-	-	-	*	-	*	-
Veldhuis et al.	2016	120	34.00	-9.30	64.00	-8.52	*	-	-	-	-	-	*	*	-	-	-	-

Table 2.5: Table of study characteristics for cross-sectional studies. *(continued)*

			Premenopausal		Postmenopausal		Fat Mass Measure											
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**WTHR**	**TBF**	**HC**	**SAF**	**VF**	**SISF**	**TF**	**ASF**	**LF**
Wang et al.	2012	1526	44.20	-6.60	56.30	-4.60	-	-	-	-	*	-	-	-	-	-	-	-
Wang et al.	2006	346	33.36	-9.20	66.75	-10.75	*	-	-	-	-	-	-	-	-	-	-	-
Wang et al.	2012	1143	49.13	-2.72	64.72	-7.61	*	-	*	*	-	*	-	-	-	-	-	-
Wee et al.	2013	283	45.81	-1.12	56.80	-1.84	*	-	-	-	-	-	-	-	-	-	-	-
Williams et al.	1997	115	32.70	-10.90	63.90	-11.60	*	-	-	-	-	-	-	-	-	-	-	-
Wing et al.	1991	340	NA	NA	NA	NA	*	*	-	-	-	-	-	-	*	-	-	-
Xu et al.	2010	252	44.70	-4.10	70.70	-6.30	*	*	-	-	-	-	-	-	-	-	-	-
Yamatani et al.	2013	40	42.60	-7.35	60.60	-7.50	*	*	-	-	-	-	*	*	-	-	-	-
Yannakoulia et al.	2007	114	38.60	-7.70	57.50	-6.20	*	*	*	*	*	-	-	-	-	-	-	-
Yoldemir et al.	2012	190	45.27	-2.93	57.02	-6.15	*	*	-	*	-	-	-	-	-	-	-	-
Yoo et al.	2012	358	34.20	-9.70	61.10	-7.70	*	*	*	*	*	-	*	*	-	-	-	-
Yoo et al.	1998	306	NA	NA	NA	NA	*	*	-	-	-	-	-	-	-	-	-	-
Yoshimoto et al.	2011	278	41.80	-6.20	62.10	-8.20	*	*	-	-	-	-	-	-	-	-	-	-
Zhong et al.	2005	676	NA	NA	NA	NA	*	*	-	-	-	-	-	-	-	-	-	-
Zhou et al.	2010	729	42.20	-3.80	53.80	-2.80	*	-	-	-	-	-	-	-	-	-	-	-
Zhou et al.	2015	6324	44.10	-4.80	60.00	-7.80	*	*	*	*	-	-	-	-	-	-	-	-
Zivkovic et al.	2011	271	37.00	-5.30	54.00	-4.50	*	-	*	-	-	-	-	-	-	-	-	-

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; BMI, Body Mass Index; BW, Body Weight; WC, Waist Circumference; WTHR, Waist to Hip Ratio; TBF, Total Body Fat Percentage; HC, Hip Circumference; AF, Subcutaneous Abdominal Fat; VF, Visceral Fat; SSIF, Suprailliac Skinfold Thickness; TF, Trunk Fat Percentage; SAF, Abdominal Skinfold Thickness; LF, Total Leg Fat Percentage; SD, Standard Deviation. Note: * indicates inclusion of measure.

Table 2.6: Table of study characteristics for longitudinal studies.

			Premenopausal		Postmenopausal		Fat Mass Measure					
Study	**Year**	**Sample size**	**Mean age**	**SD**	**Mean age**	**SD**	**BMI**	**BW**	**WC**	**TBF**	**SAF**	**VF**
Abdulnour et al.	2012	13	50.65	2.26	52.76	2.16	-	-	-	-	*	*
Akahoshi et al.	2001	48	39.40	1.60	45.30	1.50	*	-	-	-	-	-
Akahoshi et al.	2001	388	44.20	1.60	50.10	1.50	*	-	-	-	-	-
Akahoshi et al.	2001	565	48.30	1.70	54.20	1.70	*	-	-	-	-	-
Ford et al.	2005	74	40.07	4.43	45.77	4.62	*	-	-	-	-	-
Franklin et al.	2009	8	49.30	1.70	57.00	2.26	*	*	*	*	-	-
Janssen et al.	2008	859	46.81	2.52	52.29	2.86	*	-	*	-	-	-
Lee et al.	2009	69	50.60	2.60	54.70	2.60	*	*	-	*	*	*
Liu-Ambrose et al.	2006	53	40.50	4.70	53.20	4.70	-	*	-	-	-	-
Lovejoy et al.	2008	51	48.10	0.30	52.10	0.30	-	*	-	*	*	*
Macdonald et al.	2005	248	47.72	1.40	54.13	1.52	*	*	-	-	-	-
Razmjou et al.	2018	48	49.77	1.80	59.97	1.78	*	*	*	*	-	-
Soreca et al.	2009	48	47.98	1.32	67.98	1.32	*	*	-	-	-	-

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; BMI, Body Mass Index; BW, Body Weight; WC, Waist Circumference; TBF, Total Body Fat Percentage; SAF, Subcutaneous Abdominal Fat; VF, Visceral Fat; SD, Standard Deviation.
Note: * indicates inclusion of measure.

Table 2.7: Quality assessment of individual cross-sectional studies.

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Abate et al.	2014	-	*	-	*	*	*	*	*	*	7
Abdulnour et al.	2012	*	*	-	*	*	*	*	*	*	8
Abildgaard et al.	2013	*	*	-	*	*	*	*	*	*	8
Adams-Campbell et al.	1996	*	*	*	*	-	-	-	-	*	5
Agrinier et al.	2010	*	*	*	*	-	*	*	*	*	8
Aguado et al.	1996	-	*	-	*	-	-	-	*	*	4
Albanese et al.	2009	*	*	-	*	*	*	*	*	*	8
Allali et al.	2009	*	*	-	*	-	-	-	-	-	3
Aloia et al.	1995	*	*	-	*	-	-	-	-	-	3
Amankwah et al.	2013	*	*	*	*	-	*	*	*	*	8
Amarante et al.	2011	-	-	-	*	*	-	*	-	*	4
Amiri et al.	2014	*	*	*	*	-	-	*	*	*	7
Angsuwanthana et al.	2007	*	*	*	*	*	*	*	*	*	9
Armellini et al.	1996	*	*	-	-	-	-	-	*	*	4
Arthur et al.	2013	*	*	-	*	-	*	*	*	*	7
Aydin et al.	2010	*	*	*	*	*	*	*	*	*	9
Ayub et al.	2006	-	-	-	*	*	-	-	*	*	4
Bancroft et al.	1996	*	*	*	*	*	*	*	*	*	9

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Bednarek-Tupikowska et al.	2006	-	-	-	*	*	-	-	*	*	4
Bell et al.	2007	*	*	-	*	-	*	*	*	*	7
Ben-Ali et al.	2016	*	*	-	*	-	-	*	*	*	6
Ben-Ali et al.	2014	*	*	-	*	-	-	*	*	*	6
Ben-Ali et al.	2011	*	*	-	*	-	*	*	*	*	7
Berg et al.	2004	-	-	-	*	-	*	*	*	*	5
Berge et al.	1994	*	*	*	*	-	*	*	-	-	6
Berger et al.	1995	-	*	-	*	*	*	*	*	*	7
Berstad et al.	2010	*	*	*	*	-	*	*	-	*	7
Bhagat et al.	2010	*	*	-	*	-	*	*	*	*	7
Bhurosy et al.	2013	*	*	-	*	-	*	*	*	*	7
Blumenthal et al.	1991	*	*	*	*	*	*	*	-	-	7
Bonithon-Kopp et al.	1990	*	*	-	*	*	*	*	-	-	6
Caire-Juvera et al.	2008	*	*	-	*	-	*	*	*	*	7
Campesi et al.	2016	-	-	-	*	-	*	*	-	-	3
Carr et al.	2000	*	*	-	*	-	*	*	-	-	5
Castracane et al.	1998	-	-	-	*	-	*	-	-	-	2
Catsburg et al.	2014	*	*	-	*	-	-	-	-	*	4

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Cecchini et al.	2012	*	*	-	-	-	*	*	*	*	6
Cervellati et al.	2009	-	-	-	*	-	*	*	*	*	5
Chain et al.	2017	*	*	-	*	*	-	*	*	*	7
Chang et al.	2000	*	*	-	*	-	*	*	*	*	7
Cho et al.	2008	*	*	-	*	-	-	*	*	*	6
Cifkova et al.	2008	*	*	-	*	*	*	*	*	*	8
Copeland et al.	2006	*	*	-	*	-	*	*	*	*	7
Cremonini et al.	2013	*	*	-	*	-	*	*	*	*	7
Cui et al.	2007	*	*	-	*	-	*	*	*	*	7
D'haeseleer et al.	2011	-	-	*	*	*	*	*	-	*	6
Da Camara et al.	2015	*	*	*	*	*	*	*	*	*	9
Dallongeville et al.	1995	*	*	-	*	*	-	*	*	*	7
Dancey et al.	2001	*	*	-	*	-	*	*	-	-	5
Davis et al.	1994	*	*	-	*	*	*	*	-	-	6
De Kat et al.	2017	*	*	-	*	-	*	*	*	*	7
Den Tonkelaar et al.	1990	*	*	-	*	-	-	*	*	*	6
Dmitruk et al.	2018	*	*	-	*	-	*	*	*	*	7
Donato et al.	2006	*	*	*	*	*	*	*	*	*	9

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Douchi et al.	1997	*	*	-	*	-	*	-	*	*	6
Douchi et al.	2002	*	*	-	*	-	*	*	*	*	7
Douchi et al.	2007	*	*	-	*	-	-	*	*	*	6
Dubois et al.	2001	-	*	-	*	-	*	*	-	-	4
Engmann et al.	2017	*	*	-	*	-	*	*	-	*	6
Ertungealp et al.	1999	*	-	-	-	-	-	-	-	-	1
Feng et al.	2008	*	*	*	*	-	*	*	*	*	8
Formica et al.	1995	*	*	-	*	-	-	-	-	-	3
Friedenreich et al.	2007	*	*	-	*	-	*	*	*	*	7
Friedenreich et al.	2002	*	*	*	*	-	*	*	*	*	8
Fu et al.	2011	*	*	-	*	-	*	*	*	*	7
Fuh et al.	2003	*	*	-	*	*	*	*	*	*	8
Gambacciani et al.	1999	*	*	-	*	-	*	*	*	*	7
Genazzani et al.	2006	*	*	-	*	-	*	*	*	*	7
Ghosh et al.	2008	*	*	-	*	-	*	*	*	*	7
Ghosh et al.	2010	*	*	-	*	-	*	*	*	*	7
Gram et al.	1997	*	*	-	*	*	-	*	*	*	7
Guo et al.	2015	*	*	-	*	-	*	*	*	*	7

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Gurka et al.	2016	*	*	*	*	*	*	*	-	-	7
Hadji et al.	2000	*	*	-	*	-	*	*	*	*	7
Hagner et al.	2009	*	*	-	*	-	*	*	*	*	7
Han et al.	2006	*	*	-	*	-	-	*	*	*	6
Harting et al.	1984	*	*	-	*	-	*	-	-	-	4
He et al.	2012	*	*	-	*	*	*	*	*	*	8
Hirose et al.	2003	*	*	-	*	-	-	-	-	*	4
Hjartaker et al.	2005	*	*	-	*	*	*	*	-	*	7
Ho et al.	2010	*	*	*	-	-	*	*	*	*	7
Hsu et al.	2006	*	*	-	*	-	-	-	*	*	5
Hu et al.	2016	*	*	-	-	-	-	-	*	*	4
Hunter et al.	1996	*	*	-	*	-	-	*	*	*	6
Iida et al.	2011	*	*	-	*	-	-	-	*	*	5
Ilich-Ernst et al.	2002	-	-	-	*	-	-	-	*	*	3
Ito et al.	1994	-	-	-	*	-	*	*	-	-	3
Jaff et al.	2015	*	*	-	*	*	*	*	*	*	8
Jasienska et al.	2005	*	*	-	*	*	-	-	*	*	6
Jeenduang et al.	2014	*	*	-	*	-	-	*	*	*	6

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Jeon et al.	2011	*	*	-	*	*	*	*	*	*	8
Jurimae et al.	2007	-	-	-	*	-	*	*	*	*	5
Kadam et al.	2010	*	*	-	*	*	*	*	*	*	8
Kang et al.	2016	*	*	-	*	-	-	-	*	*	5
Kaufer-Horwitz et al.	2005	*	*	-	*	-	*	*	*	*	7
Kim et al.	2007	*	*	-	*	-	-	*	*	*	6
Kim et al.	2012	*	*	-	*	-	-	-	*	*	5
Kim et al.	2013	*	*	*	*	-	-	*	*	*	7
Kim et al.	2016	*	*	-	*	-	-	-	*	*	5
Kirchengast et al.	1996	*	*	*	*	-	*	*	*	*	8
Kirchengast et al.	1998	*	*	*	*	-	*	*	*	*	8
Knapp et al.	2001	*	-	-	*	-	-	-	-	-	2
Koh et al.	2008	*	*	-	*	-	*	*	*	*	7
Konrad et al.	2011	*	*	-	*	*	-	*	*	*	7
Kontogianni et al.	2004	*	*	*	*	*	-	*	*	*	8
Konukoglu et al.	2000	-	-	*	*	-	-	*	-	-	3
Koskova et al.	2007	*	*	*	*	-	*	*	*	*	8
Kotani et al.	2011	-	-	-	*	-	-	*	*	*	4

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Kraemer et al.	2001	*	*	-	*	-	-	-	-	-	3
Kuk et al.	2005	*	*	-	*	-	-	-	*	*	5
Laitinen et al.	1991	*	*	-	*	-	-	-	-	-	3
Lejskova et al.	2012	*	*	-	*	*	*	*	*	*	8
Leon-Guerrero et al.	2017	*	*	-	*	-	*	*	*	*	7
Ley et al.	1992	*	*	-	*	-	*	*	*	*	7
Lin et al.	2006	*	*	-	*	*	-	*	*	*	7
Lindquist et al.	1980	*	*	*	*	*	*	*	*	*	9
Lindsay et al.	1992	*	*	-	*	-	-	-	*	*	5
Lovejoy et al.	2008	*	*	*	*	*	-	*	*	*	8
Lyu et al.	2001	*	*	-	*	*	-	*	*	*	7
Maharlouei et al.	2013	*	*	-	*	-	*	*	*	*	7
Malacara et al.	2002	*	*	*	*	*	*	*	-	*	8
Manabe et al.	1999	-	*	-	*	-	-	-	*	*	4
Manjer et al.	2001	*	*	-	*	-	*	*	*	*	7
Mannisto et al.	1996	*	*	*	*	-	-	-	*	*	6
Martini et al.	1997	*	*	-	*	-	-	*	*	*	6
Marwaha et al.	2013	*	*	-	*	-	*	*	*	*	7

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Matsushita et al.	2003	*	*	-	*	-	*	-	*	*	6
Matsuzaki et al.	2017	*	*	-	*	-	-	-	*	*	5
Matthews et al.	1989	*	*	*	*	*	*	*	-	-	7
Mesch et al.	2006	-	-	-	*	-	*	*	*	*	5
Meza-Munoz et al.	2006	*	*	-	*	-	*	*	*	*	7
Minatoya et al.	2014	*	*	-	-	-	-	-	-	-	2
Mo et al.	2017	*	*	-	*	-	-	-	*	*	5
Muchanga et al.	2014	*	*	*	*	*	*	*	*	*	9
Muti et al.	2000	*	*	-	*	-	-	*	*	*	6
Nitta et al.	2016	*	*	-	*	-	-	-	-	-	3
Noh et al.	2013	*	*	*	*	-	*	*	*	*	8
Nordin et al.	1992	-	-	-	*	-	-	-	-	-	1
Ohta et al.	2010	*	*	*	*	-	-	-	*	*	6
Oldroyd et al.	1998	-	-	-	*	-	-	-	-	-	1
Pacholczak et al.	2016	*	*	-	*	-	-	*	*	*	6
Park et al.	2012	*	*	-	*	-	-	-	*	*	5
Park et al.	2017	*	*	-	*	-	*	*	-	*	6
Pavicic et al.	2010	*	*	-	*	-	*	*	*	*	7

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Pavlica et al.	2013	*	*	-	*	-	-	-	*	*	5
Phillips et al.	2008	*	*	-	*	-	-	*	*	*	6
Polesel et al.	2015	*	*	*	*	-	*	*	*	*	8
Pollan et al.	2012	*	*	-	*	*	*	*	*	*	8
Portaluppi et al.	1997	-	*	*	*	*	*	*	*	*	8
Priya et al.	2013	*	*	-	*	-	-	*	*	*	6
Rantalainen et al.	2010	-	-	-	*	-	*	-	*	*	4
Reina et al.	2015	-	*	-	*	-	-	-	-	-	2
Revilla et al.	1997	*	-	-	*	-	*	*	*	*	6
Revilla et al.	1997	*	*	-	*	-	*	*	*	*	7
Rice et al.	2015	*	*	-	*	-	*	*	-	*	6
Rico et al.	2001	*	-	*	*	-	*	*	*	*	7
Rico et al.	2002	*	-	*	*	-	*	*	*	*	7
Roelfsema et al.	2016	*	-	-	*	-	*	*	*	*	6
Rosenbaum et al.	1996	-	-	-	*	-	*	*	*	*	5
Salomaa et al.	1995	*	*	-	*	-	*	*	*	*	7
Sarrafzadegan et al.	2013	*	*	-	*	-	-	-	*	*	5
Schaberg-Lorei et al.	1990	-	-	-	*	-	-	-	*	*	3

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Schwarz et al.	2007	*	*	-	*	-	*	*	*	*	7
Sherk et al.	2011	-	-	-	*	-	-	-	*	*	3
Shibata et al.	1979	-	*	-	*	*	-	-	-	-	3
Sieminska et al.	2006	-	-	-	*	-	*	*	-	-	3
Skrzypczak et al.	2005	*	*	-	*	-	*	*	*	*	7
Skrzypczak et al.	2007	*	*	-	*	-	*	*	*	*	7
Soderberg et al.	2002	*	*	-	*	-	*	*	*	*	7
Son et al.	2015	*	*	-	*	*	*	*	*	*	8
Soriguer et al.	2009	*	*	-	*	-	-	*	*	*	6
Staessen et al.	1989	-	-	-	*	-	-	*	*	*	4
Suarez-Ortegon et al.	2012	-	-	-	*	*	-	-	*	*	4
Suliga et al.	2016	*	*	-	*	*	-	*	*	*	7
Sumner et al.	1998	-	-	-	*	-	-	*	*	*	4
Tanaka et al.	2015	-	-	-	*	-	*	*	*	*	5
Thomas et al.	2000	*	*	-	*	-	-	*	*	*	6
Torng et al.	2000	*	*	-	*	-	-	*	*	*	6
Toth et al.	2000	-	*	*	*	*	*	*	*	*	8
Tremollieres et al.	1996	*	*	*	*	*	-	*	*	*	8

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Trikudanathan et al.	2013	*	*	*	*	*	-	*	*	*	8
Van-Pelt et al.	1998	-	-	*	*	-	*	*	*	*	6
Veldhuis et al.	2016	*	*	*	*	-	-	*	*	*	7
Wang et al.	2012	*	*	-	*	-	-	-	*	*	5
Wang et al.	2006	*	*	-	*	-	-	*	*	*	6
Wang et al.	2012	*	*	-	*	-	*	*	-	*	6
Wee et al.	2013	-	*	-	*	-	*	*	*	*	6
Williams et al.	1997	*	*	-	*	-	*	*	*	*	7
Wing et al.	1991	*	*	-	-	-	*	*	*	*	6
Xu et al.	2010	*	*	*	*	-	*	*	*	*	8
Yamatani et al.	2013	*	*	*	*	-	-	*	*	*	7
Yannakoulia et al.	2007	*	*	*	*	-	*	*	*	*	8
Yoldemir et al.	2012	*	*	*	*	-	*	*	*	*	8
Yoo et al.	2012	*	*	*	*	-	-	*	*	*	7
Yoo et al.	1998	*	*	*	-	-	*	*	*	*	7
Yoshimoto et al.	2011	*	*	-	*	-	-	-	-	-	3
Zhong et al.	2005	*	*	-	-	-	-	-	*	*	4
Zhou et al.	2010	*	*	*	*	-	*	*	*	*	8

Table 2.7: Quality assessment of individual cross-sectional studies. *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			**Comparability**				**Outcome**		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Zhou et al.	2015	*	*	-	*	-	-	*	*	*	6
Zivkovic et al.	2011	*	*	-	*	-	-	*	*	*	6

Note: * indicates the study met the criterion for the question.

Table 2.8: Quality assessment of individual longitudinal studies.

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	**Year**	**Q1**	**Q2**	**Q3**	**Q4a**	**Q4b**	**Q5**	**Q6**	**Q7**	**Q8**	**Total score (of 9)**
Abdulnour et al.	2012	*	*	-	*	*	*	*	*	*	8
Akahoshi et al.	2001	*	*	*	*	*	*	*	*	*	9
Ford et al.	2005	*	-	*	*	*	*	*	*	*	8
Franklin et al.	2009	-	-	-	*	*	-	*	*	-	4
Janssen et al.	2008	*	*	-	*	*	*	*	*	*	8
Lee et al.	2009	*	*	-	*	*	*	*	*	*	8
Liu-Ambrose et al.	2006	*	*	-	*	*	*	*	*	*	8
Lovejoy et al.	2008	*	*	*	*	*	-	*	*	*	8
Macdonald et al.	2005	*	*	-	*	*	*	*	*	*	8
Razmjou et al.	2018	*	*	-	*	*	*	*	*	*	8
Soreca et al.	2009	*	*	-	*	*	*	-	*	*	7

Note: * indicates the study met the criterion for the question.

Table 2.9: Output for cross-sectional studies.

		Total sample size		Mean age (SD)		Mean fat mass (SD)		Unstandardised		Standardised	
Fat mass measure	**k (Samples)**	**PreM**	**PostM**	**PreM**	**PostM**	**PreM**	**PostM**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Body mass index	171 (181)	453 036	523 796	41.96 (3.69)	59.42 (3.06)	24.75 (1.60)	26.64 (1.25)	1.14 (0.95 - 1.32)	<0.0001	0.28 (0.23, 0.33)	<0.0001
Bodyweight	109 (122)	113 603	204 845	43.36 (4.71)	59.55 (3.27)	64.82 (7.91)	66.12 (9.17)	1.00 (0.44 – 1.57)	0.0005	0.08 (0.03, 0.14)	0.0040
Waist circumference	70 (72)	214 712	326 639	42.28 (3.65)	59.07 (1.91)	78.58 (4.24)	83.61 (3.19)	4.63 (3.90 - 5.35)	<0.0001	0.45 (0.37, 0.52)	<0.0001
Waist-to-hip ratio	47 (50)	199 140	309 797	42.39 (3.44)	59.09 (1.42)	0.78 (0.03)	0.81 (0.03)	0.04 (0.03 - 0.05)	<0.0001	0.65 (0.52, 0.77)	<0.0001
Body fat percentage	46 (52)	58 605	113 226	43.81 (4.67)	59.55 (3.81)	32.44 (3.47)	35.69 (3.84)	2.88 (2.13 - 3.63)	<0.0001	0.90 (0.09, 1.71)	0.0292
Hip circumference	25 (25)	185 885	297 189	42.48 (3.08)	59.15 (0.95)	100.30 (2.66)	102.73 (2.25)	2.01 (1.36 - 2.65)	<0.0001	0.20 (0.13, 0.27)	<0.0001
Subcutaneous abdominal fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	194.05 (23.65)	221.21 (32.09)	28.73 (8.56 - 48.91)	0.0053	0.85 (-0.50, 2.21)	0.2176
Visceral fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	69.22 (15.75)	104.36 (13.92)	26.90 (13.12 - 40.68)	0.0001	0.59 (0.20, 0.98)	0.0028
Suprailiac skinfold thickness	9 (10)	1103	745	39.76 (4.41)	61.89 (4.77)	22.16 (7.04)	24.55 (9.90)	2.65 (0.45 - 4.85)	0.0181	0.28 (0.05, 0.50)	0.0149
Trunk fat percentage	7 (7)	39 335	95 756	45.28 (6.61)	59.68 (3.41)	31.27 (4.78)	33.74 (5.36)	5.49 (3.91 - 7.06)	<0.0001	0.68 (0.52, 0.83)	<0.0001
Abdominal skinfold thickness	4 (5)	199	359	40.64 (6.32)	62.99 (5.16)	26.65 (8.14)	29.43 (9.82)	6.46 (0.51 - 12.42)	0.0335	0.61 (0.05, 1.18)	0.0338
Total leg fat percentage	3(3)	991	524	36.96 (1.13)	55.18 (5.17)	36.33 (5.47)	36.00 (2.62)	-3.19 (-5.98 - -0.41)	0.0246	-0.51 (-0.95, -0.07)	0.0227

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; k = number of studies; SD, Standard Deviation; CI, Confidence Interval. Note: Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. $p < 0.05$ considered significant.

Table 2.10: Output for longitudinal studies.

			Mean age (SD)		Mean fat mass (SD)		Unstandardised		Standardised	
Fat mass measure	**k (Samples)**	**Total sample size**	**PreM**	**PostM**	**PreM**	**PostM**	**Estimate (95% CI)**	**p-value**	**Estimate (95% CI)**	**p-value**
Body mass index	8 (10)	2 355	46.67 (2.53)	52.80 (3.71)	24.30 (1.97)	25.03 (2.37)	0.93 (0.26 - 1.59)	0.0061	0.21 (0.07, 0.35)	0.0036
Bodyweight	7 (7)	525	47.64 (3.06)	55.76 (5.08)	66.11 (3.89)	69.19 (3.71)	2.99 (1.36 - 4.63)	0.0003	0.39 (0.12, 0.66)	0.0049
Body fat percentage	4 (4)	176	49.59 (1.24)	55.49 (3.65)	36.29 (4.88)	37.84 (3.33)	2.18 (0.21 - 4.16)	0.0299	0.28 (0.13, 0.42)	0.0001
Waist circumference	3 (3)	915	46.99 (2.04)	52.73 (5.17)	80.79 (3.62)	84.06 (2.61)	3.82 (0.87 - 6.77)	0.0111	0.38 (-0.07, 0.84)	0.1004
Subcutaneous abdominal fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	215.14 (66.15)	242.28 (77.34)	18.53 (-3.64 - 40.69)	0.1014	0.52 (-0.31, 1.35)	0.2168
Visceral fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	78.63 (14.45)	92.23 (12.77)	12.95 (8.65 – 17.25)	<0.0001	0.49 (-0.03, 1.01)	0.0629

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; k = number of studies; SD, Standard Deviation; CI, Confidence Interval. Note: Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. $p < 0.05$ considered significant.

3 Lipid profile differences during menopause: a review with meta-analysis

3.1 Abstract

Objectives: The aim of the study was to determine lipid profile differences between premenopausal and postmenopausal women.

Methods: The present review utilised a meta-analytic approach. Sixty-six studies were included, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal.

Results: The main findings were that (1) lipoproteins were significantly higher in postmenopausal women compared to premenopausal women including triglycerides (0.27 mmol/L, 95% confidence interval, 0.22 to 0.31), total cholesterol (0.58, 0.50 to 0.65), low-density lipoprotein (0.45, 0.38 to 0.53) and total cholesterol to high-density lipoprotein levels (0.39, 0.16 to 0.62), (2) there was no difference in high-density lipoprotein levels between premenopausal and postmenopausal women (0.02, -0.00 to 0.04) and (3) the differences in lipid levels was partly attributable to the mean age difference between premenopausal and postmenopausal women.

Conclusions: These findings are important as they provide precise estimates and trajectories of lipid changes in women around menopause. Furthermore the results suggest that the unfavourable lipid profile that develops in postmenopausal women puts them at higher risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

3.2 Introduction

Menopause is characterised by the progressive decline of endogenous estrogen levels and is defined as the final menstrual period (Harlow et al., 2012). As women progress from a premenopausal to postmenopausal state, deleterious changes in serum lipid profiles have been shown to occur, as demonstrated by the increased levels of low-density lipoprotein (LDL), total cholesterol (TC) and triglycerides (TG) (Derby et al., 2009; Jensen et al., 1990). Previous narrative reviews that have discussed lipid changes in women around menopause have been limited by a paucity of quantitative estimates (Carr, 2003; Gaspard et al., 1995; Kolovou & Bilianou, 2008), which are typically made available through a systematic review of the literature with meta-analyses. This has not yet been done for serum lipids, perhaps

because the extant literature on this topic may be too large to systematically review. We have recently conducted a meta-analyses on fat mass differences between premenopausal and postmenopausal women (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019) and in this process we have also extracted relevant lipid profile data. Given that lipid profiles are highly related to fat mass, particularly central obesity (Hodson et al., 2015), the data extracted from our previous review provides a useful representation of lipid changes in women around menopause. It is therefore within this context that we are reviewing data and reporting precise quantitative estimates on lipid profile differences between premenopausal and postmenopausal women to address this gap in the literature. This review will provide important information to clinicians as well as critical evidence on lipid trajectories, which can guide the development of targeted interventions to facilitate positive health outcomes for postmenopausal women.

3.3 Methods

The methodology of the initial meta-analyses is reported elsewhere in detail (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019) and was registered prospectively in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643). Briefly the PubMed database was searched (to May 2018) with filters applied to exclude both non-human and non-English studies. In addition, the criteria and methods described in the following sections were used.

3.3.1 Inclusion and exclusion criteria

Both longitudinal and cross-sectional studies that investigated healthy premenopausal and healthy postmenopausal women were included, whereas studies that exclusively investigated clinical/pathophysiological populations or had fewer than 40 participants were excluded. The sample size cutoff was established to avoid extreme sampling bias and ensure that small studies, which are more likely to be methodologically less robust, are not included.

3.3.2 Data extraction

Available lipid data that was extracted from each study included high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglycerides (TG) and TC to HDL ratio. The International System of Units (SI) mmol/L was used to express lipid levels. Articles that reported lipids as mg/dl were converted to mmol/L by multiplying the values by 0.02586 (for HDL, LDL and TC) or by 0.01129 (for TG). Two authors (AA and EW) double extracted all data from included articles to avoid transcription errors with any disagreement resolved by consensus.

3.3.3 Statistics

R (version 3.3.3) (R. C. Team, 2016) operating within RStudio (version 1.0.143) (Rs. Team, 2012) was used to conduct all statistical analysis. The metafor package (version 2.0.0) (Viechtbauer, 2010) was used for the meta-analysis.

3.3.4 Meta-analysis

Becasue the sampling of populations and methodology varied across studies, heterogeneity was assumed, which resulted in a distribution of effect sizes (Borenstein et al., 2010). Therefore, all analyses used a Random Effects Model (using the restricted maximum likelihood estimator) to estimate the mean of the distribution of these effect sizes.

Cochran's Q statistic (with $p < 0.01$ indicative of significant heterogeneity) and the I^2 statistic (values 25%, 50% and 75% suggestive of low, moderate and high heterogeneity respectively) were used to assess heterogeneity across studies (J. P. Higgins et al., 2003). Sensitivity analyses using the leave-one-out-method were conducted to identify studies that excessively contributed to heterogeneity. Meta-regression analyses using a mixed effect model were conducted to determine the influence of moderators, such as ageing.

3.3.5 Bias

Funnel plots and Egger regression test were used to investigate the possible impact of publication bias (Egger et al., 1997). The trim and fill method was also used to estimate the number of studies that may be missing from the meta-analysis and to estimate adjusted effect sizes (Duval & Tweedie, 2000a, 2000b).

3.4 Results

3.4.1 Effect sizes

The unstandardized raw mean differences (i.e. estimate) for each lipid measure between postmenopausal and premenopausal women are presented in Table 3.1. Some studies included multiple sub-cohorts of premenopausal and postmenopausal women. In these cases, sub cohorts were extracted separately and treated as discrete samples. 3 longitudinal studies were identified, however, such studies did not report compatible measures and therefore were not suitable for meta-analysis. Therefore, 66 cross-sectional studies reporting on 67 sample populations were included in the analyses (see Table 3.3, which includes study characteristics).

Table 3.1: Output for cross-sectional studies.

		Total sample size		Mean age (SD)		Mean (SD)	Mean lipid level (SD)		Unstandardised	
Lipid measure	**k (Samples)**	**PreM**	**PostM**	**PreM**	**PostM**	**Age difference**	**PreM**	**PostM**	**Estimate (95% CI)**	**p-value**
HDL	58 (59)	64 330	42 650	38.98 (5.74)	56.41 (3.58)	15.74 (7.62)	1.53 (0.18)	1.55 (0.20)	0.02 (-0.00, 0.04)	0.0973
TG	57 (58)	24 365	25 642	42.36 (6.00)	57.14 (4.04)	13.71 (8.35)	1.28 (0.29)	1.57 (0.34)	0.27 (0.22, 0.31)	<0.0001
TC	56 (56)	66 062	41 940	39.19 (5.69)	56.57 (3.50)	15.71 (7.37)	4.77 (0.35)	5.57 (0.46)	0.58 (0.50, 0.65)	<0.0001
LDL	49 (49)	63 246	39 176	38.90 (5.71)	56.55 (3.65)	16.01 (7.63)	2.90 (0.25)	3.46 (0.32)	0.45 (0.38, 0.53)	<0.0001
TC:HDL	10 (10)	1 982	1 803	43.05 (4.67)	58.39 (4.43)	14.85 (7.82)	3.74 (0.24)	4.27 (0.51)	0.39 (0.16, 0.62)	0.0008

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; TC:HDL, total cholesterol to high-density lipoprotein ratio; k = number of studies; SD, Standard Deviation; CI, Confidence Interval. Note: $p < 0.05$ considered significant. Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. For HDL, TC and LDL, to convert values from SI units (mmol/L) to mg/dl, multiply by 38.67, however, for TG, multiply by 88.57.

3.4.2 Meta-analysis results

3.4.2.1 High-density lipoprotein Fifty-seven studies examined the association between HDL and menopausal status. There were no significant mean HDL differences between premenopausal and postmenopausal women (Table 3.1 and Figure 3.1).

3.4.2.2 Triglycerides Fifty-seven studies examined the association between TG and menopausal status. The mean TG change was 0.27 mmol/L (SE = 0.02; Table 3.1 and see Figure 3.4, which illustrates a forest plot for TG), with an annual difference 0.02 mmol/L/yr.

3.4.2.3 Total cholesterol Fifty-five studies examined the association between TC and menopausal status. The mean TC change was 0.58 mmol/L (SE = 0.04; Table 3.1 and see Figure 3.5, which illustrates a forest plot for TC), with an annual difference of 0.04 mmol/L/yr.

3.4.2.4 Low-density lipoprotein Forty-eight studies examined the association between LDL and menopausal status. The mean LDL change was 0.46 mmol/L (SE = 0.04; Table 3.1 and Figure 3.2), with an annual difference of 0.03 mmol/L/year.

3.4.2.5 Total cholesterol to high-density lipoprotein ratio Ten studies examined the association between TC to HDL ratio and menopausal status. The mean TC to HDL change was 0.39 mmol/L (SE = 0.12; Table 3.1 and see Figure 3.6, which illustrates a forest plot for TC to HDL ratio), with an annual difference of 0.03 mmol/L/year.

3.4.3 Sensitivity analyses

In all meta-analyses performed, significant heterogeneity was found and the proportion of real variance that was not related to random error between studies (I^2) was high for all analyses. Leave-one-out-analyses revealed no particularly influential study and showed relative consistency in reported estimates.

3.4.4 Publication bias

The trim and fill test and funnel plot diagnostics revealed some evidence of publication bias. Eggers regression test was significant for TC and LDL analyses, indicating some asymmetry. The trim and fill analyses identified one missing study for HDL and five for LDL (Figure 3.3). Whilst these results suggest that some publication bias is likely to be present, the differences between actual and reported estimates were generally quite small. The inclusion of missing studies did not change the relationship or significance of the results.

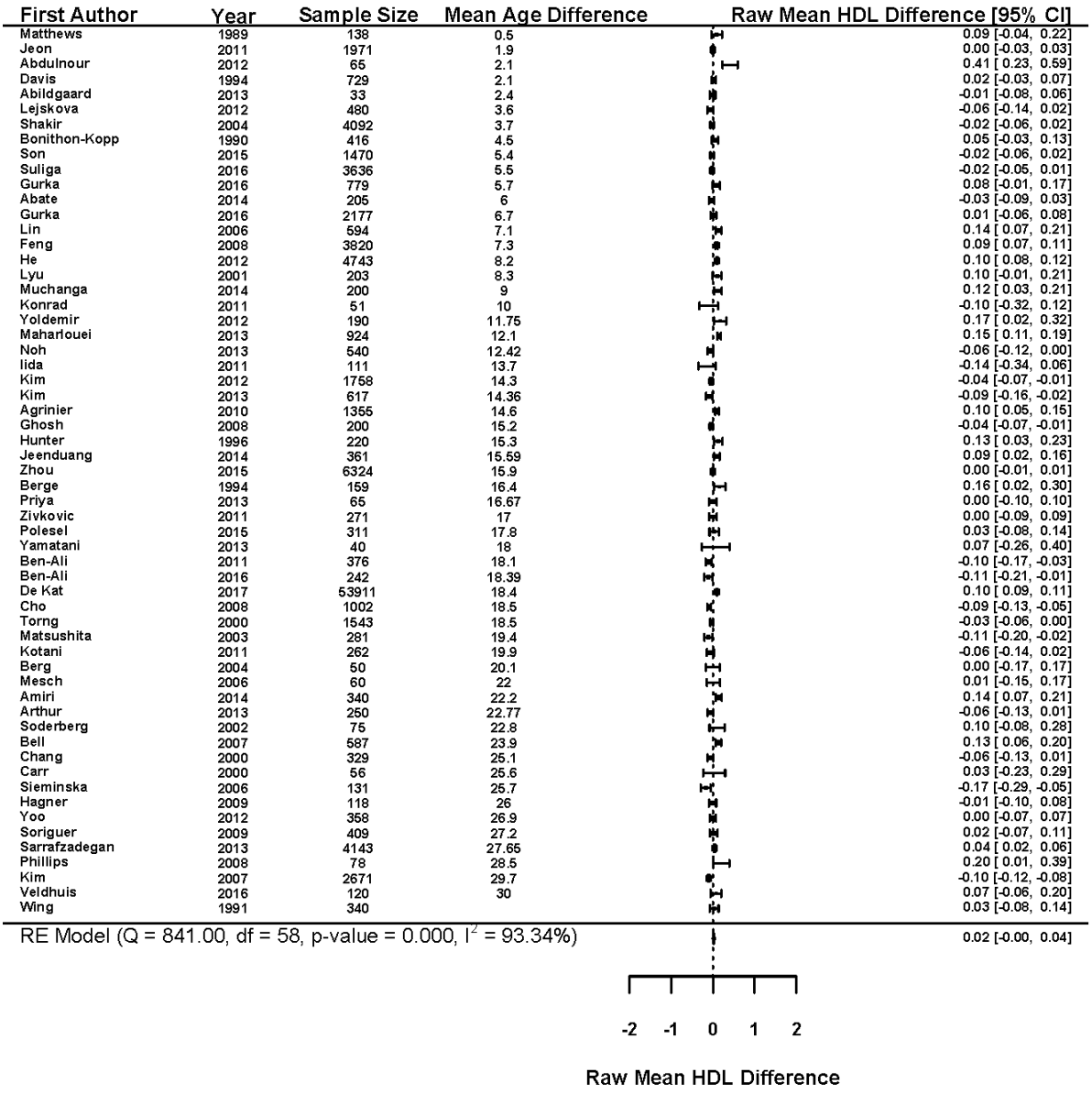

Figure 3.1: Forest plot of the raw mean high-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: HDL, high-density lipoprotein; CI, Confidence Interval; RE Model, Random Effects Model.

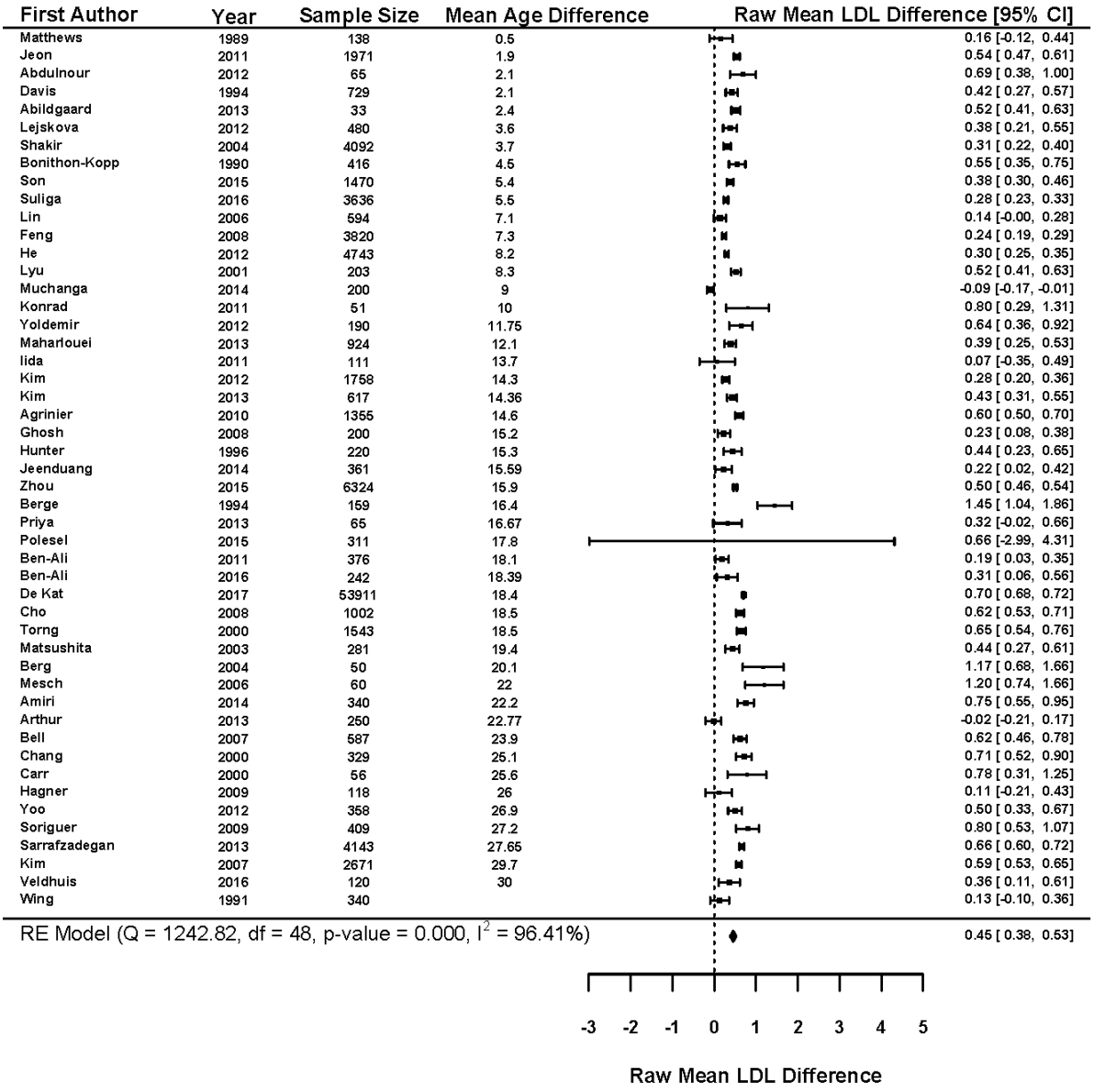

Figure 3.2: Forest plot of the raw mean low-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: LDL, low-density lipoprotein; CI, Confidence Interval; RE Model, Random Effects Model.

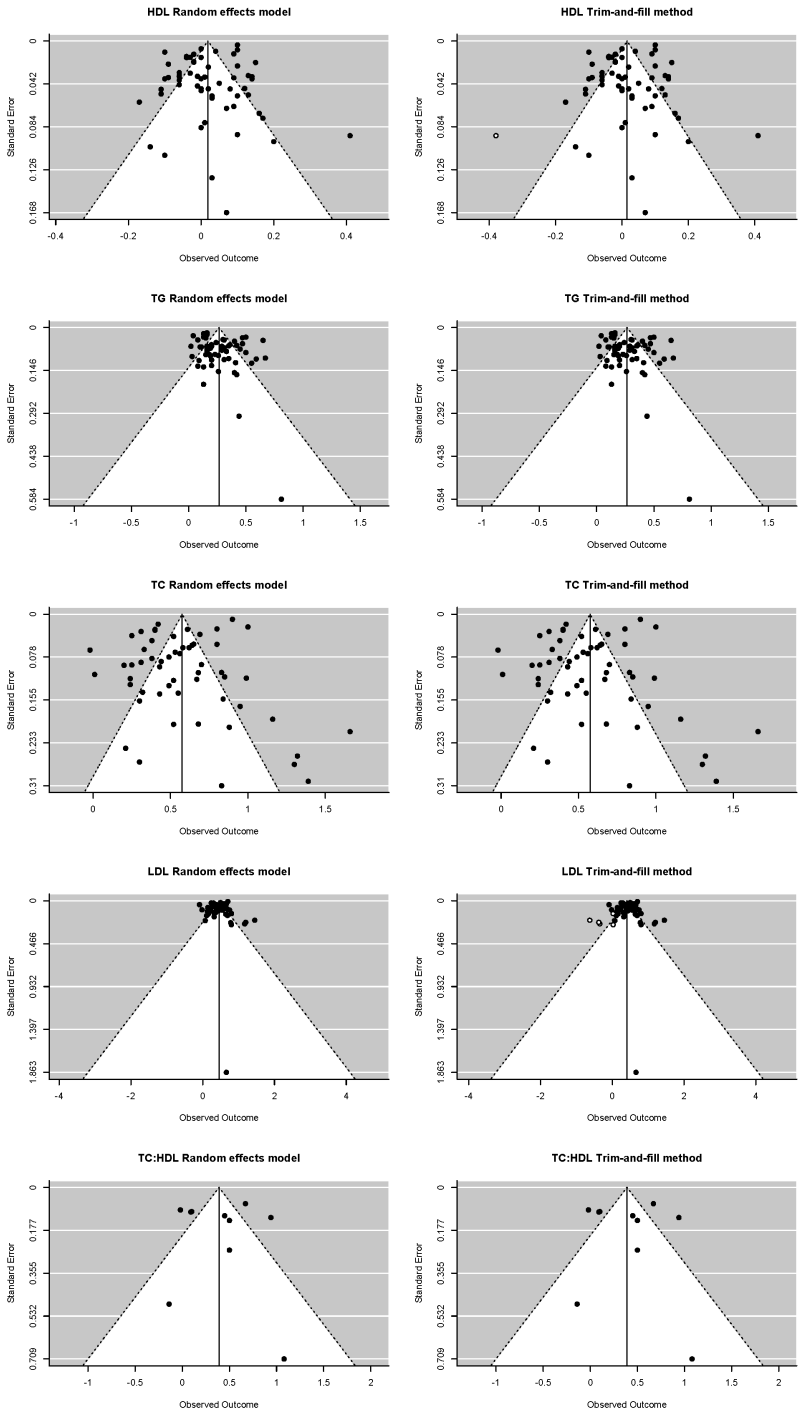

Figure 3.3: Funnel plots using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride; TC:HDL, total cholesterol to high-density lipoprotein ratio.

Table 3.2: Metaregression analyses after removal of the effect that is attributable to normal aging.

			Unstandardised	
Lipid measure	**Samples**	R^2	**Estimate (95% CI)**	**p-value**
TG	57	36.61	0.0103 (0.0059, 0.0147)	<0.0001
TC	55	9.71	0.0113 (0.0021, 0.0205)	0.0164
LDL	48	10.13	0.0088 (0.0006, 0.0171)	0.0351
TC:HDL	10	40.08	0.0243 (0.0025, 0.0462)	0.0289

Abbreviations: TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; TC:HDL, total cholesterol to high-density lipoprotein ratio; R^2, proportion of observed variance explained by the model; CI, Confidence Interval. Note: $p < 0.05$ considered significant. Studies that did not report age were omitted from model fitting. For TC and LDL, to convert values from SI units (mmol/L) to mg/dl, multiply by 38.67, however, for TG, multiply by 88.57.

3.4.5 Meta-regression and subgroup analyses

Ageing (i.e. the mean age difference between premenopausal and postmenopausal women) significantly predicted the unexplained variance (9.71 – 40.08%) in lipid estimates (Table 3.2). More specifically, the meta-regression (which used a mixed effects model) indicated that for every year difference between premenopausal and postmenopausal women, there was a 0.01 mmol/L increase in TG, TC, LDL and a 0.02 mmol/L increase in TC to HDL ratio (Table 3.2). The inclusion of women using hormone therapy had no significant effect on the overall estimates.

Subgroup analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women (compared to studies with a mean age difference greater than 5 years) revealed no significant differences for HDL, LDL, TC and TC to HDL ratio. However, studies that had a mean age difference greater than five years had a 0.1295 mmol/L increase in TG (SE 0.06, 95% CI from 0.02 to 0.24). Notably, I^2 remained high across all subgroup analyses. Furthermore, subset analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women revealed no difference in the direction or significance of effects compared to initial estimates. The magnitude of estimates for most measures was also very similar (see Table 3.4, which illustrates subset analyses). Notably, however, the magnitude of effect decreased for triglycerides (initial estimate: 0.27 mmol/L, 95% confidence interval 0.22 to 0.31; less than 5 years mean difference estimate: 0.14, 0.09 to 0.19) and could not be investigated in the total cholesterol to high-density lipoprotein levels due to insufficient studies available for subset analyses. Furthermore, the heterogeneity

remained high (i.e. above 75%) across all analyses (see Table 3.5, which illustrates heterogeneity for subset analyses), except for triglycerides (88.68% to 55.28%) and low-density lipoprotein (96.41% to 69.73%).

3.5 Discussion

The current review investigated the differences in lipid levels between healthy premenopausal and postmenopausal women. The main findings of this review were that (1) TG, TC, LDL and TC to HDL ratio levels were significantly higher in postmenopausal women compared to premenopausal women, (2) there was no difference in HDL levels between premenopausal and postmenopausal women and (3) the differences in lipid levels was partly attributable to the mean age difference between premenopausal and postmenopausal women.

It is important to determine why an unfavourable lipid profile develops in postmenopausal women comparatively to premenopausal women. Whilst both ageing and menopause are potentially implicated, it can be difficult to delineate the individual influence of each since both progress concurrently. Previous research indicates that for women aged 18-45 years the typical trends for TG, TC and LDL is 0.070 mmol/year, 0.010 mmol/year and 0.003 mmol/year respectively (Siervogel et al., 1998). The analyses presented in this paper reflect consistent but comparatively smaller annual estimates for TG (0.02 mmol/year), yet larger annual estimates for TC (0.04 mmol/year) and LDL (0.03 mmol/year), which would suggest that the annual rate of change does not remain the same throughout early adulthood and middle age. However, whilst the current study has identified ageing as a key predictor of the difference in lipid levels between premenopausal and postmenopausal women, which explains a portion of the variance (9.71 – 40.08%), there are other possible genetic and environmental factors that may account for the remaining variance and inconsistencies between estimates. For example, a longitudinal study revealed that lipid profiles fluctuated in premenopausal women depending on the stage of their menstrual cycle, with the follicular phase (indicative of high endogenous estrogen levels), associated with decreased TC, LDL and TG (Gaskins et al., 2010). Furthermore, the use of estrogen alone hormone therapy has been linked with raised HDL and lowered LDL and TC levels (Godsland, 2001). Taken together, these findings suggest that the decline in estrogen levels that accompany menopause may have a harmful impact on the overall lipid profile of postmenopausal women. However, our previous meta-analysis demonstrated that increases in fat mass between premenopausal and postmenopausal women were largely attributable to ageing (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). Therefore, it is also possible that the age related changes in lipid profiles are linked with similar factors as those associated with increased fat mass including poor diet and low levels of

physical activity. Further insights regarding the precise influence of these modifiable lifestyle factors on overall lipid changes in women around menopause will result in the development of focused and effective holistic intervention programs that seek to mitigate the identified risks for women.

Although the recommended cholesterol ranges and thresholds vary as a function of individual risk for developing lipid related disorders, the recommended LDL levels are <3.36 mmol/L for individuals with moderate coronary heart disease (CHD) risk (i.e. a clustering of 2 lifestyle risk factors including obesity, physical inactivity, elevated triglyceride, low HDL cholesterol or metabolic syndrome) (Grundy et al., 2004). In this study, it is important to note that the mean LDL cholesterol level for premenopausal women is 2.90 mmol/L, whereas postmenopausal women are above the recommended levels (3.46 mmol/L) for individuals with moderate CHD risk. This suggests that postmenopausal women who have a clustering of risk factors for CHD should be especially observant to changes in cholesterol after menopause, given that an unfavourable lipid profile develops at this time. Interestingly, whilst some studies report that HDL levels decrease after menopause onset (Jensen et al., 1990), the current review aligns with studies that suggest that HDL levels remain unchanged (Fukami et al., 1995; J.-L. Zhou et al., 2010).

3.5.1 Strengths and limitations

A key strength of the present study was that a large number of individuals were included in the analyses, resulting in a comprehensive assessment of lipid profile changes between premenopausal and postmenopausal women. Specifically, 66 cross-sectional studies were included in the meta-analyses, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal. Furthermore, as far as we are aware, this review is the first to provide precise quantitative estimates about lipid profile differences between premenopausal and postmenopausal women.

Notable limitations included the fact that there were insufficient longitudinal studies available for meta-analyses. Furthermore, the literature was not systematically reviewed prior to conducting the meta-analyses, which increased the possibility of publication bias in reported findings. However, publication bias analyses were conducted and revealed only small differences between actual and reported estimates, which did not change the relationship or significance of the results.

3.5.2 Future Directions

Given the heterogeneity of findings and that a large amount of unexplained variance remains to be investigated, future systematic reviews should investigate the role of moderators on cholesterol changes in women, including age of menopause onset, ethnicity, physical activity levels, genetic factors, diet, obesity and hormone therapy use. Once identified, the extent to which potential risk factors contribute to deleterious lipid profile changes should be precisely quantified and ranked in order of influence/weight and potential for modification, such that informed intervention programs, which seek to mitigate the identified risks for women and ensure that lipid levels are kept in the normal range, can be effectively developed. Additionally, more longitudinal studies that investigate changes in lipid levels as women progress from premenopausal to postmenopausal states are required so that additional insights can be provided regarding changes that occur during perimenopause.

3.6 Conclusion

The current analyses revealed that postmenopausal women develop an unfavourable lipid profile compared to premenopausal women, which is partly attributed to mean age differences between these groups. These findings are important as they provide precise estimates of lipid changes in women around menopause. Furthermore the results suggest that particular attention should be paid to changes in lipid levels after menopause due to the development of an unfavourable lipid profile that can increase the risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

3.7 Supplementary materials

The supplementary materials for Chapter 3 include:

- **Figure 3.4** Forest plot of the raw mean triglyceride difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TG, triglyceride; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 3.5** Forest plot of the raw mean total cholesterol difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TC, total cholesterol; CI, Confidence Interval; RE Model, Random Effects Model.
- **Figure 3.6** Forest plot of the raw mean total cholesterol to high-density lipoprotein ratio difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TC:HDL, total cholesterol to high-density lipoprotein ratio; CI, Confidence Interval; RE Model, Random Effects Model.
- **Table 3.3** Table of study characteristics for cross-sectional studies.
- **Table 3.4** Output for cross-sectional studies in subset analyses.
- **Table 3.5** Measures of heterogeneity for cross-sectional studies in subgroup analyses.

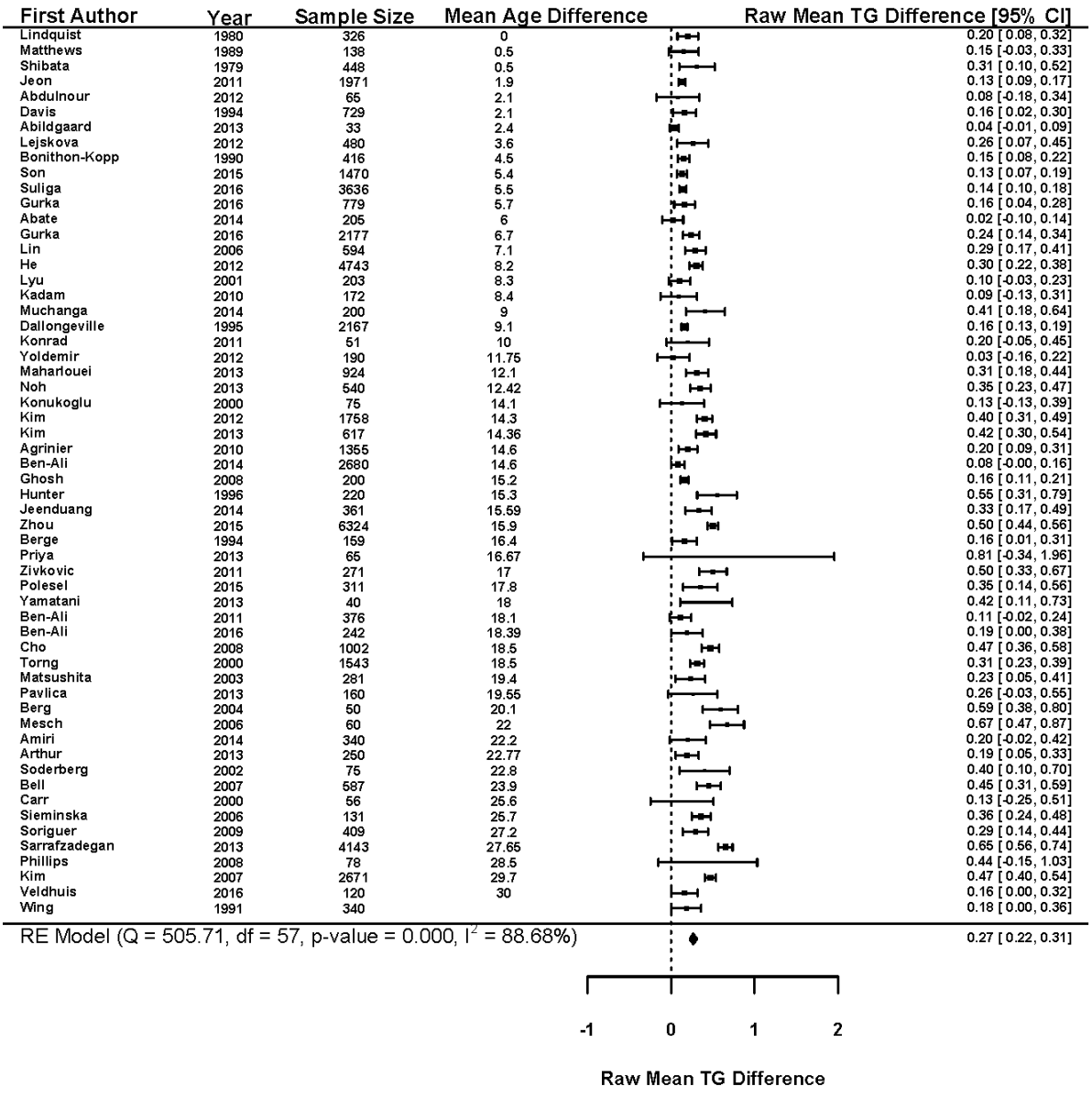

Figure 3.4: Forest plot of the raw mean triglyceride difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TG, triglyceride; CI, Confidence Interval; RE Model, Random Effects Model.

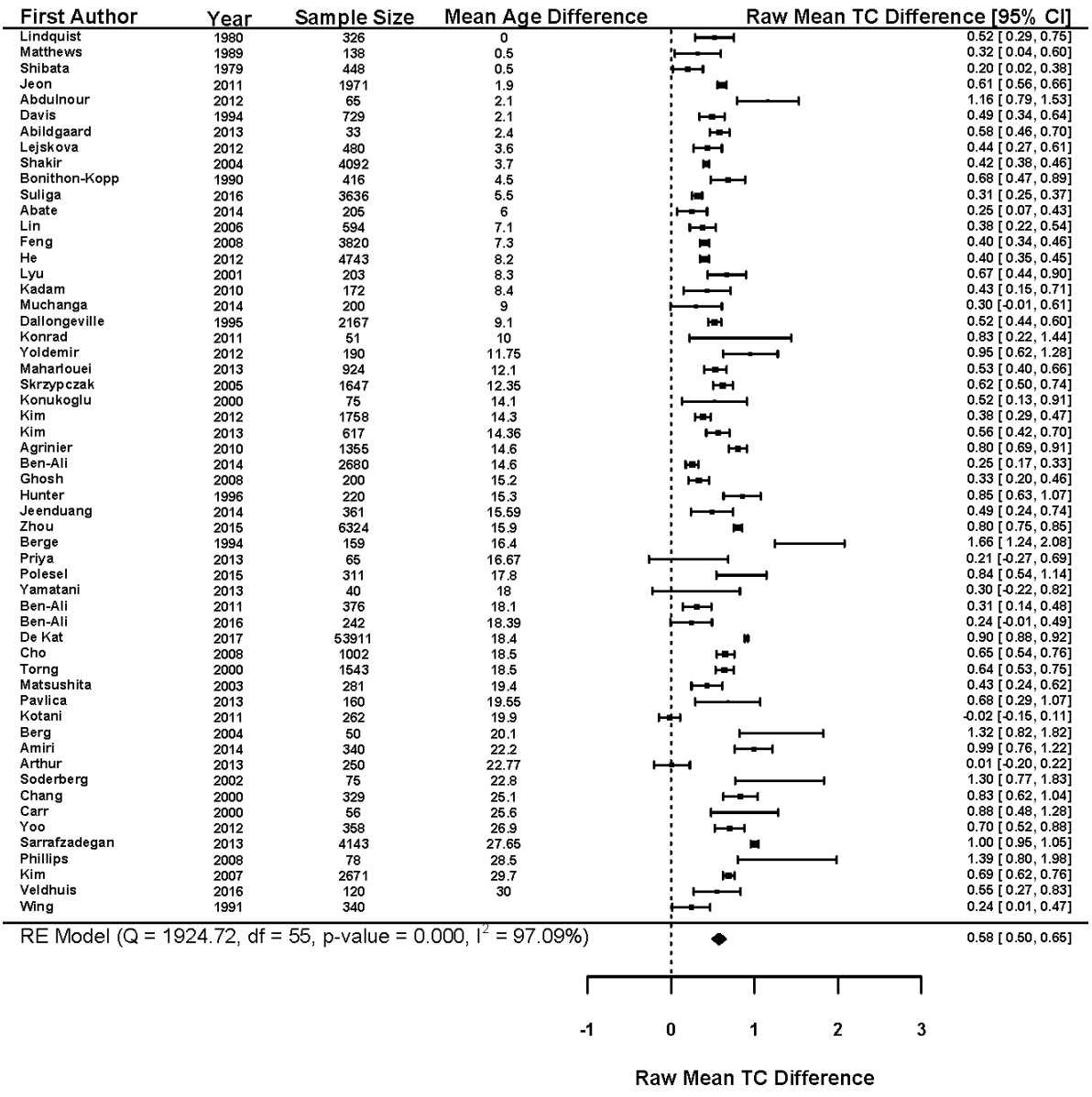

Figure 3.5: Forest plot of the raw mean total cholesterol difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TC, total cholesterol; CI, Confidence Interval; RE Model, Random Effects Model.

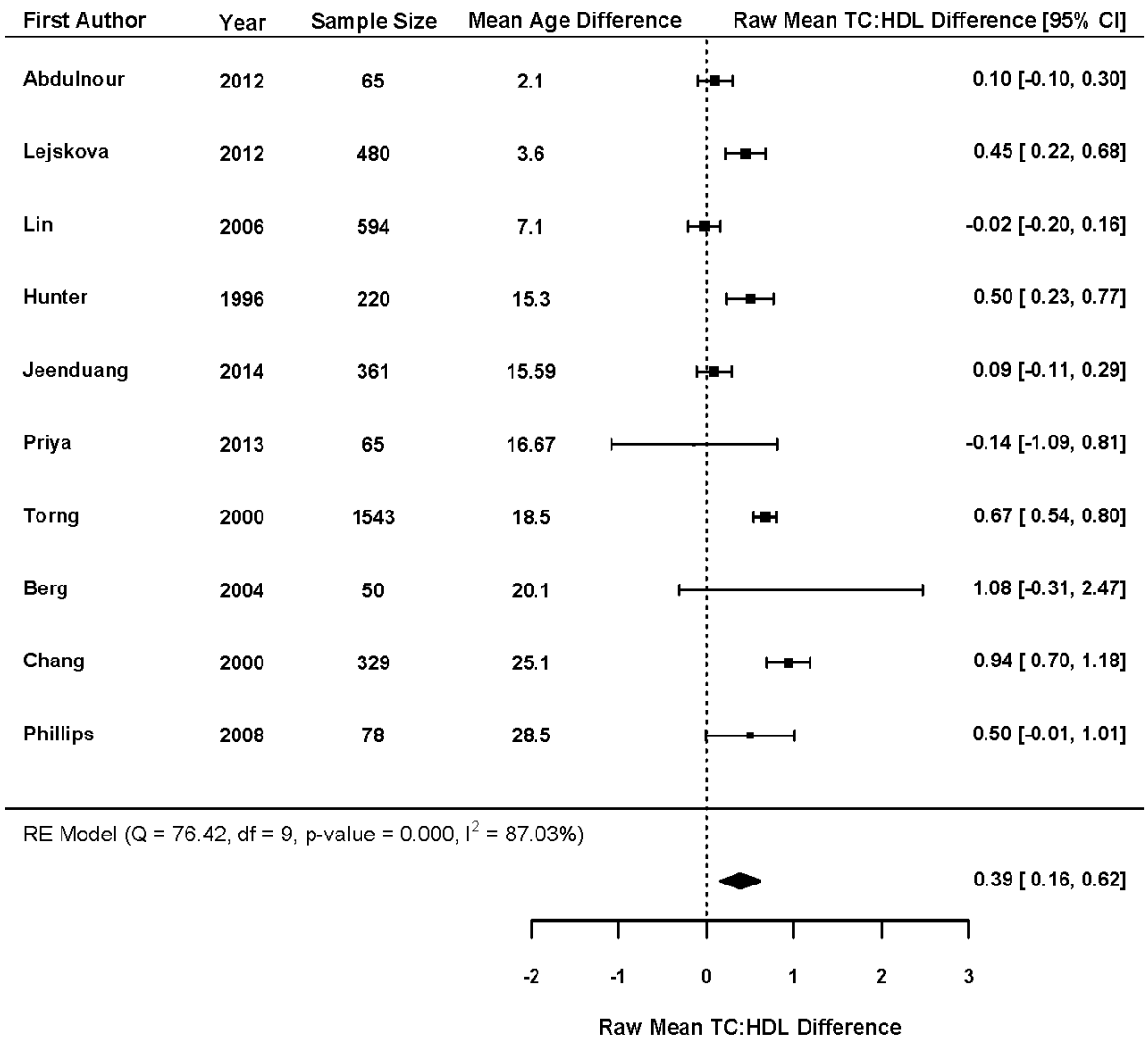

Figure 3.6: Forest plot of the raw mean total cholesterol to high-density lipoprotein ratio difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. Abbreviations: TC:HDL, total cholesterol to high-density lipoprotein ratio; CI, Confidence Interval; RE Model, Random Effects Model.

Table 3.3: Table of study characteristics for cross-sectional studies.

		Premenopausal		Postmenopausal		Lipid Measure				
Study	**Year**	**Mean age**	**SD**	**Mean age**	**SD**	**HDL**	**TG**	**TC**	**LDL**	**TC:HDL**
Abate et al.	2014	46.70	(1.9)	52.70	(3.4)	*	*	*	-	-
Abdulnour et al.	2012	52.30	(0.5)	54.40	(2)	*	*	*	*	*
Abildgaard et al.	2013	49.60	(1.8)	52.00	(2)	*	*	*	*	-
Agrinier et al.	2010	42.80	(4.4)	57.40	(5.4)	*	*	*	*	-
Amiri et al.	2014	36.80	(11.52)	59.00	(7.48)	*	*	*	*	-
Arthur et al.	2013	34.48	(8.85)	57.25	(8.28)	*	*	*	*	-
Bell et al.	2007	38.90	(7.9)	62.80	(8.3)	*	*	-	*	-
Ben-Ali et al.	2016	39.48	(7.79)	57.87	(7.65)	*	*	*	*	-
Ben-Ali et al.	2014	42.90	(5)	57.50	(7.3)	-	*	*	-	-
Ben-Ali et al.	2011	35.30	(7.6)	53.40	(6.2)	*	*	*	*	-
Berg et al.	2004	36.90	(4.1)	57.00	(5.3)	*	*	*	*	*
Berge et al.	1994	38.90	(7.2)	55.30	(6.1)	*	*	*	*	-
Bonithon-Kopp et al.	1990	47.80	(2.2)	52.30	(1.8)	*	*	*	*	-
Carr et al.	2000	35.40	(8.6)	61.00	(4.1)	*	*	*	*	-
Chang et al.	2000	36.10	(6.5)	61.20	(6.2)	*	-	*	*	*
Cho et al.	2008	40.50	(7.8)	59.00	(6.6)	*	*	*	*	-
Dallongeville et al.	1995	48.30	(3.4)	57.40	(3.9)	-	*	*	-	-
Davis et al.	1994	48.10	(1.7)	50.20	(1.7)	*	*	*	*	-
De Kat et al.	2017	36.90	(8.1)	55.30	(7.4)	*	-	*	*	-
Feng et al.	2008	43.70	(3)	51.00	(2.6)	*	-	*	*	-
Ghosh et al.	2008	40.20	(6.5)	55.40	(5.2)	*	*	*	*	-
Gurka et al.	2016	47.60	(3.4)	54.30	(3.6)	*	*	-	-	-
Gurka et al.	2016	47.40	(2.1)	53.10	(4.1)	*	*	-	-	-
Hagner et al.	2009	36.50	(5.17)	62.50	(5.43)	*	-	-	*	-
He et al.	2012	45.80	(3.6)	54.00	(3.6)	*	*	*	*	-

Table 3.3: Table of study characteristics for cross-sectional studies.
(continued)

		Premenopausal		Postmenopausal		Lipid Measure				
Study	**Year**	**Mean age**	**SD**	**Mean age**	**SD**	**HDL**	**TG**	**TC**	**LDL**	**TC:HDL**
Hunter et al.	1996	36.20	(9)	51.50	(10.2)	*	*	*	*	*
Iida et al.	2011	47.60	(3.8)	61.30	(6.6)	*	-	-	*	-
Jeenduang et al.	2014	42.58	(6.62)	58.17	(9.65)	*	*	*	*	*
Jeon et al.	2011	49.30	(8.5)	51.20	(9)	*	*	*	*	-
Kadam et al.	2010	45.60	(4.8)	54.00	(7.1)	-	*	*	-	-
Kim et al.	2007	35.40	(8.1)	65.10	(9.3)	*	*	*	*	-
Kim et al.	2012	50.70	(2.8)	65.00	(7.4)	*	*	*	*	-
Kim et al.	2013	42.12	(6.22)	56.48	(6.55)	*	*	*	*	-
Konrad et al.	2011	43.00	(5)	53.00	(4)	*	*	*	*	-
Konukoglu et al.	2000	35.40	(8.3)	49.50	(4.7)	-	*	*	-	-
Kotani et al.	2011	44.70	(4.9)	64.60	(4.4)	*	-	*	-	-
Lejskova et al.	2012	48.60	(2.4)	52.20	(2)	*	*	*	*	*
Lin et al.	2006	46.00	(3.6)	53.10	(4.4)	*	*	*	*	*
Lindquist et al.	1980	50.00	(NA)	50.00	(NA)	-	*	*	-	-
Lyu et al.	2001	45.10	(3.4)	53.40	(5)	*	*	*	*	-
Maharlouei et al.	2013	46.50	(5)	58.60	(6.7)	*	*	*	*	-
Matsushita et al.	2003	43.00	(6.3)	62.40	(7.9)	*	*	*	*	-
Matthews et al.	1989	47.30	(1.5)	47.80	(1.6)	*	*	*	*	-
Mesch et al.	2006	33.00	(5.6)	55.00	(5.6)	*	*	-	*	-
Muchanga et al.	2014	44.00	(3)	53.00	(4)	*	*	*	*	-
Noh et al.	2013	46.92	(4.7)	59.34	(5.82)	*	*	-	-	-
Pavlica et al.	2013	38.87	(9.81)	58.42	(1.01)	-	*	*	-	-
Phillips et al.	2008	32.90	(9.14)	61.40	(10.73)	*	*	*	-	*
Polesel et al.	2015	34.83	(8.4)	52.63	(5.72)	*	*	*	*	-

Table 3.3: Table of study characteristics for cross-sectional studies.
(continued)

		Premenopausal		Postmenopausal		Lipid Measure				
Study	**Year**	**Mean age**	**SD**	**Mean age**	**SD**	**HDL**	**TG**	**TC**	**LDL**	**TC:HDL**
Priya et al.	2013	38.65	(6.21)	55.32	(6.32)	*	*	*	*	*
Sarrafzadegan et al.	2013	32.15	(9.22)	59.80	(10.39)	*	*	*	*	-
Shakir et al.	2004	53.20	(1.6)	56.90	(2.9)	*	-	*	*	-
Shibata et al.	1979	46.90	(1.4)	47.40	(1.4)	-	*	*	-	-
Sieminska et al.	2006	28.20	(4.1)	53.90	(3.2)	*	*	-	-	-
Skrzypczak et al.	2005	43.66	(4.07)	56.01	(7.08)	-	-	*	-	-
Soderberg et al.	2002	37.90	(7.9)	60.70	(6.1)	*	*	*	-	-
Son et al.	2015	46.80	(2.5)	52.20	(3.1)	*	*	-	*	-
Soriguer et al.	2009	36.90	(7.5)	64.10	(5.2)	*	*	-	*	-
Suliga et al.	2016	49.70	(3.1)	55.20	(3)	*	*	*	*	-
Torng et al.	2000	42.70	(5.8)	61.20	(9.5)	*	*	*	*	*
Veldhuis et al.	2016	34.00	(9.3)	64.00	(8.52)	*	*	*	*	-
Wing et al.	1991	NA	(NA)	NA	(NA)	*	*	*	*	-
Yamatani et al.	2013	42.60	(7.35)	60.60	(7.5)	*	*	*	-	-
Yoldemir et al.	2012	45.27	(2.93)	57.02	(6.15)	*	*	*	*	-
Yoo et al.	2012	34.20	(9.7)	61.10	(7.7)	*	-	*	*	-
Zhou et al.	2015	44.10	(4.8)	60.00	(7.8)	*	*	*	*	-
Zivkovic et al.	2011	37.00	(5.3)	54.00	(4.5)	*	*	-	-	-

Abbreviations: HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; TC:HDL, total cholesterol to high-density lipoprotein ratio. Note: * indicates inclusion of measure.

Table 3.4: Output for cross-sectional studies in subset analyses.

		Total sample size		Mean age (SD)		Mean (SD)	Mean fat mass (SD)		Unstandardised		
Lipid measure	**k (Samples)**	**PreM**	**PostM**	**PreM**	**PostM**	**Age difference**	**PreM**	**PostM**	**Estimate (95% CI)**	**Standard error**	**p-value**
HDL	59	64 330	42 650	38.98 (5.74)	56.41 (3.58)	15.74 (7.62)	1.53 (0.18)	1.55 (0.20)	0.02 (-0.00, 0.04)	0.0114	0.0973
HDL (<=5)	8	2 748	5 176	49.55 (2.09)	55.14 (3.91)	3.07 (1.16)	1.63 (0.11)	1.70 (0.11)	0.04 (-0.03, 0.11)	0.0359	0.3002
HDL (>5)	50	61 303	37 413	38.50 (5.21)	56.59 (3.68)	16.76 (6.80)	1.52 (0.19)	1.53 (0.20)	0.02 (-0.01, 0.04)	0.0126	0.1882
TG	58	24 365	25 642	42.36 (6.00)	57.14 (4.04)	13.71 (8.35)	1.28 (0.29)	1.57 (0.34)	0.27 (0.22, 0.31)	0.0216	<0.0001
TG (<=5)	9	2754	1852	48.61 (1.05)	50.81 (1.63)	2.04 (1.36)	1.12 (0.32)	1.24 (0.34)	0.14 (0.09, 0.19)	0.0262	<0.0001
TG (>5)	50	21 332	23 729	41.55 (5.91)	57.64 (3.73)	14.90 (7.82)	1.31 (0.28)	1.60 (0.33)	0.29 (0.24, 0.34)	0.0245	<0.0001
TC	56	66 062	41 940	39.19 (5.69)	56.57 (3.50)	15.71 (7.37)	4.77 (0.35)	5.57 (0.46)	0.58 (0.50, 0.65)	0.0397	<0.0001
TC (<=5)	10	3 246	5 452	49.30 (2.07)	54.83 (4.10)	2.82 (1.42)	5.27 (0.60)	6.03 (0.57)	0.52 (0.40, 0.64)	0.0602	<0.0001
TC (>5)	45	62 537	36 427	38.67 (5.16)	56.83 (3.52)	16.84 (6.31)	4.75 (0.30)	5.50 (0.41)	0.59 (0.50, 0.69)	0.0473	<0.0001
LDL	49	63 246	39 176	38.90 (5.71)	56.55 (3.65)	16.01 (7.63)	2.90 (0.25)	3.46 (0.32)	0.45 (0.38, 0.53)	0.0366	<0.0001
LDL (<=5)	8	2 748	5 176	49.55 (2.09)	55.14 (3.91)	3.07 (1.16)	3.12 (0.31)	3.61 (0.25)	0.45 (0.36, 0.53)	0.0453	<0.0001
LDL (>5)	40	60 219	33 939	38.42 (5.14)	56.76 (3.78)	17.10 (6.67)	2.89 (0.24)	3.44 (0.33)	0.47 (0.38, 0.55)	0.0443	<0.0001
TC:HDL	10	1 982	1 803	43.05 (4.67)	58.39 (4.43)	14.85 (7.82)	3.74 (0.24)	4.27 (0.51)	0.39 (0.16, 0.62)	0.1156	0.0008
TC:HDL (<=5)	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Abbreviations: PreM, Premenopausal; PostM, Postmenopausal; HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; TC:HDL, total cholesterol to high-density lipoprotein ratio; k = number of samples; SD, Standard Deviation; CI, Confidence Interval. Note: $p < 0.05$ considered significant. Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. For HDL, TC and LDL, to convert values from SI units (mmol/L) to mg/dl, multiply by 38.67, however, for TG, multiply by 88.57. <= 5; studies that had a mean age difference less than or equal to 5. >5; studies that had a mean age difference greater than 5 years.

Table 3.5: Measures of heterogeneity for cross-sectional studies in subgroup analyses.

Lipid measure	Tau^2 **(SE)**	I^2	H^2	**Q (df)**	**p-value**
HDL	0.0056 (0.0014)	93.34	15.02	840.9972 (58)	<0.0001
HDL (<=5)	0.0085 (0.0055)	90.49	10.51	26.8719 (7)	0.0004
HDL (>5)	0.0058 (0.0015)	94.02	16.72	794.0251 (49)	<0.0001
TG	0.0201 (0.0049)	88.68	8.83	505.7093 (57)	<0.0001
TG (<=5)	0.0026 (0.0028)	55.28	2.24	15.6015 (8)	0.0345
TG (>5)	0.0214 (0.0057)	88.51	8.70	419.7883 (47)	<0.0001
TC	0.0740 (0.0166)	97.09	34.38	1924.7162 (55)	<0.0001
TC (<=5)	0.0275 (0.0168)	90.75	10.81	63.5598 (9)	<0.0001
TC (>5)	0.0848 (0.0211)	97.30	37.00	1574.5317 (44)	<0.0001
LDL	0.0537 (0.0131)	96.41	27.82	1242.8152 (48)	<0.0001
LDL (<=5)	0.0099 (0.0085)	69.73	3.30	25.7254 (7)	0.0006
LDL (>5)	0.0652 (0.0173)	97.26	36.56	1188.8169 (39)	<0.0001
TC:HDL	0.0978 (0.0599)	87.03	7.71	76.4228 (9)	<0.0001
TC:HDL (<=5)	NA	NA	NA	NA	NA

Abbreviations: HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; LDL, low-density lipoprotein; TC:HDL, total cholesterol to high-density lipoprotein ratio; Tau^2, estimated amount of total heterogeneity; SE, standard error; I^2, total heterogeneity divided by total variability; H^2, total variability divided by the sampling variability; Q = Cochrane's Q test; df, degrees of freedom. Note: $p < 0.05$ considered significant. <= 5; studies that had a mean age difference less than or equal to 5. >5; studies that had a mean age difference greater than 5 years.

4 A review of menopause nomenclature

4.1 Abstract

Objectives: Menopause nomenclature varies in the scholarly literature making synthesis and interpretation of research findings difficult. Therefore, the present study aimed to review and discuss critical developments in menopause nomenclature; determine the level of heterogeneity amongst menopause definitions and compare them with the Stages of Reproductive Aging Workshop criteria.

Methods: Definitions/criteria used to characterise premenopausal and postmenopausal status were extracted from 210 studies and 128 of these studies were included in the final analyses.

Results: The main findings were that 39.84% of included studies were consistent with STRAW classification of *premenopause*, whereas 70.31% were consistent with STRAW classification of *postmenopause*. Surprisingly, major inconsistencies relating to premenopause definition were due to a total lack of reporting of any definitions/criteria for premenopause (39.84% of studies). In contrast, only 20.31% did not report definitions/criteria for postmenopause.

Conclusion: There is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. We propose three key suggestions/recommendations, which can be distilled from these findings. Firstly, premenopause should be transparently operationalised and reported. Secondly, as a minimum requirement, regular menstruation should be defined as the number of menstrual cycles in a period of at least 3 months. Finally, the utility of introducing normative age-ranges as supplementary criterion for defining stages of reproductive ageing should be considered. The use of consistent terminology in research will enhance our capacity to compare results from different studies and more effectively investigate issues related to women's health and ageing.

4.2 Introduction

Menopause is a critical stage of female reproductive ageing and health, with important implications relating to fat mass and its distribution (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019), dyslipidemia (Ambikairajah, Walsh, & Cherbuin, 2019) and neurodegeneration (Ambikairajah et al., 2021, 2020). In this context, it is likely that some of the biological changes co-occurring with menopause, contribute to the well-documented higher risk of dementia in women (GBD 2019 Collaborators, 2021), as well as the observed increase in cardiovascular disease whose pattern becomes more similar to that of men at older ages

despite its lower prevalence at younger ages (McAloon et al., 2016; Mikkola et al., 2013). However, the contributions of menopause to health have been historically understudied in the context of ageing (Taylor et al., 2019). For example, over a period of 23 years (1995 to 2017), peer-reviewed neuroimaging articles which focused on menopause only accounted for approximately 2% of the ageing literature (Taylor et al., 2019). There are many possible explanations (including sex biases in research), however, a critical challenge for menopause research has been the operationalisation of menopause nomenclature.

The meaning of *menopause* is widely understood, but often imprecisely defined in research. The standards for defining menopause nomenclature, such as *premenopause* and *postmenopause* vary substantially across publications. Although, the precise extent of this heterogeneity remains to be established - perhaps because the extant literature on this topic may be too large to systematically review - it is clear that such variability across studies makes the synthesis and comparison of findings difficult. In recognition of this issue, there have been a number of attempts by international experts to collaboratively develop a comprehensive standardised set of criteria to describe terminology associated with menopause (Harlow et al., 2007; Harlow et al., 2012; Soules et al., 2001; Utian, 1999; World Health Organization, 1980, 1996). Whilst promising developments have been made in recent decades, a follow-up investigation regarding the frequency and consistency of uptake and use of the proposed criteria have not been adequately investigated. Therefore, the degree to which standardised criteria have been successfully implemented in publications relating to menopause research remains unknown.

To address this gap we have leveraged on our recent systematic review with meta-analysis focused on fat mass differences between premenopausal and postmenopausal women, which included 210 studies consisting of 1,052,391 women, by extracting definitions used to characterise premenopausal and postmenopausal status in a broad cross-section of peer-reviewed literature (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). The present study aims to first review and discuss critical developments in menopause nomenclature, with a particular emphasis placed on the implications that current criteria have for menopause research. Then, to assess the level of heterogeneity in menopause nomenclature identified through our previous systematic review (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). Finally, to contrast the extracted definitions against the Stages of Reproductive Aging Workshop (STRAW) criteria (Harlow et al., 2012; Soules et al., 2001; Utian, 1999).

4.2.1 WHO (1981 - 1999)

According to the more recently established guidelines by a World Health Organization (WHO) "Scientific Group on Research in the Menopause", natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity (World Health Organization, 1980, 1996). Furthermore, natural menopause is deemed to have occurred after 12 consecutive months of amenorrhea, for which no other obvious pathological or physiological causes could be determined. As seen in Figure 4.1, menopause occurs at the final menstrual period (FMP), which can only be known with certainty retrospectively, a year or more after the event. Induced menopause, however, is defined as the cessation of menstruation following either surgical removal of both ovaries (i.e. oophorectomy), or iatrogenic ablation of ovarian function (i.e. chemotherapy or irradiation).

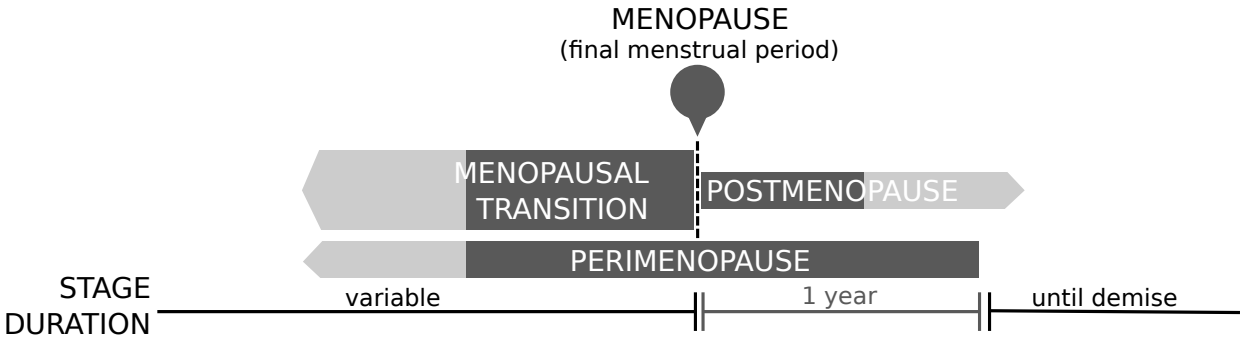

Figure 4.1: Visual representation of the relationship between different time periods surrounding menopause as established by a World Health Organization Scientific Group on Research in the Menopause. Figure is a modification of work found in World Health Organization (1996).

The WHO (1996) highlighted that *premenopause* was often used ambiguously by researchers, either to refer to the 1 or 2 years immediately before menopause or alternatively, to encompass the entire reproductive period up to the FMP, which was the recommended use of the term. Other critical stages defined by the WHO included *postmenopause* (i.e. the period following the FMP regardless of whether menopause was induced or spontaneous); perimenopause (i.e. the period immediately prior to the FMP when endocrinological, biological and clinical features of approaching menopause commence, as well as the first year after menopause); and the menopausal transition (i.e. the period of time before FMP, when variability in the menstrual cycle is usually increased). Finally, it was strongly recommended that the term *climacteric*, which was previously used interchangeably with *perimenopause*, should be abandoned to avoid confusion. However, due to widespread popularity and the prevailing use of the word, *climacteric* was reinstated by The Council of Affiliated Menopause Societies

(CAMS) in 1999 and was defined as a phase which incorporates perimenopause, but extends for a longer variable period before and after perimenopause and marks the transition from the reproductive to non-reproductive states (Figure 4.2) (Utian, 1999).

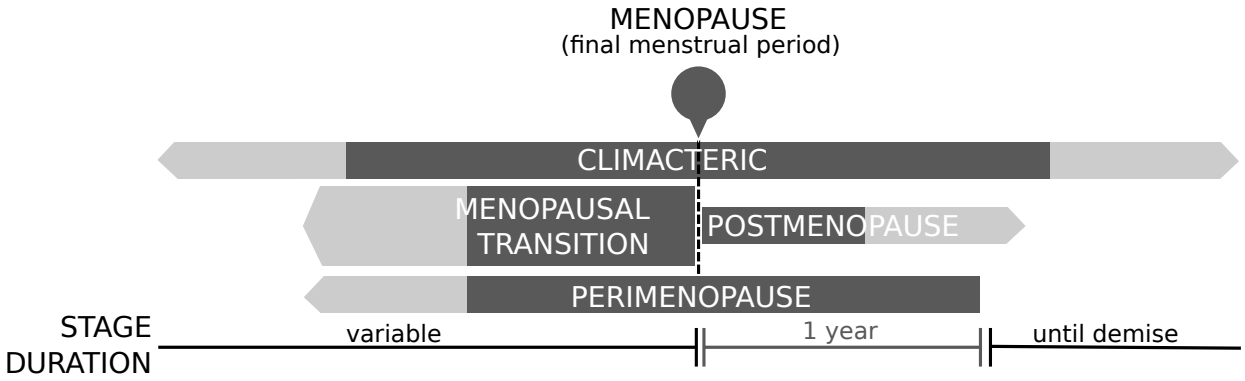

Figure 4.2: Updated visual representation of the relationship between different time periods surrounding menopause, which includes the term *Climacteric* as defined by The Council of Affiliated Menopause Societies. Figure is a modification of work found in Utian (1999).

4.2.2 STRAW (2001)

The nomenclature established thus far facilitated a scientific consensus for describing female reproductive ageing, however, there were still limitations that needed to be addressed. For example, the WHO and CAMS definitions had vague starting points and used terms such as premenopause, perimenopause, menopausal transition and climacteric which, to some extent, had overlapping time periods. This lack of clear, objective criteria to describe the stages of female reproductive ageing led to the Stages of Reproductive Ageing Workshop (STRAW) in 2001. The ensuing STRAW criteria separated the stages of female reproductive ageing into seven distinct segments (Figure 4.3), with a particular focus on healthy women undergoing natural menopause. Furthermore, menstrual cycles, endocrine/biochemical factors, signs/symptoms in other organ systems, and uterine/ovarian anatomy were used to define the stages of female reproductive ageing.

Within the STRAW criteria, menopause is central to the staging system and was labelled as point zero (0). There are five stages preceding the FMP (-5 to -1) and two following it (+1 to +2). Stages -5 to -3 encompassed the Reproductive Interval; -2 to -1 reflected the Menopausal Transition; and +1 to +2 defined Postmenopause (Soules et al., 2001). The menopausal transition (-2 to -1) began with a variation in menstrual cycle length and rise in follicle stimulating hormone (FSH) and ended with the FMP. Early postmenopause (+1) was defined as within 5 years since the FMP and was further subdivided into segments ‘a’; the

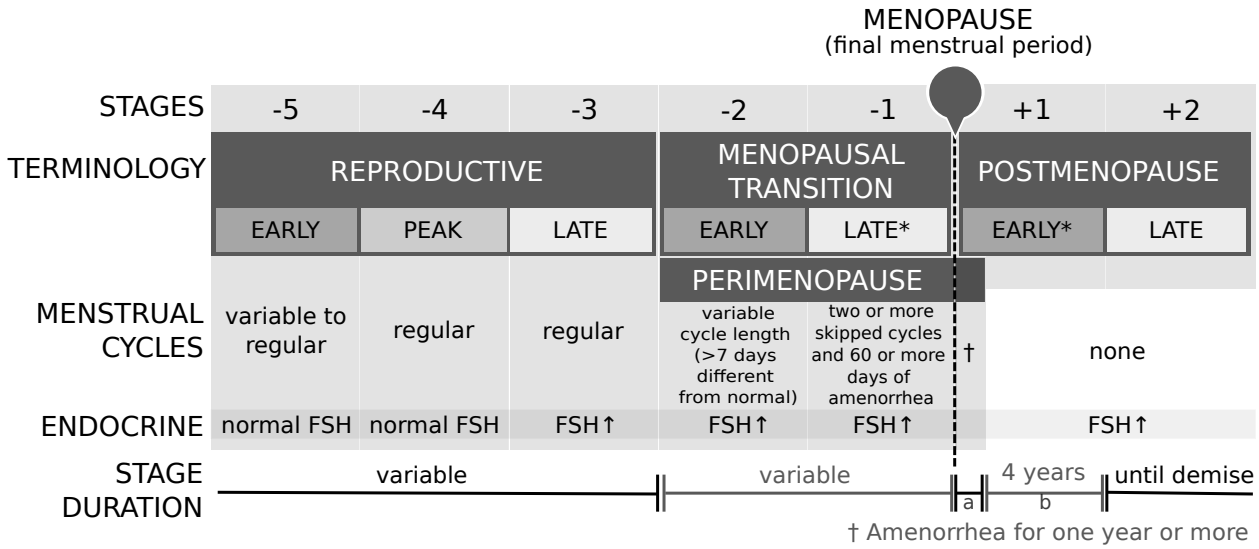

Figure 4.3: STRAW staging system. *Stages most likely to be characterised by vasomotor symptoms; FSH, follicle stimulating hormone; ↑, elevated. Figure is a modification of work found in Soules et al. (2001).

first 12 months after the FMP and 'b'; the following four years. Whereas late postmenopause (+2) was defined as having a variable duration since it ended with a woman's death. Finally, the STRAW criteria defined perimenopause (-2 to +1a) as ending 12 months after the FMP. Furthermore, it was suggested that the terms perimenopause and climacteric should be synonymous in meaning and used with patients or the public, but not in scientific papers, in accordance with the WHO recommendations.

Importantly, the validity and reliability of the STRAW recommendations has been evaluated and was broadly supported by the ReSTAGE Collaboration, which conducted empirical analyses on four cohort studies including the TREMIN study, the Seattle Midlife Women's Health Study, the Study of Women's Health Across the Nation (SWAN) and the Melbourne Women's Midlife Health Project (Harlow et al., 2007; Harlow et al., 2008; Harlow et al., 2006). However, particular limitations have also been noted and modifications to the STRAW criteria were suggested by the ReSTAGE collaboration. In particular, when the STRAW criteria were first established, there was a lack of multiethnic cohort studies available, which limited the generalisability of the staging system to diverse populations (Harlow et al., 2012). Furthermore, the initial STRAW criteria only considered FSH as a biomarker, with relatively little clarification about the precise timing of change in FSH levels or quantitative criteria for FSH, due to insufficient data (Harlow et al., 2012). As a result, the initial STRAW criteria focused primarily on menstrual bleeding patterns and qualitative FSH levels. Other important limitations of the original STRAW criteria included their exclusive applicability to healthy

women, with explicit recommendations against applying the criteria to women who either (i) smoked, (ii) had a BMI greater than $30kg/m^2$ or less than 18 kg/m^2, (iii) engaged in heavy exercise (greater than 10 hours per week of aerobic exercise), (iv) had chronic menstrual cycle irregularity, (v) had a prior hysterectomy, (vi) had abnormal uterine anatomy (e.g. fibroids) or (vii) had abnormal ovarian anatomy (e.g. endometrioma).

4.2.3 STRAW + 10 (2011)

In 2011, the STRAW + 10 criteria (Harlow et al., 2012) were established to reflect significant advances in the field of female reproductive ageing and to provide updated recommendations that addressed certain limitations present in the initial staging criteria.

The STRAW + 10 staging system suggested that the late reproductive stage (-3) should be subdivided into two stages (-3b and -3a) based on menstrual cycle characteristics and FSH levels (Figure 4.4). This was done to recognise subtle changes in menstrual cycle flow and also shorter cycle lengths in stage -3a, in addition to an increased variability in FSH levels (Harlow et al., 2012). Secondly, the new recommendations incorporated the suggestions provided by the ReSTAGE Collaboration, which proposed that more precise menstrual cycle criteria should be used to describe the early (-2) and late (-1) menopausal transition, in addition to the quantification of FSH levels in late menopausal transition (Harlow et al., 2007). Specifically, the early menopausal transition (-2) was discernible from the late reproductive stage (-3a) due to an increased variability in menstrual cycle length (defined as a difference of 7 days or more in length of a menstrual cycle that is persistent i.e. reoccurs within 10 cycles of the first variable length cycle). Furthermore, late menopausal transition (-1) was marked by an interval of amenorrhea greater or equal to 60 days, in addition to an increased FSH level greater than 25 IU/L (Harlow et al., 2007; Harlow et al., 2012). Finally, early postmenopause (+1) was further subdivided into 3 stages (+1a, +1b, +1c) to account for the continual increase in FSH and decrease in estradiol for 2 years after FMP, whereby +1a corresponded with 12 months after FMP i.e. end of perimenopause and +1b referred to the year prior to the stabilisation of high FSH and low estradiol levels (+1c).

The STRAW + 10 staging system has been found to be applicable to most women regardless of age, demographic, body mass index (BMI) or lifestyle characteristics (Harlow et al., 2012). However there are still significant areas of scientific research that need to be prioritised to strengthen future criteria including (i) the use of standardised assays for key biomarkers (e.g. Anti-Mullerian hormone), (ii) further empirical analysis across multiple cohorts to specify menstrual cycle criteria for the late reproductive stage, and (iii) further research aimed at better understanding reproductive ageing in women who have had either the removal of a

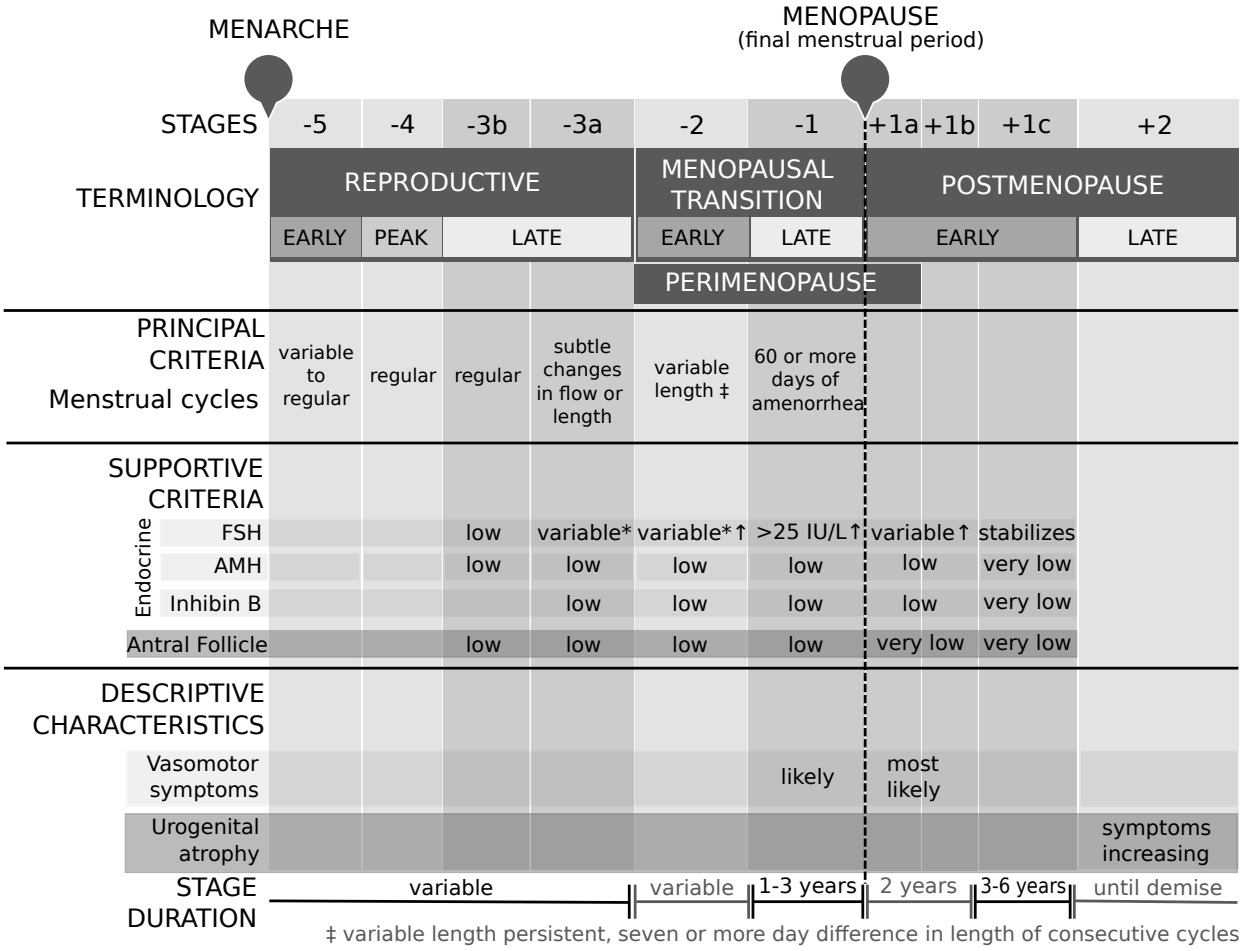

Figure 4.4: STRAW + 10 staging system. $*$, blood drawn on cycle days 2-5; FSH, follicle stimulating hormone; AMH, anti-mullerian hormone; $\uparrow$, elevated. Figure is a modification of work found in Harlow et al. (2012).

single ovary and/or a hysterectomy, chronic illness such as HIV infection, cancer treatment, polycystic ovary syndrome or premature ovarian failure (Harlow et al., 2012). Another critical limitation of the STRAW + 10 criteria is that they do not apply to women who are using exogenous hormones, such as hormone replacement therapy (HRT). Likely because HRT use may confound the accurate classification of women into distinct reproductive stages. This is a key consideration that needs to be appropriately accounted for in studies that are interested in investigating varying outcomes in women at different stages of reproductive ageing.

Despite these limitations, the STRAW criteria has significantly advanced our understanding of women's health and is widely considered the current gold standard for defining terms related to female reproductive ageing. However, the uptake and use of the STRAW criteria in publications relating to menopause research remains unknown and is addressed next.

4.3 Methods

The definitions of premenopausal and postmenopausal women were extracted from the 210 studies (Supplementary Tables 1 and 2) (Abate et al., 2014; Abdulnour et al., 2012; Abildgaard et al., 2013; Adams-Campbell et al., 1996; Agrinier et al., 2010; Aguado et al., 1996; Akahoshi et al., 2001; C. V. Albanese et al., 2009; Allali et al., 2009; Aloia et al., 1995; Amankwah et al., 2013; Amarante et al., 2011; Amiri et al., 2014; Angsuwathana et al., 2007; Armellini et al., 1996; Arthur et al., 2013; Aydin, 2010; Ayub et al., 2006; Bancroft & Cawood, 1996; Bednarek-Tupikowska et al., 2006; Bell et al., 2007; Ben Ali et al., 2011, 2014; Ben Ali et al., 2016; Berg et al., 2004; Berge et al., 1994; Berger et al., 1995; Berstad et al., 2010; Bhagat et al., 2010; Bhurosy & Jeewon, 2013; Blumenthal et al., 1991; Bonithon-Kopp et al., 1990; Caire-Juvera et al., 2008; Campesi et al., 2016; Carr et al., 2000; Castracane et al., 1998; Catsburg et al., 2014; Cecchini et al., 2012; Cervellati et al., 2009; Chain et al., 2017; Chang et al., 2000; Cho et al., 2008; Cifkova et al., 2008; Copeland et al., 2006; Cremonini et al., 2013; Cui et al., 2007; D'Haeseleer et al., 2011; da Câmara et al., 2015; Dallongeville et al., 1995; Dancey et al., 2001; C. E. Davis et al., 1994; De Kat et al., 2017; den Tonkelaar et al., 1990; Dmitruk et al., 2018; Donato et al., 2006; Douchi et al., 1997; Douchi et al., 2002; Douchi et al., 2007; Dubois et al., 2001; Engmann et al., 2017; Ertungealp et al., 1999; Feng et al., 2008; Ford et al., 2005; Formica et al., 1995; Franklin et al., 2009; C. Friedenreich et al., 2007; C. M. Friedenreich et al., 2002; Fu et al., 2011; Fuh et al., 2003; Gambacciani et al., 1999; Genazzani & Gambacciani, 2006; Ghosh, 2008; Ghosh & Bhagat, 2010; Gram et al., 1997; Guerrero et al., 2017; Guo et al., 2015; Gurka et al., 2016; Hadji et al., 2000; Hagner et al., 2009; Han et al., 2006; Harting et al., 1984; He et al., 2012; Hirose et al., 2003; Hjartaker et al., 2005; Ho et al., 2010; Hsu et al., 2006; Hu et al., 2005; Hunter et al., 1996; Iida et al.,

2011; Ilich-Ernst et al., 2002; Ito et al., 1994; Jaff et al., 2015; Janssen et al., 2008; Jasienska et al., 2005; Jeenduang et al., 2014; Jeon et al., 2011; Jurimae & Jurimae, 2007; Kadam et al., 2010; Kang et al., 2016; Kaufer-Horwitz et al., 2005; H. M. Kim et al., 2007; J. H. Kim et al., 2012; S. Kim et al., 2013; Y. M. Kim et al., 2016; Kirchengast et al., 1996, 1998; Knapp et al., 2001; Koh et al., 2008; Konrad et al., 2011; Kontogianni et al., 2004; Konukoglu et al., 2000; Koskova et al., 2007; Kotani et al., 2011; Kraemer et al., 2001; Kuk et al., 2005; Laitinen et al., 1991; Lee et al., 2009; Lejskova et al., 2012; Ley et al., 1992; W. Y. Lin et al., 2005; Lindquist & Bengtsson, 1980; Lindsay et al., 1992; Liu-Ambrose et al., 2006; Lovejoy et al., 2005, 2005; Lyu et al., 2001; Macdonald et al., 2005; Maharlouei et al., 2013; Malacara et al., 2002; Manabe et al., 1999; Manjer et al., 2001; Mannisto et al., 1996; Martini et al., 1997; Marwaha et al., 2013; Matsushita et al., 2003; Matsuzaki et al., 2017; Matthews et al., 1989; Mesch et al., 2006; Meza-Munoz et al., 2006; Minatoya et al., 2014; Mo et al., 2017; Muchanga Sifa et al., 2014; Muti et al., 2000; Nitta et al., 2016; Noh et al., 2013; Nordin et al., 1992; Ohta et al., 2010; Oldroyd et al., 1998; Pacholczak et al., 2016; J.-H. Park et al., 2012; Y. M. Park et al., 2017; Pavlica et al., 2013; Phillips et al., 2008; Polesel et al., 2015; Pollan et al., 2012; Portaluppi et al., 1997; Priya et al., 2013; Rantalainen et al., 2010; Razmjou et al., 2018; Reina et al., 2015; Revilla, Villa, Hernandez, et al., 1997, 1997; Rice et al., 2015; Rico et al., 2001, 2002; Roelfsema & Veldhuis, 2016; Rosenbaum et al., 1996; Salomaa et al., 1995; Sarrafzadegan et al., 2013; Schaberg-Lorei et al., 1990; Schwarz et al., 2007; Shakir et al., 2004; Sherk et al., 2011; Shibata et al., 1979; Sieminska et al., 2006; Skrzypczak et al., 2007; Skrzypczak & Szwed, 2005; Soderberg et al., 2002; Son et al., 2015; Soreca et al., 2009; Soriguer et al., 2009; Staessen et al., 1989; Suarez-Ortegon et al., 2012; Suliga et al., 2016; Sumner et al., 1998; Tanaka et al., 2015; T. Thomas et al., 2000; Torng et al., 2000; Toth et al., 2000; Tremollieres et al., 1996; Trikudanathan et al., 2013; Van Pelt et al., 1998; Veldhuis et al., 2016; F. Wang et al., 2012; W. Wang et al., 2005; W. S. Wang et al., 2012; Wee et al., 2013; P. T. Williams & Krauss, 1997; Wing et al., 1991; Xu et al., 2010; Yamatani et al., 2013; Yannakoulia et al., 2007; Yoldemir & Erenus, 2012; H. J. Yoo et al., 2012; K. Y. Yoo et al., 1998; Yoshimoto et al., 2011; Žeželj et al., 2010; Zhong et al., 2005; J.-L. Zhou et al., 2010; Y. Zhou et al., 2015; Zivkovic et al., 2011) that were eligible for inclusion in the meta-analysis from a previous systematic review, which aimed to identify all peer-reviewed articles reporting on changes in fat mass around menopause (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). Given that the focus of the present study is the relationship between definitions used in the current literature and the STRAW criteria, only studies published four years after the establishment of the STRAW criteria in 2001 (i.e. 2005 onwards) have been included in the analysis. The four-year lag time was implemented to conservatively account for the 'study inception to publication' timeframe, which may have limited the ability for certain studies

published between 2001 and 2005 to effectively implement the STRAW criteria. Similarly, longitudinal studies, which had baseline assessments prior to 2005, were excluded. Therefore, 128 studies were included in the final analyses.

4.3.1 Protocol and registration

The methodology of the initial meta-analyses is reported elsewhere in detail (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019) and was pre-registered in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643).

4.3.2 Search string

The PubMed database was used to conduct a systematic search and retrieve all studies that reported fat mass differences in quantity or distribution between premenopausal and postmenopausal women. The following search string was used: ("adipose tissue" OR "adiposity" OR "subcutaneous fat" OR "obesity" OR "overweight" OR "body weight" OR "body fat distribution" OR "body mass index" OR "BMI" OR "DEXA" OR "DXA" OR "dual energy x-ray absorptiometry" OR "waist to hip ratio" OR "waist-hip ratio" OR "waist circumference" OR "x-ray computed tomography" OR "computed tomography" OR "CT scan" OR "caliper" OR "skinfold" OR "skin fold" OR "abdominal MRI" OR "abdominal magnetic resonance imaging" OR "intra-abdominal fat") AND ("menarche" OR "pre-menopause" OR "premenopause" OR "pre-menopausal" OR "premenopausal" OR "reproductive" OR "menopausal transition") AND ("post-menopause" OR "postmenopause" OR "post-menopausal" OR "postmenopausal" OR "non-reproductive"). PubMed filters were used to exclude non-human and non-English studies. No time restrictions were applied to the literature search, which was conducted in May 2018.

4.3.3 Inclusion and exclusion criteria

Studies that investigated both healthy premenopausal and healthy postmenopausal women were included, whereas studies that (i) exclusively investigated clinical/pathophysiological populations or (ii) had fewer than 40 participants were excluded.

4.3.4 Data extraction

Available definitions/criteria used to describe premenopausal and postmenopausal women were extracted from each study. Where data was missing or unclear, authors were contacted via email to obtain relevant information. All data from included articles was double extracted

by two authors (AA and EW) to avoid transcription errors with any disagreement resolved by consensus.

4.3.5 Quality assessment

The quality of included studies was independently assessed by two authors (AA and EW), using an adapted version of the Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). More information on the quality of included studies can be found in our recent systematic review with meta-analysis (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). In short, the NOS for cohort studies utilised three categories to evaluate individual study quality including (1) the selection of participants, (2) the comparability of groups and (3) the assessment/ascertainment of the outcome of interest. Notably, a clear definition of premenopausal and postmenopausal women was included as a criterion when assessing study quality, specifically for the comparability of groups. Any discrepancy in quality assessment was resolved by consensus. If consensus decisions were not possible a third rater was used.

4.4 Results

The raw extracted definitions for studies are presented in Supplementary Tables 1 and 2. The consistency of definitions with STRAW criteria for included studies is presented in Figure 4.5.

4.4.1 Premenopausal women

4.4.1.1 Cycle regularity A total of 41 studies included the criterion *regular menstruation*, three included *regular menstruation in the last 5 years*, 1 included *regular menstruation in the past 2 years* and 1 included *regular menstruation in the past year*. Therefore, 46 studies (35.94%) were consistent with STRAW classification of premenopause, based on menstrual cycles.

Two studies used *still cycling*, 2 used *no increase in cycle irregularity* and 2 used *no change in flow* when characterising premenopausal women. Cycle regularity was further quantified by the use of cycles per month(s) or cycles per year(s). Three studies included the criteria *one menstruation in the past 33 days*, 2 included *two menstruations in the last 3 months*, 1 included *at least one menstruation in the last 3 months*, 1 included *11 to 13 cycles per year*, 1 included *8 menses in the last year*, 2 included *one menstrual cycle in the last 12 months* and 1 included *one menstrual cycle in the last 2 years*. One study identified premenopause as *the whole reproductive period up until menopause*.

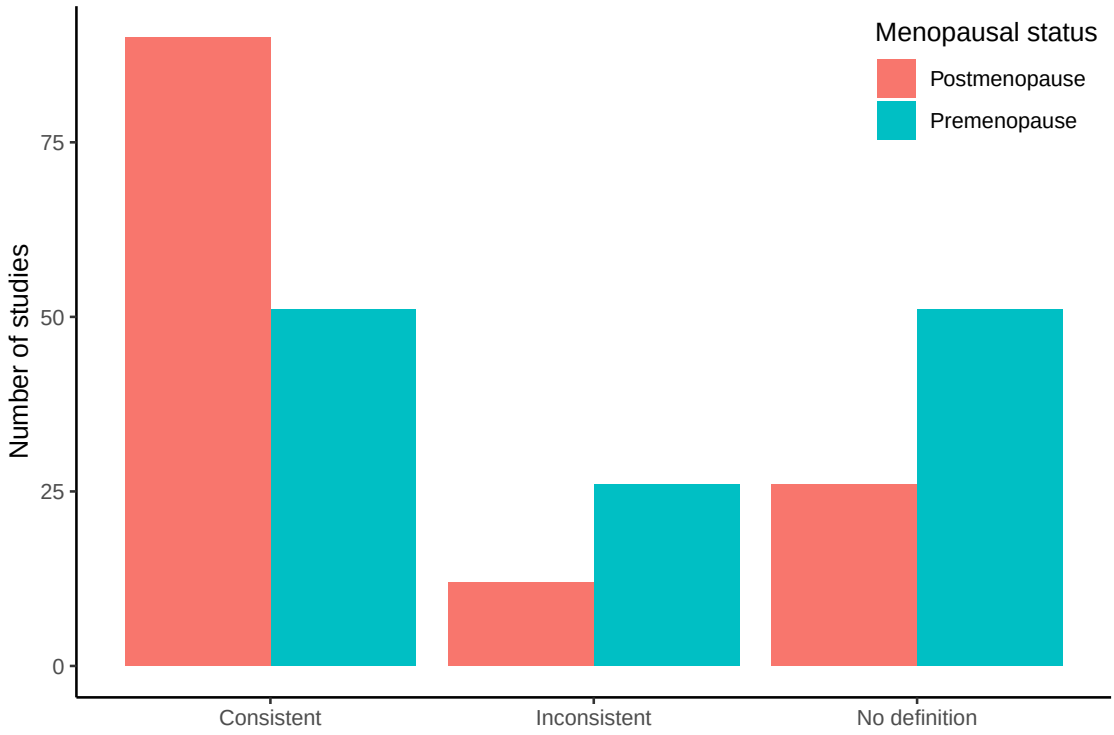

Figure 4.5: Consistency of definitions with STRAW criteria.

4.4.1.2 Hormone levels Six studies 4.69% used FSH levels as one of the criteria, consistent with STRAW classification of premenopause, based on hormone levels. Of these 6 studies, 1 used *regular menstruation* as an additional criterion, whereas the other 5 attempted to quantify cycle regularity. The threshold for FSH levels ranged from less than 20IU/L to less than 40IU/L.

4.4.1.3 Age Four studies included women over a specific age ranging from 40 to 44. However all 4 studies also included other subcategories such as *regular menstruation*. Two studies used age brackets that included *25 to 45*, and *45 to 55*. Ten studies included women who were less than a specific age, which ranged from 35 to 55 years. Of these 3 studies used *age* as the only criterion to define premenopause. One study included *age* as a subcategory of their definition, however, did not define it precisely.

4.4.1.4 Not postmenopausal or pregnant Five studies included *no criteria for postmenopause*, 4 included *no symptoms of menopause*, 4 included *no climacteric complaints*, 3 included *no HRT use* and 3 included *no hysterectomy or ovaries removed* as criteria for categorising premenopause. One study used pregnancy as a criterion for defining premenopause.

4.4.1.5 No definition Of the 128 studies included, 51 (39.84%) did not report definitions/criteria for premenopause.

4.4.2 Postmenopausal women

4.4.2.1 Amenorrhea or the final menstrual period Eighty studies included the criterion *at least 12 months of amenorrhea*, 1 included *less than 2 years from the FMP*, 1 included *1 to 5 years since the FMP*, 1 included *0 to 6 years after the FMP*, 1 included *greater than 1 but less than 7 years of amenorrhea*, 1 included *greater than 2 but less than 7 years amenorrhea* and 2 included *2 years after the FMP*. Therefore, 87 studies (67.97%) were consistent with STRAW classification of postmenopause, based on menstrual cycles.

Two studies included *at least 6 months of amenorrhea* and 1 included *at least 11 months of amenorrhea*. Three studies included the term *no menstrual cycles or periods or no menstrual bleeding* however, further detail regarding the duration of amenorrhea was not provided.

4.4.2.2 Hormone levels Fourteen studies (10.94%) used FSH levels as a criterion, consistent with STRAW classification of postmenopause, based on hormone levels. Of these 11 studies used menstrual criteria consistent with STRAW, 2 used hormonal criterion alone and 1 included *no menstrual bleeding*. For hormone thresholds, of the 14 studies, 8 used the threshold for FSH levels *as greater than 30IU/L* and 2 used *greater than 40 IU/L*. One study did not report FSH thresholds, whereas the remaining 3 studies had FSH levels that included *greater than 20IU/L, greater than 55IU/L* and *between 22 to 138IU/L*. Two studies used estradiol levels with thresholds ranging from *less than 20pg/ml* to *less than 50pg/ml*. One study also used Luteinizing Hormone (LH) levels *greater than 30IU/L*.

4.4.2.3 Natural or surgical menopause Twelve studies specifically stated *natural menopause*, 3 stated *no surgical removal of ovaries and/or uterus* and 2 stated *not due to surgery or any other biological or physiological causes*. Twelve studies included the criteria *bilateral oophorectomy*, 2 included *hysterectomy* and 1 included *cessation of menses induced by surgery*.

4.4.2.4 Age Twelve studies included women over a specific age, ranging from *40 to 55*. Of these 2 studies used age as the only criterion to define postmenopausal women.

4.4.2.5 Hormone replacement therapy Five studies included *women not taking HRT*, whereas 4 studies included *women taking HRT*, and 1 study included *women taking ovarian suppressing drugs or contraception eliminating menstruation*.

4.4.2.6 No definition Of the 128 studies included, 26 (20.31%) did not report any definitions/criteria for postmenopause.

4.5 Discussion

To our knowledge, this review is the first to assess the uptake and use of the STRAW criteria by extracting definitions used to characterise premenopausal and postmenopausal status in a broad cross-section of peer-reviewed literature from our recent systematic review with meta-analysis (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). The main findings were that 39.84% of included studies were consistent with STRAW classification of *premenopause*, whereas 70.31% were consistent with STRAW classification of *postmenopause* (Figure 4.5). Furthermore, 39.84% did not report definitions/criteria for premenopausal women, whereas, 20.31% did not report definitions/criteria for postmenopausal women.

For menstrual cycle variability, 35.94% of studies were consistent with STRAW classification of *premenopause* and 67.97% for *postmenopause*. Notably, STRAW + 10 later distinguished menstrual cycle variability as the most important criteria for the reproductive staging system (Harlow et al., 2012), which is reflective of its use in the literature. For *postmenopause*, the current results reflect a conceptualisation consistent with the STRAW criteria, which require the relationship between the FMP and start of *postmenopause* to be explicitly defined. However, this same level of consistency was not observed for *premenopause*. One possible explanation relates to the term *premenopause* not having been explicitly used in the STRAW criteria (Harlow et al., 2012; Soules et al., 2001). Instead, it is inferred to be synonymous with *reproductive stage*. Given its wide clinical and scientific use, our recommendation is that the transparent operationalisation of *premenopause* may improve the consistency and application of the STRAW criteria (Figure 4.6). Another possibility is the degree of uncertainty regarding the precise meaning of *regular menstruation*. Specifically, 14.29% of studies that defined *premenopause* attempted to quantify regular menstruation as the number of menstrual cycles per days, month(s) or year(s). This uncertainty may reflect a key limitation of the STRAW (Soules et al., 2001) and more recent STRAW + 10 (Harlow et al., 2012) criteria, which principally describe the reproductive period as having *regular menstrual cycles*, with no guidelines provided regarding the interpretation of *regular*. Moreover, previous research has demonstrated the lack of clear clinical definitions for reproductive stages can significantly decrease the accuracy of participant's self-report (Smith-DiJulio et al., 2005). Since menstrual cycles can be skipped due to reasons unrelated to menopause including extreme exercise, pregnancy, weight fluctuations or illness it would be highly preferable if *regular menstruation* was specifically and consistently defined for a defined period. We

recommend that defining regular menstruation as the number of menstrual cycles per 3 months, as a minimum requirement, would be a practical reporting timeframe both clinically and for women to recall accurately (Figure 4.6).

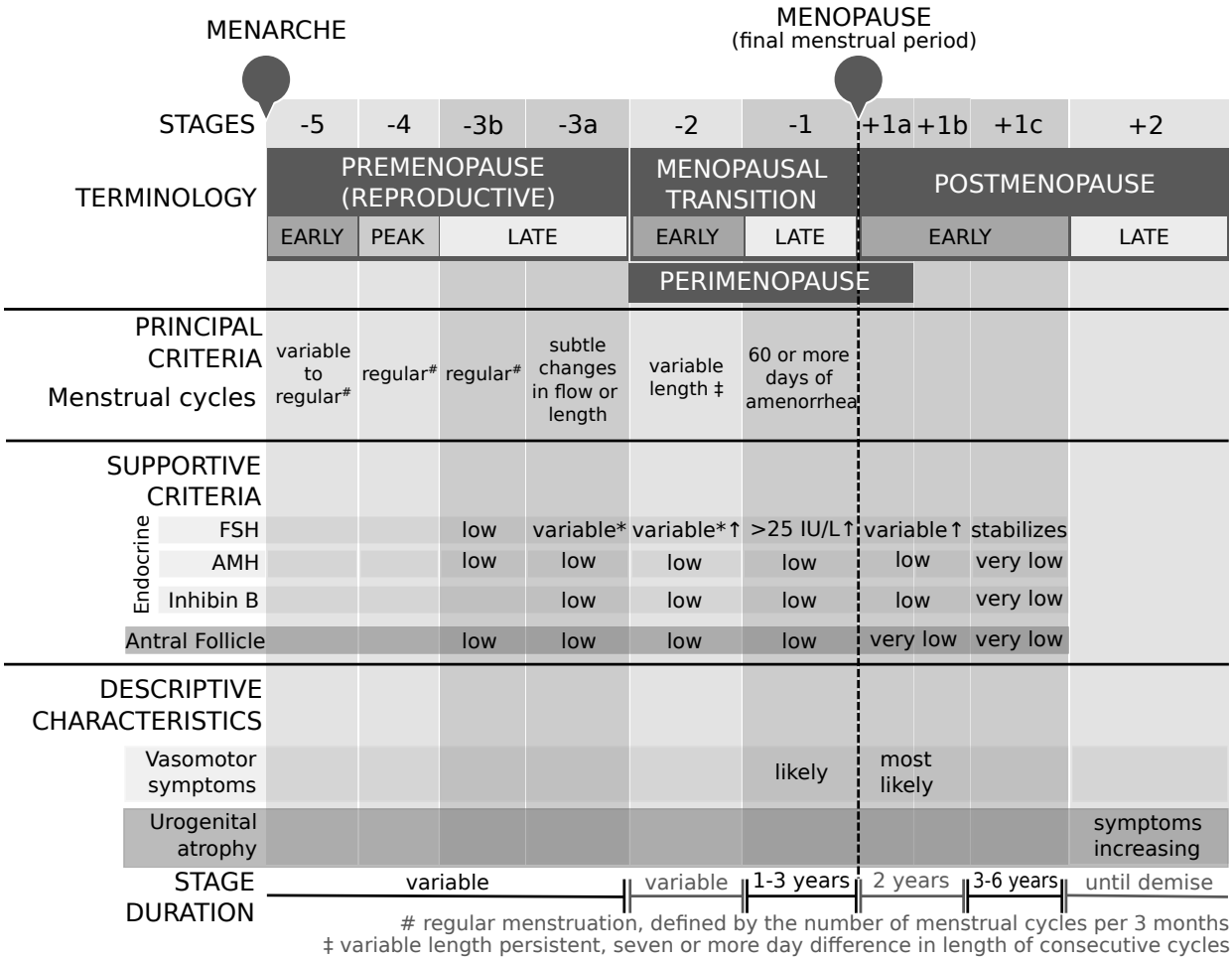

Figure 4.6: Recommended revision to the STRAW + 10 staging system to include the transparent operationalisation of *premenopause* and define *regular menstruation* as the number of menstrual cycles per 3 months, as a minimum requirement, which would be a practical reporting timeframe both clinically and for women to recall accurately. $*$, blood drawn on cycle days 2-5; FSH, follicle stimulating hormone; AMH, anti-mullerian hormone; ↑, elevated. Figure is a modification of work found in Harlow et al. (2012).

For hormone levels, 4.69% of studies were consistent with STRAW classification of premenopause and 10.94% for postmenopause. STRAW + 10 later distinguished hormone levels as a supportive criterion for the reproductive staging system given the lack of international standardisation of biomarker assays as well as their cost and/or invasiveness and inequity across low-socioeconomic countries (Harlow et al., 2012). Notably, Anti-Mullerian hormone (AMH) has emerged as a primary candidate for developing an international standard biomarker

since it is detectable in peripheral circulation (Kevenaar et al., 2006) and does not change in response to an acute endogenous rise in hormones such as FSH and estrogen (de Vet et al., 2002; Feyereisen et al., 2006; van Rooij, 2002). Whilst promising, insights about staging reproductive ageing can also be drawn from research that aims to predict age of menopause. Unsurprisingly, age is a useful predictor of menopausal status (Depmann et al., 2018), given ageing and menopause co-occur (Schoenaker et al., 2014). However, evidence suggests that the combination of hormones, such as AMH and age does not provide a statistically significant improvement to predictions of time to menopause than age alone (Age C-statistic = 84%, 95% CI = 83 to 86%; Age + AMH C-statistic = 86%, 95% CI = 85 to 87%) (Depmann et al., 2018). These findings indicate that there is utility in introducing normative age-ranges as a supplementary criterion for defining stages of reproductive ageing. Compared with the establishment of standardised biomarker assays, the use of normative age-ranges can be done relatively quickly and reliably, using available evidence from multiple large population studies, such as the UK Biobank study (Sudlow et al., 2015). This need is recognised by the number of studies in this review with a definition that has attempted to use age to further clarify menopausal status (Premenopause: 19.48%; Postmenopause: 11.76%). Moreover, the use of age as an additional component of the supportive criteria for determining reproductive stage becomes further evident when women who use HRT or suffer from chronic illness are considered. For example, a systematic review with meta-analysis of randomised controlled trials showed that the incidence of chemotherapy induced amenorrhea is 61% (95% CI: 51 to 68%) for women with breast cancer (Zavos & Valachis, 2016). For these women, the current use of principal criteria, which relies solely on menstrual cycles, is inadequate. This emphasises the urgent need to expand the supportive criteria to ensure STRAW + 10 can be utilised by women using HRT or suffering from chronic illness that impacts menstrual cycles.

Altogether, 33.77% of studies that defined premenopause and 11.76% of studies that defined postmenopause used criteria inconsistent with STRAW criteria. The disproportionate use of additional criteria for defining *premenopause* compared with *postmenopause* is further indication that the term *premenopause* is not precisely and systematically defined by the STRAW criteria. This has prompted researchers to use additional/alternative criteria to achieve clarity. Unfortunately, the consequence of non-standardised criteria is increased heterogeneity, which can lead to the synthesis of imprecise estimates. Moreover, of the 128 included studies, 39.84% did not report definitions/criteria for premenopausal women, whereas, only 20.31% did not report definitions/criteria for postmenopausal women. This difference may reflect a belief that the definition/criteria for premenopausal women is widely understood, with no need for further clarification by authors. However, in the context of the findings presented in this review, it is more likely these trends reflect a poor understanding of

the term *premenopause* compared with *postmenopause*.

4.6 Conclusion

There is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. We propose three key suggestions/recommendations, which can be distilled from these findings. Firstly, premenopause, which is not currently explicitly stated in STRAW or STRAW + 10, should be transparently operationalised and reported. Secondly, as a minimum requirement, regular menstruation should be defined as the number of menstrual cycles in a period of at least 3 months. Finally, the utility of introducing normative age-ranges as supplementary criterion for defining stages of reproductive ageing should be considered. The use of consistent terminology in research will enhance our capacity to compare results from different studies and more effectively investigate issues related to women's health and ageing.

4.7 Supplementary materials

The supplementary materials for Chapter 4 include:

- **Table 4.1** Premenopause definitions.
- **Table 4.2** Postmenopause definitions.

Table 4.1: Premenopause definitions.

Study	Year	Premenopause definition
Abate et al.	2014	Women older than 44 who had regular menstrual cycles
Abdulnour et al.	2012	Two menstruations in the last 3 months, no increase in cycle irregularity in the 12 months before testing and FSH <30IU/L.
Abildgaard et al.	2013	Menstrual bleeding within the last 12 months, and FSH <20IU/L
Adams-Campbell et al.	1996	Unclear
Agrinier et al.	2010	Pregnant, or regular menstruation under 40 years, or irregular menstruation under 40 years, regular menstruation over 40 with no progestin use.
Aguado et al.	1996	Unclear
Akahoshi et al.	2001	Four years before the final menstrual period (FMP), where the FMP is amenorrhea for more than 12 months, except for pregnancy
Albanese et al.	2009	Menstrual histories indicating current and prior menstrual regularity 11 to 13 cycles per year
Allali et al.	2009	Unclear
Aloia et al.	1995	Unclear
Amankwah et al.	2013	Based on age, no hysterectomy, no menopause, no ovaries removed and no symptoms of menopause
Amarante et al.	2011	Regular menstrual cycles and had spontaneous menstrual cycle in the last month
Amiri et al.	2014	Unclear
Angsuwanthana et al.	2007	Women who were older than 40 years and did not have criteria for postmenopausal women
Armellini et al.	1996	Unclear
Arthur et al.	2013	Still menstruating irrespective of the regularities of their menses
Aydin et al.	2010	Women who were not postmenopausal (12 months past final menses), were considered premenopausal
Ayub et al.	2006	Unclear
Bancroft et al.	1996	Regular cycles and there was evidence of ovulation during the month of sampling (plasma progesterone >=10nmol/l) or irregular cycles but had ovulated during the month
Bednarek-Tupikowska et al.	2006	Unclear
Bell et al.	2007	A decision tree including - younger than 55, no stated age at menopause, regulary menstrual bleeding, no use of hormone contraception and FSH levels
Ben-Ali et al.	2016	Unclear
Ben-Ali et al.	2014	Unclear
Ben-Ali et al.	2011	Regular periods in the years preceding their examination

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Berg et al.	2004	Regular cycles
Berge et al.	1994	Cycles were regular
Berger et al.	1995	Regular menstruation, lack of menopausal symptoms and normal gonadotropin levels
Berstad et al.	2010	Women who wee still menstruatingand had not taken any hormone therapy before the reference date
Bhagat et al.	2010	Unchanged and regular menstrual pattern during the last 5 years without typical climacteric complaints
Bhurosy et al.	2013	Having regular menstrual bleeding
Blumenthal et al.	1991	Regular menstrual cycle lengths and had not taken hormones orally in the past year and FSH less than 40
Bonithon-Kopp et al.	1990	Not experienced the menopause and that their last menstrual period had occurred in the last three months
Caire-Juvera et al.	2008	Experiencing a mestrual cycle within the past 12 calandar months or having a FSH level $<$ 22 mIU/ml
Campesi et al.	2016	With regular menstrual cycles (27-29 days)
Carr et al.	2000	No change in the past year in menstrual flow amount, duration or cycle length, as well as no change in regularity since ages 20-35 without hormone use
Castracane et al.	1998	Normal cycling female subjects, with cycle length between 25 and 35 days
Catsburg et al.	2014	Unclear
Cecchini et al.	2012	Women younger than 50
Cervellati et al.	2009	Regular menstrual cycle
Chain et al.	2017	Unclear
Chang et al.	2000	Age less than 48 with regular menstruation
Cho et al.	2008	Unclear
Cifkova et al.	2008	FMP occurred less than 60 days before the interview and FSH $<$ 40IU/L
Copeland et al.	2006	Cycling regularly
Cremonini et al.	2013	Regular menstrual cycle
Cui et al.	2007	Regular menstrual cycle
D'haeseleer et al.	2011	Regular menstrual cycle
Da Camara et al.	2015	Regular menstruation
Dallongeville et al.	1995	Unclear
Dancey et al.	2001	Less than 45 years of age
Davis et al.	1994	Currently have menstrual cycles/periods

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
De Kat et al.	2017	Women with a currently regular menstrual cycle
Den Tonkelaar et al.	1990	Unclear
Dmitruk et al.	2018	Regularly menstruating women
Donato et al.	2006	Women with no change in menstrual flow or frequency
Douchi et al.	1997	Regular menstruation
Douchi et al.	2002	Regular menstruation
Douchi et al.	2007	Unclear
Dubois et al.	2001	Women who were not amenorrhoeic for at least 12 months
Engmann et al.	2017	Self-reported as pre or peri-menopausal or age <= 55
Ertungealp et al.	1999	Unclear
Feng et al.	2008	Regular menstrual period every 21-40 days without significant changes in the past year
Ford et al.	2005	Menstrual cycle in the last 12 months and not using oral contraceptive pill or other hormone products and not pregnant or lactating
Formica et al.	1995	Unclear
Franklin et al.	2009	Unclear
Friedenreich et al.	2007	Regular menses over the past 12 months pr reported using HRT and we under the age of 46
Friedenreich et al.	2002	Based on age, no hysterectomy, no menopause, no ovaries removed and no symptoms of menopause
Fu et al.	2011	Regular menstruation defines as the 25-35 day interval between menstrual on-set
Fuh et al.	2003	Regular menstruation
Gambacciani et al.	1999	Regular menstrual cycle
Genazzani et al.	2006	Regular menstrual cycle
Ghosh et al.	2008	Unchanged and regular menstrual pattern during the last 5 years without typical climacteric complaints
Ghosh et al.	2010	Unchanged and regular menstrual pattern during the last 5 years without typical climacteric complaints
Gram et al.	1997	Unclear
Guo et al.	2015	Women younger than 45 years who had not undergone a bilateral oophorectomy
Gurka et al.	2016	Women who had a menstrual period in the past 2 years but denied current menopause
Hadji et al.	2000	Women with regular periods in the year preceding their examination and/or had a serum FSH of <30IU/L and a serum estradiol of >10pg/ml
Hagner et al.	2009	FMP less than 60 days

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Han et al.	2006	Unclear
Harting et al.	1984	Not having menses due to hysterectomy without bilateral oophorectomy younger than age 40 or due to lactation
He et al.	2012	Having regular menstrual cycles during recent one year and time since their last menstruation was less than 33 days
Hirose et al.	2003	Unclear
Hjartaker et al.	2005	All women who did not report natural menopause or bilateral oophorectomy at enrolment were considered premenopausal regardless of age, hysterectomy or use of hormonal replacement therapy until they reached the age of 50, at which time they were considered postmenopausal
Ho et al.	2010	No change in menstruation pattern
Hsu et al.	2006	Unclear
Hu et al.	2016	Unclear
Hunter et al.	1996	Unclear
Iida et al.	2011	Unclear
Ilich-Ernst et al.	2002	Unclear
Ito et al.	1994	Normal and regular menstrual cycle
Jaff et al.	2015	STRAW: Regular menstrual cycle and/or with subtle changes to flow or length
Janssen et al.	2008	Bleeding in the last month
Jasienska et al.	2005	Unclear
Jeenduang et al.	2014	Unclear
Jeon et al.	2011	The women said that they were premenopausal
Jurimae et al.	2007	Regular menstrual periods
Kadam et al.	2010	Women above 40 years of age with regular menstruation
Kang et al.	2016	Unclear
Kaufer-Horwitz et al.	2005	Menstrual cycles are regular (25-28 x3) and without any recent changes
Kim et al.	2007	Unclear
Kim et al.	2012	Unclear
Kim et al.	2013	Unclear
Kim et al.	2016	Unclear
Kirchengast et al.	1996	Regular menstrual cycles

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Kirchengast et al.	1998	Regular and probably ovulatory menstrual cycles and E2 >25pg/ml and FSH levels <40 mIV/ml typical of the fertile phase of life
Knapp et al.	2001	Unclear
Koh et al.	2008	Not experiencing menopause on the basis of regularity of menstrual cycles
Konrad et al.	2011	Unclear
Kontogianni et al.	2004	Unclear
Konukoglu et al.	2000	Unclear
Koskova et al.	2007	All of the reproductive years before the onset of menopause i.e. before the cessation of reproductive functions, but with the first endocrine signs of climacterium which start around the age of 40
Kotani et al.	2011	Unclear
Kraemer et al.	2001	Unclear
Kuk et al.	2005	Unclear
Laitinen et al.	1991	Unclear
Lee et al.	2009	Have at least one menstrual period within the 3 months before enrollment
Lejskova et al.	2012	Less than 33 postmenstrual days
Leon-Guerrero et al.	2017	Women who were still menstruating at the reference date
Ley et al.	1992	Regular menstrual cycles and no menopausal symptos
Lin et al.	2006	Unclear
Lindquist et al.	1980	Those who had menstruations during the last month
Lindsay et al.	1992	Unclear
Liu-Ambrose et al.	2006	Menstruation occurred in the last 12 months
Lovejoy et al.	2008	Unclear
Lyu et al.	2001	Unclear
Macdonald et al.	2005	Regular menses
Maharlouei et al.	2013	The entire period of a women's life between menarche and perimenopause (menopausal transition) and terminates with the commencement of menopause
Malacara et al.	2002	Women with regular cycles
Manabe et al.	1999	Unclear
Manjer et al.	2001	No cessation of menses and no hormonal medication use

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Mannisto et al.	1996	Unclear
Martini et al.	1997	Unclear
Marwaha et al.	2013	Women <= 50
Matsushita et al.	2003	Regular menstrual cycling
Matsuzaki et al.	2017	Unclear
Matthews et al.	1989	Menstrual bleeding within the three previous months
Mesch et al.	2006	Women with regular cycles
Meza-Munoz et al.	2006	Women 25-45 years of age, with normal regular cycles and without hormone contraception
Minatoya et al.	2014	Unclear
Mo et al.	2017	Unclear
Muchanga et al.	2014	Women who reported unchanged or irregular menstrual pattern
Muti et al.	2000	Unclear
Nitta et al.	2016	Unclear
Noh et al.	2013	Not postmenopausal
Nordin et al.	1992	Unclear
Ohta et al.	2010	Unclear
Oldroyd et al.	1998	Unclear
Pacholczak et al.	2016	Unclear
Park et al.	2012	Unclear
Park et al.	2017	Still cycling, hysterectomy, ablation, or embolization, and <55 years old.
		Ovarian suppressing drugs or contraception that eliminated menstrual flow and <55 years of age
Pavicic et al.	2010	Women with regular periods
Pavlica et al.	2013	Unclear
Phillips et al.	2008	Unclear
Polesel et al.	2015	Ongoing menstrual cycle
Pollan et al.	2012	Regular menstruation
Portaluppi et al.	1997	Regular menstrual periods and serum FSH <50
Priya et al.	2013	Unclear
Rantalainen et al.	2010	Women below 35 years of age and assumed to be premenopausal

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Razmjou et al.	2018	Two menstruations in the last 3 months, no increase in cycle irregularity in the 12 months before testing and FSH <30IU/L
Reina et al.	2015	Unclear
Revilla et al.	1997	Menstrual histories indicated current and prior menstrual regularity 11-13 cycles per year
Revilla et al.	1997	Menstrual histories indicated current and prior menstrual regularity 11-13 cycles per year
Rice et al.	2015	Women who stated that they had not undergone menopause
Rico et al.	2001	Menstrual histories indicated current and prior menstrual regularity 11-13 cycles per year
Rico et al.	2002	Menstrual histories indicated current and prior menstrual regularity 11-13 cycles per year
Roelfsema et al.	2016	Regular periods
Rosenbaum et al.	1996	Menstruating regularly
Salomaa et al.	1995	Regular menstrual cycles
Sarrafzadegan et al.	2013	Unclear
Schaberg-Lorei et al.	1990	Unclear
Schwarz et al.	2007	WHO definition i.w. whole reproductive period up until menopause
Shakir et al.	2004	Women who still had regular menstruation
Sherk et al.	2011	Unclear
Shibata et al.	1979	Unclear
Sieminska et al.	2006	Regular menstrual cycles
Skrzypczak et al.	2005	Women who were menstruating
Skrzypczak et al.	2007	Women who were menstruating
Soderberg et al.	2002	Regular menstruation
Son et al.	2015	Regular menstrual periods
Soreca et al.	2009	Had menstruated in the previous 3 months
Soriguer et al.	2009	Unclear
Staessen et al.	1989	Unclear
Suarez-Ortegon et al.	2012	Unclear
Suliga et al.	2016	Unclear
Sumner et al.	1998	Unclear
Tanaka et al.	2015	Regular menstruation

Table 4.1: Premenopause definitions. *(continued)*

Study	Year	Premenopause definition
Thomas et al.	2000	Unclear
Torng et al.	2000	Unclear
Toth et al.	2000	The occurrence of two menses in the 3 months preceding testing, no increase in cycle irregularity in the 12 months preceeding testing and FSH < 30
Tremollieres et al.	1996	Unclear
Trikudanathan et al.	2013	Unclear
Van-Pelt et al.	1998	Normal or regular menstruation
Veldhuis et al.	2016	Unclear
Wang et al.	2012	Unclear
Wang et al.	2006	Unclear
Wang et al.	2012	45 <= age <= 55
Wee et al.	2013	Women with regular menses during the 2 years preceeding recruitment into the study
Williams et al.	1997	12-50 year olds having periods
Wing et al.	1991	Menstruated in the past 3 months
Xu et al.	2010	Regular menstruation without significant variation between the menses or in the number of days of menstrual bleeding in each period over the course of the preceeding year
Yamatani et al.	2013	Unclear
Yannakoulia et al.	2007	Regular menses
Yoldemir et al.	2012	Any women with more than 8 menses in the last year were considered to be premenopausal
Yoo et al.	2012	Unclear
Yoo et al.	1998	Regular menstrual cycle
Yoshimoto et al.	2011	Unclear
Zhong et al.	2005	Unclear
Zhou et al.	2010	Regular menstruation
Zhou et al.	2015	Unclear
Zivkovic et al.	2011	Unclear

Table 4.2: Postmenopause definitions.

Study	Year	Postmenopause definition
Abate et al.	2014	Women whose menstrual cycles had stopped for at least 2 years, but no more than 7 years
Abdulnour et al.	2012	Based on the final menstrual period and confirmed by 12 months of amenorrhea
Abildgaard et al.	2013	Based on the final menstrual period and confirmed by 12 months of amenorrhea and FSH >20IU/L
Adams-Campbell et al.	1996	Unclear
Agrinier et al.	2010	Based on the final menstrual period and confirmed by 12 months of amenorrhea
Aguado et al.	1996	Unclear
Akahoshi et al.	2001	Two years after the final menstrual period
Albanese et al.	2009	One to five years since menopause (greater than 12 months from their last menstrual bleeding)
Allali et al.	2009	Unclear
Aloia et al.	1995	Unclear
Amankwah et al.	2013	Stopped menstruation for 1 year and age was 50 or more
Amarante et al.	2011	One year or more of amenorrhea after the age of 40 years
Amiri et al.	2014	Time of cessation of menstrual periods for 12 consecutive months, not due to surgery or any other biological or physiological causes
Angsuwanthana et al.	2007	Women with bilateral oophorectomy, for hysterectomised women without bilateral oophorectomy (FSH >40) and for natural menopause,if younger than 45 the women had amenorrhea for greater than 1 year and FSH > 40 and if older than 45 years, the women had amenorrhea for >1 year
Armellini et al.	1996	Unclear
Arthur et al.	2013	Ceased menstruation for at least one year
Aydin et al.	2010	12 months past final menses
Ayub et al.	2006	Unclear
Bancroft et al.	1996	Women whose last menopausal period occurred more than 12 months previously
Bednarek-Tupikowska et al.	2006	Unclear
Bell et al.	2007	A decision tree including - older than 55, a stated age at menopause, no menstrual bleeding, potential use of hormone contraception and FSH levels
Ben-Ali et al.	2016	Women with natural menopause whose current age was >= 1 year from the final menstrual period and who did not receive hormone replacement therapy
Ben-Ali et al.	2014	Women with natural menopause whose current age was >= 1 year from the final menstrual period and who did not receive hormone replacement therapy

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Ben-Ali et al.	2011	At least 12 consecutive months of amenorrhea with no other medical cause
Berg et al.	2004	At least 1 year of spontaneous amenorrhea
Berge et al.	1994	Natural menopause occurred at least one year ago
Berger et al.	1995	Spontaneously postmenopausal with secondary amenorrhea for a minimum of 6 months, elevated gonadotropin levels and reduced oestrogen levels
Berstad et al.	2010	FMP occurred >12 months before the reference date and had not used hormone therapy before or during the 12month interval after the FMP, or if she had undergone bilateral oophorectomy
Bhagat et al.	2010	Reporting last menses to be at least 12 months previously (i.e. no menstruation for at least 1 year)
Bhurosy et al.	2013	Those who had their last menstrual bleeding at least one year before
Blumenthal et al.	1991	No menses in the 12 months prior to participating in the study and had FSH levels greater than 40
Bonithon-Kopp et al.	1990	Passed the menopause and their periods has stopped spontaneously more than three months before examination
Caire-Juvera et al.	2008	No menstrual cycle within the past 12 months or FSH level between 22 and 138 mIU/mL
Campesi et al.	2016	At least 1 year without menstrual cycle
Carr et al.	2000	12 months with no bleeding or spotting after age 35, not due to use of exogenous hormones
Castracane et al.	1998	Unclear
Catsburg et al.	2014	Unclear
Cecchini et al.	2012	Women who reported that both of her ovaries were removed or if she indicated that her menstrual periods had stopped for at least 12 months
Cervellati et al.	2009	Amenhorrea for longer than 11 months
Chain et al.	2017	Cessation of natural menses for >= 12 months
Chang et al.	2000	Amenorrhea greater than 12 months duration
Cho et al.	2008	Absence of menses for 12 consecutive months
Cifkova et al.	2008	FMP had occurred more than 365 days before the interview with FSH levels > 40IU/L
Copeland et al.	2006	One year of menses cessation and FSH levels >30 mIU/ml
Cremonini et al.	2013	Periods of amenorrhea longer than 12 months
Cui et al.	2007	At least 12 months of amenorrhea resulting from the permanent cessation of ovarian function
D'haeseleer et al.	2011	12 consecutive months of amenorrhea
Da Camara et al.	2015	Absence of menses for over one year

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Dallongeville et al.	1995	No menstruation during the 12 months before examination
Dancey et al.	2001	More than 55 years of age
Davis et al.	1994	No menstrual cycles or periods
De Kat et al.	2017	Date of last menstruation was more than 1 year before the visit
Den Tonkelaar et al.	1990	Menstruation had stopped spontaneously more than 12 months before
Dmitruk et al.	2018	Menostasis was longer than 12 months
Donato et al.	2006	Women presenting with 12 months or more of amenorrhea, or as a result of medical interventions, such as bilateral oophorectomy
Douchi et al.	1997	Unclear
Douchi et al.	2002	No menstruation for 12 months before the investigation
Douchi et al.	2007	No menstruation for 12 months before the investigation
Dubois et al.	2001	Women who were amenorrhoeic for at least 12 months
Engmann et al.	2017	Self-reported as postmenopausal (natural or both ovaries removed), or age 55+ or current HRT use
Ertungealp et al.	1999	Unclear
Feng et al.	2008	Menstruation stopped for at least 12 months
Ford et al.	2005	Absence of a menstrual bleed for a 12-month period or a history of bilateral oophorectomy
Formica et al.	1995	Unclear
Franklin et al.	2009	No menses for 1 year
Friedenreich et al.	2007	Not having had any menses over the past 12 months or if they had a bilateral oophorectomy or if they were using HRT and over the age of 55
Friedenreich et al.	2002	Stopped menstruation for 1 year and age was 50 or more
Fu et al.	2011	Complete natural cessation of menses for more than 12 months
Fuh et al.	2003	No menstruation within the previous 12 months
Gambacciani et al.	1999	No menstruation for 6 or more months prior to the study
Genazzani et al.	2006	No menstruation for 6 or more months prior to the study
Ghosh et al.	2008	Reporting last menses to be at least 12 months previously (i.e. no menstruation for at least 1 year)
Ghosh et al.	2010	Reporting last menses to be at least 12 months previously (i.e. no menstruation for at least 1 year)
Gram et al.	1997	Stopped menstruation for at least 1 year
Guo et al.	2015	Women older than 53 years at recruitments and/or had had both ovaries removed were categorized as postmenopausal

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Gurka et al.	2016	Women who had not had a period in the past 2 years and did not have durgical removal of ovaries or uterus
Hadji et al.	2000	Women with a hysterectomy and bilateral oophorectomy and/or no menstrual periods in the year preceding their examination and/or a serum FSH level of <10pg/ml
Hagner et al.	2009	FMP more than 365 days before examination
Han et al.	2006	Menses had ceased permanently and naturally or bilateral oophorectomy, hysterectomy without the removal of ovaries and older than 50
Harting et al.	1984	Unclear
He et al.	2012	Menstruation had naturally stopped for at least one year without bilateral oophorectomy, simple hysterectomy, hormone therapy or currently pregnant
Hirose et al.	2003	Unclear
Hjartaker et al.	2005	Only women who reported natural menopause or bilateral oophorectomy or over the age of 50
Ho et al.	2010	At least 12 months since the last menses
Hsu et al.	2006	Unclear
Hu et al.	2016	Unclear
Hunter et al.	1996	Absence of menses for one year
Iida et al.	2011	Unclear
Ilich-Ernst et al.	2002	Unclear
Ito et al.	1994	Absence of menstrual period for at least 6 months
Jaff et al.	2015	STRAW: 0-6 years after the final menstrual period
Janssen et al.	2008	Bleeding was more than 12 months ago
Jasienska et al.	2005	Unclear
Jeenduang et al.	2014	Absence of menstruation for a preceding 12 months minimum
Jeon et al.	2011	Cessation of menstruation for at least 1 year
Jurimae et al.	2007	Postmenopausal for >1 year but <7 years
Kadam et al.	2010	Permanent cessation of menstrual periods that occurs naturally or is induced by surgery in accordance with the definition by WHO
Kang et al.	2016	Unclear
Kaufer-Horwitz et al.	2005	>12 months of amenorrhea
Kim et al.	2007	A woman with natural menopause whose current age was >= 1 year than her age of menopause who did not receive HRT

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Kim et al.	2012	Unclear
Kim et al.	2013	Cessation of menstruation for at least 1 year, with a FSH level greater than 30
Kim et al.	2016	Unclear
Kirchengast et al.	1996	Menopause had occurred spontaneously
Kirchengast et al.	1998	Spontaneous menstrual bleeding had occurred at least 1 year before the investigation with estradiol <25pg/ml and FSH >40miV/ml
Knapp et al.	2001	Unclear
Koh et al.	2008	Had menses >1 year before the study
Konrad et al.	2011	Cessation of menses for at least 12 consecutive months
Kontogianni et al.	2004	Absence of menses for more than 6 months and by elevated serum FSH levels (FSH>40 U/L)
Konukoglu et al.	2000	Absence of menstruation for at least 6 months and a serum concentration of FSH of >40 IU/ml
Koskova et al.	2007	The last physiological endometrial bleeding and can be assessed retrospectively after 1 year of absence of bleeding
Kotani et al.	2011	Cessation of menses for a period of 12 months or longer
Kraemer et al.	2001	Unclear
Kuk et al.	2005	Unclear
Laitinen et al.	1991	Unclear
Lee et al.	2009	The lack of menstrual periods for at least 12 consecutive months
Lejskova et al.	2012	More than 365 postmenstrual days
Leon-Guerrero et al.	2017	Women whose most recent preiod was more than 12 months before the reference date
Ley et al.	1992	Amenorrhea and elevated gonadotrophin concentrations
Lin et al.	2006	Menopause is defined as the absence of menstruation for 12 consecutive months, which is not due to surgical resection of the uterus or ovaries
Lindquist et al.	1980	Those who had no menstruation during a period fo >= 6 months before the study
Lindsay et al.	1992	Unclear
Liu-Ambrose et al.	2006	No menstruation had occurred in the last 12 months
Lovejoy et al.	2008	No menstrual cycles in the past year and FSH>30mIU/ml
Lyu et al.	2001	Having no menstrual bleeding for >= 1year
Macdonald et al.	2005	Women who had ceased menstruating for at least 1 year and had never taken HRT
Maharlouei et al.	2013	The cessation of menses for a minimum of 12 months and encompasses the entire period in a

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
		women's life that takes place after her last period (menopause)
Malacara et al.	2002	Women with previous regular cycles, without menses in previous 12 months
Manabe et al.	1999	Unclear
Manjer et al.	2001	Women whose menses have ceased or are taking HRT
Mannisto et al.	1996	Unclear
Martini et al.	1997	No menstrual bleeding for at least 6 months preceeding
Marwaha et al.	2013	Woman >= 50
Matsushita et al.	2003	Unclear
Matsuzaki et al.	2017	Unclear
Matthews et al.	1989	Stopped menstruating for at least 12 months
Mesch et al.	2006	Women with 1 year of spontaneous amenorrhea
Meza-Munoz et al.	2006	Women older than 48 with at least 1 year since their last menses, with previously regular cycles
Minatoya et al.	2014	Unclear
Mo et al.	2017	Unclear
Muchanga et al.	2014	Women who reported their last menses to be at least 12 months prior to this study
Muti et al.	2000	The absence of menstrual bleeding for at least 12 months
Nitta et al.	2016	Unclear
Noh et al.	2013	No menstruation for the last 12 months and met one of the following conditions: (1) reported natural menopause, (2) received bilateral oophorectomy, (3) had ever taken HRT, (4) had an FSH level >30 or (5) was older than 55
Nordin et al.	1992	Unclear
Ohta et al.	2010	Unclear
Oldroyd et al.	1998	Unclear
Pacholczak et al.	2016	No menses for 12 months or bilateral oophorectomy or hysterectomy
Park et al.	2012	Unclear
Park et al.	2017	No menstrual periods in the last 12 months or had both ovaries removed, chemotherapy/radiation that stopped periods, hysterectomy, ablation, or embolization and >55 years of age, ovarian suppressing drugs or contraception that eliminated menstrual flow and >=55 years of age
Pavicic et al.	2010	One year of amenorrhoea
Pavlica et al.	2013	Unclear

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Phillips et al.	2008	Absence of menstruation for at least one year
Polesel et al.	2015	Amenorrhea for more than 1 year and FSH and LH concentrations higher than 30l
Pollan et al.	2012	Absence of menstruation in the last 12 months
Portaluppi et al.	1997	Women with last menstrual period at least 12 months before they entered and FSH >50
Priya et al.	2013	At least 1 year of cessation of menses
Rantalainen et al.	2010	Self-report
Razmjou et al.	2018	Based on the final menstrual period and confirmed by 12 months of amenorrhea.
Reina et al.	2015	Unclear
Revilla et al.	1997	No menstrual periods for at least 12 months
Revilla et al.	1997	No menstrual periods for at least 12 months
Rice et al.	2015	Women who had undergone menopause defined as the permanent cessation of periods for more than 12 months
Rico et al.	2001	No menstrual period for at least 12 months and serum FSH levels >30
Rico et al.	2002	No menstrual period for at least 12 months and serum FSH levels >30
Roelfsema et al.	2016	Based on medical history and FSH >30
Rosenbaum et al.	1996	No menstruation for at least 7 years
Salomaa et al.	1995	No menstrual cycles
Sarrafzadegan et al.	2013	Unclear
Schaberg-Lorei et al.	1990	Unclear
Schwarz et al.	2007	12 consecutive months of amenorrhea and is not due to causes and procedures such as hysterectomy that would be associated with cessation of menses
Shakir et al.	2004	Women whose menstruation had ceased more than 12 months ago
Sherk et al.	2011	Unclear
Shibata et al.	1979	Unclear
Sieminska et al.	2006	Amenorrhoea for at least 1 year
Skrzypczak et al.	2005	Women whose last menstruation occurred earlier than 12 months before the participation of the study
Skrzypczak et al.	2007	Women whose last menstruation occurred earlier than 12 months before the participation of the study
Soderberg et al.	2002	More than 6 months since last menstruation
Son et al.	2015	The period after 12 consecutive months of amenorrhea

Table 4.2: Postmenopause definitions. *(continued)*

Study	Year	Postmenopause definition
Soreca et al.	2009	Unclear
Soriguer et al.	2009	6 months of amenorrhea
Staessen et al.	1989	Definitive cessation of periods or cessation of periods following a gynecological operation
Suarez-Ortegon et al.	2012	Unclear
Suliga et al.	2016	Women with amenorrhea for at least 12 months
Sumner et al.	1998	Women who had not menstruated for 1 year OR women with hysterectomy IF she was older than 55
Tanaka et al.	2015	Absence of menstruation for the last 2 years
Thomas et al.	2000	Documented bilateral oophorectomy or a duration longer than 6 months without a menstrual period
Torng et al.	2000	Women with secondary amenorrhea of at least 1 year
Toth et al.	2000	Absence of menses for at least 6 months and a FSH level >30
Tremollieres et al.	1996	Amenorrhea of >=6 months and estradiol <20 and FSH > 30
Trikudanathan et al.	2013	Periods stopped for 1 year or more
Van-Pelt et al.	1998	FSH >30 and absence of menses
Veldhuis et al.	2016	FSH >30 and E2 <50pg/ml
Wang et al.	2012	Unclear
Wang et al.	2006	No menses for at least 12 months
Wang et al.	2012	Age >= 55
Wee et al.	2013	Cessation of menses for at least 12 months prior to the study
Williams et al.	1997	>= 40 years old and not having periods
Wing et al.	1991	Stopped menstruating for at least 12 months, did not have surgical menopause or HRT in the last year
Xu et al.	2010	Have not experienced any menstrual flow for a minimum of 12 months and FSH >30
Yamatani et al.	2013	Amenorrhea for at least 12 months, and FSH > 30 and E2 lower than 20
Yannakoulia et al.	2007	Women who had ceased menstruating for at least 12 months
Yoldemir et al.	2012	Absence of menstruation for the preceeding 12 months or more
Yoo et al.	2012	At least 12 months of amenorrhea resulting in permanent cessation of ovarian function
Yoo et al.	1998	Women whose last menstrual cycle occurred at least six months prior to the survey and aged over 35
Yoshimoto et al.	2011	Unclear
Zhong et al.	2005	Unclear

Table 4.2: Postmenopause definitions. *(continued)*

Study	**Year**	**Postmenopause definition**
Zhou et al.	2010	Having 12 consecutive months of amenorrhea with no other causes
Zhou et al.	2015	Women who reported menses had ceased for 1 year or more
Zivkovic et al.	2011	Women less than 2 years from menopause, where menopause is 12 months of amenorrhea

5 Longitudinal changes in fat mass and the hippocampus

5.1 Abstract

Objectives: To investigate cross-sectional and longitudinal associations between fat mass (i.e. body mass index [BMI], waist circumference [WC] and waist-to-hip ratio [WTHR]) and hippocampal volumes.

Methods: UK Biobank participants (n = 20,395) aged 40-70 (mean follow-up = 7.66 years), were included and categorised into one of four groups, which represented their baseline fat mass status and trajectory of change by follow-up assessment: normal to overweight/obese (NO), overweight/obese to normal (ON), normal stable (NS) or overweight/obese stable (OS). Regression models used NS (WC: $<$ 80 cm in women and $<$ 94 cm in men; WTHR: $<$ 0.85 in women and $<$ 0.90 in men and BMI: $<$ 25 kg/m^2 in women and men), as the reference group. Hippocampal volumes were automatically segmented using FMRIB Software Library.

Results: Compared to NS, OS (BMI: β = -62.23, standard error [SE] = 16.76; WC: β = -145.56, SE = 16.97 and WTHR: β = -101.26, SE = 19.54) and ON (BMI: β = -61.1, SE = 30.3; WC: β = -93.77, SE = 24.96 and WTHR: β = -69.92, SE = 26.22) had significantly lower hippocampal volumes.

Conclusions: The detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

5.2 Introduction

The prevalence of overweight and obesity has accelerated in recent decades, with current global estimates indicating that the proportion of adults with a body mass index (BMI) greater than 25 kg/m^2 (i.e. overweight) is one in three (M. Ng et al., 2014; Stevens et al., 2012). These findings are of particular importance within the context of our globally ageing population given that previous research has demonstrated that, in addition to being associated with a number of unfavourable health and wellbeing outcomes including, type 2 diabetes mellitus, cancer and cardiovascular disease (Guh et al., 2009), overweight BMI in midlife confers a 35% increased risk of developing Alzheimer's disease (AD), compared with normal BMI (Anstey et al., 2011).

The hippocampus is a brain region which is sensitive to changes, particularly in the early stages of neurodegeneration (Braak & Braak, 1991; Karas et al., 2004; Zakzanis et al., 2003). Notably,

the accumulation of fat tissue, particularly visceral fat, which is often prevalent in individuals with overweight/obesity, is known to be closely linked with elevated levels of pro-inflammatory cytokines (Fontana et al., 2007; Gregor & Hotamisligil, 2011; A. A. Miller & Spencer, 2014), which have been associated with smaller hippocampal volumes (Sudheimer et al., 2014). In animal models, obesity in ageing is associated with a heightened state of systemic inflammation, which exacerbates blood brain barrier disruption, neuroinflammation and oxidative stress in the mouse hippocampus (Tucsek et al., 2014). These pathophysiological consequences of overweight/obesity have been closely linked with impaired hippocampal integrity in humans (Montagne et al., 2015; Sudheimer et al., 2014). Interestingly, a post-mortem study of non-demented elderly individuals revealed that those with obesity had neuropathological hallmarks of AD, such as higher levels of hippocampal amyloid-beta peptides, amyloid precursor protein and hyperphosphorylated tau protein, compared with those without obesity (Mrak, 2009). However, neuroimaging studies have revealed that the association between fat mass and hippocampal volume in middle to early-old aged adults has been less consistent with studies reporting negative (Bruehl et al., 2009; Cherbuin et al., 2015; Jagust et al., 2005; Raji et al., 2010), positive (Widya et al., 2011) or no association (Bobb et al., 2014; Driscoll et al., 2012; Hamer & Batty, 2019).The heterogeneous results may be explained by the typical use of BMI, which does not precisely index changes in visceral fat and is inherently biased by the ageing process (Romero-Corral et al., 2008). Therefore, other cost-effective, feasible and useful clinical measures, including waist circumference (WC) and/or waist-to-hip ratio (WTHR) may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in WC and WTHR have not been adequately investigated in previous studies that have examined the relationship between fat mass and hippocampal volume (Bobb et al., 2014; Cherbuin et al., 2015; Croll et al., 2019; Driscoll et al., 2012).

The current study aimed to rectify these shortcomings by investigating the associations between fat mass (i.e. BMI, WC and WTHR) and changes in fat mass over time with hippocampal volumes in middle to early-old aged women and men. Secondary aims were to determine (1) whether these associations differed between measures of fat mass and (2) which measure(s) of fat mass were most strongly associated with total body fat and visceral fat as measured by the gold standard tool, dual-energy x-ray absorptiometry (DEXA). It was hypothesised that any observed associations between fat mass and the hippocampus would be dependent on i) baseline fat mass status (i.e. normal, overweight or obese), ii) the trajectory of change and iii) the measure of fat mass used. It was predicted that individuals who were classified as chronically overweight/obese (and thereby experience chronic, low grade systemic inflammation as well as other comorbidities), would have lower hippocampal volumes than those who progressed from normal weight to overweight/obese categories, or maintained their

weight within the normal range. Furthermore, it was hypothesised that these results would be best represented by the fat mass measure which was most suited for indexing changes in visceral fat.

5.3 Methods

5.3.1 Participants

A total of 502536 participants aged 37-73 years at baseline (2006 - 2010) were from the UK Biobank study (Sudlow et al., 2015) and considered for inclusion. Participants were recruited from the National Health Service central registers. Of those considered, as a minimum requirement, only those who had completed a structural MRI scan (21390) and had a measure of BMI, WC and hip circumference (HC) at baseline and follow-up assessment (2014 +) were included (20849). After excluding participants with neurological disorders, including stroke (n = 256) or those who were underweight i.e. BMI <18.5 kg/m^2 (n = 179), or had extreme obesity i.e. BMI > 50 kg/m^2 (n = 20), 20395 participants remained for analysis in the present study. None of the included participants had dementia.

5.3.2 Ethical approval

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/0382). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

5.3.3 Fat mass measures

BMI, WC and WTHR were measured at baseline, first follow-up assessment and second follow-up assessment (Figure 5.1). Trained staff used standardised procedures to obtain body size measurements. Participants were asked to remove shoes, socks and heavy outer clothing before body weight was measured with the Tanita BC-418 MA body composition analyser (Tanita, Tokyo, Japan) and standing height was measured using a Seca 202 height measure (Seca, Hamburg, Germany). BMI was calculated with the formula: $weight(kg)/height^2(m^2)$. WC was measured with a Wessex non-stretchable sprung tape measure (Wessex, United Kingdom) at the level of the umbilicus, while HC was measured at the widest point. WTHR was computed (i.e. WC (cm) / HC (cm)). Total body fat and visceral fat was measured (for 4,482 and 4,431 participants respectively) using a dual-energy x-ray absorptiometry (DEXA) device, specifically, the GE-Lunar iDXA (GE Healthcare, Chicago, Illinois, Unites States of America).

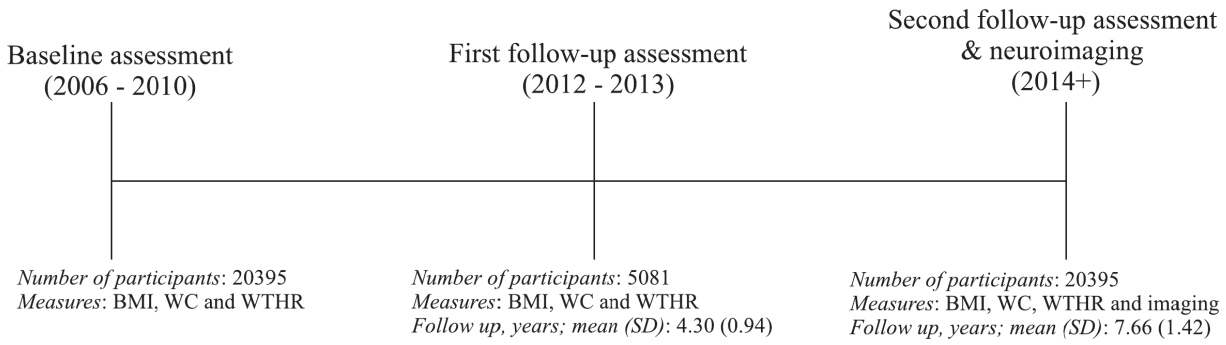

Figure 5.1: Timeline of UK Biobank study. Abbreviations: BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio; SD, Standard Deviation.

Of the 20,395 participants included in the study, 5,080 had an additional follow-up measure of fat mass (Figure 5.1). For these participants, annual changes in fat mass was calculated with the formula:

$$y = \beta_0 + \beta_1 followup(years)$$

Where β_0 is the fat mass at each timepoint and β_1 is the annual change in fat mass.

For each measure of fat mass, participants were then categorised into one of four groups, which represented their baseline fat mass status and their trajectory of change by follow-up assessment i.e. normal to overweight/obese (NO), overweight/obese to normal (ON), normal stable (NS) or overweight/obese stable (OS). Standardised criteria from the International Diabetes Federation (Alberti et al., 2006) and the World Health Organization (World Health Organization, 2000, 2011) were used to classify normal and overweight/obese groups. Specifically, BMI for men and women: overweight/obese $>= 25\ kg/m^2$, normal $< 25\ kg/m^2$; WC for women: overweight/obese >= 80 cm, normal < 80 cm; WC for men: overweight/obese >= 94 cm, normal < 94 cm; WTHR for women: overweight/obese >= 0.85, normal < 0.85 and WTHR for men: overweight/obese >= 0.90, normal < 0.90.

5.3.4 Covariates

Covariates included sex, follow-up period, self-reported age and educational attainment, vascular/heart problems (i.e. heart attack, angina or hypertension) and diabetes, diagnosed by doctor. Participants were classified as having hypertension if they were using blood pressure medication and also, as having diabetes if they were using oral anti-diabetic medication or insulin. Further covariates included self-reported physical activity (i.e. number of days per week spent doing at least 10 minutes of continuous vigorous activity), smoking (i.e. ever or

never) and frequency of alcohol intake.

5.3.5 Image acquisition

Magnetic resonance imaging (MRI) scans were acquired at the second follow-up assessment (Figure 5.1). All participants were imaged across three imaging centres with identical scanners (3T Siemens Skyra; software platform VD13) using a 32-channel head coil (K. L. Miller et al., 2016). T1-weighted images were acquired in the sagittal orientation using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence over a duration of 5 minutes; resolution = 1 x 1 x 1 mm; field of view = 208 x 256 x 256 matrix (K. L. Miller et al., 2016).

5.3.6 Segmentation and image analysis

Images were processed and analysed by the UK Biobank imaging team using FMRIB Software Library (FSL) v6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard MRI analysis protocols have been reported elsewhere (Alfaro-Almagro et al., 2018; K. L. Miller et al., 2016), however, we have included an overview of key steps. The UK Biobank processing pipeline included a linear and then non-linear registration to a 1mm resolution version of the MNI152 template. Automated tissue segmentation was conducted and subcortical structures, such as the hippocampus, were modelled. Raw hippocampal volumes were multiplied by the overall volumetric head-size scaling factor to obtain normalised volumes, which were subsequently used for all analyses.

5.3.7 Statistical methods

All statistical analyses were conducted using R (version 3.6.1), in RStudio (version 1.1.419). Pearson's correlation coefficients were used to measure the strength of the associations between BMI, WC, WTHR and DEXA measurements of total body fat and visceral fat. Multiple linear hierarchical regression models were then computed to quantify the association between fat mass and changes in fat mass and hippocampal volumes, while controlling for age and sex (Model 1). Model 2 further controlled for education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. Analysis which investigated the associations between fat mass categories (i.e. NO, ON, NS and OS) and the hippocampus also adjusted for length of follow-up (years). Within each fat mass category, longitudinal changes in fat mass and the hippocampus were assessed. Since the fat mass thresholds for categorisation differed between men and women (particularly for WC and WTHR), these analyses were repeated separately. Both unstandardised beta-coefficients and annual percentage change in fat mass were utilised in the reporting and interpretation of results, where appropriate.

Annual percentage change was calculated by dividing the annual change in fat mass by the baseline fat mass, multiplied by 100. The alpha level was set at < 0.05. Non-linear associations were explored by fitting a squared term for fat mass. Assumptions of linearity, including homoscedasticity and normality of residuals were examined.

5.4 Results

The participants' demographic and health characteristics are presented in Table 5.1. Differences between those who were included and excluded have been reported in Table 5.4. For those included, participants were on average 54.86 years (standard deviation [SD] = 7.48) with a mean follow-up of 7.66 years (SD = 1.42) at baseline. The average total hippocampal volume was 7709.73 mm^3, (SD = 867.92 mm^3). On average, participants lost 68.6 grams/year over the follow-up period. Boxplots of fat mass change over the follow-up between NS, NO, OS and ON groups are presented in Figure 5.2. Demographic information for NS, NO, OS and ON groups for each fat mass measure are presented in Table 5.5 - Table 5.7.

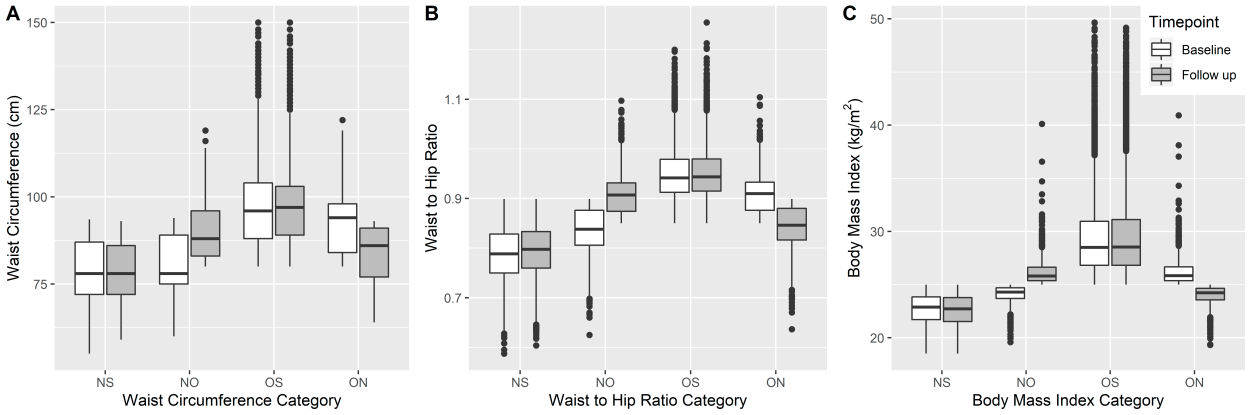

Figure 5.2: Fat mass change over follow-up for each group. Abbreviations: NS, Normal stable; NO, Normal to overweight/obese; OS, Overweight/obese stable; ON, Overweight/obese to normal.

Table 5.1: Demographic and health characteristics.

Characteristics	**Value**
Sample size; N	20395
Age, years; mean, (SD)	54.86 (7.48)
Follow up period, years; mean (SD)	7.66 (1.42)
Female; N (%)	10658 (52.26)
Body Mass Index, kg/m^2; mean (SD)	26.67 (4.16)
Waist Circumference, cm; mean (SD)	88.12 (12.44)
Waist to Hip Ratio; mean (SD)	0.86 (0.087)
Education college/degree; N (%)	9491 (46.54)
Hypertension; N (%)	4240 (20.79)
Diabetes; N (%)	544 (2.67)
Ever smoker; N (%)	11623 (56.99)
Total hippocampal volume, mm^3; mean (SD)	7709.73 (867.92)

Abbreviations: N, number; SD, standard deviation. Note: There were 109 (0.53%) missing for education, 147 (0.72%) missing for hypertension, 4 (0.02%) missing for diabetes and 44 (0.22%) missing for smoking status.

Cross-sectional analyses revealed that after adjusting for all covariates, higher BMI, WC and WTHR were each individually associated with lower hippocampal volumes (Table 5.8; BMI: B = -9.61, standard error [SE] = 1.77; WC: B = -6.74, SE = 0.69 and WTHR: B = -690.78, SE = 119.13).

Overall, longitudinal changes in continuous BMI, WC or WTHR were not significantly associated with lower hippocampal volumes (Table 5.9), however, compared to participants who were NS for BMI, WC or WTHR, those who remained OS (BMI: B = -62.23, SE = 16.76; WC: B = -145.56, SE = 16.97 and WTHR: B = -101.26, SE = 19.54) or were ON (BMI: B = -61.1, SE = 30.3; WC: B = -93.77, SE = 24.96 and WTHR: B = -69.92, SE = 26.22) had significantly lower hippocampal volumes across all three measures of fat mass (Table 5.2). Participants who were NO for WC or WTHR also had significantly lower hippocampal volumes than those who were NS (WC: B = -74.39, SE = 25.51 and WTHR: B = -62.09, SE = 22.52). However, participants who were NO for BMI had no significant difference in hippocampal volume compared to those who were NS.

Table 5.2: Longitudinal categorical analysis results for total hippocampus.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal to overweight/obese (NO)	-45.94	32.24	-109.14 – 17.25	0.154	0.155
	Overweight/obese stable (OS)	-62.33	16.76	-95.17 – -29.48	<0.001	-
	Overweight/obese to normal (ON)	-61.15	30.30	-120.55 – -1.76	0.044	-
WC	Normal to overweight/obese (NO)	-74.40	25.51	-124.40 – -24.41	0.004	0.157
	Overweight/obese stable (OS)	-145.68	16.97	-178.95 – -112.41	<0.001	-
	Overweight/obese to normal (ON)	-93.81	24.96	-142.73 – -44.89	<0.001	-
WTHR	Normal to overweight/obese (NO)	-62.12	22.52	-106.27 – -17.98	0.006	0.155
	Overweight/obese stable (OS)	-101.44	19.54	-139.75 – -63.13	<0.001	-
	Overweight/obese to normal (ON)	-69.95	26.22	-121.35 – -18.56	0.008	-

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, sex, follow up (years), education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. $mm3$.

Analyses were repeated separately for women and men (Table 5.10 and 5.11). For men, OS (BMI: B = -92.17, SE = 26.55; WC: B = -206.02, SE = 25.69 and WTHR: B = -114.98, SE = 29.08) and ON (BMI: B = -97.79, SE = 45.76; WC: B = -91.18, SE = 34.5 and WTHR: B = -96.29, SE = 40.49) groups were consistently associated with lower hippocampal volumes compared with NS across all measures of fat mass. However, no significant differences in hippocampal volumes were consistently found between the NO and NS groups. For women, OS groups had consistently lower hippocampal volumes than NS across all measures of fat mass (BMI: B = -45.19, SE = 21.52; WC: B = -101.73, SE = 22.5 and WTHR: B = -70.54, SE = 28.67). For WC and WTHR, the NO group had lower hippocampal volumes than the NS group (WC: B = -84, SE = 32.43 and WTHR: B = -103.79, SE = 28.43), however, these differences were not found for BMI. ON participants had significantly lower hippocampal volumes compared to the NS group for WC (B = -113.16, SE = 36.51), however, this difference was not observed for WTHR or BMI.

For each individual subgroup (i.e. NS, NO, OS, ON), annual change in BMI, WC or WTHR had no significant association with hippocampal volume (Table 5.12). This was consistently observed between women and men (Table 5.13 and 5.14).

As seen in Table 5.3, WC was most correlated with visceral fat (r = 0.83), compared to WTHR (r = 0.73) and BMI (r = 0.69). However, BMI was most correlated with total body fat (r = 0.90), compared to WC (r = 0.72) and WTHR (r = 0.29).

Table 5.3: Simple Pearson correlation analysis results for between WC, WTHR, BMI and DEXA .

	TBF	**Estimate (95% CI)**	**p-value**	**VF**	**Estimate (95% CI)**	**p-value**
BMI	0.897	0.891 – 0.903	<0.001	0.688	0.672 – 0.703	<0.001
WC	0.719	0.706 – 0.734	<0.001	0.827	0.817 – 0.836	<0.001
WTHR	0.291	0.264 – 0.318	<0.001	0.728	0.714 – 0.742	<0.001

Abbreviations: CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio; VF, Visceral Fat; TBF, Total Body Fat; DEXA, Dual-Energy X-ray Absorptiometry. Note: TBF and VF were measured for 4482 and 4431 participants, respectively, using DEXA.

5.5 Discussion

This study aimed to investigate the association between fat mass and longitudinal changes in fat mass with hippocampal volumes in middle to early-old aged women and men. To better understand these relationships, the current study also aimed to determine whether observed associations differed between measures of fat mass and to identify which measure(s) of fat mass were most strongly associated with total body fat and visceral fat, as indicated by DEXA. The key findings were that (1) WC was most strongly correlated with visceral fat (r = 0.83), compared to WTHR (r = 0.73) and BMI (r = 0.69), (2) individuals with chronic overweight/obesity had significantly lower hippocampal volumes (specifically, WC: 1.13%; WTHR: 0.79% and BMI: 0.49% smaller after adjusting for all covariates) when compared with those who maintained a normal level of fat mass (i.e. WC: < 80 cm in women and < 94 cm in men; WTHR: < 0.85 in women and < 0.90 in men and BMI: < 25 kg/m^2 in women and men) at baseline and follow-up (average follow-up = 7.66 years) and (3) individuals who were within a normal range of fat mass at follow-up assessment, yet were previously classified as having overweight/obesity at baseline had lower hippocampal volumes than those who remained normal stable (specifically, WC: 0.73%; WTHR: 0.55% and BMI: 0.48% smaller after adjusting for all covariates). Notably, the significant cross-sectional association between fat mass and hippocampal volume was not previously detected in a study on the same cohort (Hamer & Batty, 2019). In that particular study, the sample was half the size of the present study and depression was also considered as a covariate. Our analysis did not include depression as a covariate, partly due to the significant degree of missingness present. The current findings emphasise the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

Overweight/obesity is a complex condition which has multifactorial components (including genetic, environmental and socioeconomic factors) that underlie its aetiology. The current findings further highlight the complexity of overweight/obesity by emphasising the long term impact the condition may have on the neurological health of individuals. There are a number of possible biological mechanisms, which may explain the consistent finding that those who were OS or ON had lower hippocampal volumes than those who were NS, across all measures of fat mass. For example, previous studies have demonstrated that the accumulation of fat tissue, particularly visceral fat, is closely linked with elevated levels of pro-inflammatory cytokines (Fontana et al., 2007; Gregor & Hotamisligil, 2011; A. A. Miller & Spencer, 2014), which have been associated with smaller hippocampal volumes (Sudheimer et al., 2014). This is of particular importance as the current results revealed that (1) WC was most strongly

associated with visceral fat and (2) the largest effect was consistently found for WC, as those who were OS and ON had 1.13% and 0.73% smaller hippocampal volumes than NS for WC, respectively, compared with WTHR (OS: 0.79% and ON: 0.55% smaller hippocampus than NS) and BMI (OS: 0.49% and ON: 0.48% smaller hippocampus than NS). Notably, no statistical differences between NS and NO groups were found for BMI, which was lowly correlated with visceral fat levels compared to WC but was most highly correlated with total body fat, yet, for both WC and WTHR the NO group had significantly lower hippocampal volumes than NS (0.58% and 0.49% smaller respectively).

Taken together, the current findings seem to suggest that an accumulated burden of pathology may have developed in those that were OS, ON and NO, perhaps as a result of chronic, low grade systemic inflammation that persists, commonly in individuals with overweight/obesity (due to an accumulation of visceral fat tissue), or other pathological mechanisms, resulting in lower hippocampal volumes compared to those who maintained a normal level of fat mass. This is consistent with the literature which has shown that chronic obesity is associated with a cascade of potentially harmful physiological processes (including oxidative stress, inflammation and insulin resistance) which are implicated in the deterioration of metabolic homeostasis (Monteiro & Azevedo, 2010), and has been linked with accelerated neurodegeneration (Glass et al., 2010). Furthermore, previous research has demonstrated that individuals who gained weight, lost weight or remained obese had an increased risk of mortality compared with those who maintained normal amounts of body fat (C. Chen et al., 2019). Therefore, these results appear to indicate that it is the chronicity of overweight/obesity which is associated with lower hippocampal volumes. However, an alternative explanation is that, for reasons not well understood, those who were ON or OS had lower hippocampal volumes at baseline. Whilst possible, this explanation is less likely given the substantial amount of evidence in the literature that has demonstrated the link between obesity and neurodegeneration (Anstey et al., 2011; Beydoun et al., 2008; Livingston et al., 2017), which also aligns with experimental data in animals showing that obesity in mice can lead to decreased neurogenesis and accelerated neurodegeneration, resulting in dementia pathology (Cai, 2013; Julien et al., 2010). Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present and future research should investigate this further.

The use of BMI, WC and WTHR enabled the comparison of results across three commonly used clinical measures/indices of fat mass. Whilst more precise technology for measuring fat mass exists, such as DEXA and MRI (Borga et al., 2018), these tools require relatively large investments of time, money and resources, compared to BMI, WC and WTHR. Furthermore, longitudinal measures of fat mass using DEXA or MRI are currently not available in the UK

Biobank dataset. As a result, an important question raised by these findings is which clinical measure (i.e. BMI, WC or WTHR) best represents the association between fat mass and the hippocampus and may therefore be a better predictor of future neurodegeneration. Firstly, as previously noted, correlation analysis indicated that WC was most strongly associated with visceral fat (r = 0.83), compared to WTHR (r = 0.73) and BMI (r = 0.69). This may provide a theoretical rationale for its use as a clinical measure to assess the association between fat mass and the hippocampus. Furthermore, subgroup analysis in women revealed statistically significant differences between NO, OS, ON groups and those who were NS for WC, however, these differences were not consistently found for WTHR and BMI (Table 5.10). Several possible reasons may account for these findings. For example, previous research has demonstrated that women tend to accumulate central fat (specifically visceral fat), during midlife (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019), which may explain the observed associations, given that WC was most strongly correlated with visceral fat, which has been previously linked to neurodegeneration through the elevation of pro-inflammatory cytokines (Sudheimer et al., 2014). Another possibility is that the individuals who were in each fat mass group (i.e. NS, NO, OS and ON) varied to a certain degree between measures due to the differences with the standardised cutoff points used for categorisation. Therefore, the observed differences in results may reflect the sensitivity of the fat mass thresholds for each category (i.e. NS, NO, OS and ON) to better capture individuals who had healthier hippocampal volumes than others. To assess this, post-hoc analysis was conducted whereby a fifth group was established, which included individuals (n = 3998) who were consistently normal stable for all of BMI, WC and WTHR (henceforth called consistently normal stable i.e. CNS). Interestingly, for WC, no difference was found between those who were NS or CNS. Furthermore, the magnitude and significance of effects remained consistent between NS and NO, OS and ON groups with and without the inclusion of a CNS group (Table 5.15). Alternatively, for WTHR and BMI the CNS group had significantly larger hippocampal volumes than those who were NS. Furthermore, the differences between ON and OS groups with NS for BMI were no longer detected once the CNS group was included. A similar result was observed for the ON and NO groups for WTHR. Therefore the CNS group was likely capturing the individuals with larger hippocampal volumes for BMI and WTHR, but not WC. This may be because BMI and WTHR measures reflect body size and on average head size, which is itself associated with hippocampal volume. These findings seem to further demonstrate the robustness and sensitivity of WC for assessing the relationship between visceral fat and hippocampal volume. Taken together, these results align with and extend upon previous studies, which have noted that WC is a more sensitive indicator for determining the adverse effects of overweight and obesity on brain health than BMI, particularly in females

(Kurth et al., 2013).

5.5.1 Strengths and limitations

Key strengths of the current study include (1), the large cohort of middle to early-old aged adults (specifically 20,395 individuals) that included both men and women, (2) the use of longitudinal changes in fat mass and (3), the use of multiple commonly used clinical measures/indices of fat mass (including BMI, WC and WTHR) to address the questions of interest. Furthermore, due to the large sample size, a large number of relevant covariates could be adjusted for (including age, sex, follow-up period, educational attainment, vascular/heart problems i.e. heart attack, angina or hypertension, diabetes, physical activity, smoking and alcohol intake), which ensured that observed associations were unlikely driven by common comorbid conditions that are often associated with obesity, such as diabetes, hypertension and physical activity levels. Notably, previous studies that have examined longitudinal changes in fat mass with hippocampal volumes in middle to early aged adults have been limited by sample size (Bobb et al., 2014; Cherbuin et al., 2015; Driscoll et al., 2012). Two of the three studies used BMI as their only measure of fat mass (Bobb et al., 2014; Cherbuin et al., 2015), one of which, focused on a sample consisting only of men (Bobb et al., 2014), whereas the other used self-reported BMI (Cherbuin et al., 2015) and the third estimated BMI and WC in participants at age 50 (Driscoll et al., 2012). Given this, the current study is unique in its ability to directly measure, assess and discuss the temporal association between longitudinal changes in BMI, WC and WTHR, with the hippocampus, within a large cohort of both men and women.

A limitation of the current study is that imaging data was only available at one timepoint (Figure 5.2). Therefore, it is difficult to determine whether other age related factors could be responsible for the observed differences or, as previously discussed, whether these differences were already present a baseline. For example, if smaller hippocampal volumes were observed at baseline and were associated with longitudinal increases in adiposity, then these findings may highlight a predisposed vulnerability to external food cues driving eating behaviour. Furthermore, clear standardised thresholds for WC and WTHR that separate overweight and obese groups do not currently exist. This limited the ability to identify possible differences that may exist between overweight and obese participants for WC and WTHR. Additionally, healthy participation bias for the UK Biobank cohort indicates that these findings may not be completely representative of the broader population and require replication in other datasets (Fry et al., 2017). Our study was limited to the association between changes in fat mass and the brain, however, future studies would benefit from investigating whether the observed

results translate to differences in cognitive performance, particularly in domains related to the hippocampus, such as learning and memory.

5.6 Conclusion

The current findings emphasise the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

5.7 Supplementary materials

The supplementary materials for Chapter 5 include:

- **Table 5.4** Demographic and health characteristics of included and excluded participants.
- **Table 5.5** Demographic and health characteristics for Body Mass Index groups.
- **Table 5.6** Demographic and health characteristics for Waist Circumference groups.
- **Table 5.7** Demographic and health characteristics for Waist to Hip Ratio groups.
- **Table 5.8** Cross-sectional analysis results for total hippocampus.
- **Table 5.9** Longitudinal analysis results for total hippocampus.
- **Table 5.10** Longitudinal categorical analysis results for total hippocampus in women.
- **Table 5.11** Longitudinal categorical analysis results for total hippocampus in men.
- **Table 5.12** Longitudinal continuous analysis results for total hippocampus in subgroups.
- **Table 5.13** Longitudinal continuous analysis results for total hippocampus in women.
- **Table 5.14** Longitudinal continuous analysis results for total hippocampus in men.
- **Table 5.15** Longitudinal categorical analysis results for total hippocampus with CNS group included.

Table 5.4: Demographic and health characteristics of included and excluded participants.

Characteristics/Measures	**Excluded**	**Included**
Sample size; N	482141	20395
Age, years; mean, (SD)	56.60 (8.113)	54.86 (7.483)
Female; N (%)	262744 (54.50%)	10658 (52.26%)
Body Mass Index, kg/m^2; mean (SD)	27.46 (4.826)	26.67 (4.156)
Waist Circumference, cm; mean (SD)	90.40 (13.52)	88.12 (12.44)
Waist to Hip Ratio; mean (SD)	0.8722 (0.08999)	0.8600 (0.08664)

Abbreviations: N, number; SD, standard deviation.

Table 5.5: Demographic and health characteristics for Body Mass Index groups.

Characteristics/Measures	**NS**	**NO**	**OS**	**ON**
Sample size; N	6610	1231	11115	1439
Age, years; mean, (SD)	54.43 (7.55)	52.92 (7.50)	55.15 (7.43)	56.16 (7.17)
Follow up period, years; mean (SD)	7.69 (1.40)	7.78 (1.44)	7.63 (1.42)	7.73 (1.41)
Female; N (%)	4218 (63.81)	766 (62.23)	4958 (44.61)	716 (49.76)
Body Mass Index, kg/m^2; mean (SD)	22.69 (1.46)	24.06 (0.85)	29.39 (3.54)	26.24 (1.32)
Waist Circumference, cm; mean (SD)	77.89 (7.904)	80.85 (7.471)	95.05 (10.76)	87.76 (8.073)
Waist to Hip Ratio; mean (SD)	0.81(0.072)	0.82 (0.072)	0.89 (0.082)	0.86(0.076)
Education college/degree; N (%)	3553 (53.75)	519 (42.16)	4723 (42.49)	696 (48.37)
Hypertension; N (%)	733 (11.09)	180 (14.62)	3061 (27.54)	266 (18.49)
Diabetes; N (%)	70 (1.06)	17 (1.38)	416 (3.74)	41 (2.85)
Ever smoker; N (%)	3581 (54.18)	701 (56.95)	6520 (58.66)	821 (57.05)
Total hippocampal volume, mm^3; mean (SD)	7672.39 (853.47)	7669.30 (826.24)	7739.85 (878.18)	7683.25 (880.70)

Abbreviations: N, number; SD, standard deviation; NS, normal stable; NO, normal to overweight/obese; OS, overweight/obese stable; ON, overweight/obese to normal.

Table 5.6: Demographic and health characteristics for Waist Circumference groups.

Characteristics/Measures	**NS**	**NO**	**OS**	**ON**
Sample size; N	7528	2129	8492	2246
Age, years; mean, (SD)	54.20 (7.60)	54.02 (7.53)	55.47 (7.33)	55.50 (7.33)
Follow up period, years; mean (SD)	7.63 (1.39)	7.98 (1.40)	7.65 (1.43)	7.50 (1.43)
Female; N (%)	3726 (49.50)	1270 (59.65)	4729 (55.69)	933 (41.54)
Body Mass Index, kg/m^2; mean (SD)	23.58 (2.14)	25.08 (2.21)	29.78 (3.97)	26.83 (2.49)
Waist Circumference, cm; mean (SD)	79.11 (8.31)	81.01 (7.67)	96.79 (10.74)	92.25 (7.73)
Waist to Hip Ratio; mean (SD)	0.82 (0.08)	0.82 (0.07)	0.90 (0.08)	0.90 (0.07)
Education college/degree; N (%)	3936 (52.28)	936 (43.96)	3519 (41.44)	1100 (48.98)
Hypertension; N (%)	955 (12.69)	346 (16.25)	2498 (29.42)	441 (19.63)
Diabetes; N (%)	87 (1.16)	32 (1.50)	365 (4.30)	60 (2.67)
Ever smoker; N (%)	4081 (54.21)	1213 (56.98)	4985 (58.70)	1344 (59.84)
Total hippocampal volume, mm^3; mean (SD)	7760.52 (865.76)	7678.00 (835.70)	7657.85 (871.68)	7765.77 (878.20)

Abbreviations: N, number; SD, standard deviation; NS, normal stable; NO, normal to overweight/obese; OS, overweight/obese stable; ON, overweight/obese to normal.

Table 5.7: Demographic and health characteristics for Waist to Hip Ratio groups.

Characteristics/Measures	**NS**	**NO**	**OS**	**ON**
Sample size; N	8678	2953	6753	2011
Age, years; mean, (SD)	53.69 (7.47)	54.43 (7.5)	56.31 (7.25)	55.64 (7.38)
Follow up period, years; mean (SD)	7.64 (1.39)	7.98 (1.44)	7.65 (1.42)	7.33 (1.38)
Female; N (%)	6617 (76.25)	1535 (51.98)	1578 (23.37)	928 (46.15)
Body Mass Index, kg/m^2; mean (SD)	24.87 (3.55)	26.19 (3.64)	29.02 (3.98)	27.31 (3.90)
Waist Circumference, cm; mean (SD)	79.24 (8.39)	85.36 (8.12)	99.16 (9.61)	93.38 (8.31)
Waist to Hip Ratio; mean (SD)	0.79 (0.054)	0.84 (0.046)	0.95 (0.051)	0.91 (0.039)
Education college/degree; N (%)	4338 (49.99)	1380 (46.73)	2815 (41.69)	958 (47.64)
Hypertension; N (%)	1143 (13.17)	559 (18.93)	2108 (31.22)	430 (21.38)
Diabetes; N (%)	88 (1.01)	60 (2.03)	350 (5.18)	46 (2.29)
Ever smoker; N (%)	4550 (52.43)	1661 (56.25)	4195 (62.12)	1217 (60.52)
Total hippocampal volume, mm^3; mean (SD)	7665.94 (823.12)	7707.96 (895.30)	7760.45 (911.31)	7731.01 (856.64)

Abbreviations: N, number; SD, standard deviation; NS, normal stable; NO, normal to overweight/obese; OS, overweight/obese stable; ON, overweight/obese to normal.

Table 5.8: Cross-sectional analysis results for total hippocampus.

Predictors	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	ΔR^2
BMI (Model 1)	-9.38	1.69	-12.69 – -6.07	<0.001	0.151
BMI (Model 2)	-9.61	1.77	-13.08 – -6.14	<0.001	0.004
WC (Model 1)	-6.62	0.66	-7.92 – -5.31	<0.001	0.154
WC (Model 2)	-6.74	0.69	-8.10 – -5.38	<0.001	0.004
WTHR (Model 1)	-729.89	115.56	-956.40 – -503.38	<0.001	0.152
WTHR (Model 2)	-690.78	119.13	-924.29 – -457.27	<0.001	0.003

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.9: Longitudinal analysis results for total hippocampus.

Predictors	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	ΔR^2
BMI (Model 1)	-5.88	7.89	-21.34 – 9.58	0.456	0.150
BMI (Model 2)	-8.51	7.95	-24.09 – 7.07	0.284	0.004
WC (Model 1)	-0.49	6.65	-13.52 – 12.55	0.942	0.150
WC (Model 2)	-2.35	6.69	-15.46 – 10.77	0.726	0.004
WTHR (Model 1)	-0.03	8.15	-16.00 – 15.94	0.997	0.150
WTHR (Model 2)	-0.90	8.18	-16.93 – 15.14	0.913	0.004

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model 1 is adjusted for age and sex. Model 2 is adjusted for age, sex, education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.10: Longitudinal categorical analysis results for total hippocampus in women.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal to overweight/obese (NO)	-7.63	39.33	-84.76 – 69.47	0.846	0.058
	Overweight/obese stable (OS)	-45.19	21.52	-87.38 – -2.99	0.036	-
	Overweight/obese to normal (ON)	-34.90	40.46	-114.21 – 44.42	0.388	-
WC	Normal to overweight/obese (NO)	-84.00	32.43	-147.57 – -20.43	0.010	0.060
	Overweight/obese stable (OS)	-100.73	22.50	-144.83 – -56.64	<0.001	-
	Overweight/obese to normal (ON)	-113.16	36.51	-184.73 – -41.58	0.002	-
WTHR	Normal to overweight/obese (NO)	-103.79	28.43	-159.51 – -48.07	<0.001	0.059
	Overweight/obese stable (OS)	-70.54	28.67	-126.73 – -14.34	0.014	-
	Overweight/obese to normal (ON)	-46.46	35.23	-115.52 – 22.59	0.187	-

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, follow up (years), education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.11: Longitudinal categorical analysis results for total hippocampus in men.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal to overweight/obese (NO)	-98.93	54.57	-205.90 – 8.03	0.070	0.107
	Overweight/obese stable (OS)	-92.17	26.55	-144.22 – -40.12	0.001	-
	Overweight/obese to normal (ON)	-97.79	45.76	-187.49 – -8.09	0.033	-
WC	Normal to overweight/obese (NO)	-47.87	40.69	-127.63 – 31.88	0.239	0.112
	Overweight/obese stable (OS)	-206.02	25.69	-256.37 – -155.67	<0.001	-
	Overweight/obese to normal (ON)	-91.18	34.50	-158.80 – -23.57	0.008	-
WTHR	Normal to overweight/obese (NO)	-25.01	37.25	-98.04 – 48.01	0.502	0.107
	Overweight/obese stable (OS)	-114.98	29.08	-171.99 – -57.97	<0.001	-
	Overweight/obese to normal (ON)	-96.29	40.49	-175.66 – -16.91	0.017	-

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, follow up (years), education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.12: Longitudinal continuous analysis results for total hippocampus in subgroups.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal stable (NS)	-24.17	19.32	-62.05 – 13.70	0.211	0.144
	Normal to overweight/obese (NO)	-61.91	34.69	-129.96 – 6.15	0.075	0.192
	Overweight/obese stable (OS)	-5.60	10.94	-27.06 – 15.85	0.609	0.152
	Overweight/obese to normal (ON)	33.49	38.74	-42.50 – 109.48	0.387	0.163
WC	Normal stable (NS)	2.50	14.07	-25.09 – 30.09	0.859	0.150
	Normal to overweight/obese (NO)	-30.73	25.13	-80.02 – 18.56	0.222	0.157
	Overweight/obese stable (OS)	-0.22	11.67	-23.10 – 22.66	0.985	0.165
	Overweight/obese to normal (ON)	-17.34	29.20	-74.59 – 39.92	0.553	0.153
WTHR	Normal stable (NS)	-4.15	14.36	-32.29 – 23.99	0.773	0.104
	Normal to overweight/obese (NO)	-4.70	27.18	-58.00 – 48.59	0.863	0.148
	Overweight/obese stable (OS)	14.60	19.71	-24.03 – 53.24	0.459	0.143
	Overweight/obese to normal (ON)	2.52	35.68	-67.45 – 72.49	0.944	0.156

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, sex, education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.13: Longitudinal continuous analysis results for total hippocampus in women.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal stable (NS)	-9.09	22.37	-52.94 – 34.76	0.685	0.067
	Normal to overweight/obese (NO)	-72.41	37.90	-146.81 – 1.99	0.056	0.087
	Overweight/obese stable (OS)	-2.49	14.03	-29.99 – 25.01	0.859	0.054
	Overweight/obese to normal (ON)	38.70	45.65	-50.93 – 128.33	0.397	0.096
WC	Normal stable (NS)	1.06	19.09	-36.38 – 38.49	0.956	0.054
	Normal to overweight/obese (NO)	-37.25	29.43	-94.99 – 20.50	0.206	0.074
	Overweight/obese stable (OS)	-4.02	13.66	-30.79 – 22.76	0.769	0.057
	Overweight/obese to normal (ON)	-43.67	38.29	-118.82 – 31.49	0.254	0.101
WTHR	Normal stable (NS)	0.64	15.49	-29.72 – 31.00	0.967	0.051
	Normal to overweight/obese (NO)	5.21	33.51	-60.52 – 70.94	0.876	0.089
	Overweight/obese stable (OS)	-12.61	35.70	-82.63 – 57.42	0.724	0.063
	Overweight/obese to normal (ON)	18.49	43.65	-67.19 – 104.17	0.672	0.096

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.14: Longitudinal continuous analysis results for total hippocampus in men.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal stable (NS)	-58.42	38.11	-133.16 – 16.31	0.125	0.122
	Normal to overweight/obese (NO)	22.07	77.88	-131.01 – 175.15	0.777	0.214
	Overweight/obese stable (OS)	-1.27	17.09	-34.77 – 32.23	0.941	0.107
	Overweight/obese to normal (ON)	26.14	66.04	-103.53 – 155.80	0.692	0.109
WC	Normal stable (NS)	4.21	20.73	-36.44 – 44.86	0.839	0.115
	Normal to overweight/obese (NO)	9.90	48.86	-86.01 – 105.81	0.840	0.135
	Overweight/obese stable (OS)	12.63	21.56	-29.64 – 54.90	0.558	0.105
	Overweight/obese to normal (ON)	19.39	44.34	-67.61 – 106.39	0.662	0.109
WTHR	Normal stable (NS)	-31.03	37.13	-103.84 – 41.77	0.403	0.107
	Normal to overweight/obese (NO)	-9.75	46.90	-101.75 – 82.25	0.835	0.141
	Overweight/obese stable (OS)	27.35	23.53	-18.79 – 73.48	0.245	0.109
	Overweight/obese to normal (ON)	-5.34	59.62	-122.32 – 111.65	0.929	0.100

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

Table 5.15: Longitudinal categorical analysis results for total hippocampus with CNS group included.

Measure	**Predictors**	**Estimate**	**SE**	**Estimate (95% CI)**	**p-value**	R^2
BMI	Normal to overweight/obese (NO)	9.41	35.94	-61.04 – 79.85	0.794	0.155
	Overweight/obese stable (OS)	-8.51	22.77	-53.14 – 36.12	0.709	-
	Overweight/obese to normal (ON)	-7.29	34.01	-73.94 – 59.37	0.830	-
	Consistently normal stable (CNS)	91.43	26.25	39.97 – 142.89	<0.001	-
WC	Normal to overweight/obese (NO)	-76.07	28.91	-132.73 – -19.41	0.009	0.157
	Overweight/obese stable (OS)	-147.20	21.57	-189.47 – -104.93	<0.001	-
	Overweight/obese to normal (ON)	-95.35	28.04	-150.32 – -40.38	0.001	-
	Consistently normal stable (CNS)	-3.07	24.90	-51.88 – 45.74	0.902	-
WTHR	Normal to overweight/obese (NO)	-31.97	24.84	-80.65 – 16.71	0.198	0.156
	Overweight/obese stable (OS)	-70.96	22.20	-114.47 – -27.45	0.001	-
	Overweight/obese to normal (ON)	-39.72	28.24	-95.08 – 15.63	0.160	-
	Consistently normal stable (CNS)	64.44	22.41	20.53 – 108.36	0.004	-

Abbreviations: SE, standard error; CI, confidence interval; BMI, Body Mass Index; WC, Waist Circumference; WTHR, Waist to Hip Ratio. Note: Model is adjusted for age, sex, follow up (years), education, vascular/heart problems, diabetes, physical activity, smoking and alcohol use. All estimates are unstandardised for the hippocampus i.e. mm^3.

6 Age, menstruation history, and the brain

6.1 Abstract

Objectives: To investigate the cross-sectional association between measures of menstruation history (including menopausal status, age of menopause, age of menarche and duration of reproductive stage) and brain volume.

Methods: Women (aged 45 to 79) from the UK Biobank were included (n = 5,072) after excluding those who had (1) hysterectomy or bilateral oophorectomy, (2) ever used menopausal hormone therapy, (3) ever had a stroke, or (4) were perimenopausal. Multiple linear hierarchical regression models were computed to quantify the cross-sectional association between measures of menstruation history and brain volume. Sensitivity analysis based on propensity matching for age (and other demographic/health covariates) were applied to estimate differences in brain volumes between matched premenopausal and postmenopausal women.

Results: Postmenopausal women had 1.06% (95% confidence interval [CI]; 1.05 – 1.06) and 2.17% (95% CI, 2.12 – 2.22) larger total brain (TBV) and hippocampal volumes (HV), respectively, than premenopausal women. Sensitivity analysis with age matched samples produced consistent results (i.e. TBV: 0.82%, 95% CI, 0.25 – 1.38 ; HV: 1.33%, 95% CI, 0.01 – 2.63). For every year increase in age above 45, postmenopausal women experienced 0.23% greater reduction in TBV than premenopausal women (95% CI, -0.60 - -0.14), which was not observed for HV. Moreover, every 1 year delayed onset of menopause after 45 was associated with 0.32% (95% CI, -0.35 - -0.28) and 0.31% (95% CI, -0.40 - -0.22) smaller TBV and HV, respectively. Every additional year in age of menarche was associated with 0.10% (95% CI, 0.04 – 0.16) larger TBV, which was not detected for HV. Similarly, every 1 year increase in duration of reproductive stage was associated with 0.09% smaller TBV (95% CI, -0.15 – -0.03), which was not detected for HV.

Conclusions: Menopause may contribute to brain volume beyond typical aging effects. Furthermore, early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume. Further research is required to determine whether the negative association between age of menopause and HV is potentially an indicator of future vulnerability for dementia.

6.2 Introduction

Age-standardized global prevalence for dementia is 17% higher in women than men, indicating that the higher prevalence in women may not be solely due to age (Nichols et al., 2019).

Results from the Framingham Study revealed that the remaining lifetime risk of Alzheimer's disease (AD), the most common form of dementia, was almost twice as high for a 65 year old woman (12%) than a 65 year old man (6.3%) (Seshadri et al., 1997). The longer life span observed in women does not fully explain the sex bias for AD, but increases the overall prevalence of all-cause dementia in women among the oldest old (Podcasy & Epperson, 2016). Moreover, menstruation history may also be particularly relevant, given that it is unique to female aging.

The association between menstruation history (including menopausal status, age of menopause, age of menarche and duration of reproductive stage) and dementia is currently unclear. Some evidence indicates that younger age at menopause, later age at menarche and shorter reproductive spans are associated with elevated risk of developing dementia (Gilsanz et al., 2019). For example, women with reproductive spans less than 20 years and between 21-34 years had a 55% and 26% increased risk of dementia, respectively, compared to those with a reproductive span of 34 years or higher (Gilsanz et al., 2019). However, there is considerable heterogeneity in findings which do not support a consistent association between early menopause or a shorter reproductive period and increased dementia risk (Georgakis et al., 2016).

Considering that AD pathology begins decades prior to the presentation of clinical symptoms, the effect of menstruation history on brain health may be reflected in brain volume (Braak & Braak, 1991; Ohm et al., 1995; Zakzanis et al., 2003). Notably, brain volume loss within the hippocampus has been reliably associated with the early stages of AD (Zakzanis et al., 2003) and is also predictive of conversion to AD from mild cognitive impairment (Tabatabaei-Jafari et al., 2020; Tabatabaei-Jafari et al., 2018, 2019). Moreover, the hippocampus is particularly vulnerable to the impact of aging in healthy individuals (Burke & Barnes, 2006). However, the association between menopausal status and the hippocampus has been inconsistent. Some research has demonstrated that postmenopausal women experience greater decreases in hippocampal volume compared to premenopausal women (Goto et al., 2011; Mosconi et al., 2018) whereas others report no significant differences (G.-W. Kim et al., 2018; Sullivan et al., 2005). This may be because previous studies did not precisely match premenopausal and postmenopausal women for age, which may have confounded a possible effect of menopause with that of typical aging. Furthermore, the association between other measures of menstruation history (including age of menopause, menarche and duration of reproductive stage) and brain volume remains unclear.

Therefore, this study aimed to investigate the associations between measures of menstruation history (including menopausal status, age of menopause, age of menarche and duration of

reproductive stage) and brain volume.

6.3 Methods

6.3.1 Participants

The UK Biobank study is a large population based cohort which consists of 502,506 participants aged 37-73 years at baseline who were recruited from the National Health Service central registers (Sudlow et al., 2015). Of those participants, 11,243 women underwent a structural magnetic resonance imaging (MRI) scan and were considered for inclusion. Of those, 1960 were excluded because of missing data for menopausal status, giving a sample of 9283 women. The Stages of Reproductive Aging Workshop (STRAW) criteria defines menopause as 1 year of amenorrhea following the final menstrual period (Harlow et al., 2012; Soules et al., 2001). Women who may have been classified as perimenopausal (i.e. were not premenopausal and had reported an age of menopause less than 1 year ago), were excluded from the analyses (n = 116). This was done to ensure that a clear comparison could be made between groups, with premenopausal women acting as control participants for any effect that was observed after menopause. Furthermore, two women who had self-reported premenopausal status after the age of 70 were excluded from analyses. Of those considered, after excluding participants who had reported (1) had a hysterectomy or bilateral oophorectomy (n = 1,045), (2) ever used menopausal hormone therapy (MHT; n = 3,441) or (3) ever had a stroke (n = 76), 5,072 women with meeting inclusion criteria were available for analysis (premenopausal = 735 and postmenopausal = 4,337). Differences between those who were included and excluded have been reported in Table 6.4. A flowchart describing sample selection is presented in Figure 6.1.

6.3.2 Ethical approval

UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/0382). All participants gave written informed consent before enrolment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

6.3.3 Measures

6.3.3.1 Menstruation history Measures of menstruation history included menopausal status, age of menopause, age of menarche and duration of reproductive stage. Participants self-reported menopausal status, age of menopause and age of menarche at baseline assessment, first follow up and second follow up assessment (i.e. imaging visit). The first instance of

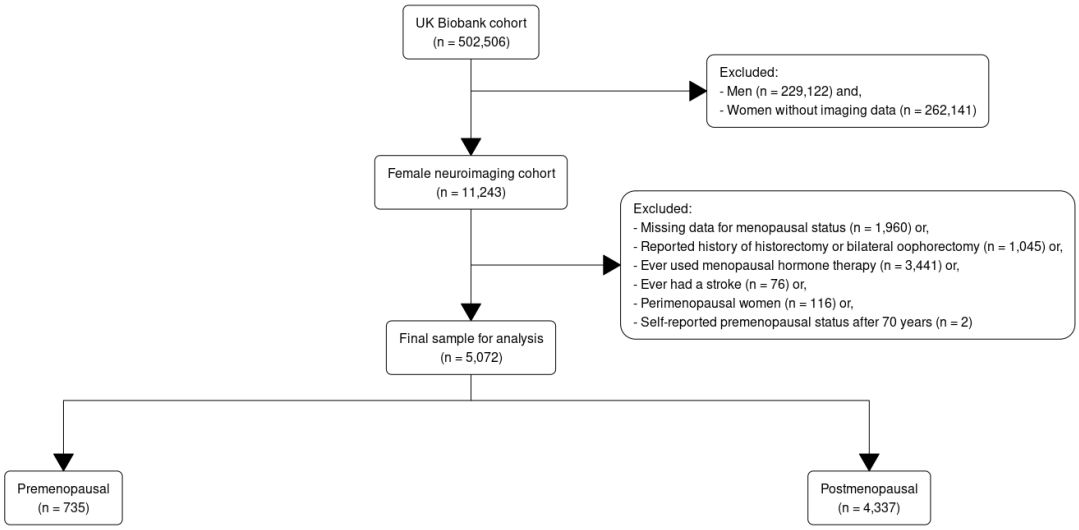

Figure 6.1: Flowchart describing sample selection.

self-reported age of menopause and age of menarche were used for all analyses. Years since menopause was computed by subtracting age of menopause from age at imaging visit. Duration of reproductive stage was calculated by subtracting age of menarche from age of menopause.

6.3.3.2 Neuroimaging

6.3.3.2.1 Image acquisition All participants were imaged across three imaging centers with identical scanners (3T Siemens Skyra running VD13A SP4) using a 32-channel head coil (K. L. Miller et al., 2016). T1-weighted images were acquired in the sagittal orientation using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence over a duration of 5 minutes; resolution = 1 x 1 x 1 mm; field of view = 208 x 256 x 256 matrix (K. L. Miller et al., 2016).

6.3.3.2.2 Segmentation and image analysis Images were processed and analyzed by the UK Biobank imaging team using the FMRIB Software Library (FSL) v6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard MRI analysis protocols have been reported elsewhere (Alfaro-Almagro et al., 2018; K. L. Miller et al., 2016). Briefly, the UK Biobank processing pipeline included a linear and non-linear registration to the MNI152 template using FLIRT and FNIRT, respectively. Brain extraction was achieved by using the inverse of the MNI152 alignment warp with a standard-space brain mask transformed into the native space and applied to the image. Automated tissue segmentation was conducted with FAST to segment the brain tissue into grey matter, white matter and cerebrospinal

fluid. As part of the segmentation, intensity bias was estimated, which generated a fully bias-field corrected version of the brain-extracted image. The external surface of the skull was then estimated from the T1-weighted image and used to normalise brain tissue volumes for head size, compared with the MNI152 template. Subcortical structures (including total hippocampal volume – i.e. left and right hippocampi combined) were derived using FIRST. Notably, all brain volumes used in subsequent analyses were normalised for head size.

6.3.3.3 Covariates Covariates included self-reported age, smoking history (i.e. ever or never), waist circumference, educational attainment, physical activity (i.e. number of days per week spent doing at least 10 minutes of continuous vigorous activity), frequency of alcohol intake (i.e. daily or almost daily, 3-4 times/week, 1-2 times/week, 1-3 times/month, special occasions only, never or prefer not to answer) and number of children. Further covariates included self-reported vascular/heart problems (including heart attack, angina or hypertension) and diabetes, diagnosed by doctor. Additionally, participants were also classified as hypertensive if they were using blood pressure medication and/or as diabetic if they were using oral anti-diabetic medication or insulin.

6.3.4 Statistical methods

All statistical analyses were conducted using R (version 4.0.0), in RStudio (version 1.3.952). Descriptive analyses were conducted using t-tests to compare premenopausal and postmenopausal women on continuous variables and Chi-square tests for categorical data.

Multiple linear hierarchical regression models were computed to quantify the association between menopausal status and brain volume (i.e. total brain volume and hippocampal volume), while controlling for age (centered on 45 years, the youngest reported age at imaging assessment), smoking history, waist circumference and diabetes history (Model 1). Model 2 further controlled for vascular/heart problems, education, physical activity, alcohol use and number of children. Interactions between menopausal status and age were also tested (Model 3). Since the age range for postmenopausal women exceeded that for premenopausal women, these analyses were repeated in an age restricted sample of 1,431 women aged 45 – 55 years (premenopausal = 720; postmenopausal = 711). To further delineate the effects of aging and menopause, sensitivity analyses using propensity matching was conducted to compare closely matched premenopausal and postmenopausal women (1:1 ratio). Exact matching was conducted for age and nearest neighbor matching for smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems and diabetes (using package MatchIt, version 3.0.2). A linear regression model

was then computed to estimate differences in total brain volume and hippocampal volume between the matched groups.

In addition, multiple linear hierarchical regression models were computed to determine the association between age, age of menopause, age of menarche, duration of reproductive stage and brain volume. Premenopausal women were excluded from analyses of age of menopause and duration of reproductive stage. For analysis concerning age of menopause, to improve interpretability, age of menopause was centered at 45 and years since menopause was used to account for current age. For duration of reproductive stage, in addition to age, age at menopause (centered on 45) was adjusted for to account for similar duration of reproductive stage lengths between women with varying ages of menopause. Due to our large sample size in this study, it was possible to resolve partial effects, even among predictors that were highly correlated. After accounting for age, Model 1 also controlled for smoking history, waist circumference and diabetes history. Model 2 further controlled for vascular/heart problems, education, physical activity, alcohol use and number of children.

The alpha level was set at < 0.05. Unstandardised beta-coefficients and proportional percentage differences in brain volume were reported. These proportions were computed by using the baseline brain volumes (i.e. when $x = 0$) and the beta-coefficients. Non-linear associations were explored by fitting a quadratic term for age. Assumptions of linearity, including homoscedasticity and normality of residuals were examined.

6.4 Results

The participants' demographic and health characteristics are presented in Table 6.1. Included participants were on average 60.32 years (standard deviation [SD] = 7.11, range = 45 to 79). On average, every year increase in age after 45 was associated with 0.34% (95% confidence interval [CI], -0.35 – -0.32) lower total brain volume and 0.26% (95% CI, -0.30 – -0.23) lower hippocampal volume, after adjusting for all covariates (Table 6.5). A scatterplot showing the distribution of total brain volume and hippocampal volume across time for premenopausal and postmenopausal women is presented in Figure 6.2.

Table 6.1: Demographic and health characteristics for premenopausal and postmenopausal women.

Characteristics/Measures	**Overall (N = 5072)**	**PreM (N = 735)**	**PostM (N = 4337)**	t/χ
Age, years; mean, (SD)	60.32 (7.11)	50.44 (2.33)	61.99 (6.23)	<0.001
Age at menopause; mean, (SD)	51.14 (3.49)	-	51.14 (3.49)	-
Years since menopause; mean, (SD)	10.86 (6.63)	-	10.86 (6.63)	-
Duration of reproductive stage; mean, (SD)	38.14 (3.86)	-	38.14 (3.86)	-
Age at menarche; mean, (SD)	13.01 (1.55)	13.13 (1.49)	12.99 (1.56)	0.024
Number of children; mean, (SD)	1.69 (1.19)	1.47 (1.16)	1.73 (1.19)	<0.001
Education college/degree; N (%)	2497 (49.23)	409 (55.65)	2088 (48.14)	<0.001
Hypertension; N (%)	672 (13.25)	56 (7.62)	616 (14.20)	<0.001
Diabetes; N (%)	87 (1.72)	10 (1.36)	77 (1.78)	0.518
Ever smoker; N (%)	2383 (46.98)	338 (45.99)	2045 (47.15)	0.523
Waist Circumference, cm; mean (SD)	81.30 (11.19)	80.64 (11.21)	81.42 (11.18)	0.083
Adjusted total hippocampal volume, mm^3; mean (SD)	10322 (997)	10478 (946)	10295 (1003)	<0.001
Adjusted total brain volume, mm^3; mean (SD)	1522864 (71618)	1567572 (60209)	1515287 (70631)	<0.001
Unadjusted total brain volume and cerebrospinal fluid, mm^3; mean (SD)	1146636 (90478)	1176811 (88738)	1141522 (89780)	<0.001

Abbreviations: N, number; SD, standard deviation; PreM, premenopausal women; PostM, postmenopausal women. Note: Of the overall sample, there were 13 (0.26%) missing for hypertension, 5 (0.10%) missing for diabetes, 17 (0.34%) missing for smoking status, 4 (0.08%) missing for waist circumference and 3 (0.06%) missing for hippocampal volume. Of postmenopausal women, there were 47 (1.08%) missing for duration of reproductive stage. Total brain volume and hippocampal volume were normalised by head size. Total hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

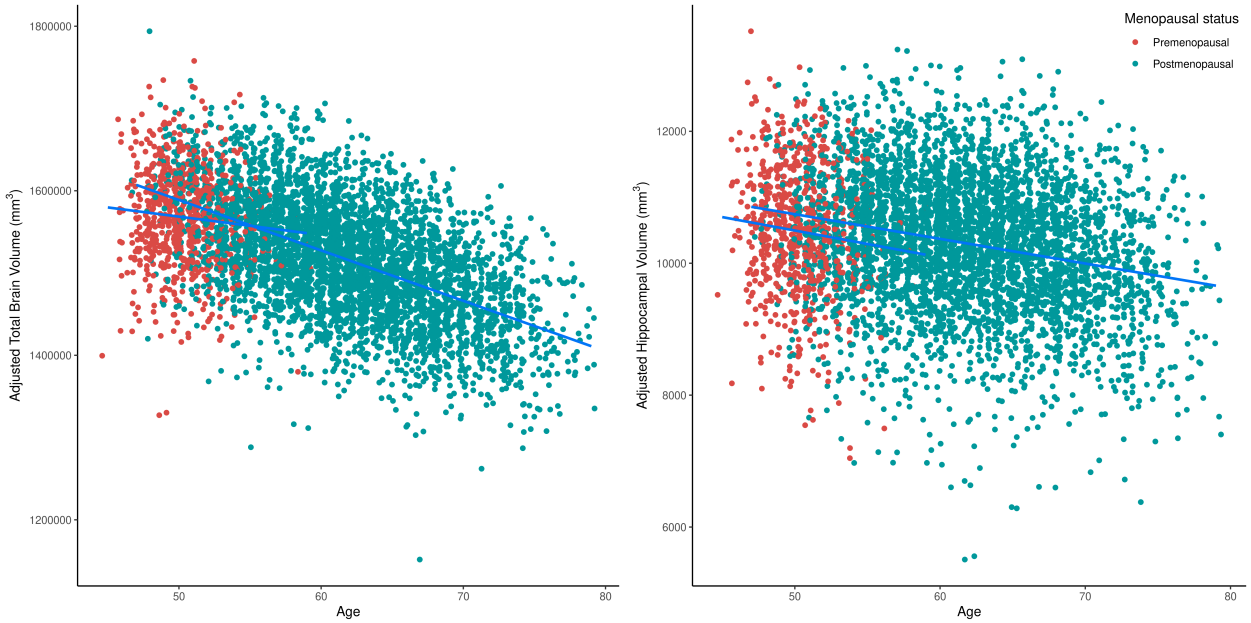

Figure 6.2: Scatterplot showing the distribution of total brain volume and hippocampal volume (adjusted for head size) across time for premenopausal and postmenopausal women..

6.4.1 Menopausal status and brain volume

After adjusting for all covariates, a significant effect of menopausal status was detected, with postmenopausal women having 1.06% (95% CI, 1.05 – 1.07) larger total brain volume and 2.17% (95% CI, 2.12 – 2.22) larger hippocampal volume than premenopausal women (Table 6.2). For total brain volume, there was a significant interaction between age and menopausal status, indicating that for every 1 year increase in age above 45, postmenopausal women experienced 0.23% greater reduction in total brain volume than premenopausal women (95% CI, -0.60 - -0.14). Similar interactive effects were not found in the hippocampus (Table 6.5). These findings were consistent in an age restricted sample of 1,431 women (premenopausal = 720; postmenopausal = 711), aged 45 to 55 (Table 6.6). Specifically, after adjusting for all covariates, postmenopausal women had 2.46% (95% CI, 2.29 – 2.62) larger total brain volume and 1.23% (95% CI, 1.17 – 2.29) larger hippocampal volume than premenopausal women (Table 6.6). For total brain volume, there was a significant interaction between age and menopausal status, indicating that for every 1 year increase in age above 45, postmenopausal women experienced 0.27% greater reduction in total brain volume than premenopausal women (95% CI, -0.71 - -0.06). Similar interactive effects were not found in the hippocampus (Table 6.6).

Table 6.2: Multiple linear hierarchical regression models were computed to generate estimates for the association between menopausal status and brain volume.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Yes – had menopause	16980	11308 – 22652	1.04	1.03 – 1.04	<0.001	0.312
	Age	-5970	-6253 – -5688	-	-	<0.001	-
Total brain volume (Model 2)	Yes – had menopause	17309	11630 – 22987	1.06	1.05 – 1.07	<0.001	0.009
	Age	-5967	-6261 – -5673	-	-	<0.001	-
Total brain volume (Model 3)	Menopause*age	-3880	-5738 – -2021	- 0.23	-0.60 - -0.14	<0.001	0.002
Hippocampal volume (Model 1)	Yes – had menopause	243	151 – 336	2.15	2.12 – 2.19	<0.001	0.056
	Age	-36	-41 – -32	-	-	<0.001	-
Hippocampal Volume (Model 2)	Yes – had menopause	244	151 – 337	2.17	2.12 – 2.22	<0.001	0.005
	Age	-36	-41 – -31	-	-	<0.001	-
Hippocampal Volume (Model 3)	Menopause*age	2	-28 – 33	0.03	-0.88 – 0.21	0.886	0.000

Abbreviations: CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff, proportional difference in brain volume between premenopausal and postmenopausal women, expressed as a percentage. Note: Model 1 is adjusted for age (centered on 45), smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. Model 3 includes an interaction term for menopausal status and age. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Sensitivity analyses based on propensity matching (participants' demographic and health characteristics are presented in Table 3), revealed a significant effect of menopausal status indicating that postmenopausal women had 0.82% (95% CI, 0.25 – 1.38) larger total brain volumes and 1.33% (95% CI, 0.01 – 2.63) larger hippocampal volumes than premenopausal women (Table 6.7).

6.4.2 Age of menopause and brain volume

For postmenopausal women, after adjusting for all covariates, age of menopause was significantly associated with total brain volume and hippocampal volume, indicating that every 1 year delay in menopause after 45 was associated with 0.32% (95% CI, -0.35 - -0.28) smaller total brain volume and 0.31% (95% CI, -0.40 - -0.22) smaller hippocampal volume (Table 6.8).

6.4.3 Age of menarche and brain volume

Age of menarche was significantly associated with total brain volume, indicating that every 1 year increase in age of menarche was associated with 0.10% larger total brain volume (95% CI, 0.04 – 0.16). This association was not observed for the hippocampus (Table 6.9).

6.4.4 Duration of reproductive stage and brain volume

In postmenopausal women, duration of reproductive stage was significantly associated with total brain volume, indicating that every 1 year increase in duration of reproductive stage was associated with 0.09% smaller total brain volume (95% CI, -0.15 - -0.03). This association was not observed for the hippocampus (Table 6.10).

6.5 Discussion

This study produced two main findings. Postmenopausal women were found to have larger brain volumes than premenopausal women but also experience greater decreases in total brain volume, but not hippocampal volume, over time. In addition, early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume.

Previous studies have found that postmenopausal women have smaller hippocampal volumes than premenopausal women (Goto et al., 2011; Mosconi et al., 2018), whereas others report no significant differences (G.-W. Kim et al., 2018; Sullivan et al., 2005). Notably, these studies did not precisely match premenopausal and postmenopausal women for age, possibly due to their limited sample size. This is of particular importance, given that aging and

menopause both progress concurrently, which can make it difficult to determine the individual contribution of each for measures of brain health. This study is unique, due to its sample size, in its capacity to conduct propensity matching for age (and other relevant covariates) and demonstrate that postmenopausal women had 0.82% and 1.33% larger total brain and hippocampal volumes than premenopausal women, respectively, which was not previously detected (Goto et al., 2011; G.-W. Kim et al., 2018; Mosconi et al., 2018; Sullivan et al., 2005). Furthermore, postmenopausal women experienced a greater reduction in total brain volume over time than premenopausal women (-0.23%/year), but not for hippocampal volume. A possible explanation for these findings is that early age of natural menopause may be detrimental for total brain volume, but not hippocampal volume given that, as age increased the differences in hippocampal volume reduction did not significantly differ between premenopausal and postmenopausal women. Another possible explanation is that increased systemic inflammation associated with menopause might explain the current results. Indeed, higher pro-inflammatory cytokine levels have been linked with the decline in estrogen with menopause (Christensen & Pike, 2015; Pfeilschifter et al., 2002). For example, previous research has demonstrated that postmenopausal women had higher levels of tumor necrosis factor-α (a pro-inflammatory cytokine) than premenopausal women, which persisted after adjustments for age and measures of fat mass (Sites et al., 2002). Larger brain volumes are typically interpreted as reflecting better cerebral health. However, it is possible that in the initial transition period to menopause, elevated systemic inflammation might lead to an increase in brain volume. Such effects have been previously demonstrated in multiple sclerosis (Cheriyan et al., 2012) and could explain the larger brain volumes detected in the present study in postmenopausal women. Furthermore, chronic inflammation has been associated with brain shrinkage which is consistent with the pattern of results observed in the present study (Jefferson et al., 2007). Future longitudinal neuroimaging/biomarker studies are required to investigate this question further. However, one alternative interpretation for the brain volume differences is that, for unknown reasons, those with larger brain volumes were more likely to have menopause earlier. Although possible, this explanation is less likely given that we were careful to control for relevant covariates in our analyses, including age, smoking history, waist circumference, diabetes, vascular/heart problems, education, physical activity, alcohol use and number of children. Furthermore, brain volumes that were unadjusted for age (and other relevant covariates), were larger in premenopausal women than postmenopausal women (Table 6.1). However, after considering the effect of age, regression analyses, age-restricted analyses and age-matched analyses all consistently demonstrated that postmenopausal women had larger total brain and hippocampal volumes than premenopausal women. Matched analysis also revealed no significant differences in unadjusted headsize between premenopausal and

postmenopausal women (Table 6.3), indicating that observed results were not attributable to headsize differences between groups. Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present.

Table 6.3: Demographic and health characteristics for the propensity matched sample of premenopausal and postmenopausal women.

Characteristics/Measures	**Overall (N = 734)**	**PreM (N = 367)**	**PostM (N = 367)**	t/χ
Age, years; mean, (SD)	52.01 (2.01)	52.01 (2.01)	52.01 (2.01)	1.000
Age at menopause; mean, (SD)	48.61 (3.03)	-	48.61 (3.03)	-
Years since menopause; mean, (SD)	3.40 (2.85)	-	3.40 (2.85)	-
Duration of reproductive stage; mean, (SD)	35.40 (3.45)	-	35.40 (3.45)	-
Age at menarche; mean, (SD)	13.21 (1.53)	13.23 (1.53)	13.18 (1.53)	0.687
Number of children; mean, (SD)	1.32 (1.14)	1.46 (1.14)	1.19 (1.12)	0.001
Education college/degree; N (%)	371 (50.54)	205 (55.86)	166 (45.23)	<0.001
Hypertension; N (%)	54 (7.36)	28 (7.63)	26 (7.08)	0.080
Diabetes; N (%)	10 (1.36)	6 (1.63)	4 (1.09)	0.750
Ever smoker; N (%)	360 (49.05)	168 (45.78)	192 (52.32)	0.090
Waist Circumference, cm; mean (SD)	78.99 (10.31)	80.00 (10.63)	77.97 (9.88)	0.008
Adjusted total hippocampal volume, mm^3; mean (SD)	10502 (951)	10432 (903)	10571 (993)	0.048
Adjusted total brain volume, mm^3; mean (SD)	1569485 (61219)	1563107 (59596)	1575862 (62229)	0.004
Unadjusted total brain volume and cerebrospinal fluid, mm^3; mean (SD)	1175093 (88370)	1177097 (87296)	1173089 (89506)	0.539

Abbreviations: N, number; SD, standard deviation; PreM, premenopausal women; PostM, postmenopausal women. Note: Total brain volume and hippocampal volume were normalised by head size. Total hippocampal volume refers to left and right hippocampi combined. Exact matching was conducted for age and nearest neighbor matching for smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems and diabetes. $p < 0.05$ considered significant.

The underlying biological mechanism between menstruation history and measures of brain health, such as brain volume, remains unclear. Previous meta-analyses have demonstrated that postmenopausal women have an unfavorable lipid profile compared to premenopausal women and also tend to accumulate adipose tissue after menopause, which has been associated with smaller hippocampal volume (Ambikairajah et al., 2020; Ambikairajah, Walsh, & Cherbuin, 2019; Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). However, these effects were predominantly attributable to aging (Ambikairajah, Walsh, & Cherbuin, 2019; Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019). Moreover, previous studies have used measures of menstruation history as a proxy for estimating estrogen exposure (de Kleijn et al., 2002; Fox et al., 2013; M. J. Prince et al., 2018). This may be because animal studies have found that estrogen potentially exerts neuroprotective effects on the brain, particularly for the hippocampus (Hara et al., 2015). Furthermore, estrogen receptors can be found throughout the brain, including the hippocampus (Almey et al., 2015; Österlund et al., 2000), a brain region that is sensitive to changes, particularly in the early stages of Alzheimer's disease (Braak & Braak, 1991; Zakzanis et al., 2003). However, exogenous estrogen use has had both positive and negative associations with the brain, depending on the time of initiation, duration and type of treatment (Boccardi et al., 2006; Erickson et al., 2005; C. Lord et al., 2008; Resnick et al., 2009; Wnuk et al., 2012). These results are part of the rationale for excluding women who self-reported MHT use in the current study. Notably, within the context of the estrogen hypothesis, our findings are not consistent with a neuroprotective role of endogenous estrogen exposure on brain volume, given that delayed age of menopause, early age of menarche and increasing duration of reproductive stage were negatively associated with brain volume. Although, it is important to note that women with similar menstruation duration may not necessarily have similar amounts of endogenous estrogen exposure. Furthermore, in addition to decreased endogenous production of estrogen, menopause is associated with changes in other hormones including progesterone, follicle-stimulating hormone, luteinizing hormone and testosterone (Al-Azzawi & Palacios, 2009; Harlow et al., 2012). Therefore, these results should be carefully interpreted, given that it is possible that observed associations between menstruation history and the brain may have been moderated by any combination of these hormones. Moreover, further research is required to determine whether the negative association between age of menopause and HV is potentially an indicator of future vulnerability for dementia.

6.5.1 Strengths and limitations

Key strengths of the current study include the large neuroimaging cohort (n = 5,072) and the use of sensitivity analyses, using propensity matching, to confirm that observed associations

were not driven by confounding factors often associated with age of menopause or aging. Furthermore, women who were classified as perimenopausal were not included in the current study. This was done to ensure that a clear comparison could be made between groups, with premenopausal women acting as control participants for any effect that was observed after menopause. However, this study had a number of limitations. Menopausal status, age of menopause and age of menarche were obtained by self-report and therefore may not be accurate. In addition, imaging data was only available at one timepoint, which limited our ability to precisely determine how brain volume changed within participants over time as they progressed from premenopause to postmenopause. Moreover, the healthy participant bias for the UK Biobank cohort (Fry et al., 2017) may have somewhat contributed to the observed results. Notably, participants included in the current study were also less likely to smoke, have diabetes or hypertension and were more likely to be younger, have a college degree and have larger hippocampal and total brain volumes compared to excluded participants (Table 6.4). Furthermore, the UK Biobank cohort included women who were 45 years of age and older, which may impact the generalisability of these findings, particularly to those who experienced early or premature menopause. Therefore further replication is required in other cohorts.

6.6 Conclusion

These findings indicate that menopause may contribute to brain volume beyond typical aging effects. Furthermore, critical female reproductive events including early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume. Further research is required to determine whether the negative association between age of menopause and HV is potentially an indicator of future vulnerability for dementia.

6.7 Supplementary materials

The supplementary materials for Chapter 6 include:

- **Table 6.4** Demographic and health characteristics of included and excluded participants.
- **Table 6.5** Demographic and health characteristics of included and excluded participants.
- **Table 6.6** Multiple linear hierarchical regression models were computed to generate estimates for the association between menopausal status and brain volume in women aged 45-55 years.
- **Table 6.7** A linear regression model was computed to generate estimates for the brain volume differences in propensity matched sample of premenopausal and postmenopausal women.
- **Table 6.8** Multiple linear hierarchical regression models were computed to generate estimates for the association between age of menopause and brain volume.
- **Table 6.9** Multiple linear hierarchical regression models were computed to generate estimates for the association between age of menarche and brain volume.
- **Table 6.10** Multiple linear hierarchical regression models were computed to generate estimates for the association between duration of reproductive stage and brain volume.

Table 6.4: Demographic and health characteristics of included and excluded participants.

	Overall	**Included**	**Excluded**	
Characteristics/Measures	**(N = 11243)**	**(N = 5072)**	**(N = 6171)**	t/χ
Age, years; mean, (SD)	61.93 (7.32)	60.32 (7.11)	63.25 (7.23)	<0.001
Age at menopause; mean, (SD)	50.17 (4.84)	51.14 (3.49)	49.21 (5.74)	<0.001
Years since menopause; mean, (SD)	13.20 (7.82)	10.86 (6.63)	15.54 (8.22)	<0.001
Duration of reproductive stage; mean, (SD)	37.21 (5.10)	38.14 (3.86)	36.27 (5.94)	<0.001
Age at menarche; mean, (SD)	12.97 (1.56)	13.01 (1.55)	12.93 (1.57)	0.005
Number of children; mean, (SD)	1.75 (1.16)	1.69 (1.19)	1.79 (1.14)	<0.001
Education college/degree; N (%)	5055 (44.96)	2497 (49.23)	2558 (41.45)	<0.001
Hypertension; N (%)	1933 (17.19)	672 (13.25)	1261 (20.43)	<0.001
Diabetes; N (%)	201 (1.79)	87 (1.72)	114 (1.85)	0.645
Ever smoker; N (%)	5561 (49.46)	2383 (46.98)	3178 (51.50)	<0.001
Waist Circumference, cm; mean (SD)	81.88 (11.16)	81.30 (11.19)	82.35 (11.11)	<0.001
Adjusted total hippocampal volume, mm^3; mean (SD)	10263 (1023)	10322 (997)	10214 (1041)	<0.001
Adjusted total brain volume, mm^3; mean (SD)	1514640 (72708)	1522864 (71618)	1507880 (72905)	<0.001
Unadjusted total brain volume and cerebrospinal fluid, mm^3; mean (SD)	1139707 (90856)	1146636 (90478)	1134013 (90778)	<0.001

Abbreviations: N, number; SD, standard deviation. Note: Total brain volume and hippocampal volume were normalised by head size. Total hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.5: Demographic and health characteristics of included and excluded participants.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Age	-6065	-6350 – -5780	-0.34	-0.35 - -0.33	<0.001	0.297
Total brain volume (Model 2)	Age	-6061	-6359 – -5763	-0.34	-0.35 – -0.32	<0.001	0.009
Hippocampal volume (Model 1)	Age	-36	-41 – -32	-0.26	-0.30 - -0.23	<0.001	0.057
Hippocampal volume (Model 2)	Age	-36	-41 – -31	-0.26	-0.30 – -0.23	<0.001	0.005

Abbreviations: CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff/year, proportional difference in brain volume for every year increase in age, expressed as a percentage. Note: Age is centered on 45 years. Model 1 is adjusted for smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.6: Multiple linear hierarchical regression models were computed to generate estimates for the association between menopausal status and brain volume in women aged 45-55 years.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Yes – had menopause	9260.00	1665 – 16854	0.57	0.50 – 0.64	0.017	0.022
	Age	-3612.00	-5179 – -2044	-	-	<0.001	-
Total brain volume (Model 2)	Yes – had menopause	40619.00	17270 – 63967	2.46	2.29 – 2.62	0.001	0.022
	Age	-1675.00	-3735 – 386	-	-	0.111	-
Total brain volume (Model 3)	Menopause*age	-4564.00	-7752 – -1377	-0.27	-0.71 - -0.06	0.005	0.000
Hippocampal volume (Model 1)	Yes – had menopause	145.00	25 – 265	1.28	1.14 – 1.44	0.018	0.015
	Age	-33.00	-58 – -8	-	-	0.010	-
Hippocampal Volume (Model 2)	Yes – had menopause	138.00	16.19 – 259.51	1.23	1.17 – 1.29	0.026	0.019
	Age	-29.00	-54.47 – -4.18	-	-	0.022	-
Hippocampal Volume (Model 3)	Menopause*age	3.18	-47 – 54	0.03	-1.04 – 0.48	0.902	0.000

Abbreviations: CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff, proportional difference in brain volume between premenopausal and postmenopausal women, expressed as a percentage. Note: Model 1 is adjusted for age (centered on 45), smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. Model 3 includes an interaction term for menopausal status and age. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.7: A linear regression model was computed to generate estimates for the brain volume differences in propensity matched sample of premenopausal and postmenopausal women.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	R^2
Total brain volume	Yes – had menopause	12756	3926 – 21586	0.82	0.25 – 1.38	0.005	0.011
Hippocampal volume	Yes – had menopause	139	1 – 277	1.33	0.01 – 2.63	0.048	0.005

Abbreviations: CI, confidence interval; R^2, the coefficient of determination; % Diff, proportional difference in brain volume between premenopausal and postmenopausal women, expressed as a percentage. Note: Exact matching was conducted for age and nearest neighbor matching for smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems and diabetes. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.8: Multiple linear hierarchical regression models were computed to generate estimates for the association between age of menopause and brain volume.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Age at menopause	-5166	-5712 – -4620	-0.32	-0.35 - -0.28	<0.001	0.300
	Years since menopause	-6155	-6443 – -5867	-	-	<0.001	-
Total brain volume (Model 2)	Age at menopause	-5063	-5620 – -4507	-0.32	-0.35 - -0.28	<0.001	0.009
	Years since menopause	-6160	-6460 – -5858	-	-	<0.001	-
Hippocampal volume (Model 1)	Age at menopause	-35	-45 – -26	-0.32	-0.41 - -0.23	<0.001	0.057
	Years since menopause	-37	-41 – -32	-	-	<0.001	-
Hippocampal Volume (Model 2)	Age at menopause	-34	-43 – -25	-0.31	-0.40 - -0.22	<0.001	0.005
	Years since menopause	-36	-41 – -31	-	-	<0.001	-

Abbreviations: CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff/year, proportional difference in brain volume for every year increase in age of menopause after 45, expressed as a percentage. Note: Age at menopause is centered on 45 years. Model 1 is adjusted for years since menopause, smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.9: Multiple linear hierarchical regression models were computed to generate estimates for the association between age of menarche and brain volume.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Age of menarche	2080	1010 – 3150	0.11	0.06 – 0.17	<0.001	0.310
	Age	-5474	-5707 – -5240	-	-	<0.001	-
Total brain volume (Model 2)	Age of menarche	1862	788 – 2937	0.10	0.04 – 0.16	0.001	0.007
	Age	-5444	-5689 – -5199	-	-	<0.001	-
Hippocampal volume (Model 1)	Age of menarche	10	-7 – 28	0.08	-0.06 - -0.22	0.248	0.052
	Age	-30	-33 – -26	-	-	<0.001	-
Hippocampal Volume (Model 2)	Age of menarche	9	-9 – 26	0.07	-0.08 – 0.21	0.342	0.005
	Age	-29	-33 – -25	-	-	<0.001	-

CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff/year, proportional difference in brain volume for every year increase in age of menarche, expressed as a percentage. Note: Model 1 is adjusted for age, smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

Table 6.10: Multiple linear hierarchical regression models were computed to generate estimates for the association between duration of reproductive stage and brain volume.

Brain volume	**Predictors**	**Estimate**	**95% CI**	**% Diff/year**	**95% CI**	**p-value**	ΔR^2
Total brain volume (Model 1)	Duration of reproductive stage	-1962	-3102 – -821	-0.10	-0.16 - -0.04	0.001	0.302
	Age	-6144	-6433 – -5854	-	-	<0.001	-
Total brain volume (Model 2)	Duration of reproductive stage	-1750	-2896 – -603	-0.09	-0.15 - -0.03	0.003	0.008
	Age	-6140	-6442 – -5837	-	-	<0.001	-
Hippocampal volume (Model 1)	Duration of reproductive stage	-10	-29 – 9	-0.07	-0.23 – 0.07	0.311	0.059
	Age	-37	-42 – -32	-	-	<0.001	-
Hippocampal Volume (Model 2)	Duration of reproductive stage	-9	-28 – 10	-0.07	-0.22 – 0.08	0.379	0.005
	Age	-36	-41 – -31	-	-	<0.001	-

Abbreviations: CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff/year, proportional difference in brain volume for every year increase in duration of reproductive stage, expressed as a percentage. Note: Model 1 is adjusted for age, age at menopause (centered on 45), smoking history, waist circumference and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use and number of children. All estimates are unstandardised i.e. mm^3. Total brain volume and hippocampal volume were normalised by head size. Hippocampal volume refers to left and right hippocampi combined. $p < 0.05$ considered significant.

7 Discussion

7.1 General discussion

Maintaining a healthy brain has been recognised as an important health challenge facing women, given global estimates indicate almost twice as many women die of dementia than men (GBD 2019 Collaborators, 2021). In part, this is due to their increased longevity, however, this does not explain all of the difference (GBD 2019 Collaborators, 2021). Other contributors include different exposure to risk factors as well as sex-related physiological differences. This thesis focused on the latter, specifically in relation to possible impacts of menopause, as this stage of life has been suggested to involve particular risks to brain health. To address this question, five studies were conducted to precisely characterise and quantify (1) changes in fat mass during menopause; (2) lipid profile differences during menopause; (3) heterogeneity of menopause nomenclature used in peer-reviewed literature; (4) changes in fat mass and the brain; and (5) menstruation history (including menopausal status and age at menopause) and the brain (Figure 7.1). Moreover, an important conceptual and theoretical question embedded throughout this thesis has been to determine how much of the observed effects were attributable to ageing, rather than a possible effect of menopause. This has been a significant challenge, given menopause and ageing co-occur.

The following sections provide a concise integrated summary of findings, followed by a discussion of the theoretical implications of these findings in the context of the existing literature. Finally, a summary of insights/recommendations that have emerged from this thesis are proposed and possible future research directions are explored.

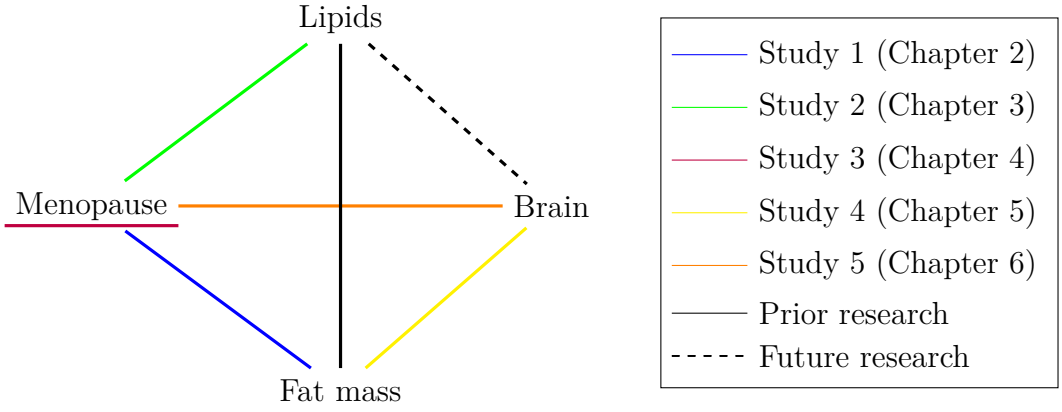

Figure 7.1: Summary of PhD research.

7.2 Integrated summary of findings

The findings from this thesis have demonstrated an association between menopause and the brain, which cannot be uniquely explained by ageing. Specifically, although menopause alone was not found to be negatively associated brain health, it was associated with somewhat poorer brain health when considered concurrently with other changes around menopause. Moreover, when considering that women tend to gain abdominal fat around menopause, as well as develop an unfavourable lipid profile, and given extensive evidence in the literature that higher abdominal fat and lipid levels are associated with a greater risk of cerebro-vascular disease and dementia, hypothesising a link between menopause and poorer brain health seems warranted but will require further confirmation in future research.

As a whole, the findings from this thesis paint an optimistic picture for women's health, since the risk factors identified and linked with deleterious brain health outcomes are modifiable. If adequate support is available at a health policy, clinical and community level, these specific risks to brain health may be reduced or prevented.

The following sections will critically evaluate and further discuss the theoretical implications of these findings in the context of the existing literature.

7.3 Integrated discussion

Menopause is a critical stage of female reproductive ageing, however, the contributions of menopause to brain health have been historically understudied in the context of ageing (Taylor et al., 2019). Over a period of 23 years (1995 to 2017), peer-reviewed neuroimaging articles which focused on menopause accounted for approximately 2% of the ageing literature (Taylor et al., 2019). There are many possible explanations (including sex biases in research), however, one key reason related to the focus of this thesis includes the statistical and methodological challenges associated with partitioning out effects due to ageing compared with menopause, given both co-occur. Therefore, the major aims and findings of this thesis address whether menopause was associated with brain health over and above ageing. Answering this question has important implications for women's health, as women will on average spend almost 40% of their lives in a postmenopausal state (Murray et al., 2015; Schoenaker et al., 2014) and are almost twice as likely to die from dementia than men (GBD 2019 Collaborators, 2021). Therefore, understanding the contributions of menopause to brain health will better inform treatment and prevention advice that directly targets women's health.

There are very good reasons why menopause and its related changes in the body may be a risk factor for brain health. Earlier menopause has been associated with greater risk of

cardiovascular disease (CVD; <50 vs 50 years; 25%, 95% CI: 15% to 35%) (Atsma et al., 2006) and increased odds of type II diabetes (< 45 vs 45-55 years; 15%, 95% CI: 4% to 26%) (Anagnostis et al., 2019). These risk factors are known to impair brain health, with well-established links to dementia (de Bruijn & Ikram, 2014; Exalto et al., 2012). In part, this is why the present thesis focused on changes in fat mass and lipids around menopause. Moreover, previous narrative reviews that have described changes in fat mass (Davis et al., 2012) and lipids (Carr, 2003; Gaspard et al., 1995; Kolovou & Bilianou, 2008) around menopause have been limited by a paucity of quantitative estimates, which are typically made available through a systematic review of the literature with meta-analyses. As a result, the first two studies of this thesis have provided important quantitative estimates regarding how fat mass and lipid profiles differ between premenopausal and postmenopausal women. Furthermore, it was previously unclear precisely how much of the changes in fat mass and lipid profiles were attributable to ageing, compared with a possible effect of menopause, which will be discussed next.

7.3.1 Fat mass and lipid changes around menopause

Converging lines of evidence from this thesis have revealed changes in total fat mass were largely attributable to increasing age, with menopause having no detectable additional influence. The progressive increase in total body fat is not unexpected since increasing fat mass coincides with age related decreases in fat-free mass (which consists of metabolically active tissues) and physical activity (Pontzer et al., 2021; Sallis, 2000). Specifically, previous research indicates that in women aged 18 to 45 years, BMI typically increases at a rate of 0.16 $kg/m^2/year$, whereas body fat percentage increases at a rate of 0.41%/year (Siervogel et al., 1998). Longitudinal results from **Chapter 2** reflect similar annual estimates for BMI (0.14 $kg/m^2/year$) and body fat percentage (0.41%/year), which indicates that the rates of change remain the same throughout early adulthood and middle age, with menopause having no detectable additional influence above and beyond the effect of ageing. Similarly, for lipid profiles, results from **Chapter 3** indicates that postmenopausal women tend to develop an unfavourable lipid profile compared to premenopausal women, which were partly attributable to the mean age difference between groups. As noted previously, lipid profiles are highly related to fat mass (Hodson et al., 2015). Therefore, it is possible that the age-related changes in lipid profiles are linked with similar factors that drive increases in fat mass including changes in energy expenditure (i.e. physical activity levels), energy intake (i.e. diet), sleep quality and quantity (Chaput & Tremblay, 2012; Roberts & Rosenberg, 2006). The results from Chapters **2** and **3** indicate that attributing increases in total body fat and the emergence of unfavourable lipid profiles to menopause may be misguided and potentially unhelpful.

Instead, age related changes in total body fat and lipids should be monitored consistently across the lifespan, with appropriate lifestyle advice/recommendations and education provided early for adequate opportunity to intervene and improve health outcomes for women.

A different pattern of results was detected for changes in fat distribution around menopause. Indeed, clear evidence of a redistribution of fat after menopause was observed. This included a decrease in total leg fat (0.17%/year) and an increase in central fat (trunk fat percentage; 0.40%/year and waist circumference (longitudinal); 0.51cm/year). The inclusion of women using hormone replacement therapy (HRT) resulted in significant increases in body fat (β = 2.46%, 95% CI: 0.16 to 4.76), but significant decreases in central fat (trunk fat percentage; β = -3.65%, 95% CI: -5.91 to -1.38), compared to analyses excluding women using HRT. This suggests a potential protective role of HRT in preventing/reducing the redistribution of fat to the abdomen, although not in preventing overall fat mass gain. These changes may, at least in part, reflect hormonal shifts that occur during midlife with women having a higher androgen (i.e. testosterone) to estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition (Janssen et al., 2015). One alternative explanation is that these findings reflect a healthy participant bias, given that women who use HRT tend to be more affluent, educated, leaner and have a better cardiovascular risk profile than non-HRT users (Matthews et al., 1996; H. D. Nelson et al., 2002). Although possible, this explanation is less likely given that the results of **Chapter 2** align with a previous meta-analysis of 8 randomised control trials, which found that postmenopausal women using HRT had less central fat, compared to placebo (Salpeter et al., 2006). The central deposition of fat is of particular clinical significance given that a 1cm increase in waist circumference has been associated with a 2% increase in risk of CVD (De Koning et al., 2007). In the present context, this suggests that postmenopausal women may have had an almost 8% increased risk of CVD than premenopausal women. Furthermore, a higher testosterone/estradiol ratio has also been associated with deleterious health consequences in women, such as CVD (Zhao et al., 2018). These findings may in part help explain why earlier menopause has been associated with greater risk of CVD (Atsma et al., 2006) and why premenopausal women have lower CVD incidence and mortality rates compared with men of the same age (Mikkola et al., 2013), whereas postmenopausal women experience higher mortality rates due to CVD compared to men of the same age (McAloon et al., 2016).

The findings from **Chapter 2** are important as they suggest women will have varied experiences in changing fat mass distribution depending on their age at menopause and history of HRT use. Despite the possible benefits associated with HRT use on body fat distribution, current guidelines suggest that HRT use is not recommended without a clear indication, such as the

treatment of menopausal symptoms, and should not be used by women who have previously had breast cancer or for the prevention of cardio-metabolic diseases (de Villiers et al., 2016; Moyer & U.S. Preventive Services Task Force, 2013). Taken together with these recommendations, it is suggested that clinicians recommend intensive lifestyle/behavioural modifications in the years preceding menopause (mean age at natural menopause = 48.78 years, SD = 1.45 years) (Schoenaker et al., 2014), to mitigate the risks associated with central fat accumulation. Notably, these recommendations have increasing importance for women who exhibit risk factors for early age at menopause, such as a history of smoking.

Findings from **Chapter 3** indicate that age explains some but not all of the differences in lipid levels observed between premenopausal and postmenopausal women (R^2 = 9.71% to 40.08%). Similar lipid profiles were observed between age restricted samples of premenopausal and postmenopausal women (mean age difference $\leq$ 5 years vs $>$ 5 years), with the exception of triglycerides, which increased with age. The remaining variability in lipid differences between premenopausal and postmenopausal women remains to be elucidated. One possibility is that menopause accounts, at least in part, for these differences. Whilst there were insufficient longitudinal studies available for meta-analysis, a longitudinal study revealed a 6% increase in total cholesterol, an 11% increase in triglycerides and a 10% increase in low density lipoprotein levels within 3 to 6 months of menopause (Jensen et al., 1990). Furthermore, there is evidence that lipid profiles fluctuate at different stages of the menstrual cycle in premenopausal women, with the follicular phase (indicative of high endogenous estrogen levels) being associated with decreased total cholesterol, low density lipoproteins and triglycerides (Gaskins et al., 2010). Additionally, a randomised controlled trial found that women who used HRT had increased high density lipoprotein and decreased low density lipoprotein levels, compared with placebo, independent of age at menopause onset, baseline lipid values and measures of fat mass (Binder et al., 2001). Surprisingly, no effect of HRT was found in **Chapter 3**. This may be explained by the well documented differences that emerge from the less robust design of cross-sectional studies, compared with randomised controlled trials. Moreover, this discrepancy may be accounted for by the complex interactions that HRT use has with the body, with varying benefits and disadvantages depending on the time of initiation, type and duration of treatment (H. D. Nelson et al., 2002). Alternatively, other unmeasured and/or unreported genetic and environmental factors, such as ethnicity, dietary changes, mood disorders and medications used in their treatment, physical activity levels, metabolic activity, and variation in sleep length and quality (Davis et al., 2012; Demerath et al., 2011; Patel et al., 2006; Sternfeld et al., 2004), which varied between premenopausal and postmenopausal women may have accounted for the differences observed in lipid profiles. Unfortunately, insufficient data from included studies limited the investigation of these specific questions. Further insights regarding the

precise influence of these modifiable lifestyle factors on overall lipid changes in women around menopause will allow for the development of targeted and holistic intervention programs that seek to mitigate the identified risks for women.

7.3.2 Menopause related changes and the brain

As noted earlier, maintaining a healthy brain has been recognised as an important health challenge facing women, given global estimates indicate almost twice as many women die from dementia than men (GBD 2019 Collaborators, 2021). Menopause and its related changes in the body have been a key focus of this thesis because of the possible risks to brain health. In this thesis, brain volume was used as a measure to assess brain health. Strong rationale underpinned the selection of the hippocampus as a region of interest (see **Brain ageing** for more details). Briefly, the hippocampus is sensitive to changes, particularly in the early stages of neurodegenerative diseases, such as dementia (Braak & Braak, 1991; Karas et al., 2004; Zakzanis et al., 2003). Furthermore, the accumulation of fat tissue, particularly visceral fat, which was previously shown to accumulate during menopause in **Chapter 2**, is known to be closely linked with elevated levels of pro-inflammatory cytokines (Fontana et al., 2007; Gregor & Hotamisligil, 2011; A. A. Miller & Spencer, 2014). Notably, higher pro-inflammatory cytokines have been associated with smaller hippocampal volumes (Sudheimer et al., 2014). Similarly, declining estrogen levels associated with menopause have been linked with higher pro-inflammatory cytokine levels and decreased density of dendritic spines and synapses in subregions of the hippocampus (Christensen & Pike, 2015; Gould et al., 1990; Pfeilschifter et al., 2002; C. Woolley et al., 1990; C. S. Woolley & McEwen, 1992). Therefore, **Chapter 5** investigated how changes in fat mass, including central fat, was associated with changes in brain volume, specifically the hippocampus, and is discussed next. **Chapter 6** investigated the relationship between menopause and the brain and is discussed in **Menopause and the brain**

The findings from **Chapter 5** suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself, emphasising the importance of maintaining normal weight for brain health. Specifically, individuals with chronic overweight/obesity had significantly lower hippocampal volumes (WC: 1.13%; WTHR: 0.79% and BMI: 0.49% smaller after adjusting for all covariates measured at baseline) when compared with those who maintained a normal level of fat mass (i.e. WC: $<$ 80 cm in women and $<$ 94 cm in men; WTHR: $<$ 0.85 in women and $<$ 0.90 in men and BMI: $<$ 25 kg/m^2 in women and men) at baseline and second follow-up (average follow-up = 7.66 years). Moreover, individuals who were within a normal range of fat mass at second follow-up assessment, yet

were previously classified as having overweight/obesity at baseline had lower hippocampal volumes than those who remained maintained fat mass within the normal range across assessments (WC: 0.73%; WTHR: 0.55% and BMI: 0.48% smaller after adjusting for all covariates measured at baseline). Therefore, these results appear to indicate that it is the chronicity of overweight/obesity that is associated with lower hippocampal volumes. When considered in conjunction with the findings from **Chapter 2**, these results have important implications for women, who tend to gain weight (particularly visceral fat) around menopause. Specifically, the impact of weight gain around menopause on the brain likely depends on an individual's previous weight status history. For example, weight gain around menopause is less likely to be harmful for brain health if this change is within the normal threshold, compared to an increase from normal to overweight/obese or within overweight/obese categories. Therefore, it is suggested that clinicians carefully consider an individual's weight status history when assessing the possible impacts that changes in fat mass around menopause may have on brain health. Moreover, weight change around menopause should be closely monitored and appropriate lifestyle/behavioural modifications should be recommended and utilised, to ensure waist circumference is within 80cm (i.e. the critical threshold used to define normal stable). Notably, the average waist circumference for postmenopausal women in **Chapter 2** was 84.06cm and the standard deviation was 2.61cm. This indicates that at least 84% of the postmenopausal women included in the meta-analysis had a waist circumference above 80cm. At a population level, this would suggest that 8 out of every 10 postmenopausal women are at risk of having a waist circumference beyond the recommended threshold for optimal brain health. This highlights the widespread impact that changes in fat mass have for women's health and should be a key consideration when designing health policy and providing clinical advice to adequately support women seeking health management plans around menopause. Furthermore, since premenopausal women have, on average, a waist circumference of 81 cm at 47 years, with menopause occurring at approximately 49 years, educational programs and interventions should occur at least in the early to mid-40s, and probably before, to mitigate risks to brain health associated with central fat accumulation around menopause.

7.3.3 Menopause and the brain

Evidence reviewed thus far provides very good reasons as to why menopause may be detrimental to brain health. As noted earlier, women are disproportionately affected by dementia (GBD 2019 Collaborators, 2021) and brain volume loss within the hippocampus has been reliably associated with the early stages of dementia, specifically Alzheimer's disease (Zakzanis et al., 2003). Moreover, women with low levels of estradiol (5 to 11.9 pg/ml) are four times more likely to have Alzheimer's disease compared to women with high amounts of estradiol

(19.9 mg/ml to 77 pg/ml), after adjusting for age, education, ethnicity, body mass index and presence of *APOE* $\epsilon 4$ allele (Manly et al., 2000). Additionally, menopause is associated with changes in other hormones, including lower progesterone levels, which have been associated with Alzheimer's disease pathogenesis (C. J. Pike et al., 2009). However, the association between menopausal status and brain health in middle to early old-age adults has been inconsistent. Some research has demonstrated postmenopausal women experience greater decreases in hippocampal volume compared to premenopausal women (Goto et al., 2011; Mosconi et al., 2018), whereas others report no significant differences (G.-W. Kim et al., 2018; Sullivan et al., 2005). As noted in **Chapter 4**, one possibility is that the standards for defining menopause nomenclature, such as *premenopause* vary substantially across publications. Such variability makes the synthesis and comparison of findings difficult. Another possibility is that previous studies did not precisely match premenopausal and postmenopausal women for age, possibly due to their limited sample size, which may have confounded a possible effect of menopause with that of typical ageing. It was hypothesised that appropriate statistical considerations for age would reveal a possible negative association between menopause and brain health.

The findings from **Chapter 6** indicated an association between menopause and the brain, which cannot be uniquely explained by ageing. Contrary to the proposed hypothesis, converging lines of evidence revealed that postmenopausal women had larger hippocampal and total brain volumes than premenopausal women. Importantly, several statistical analyses that carefully considered an effect of age were used (explained in detail in **Chapter 6**), including multiple regression analyses, propensity matching analysis (with exact matching for age), and age-restricted analyses, which all yielded consistent findings (i.e. larger brain volumes in postmenopausal women) that were not previously detected (Goto et al., 2011; G.-W. Kim et al., 2018; Mosconi et al., 2018; Sullivan et al., 2005). This result was surprising, since **Chapter 1** presented strong theoretical reasons for a negative influence of menopause on brain health. However, increased systemic inflammation associated with menopause might help explain the current results. Higher pro-inflammatory cytokine levels have been linked with the decline in estrogen with menopause (Christensen & Pike, 2015; Pfeilschifter et al., 2002). For example, previous research has demonstrated that postmenopausal women had higher levels of tumour necrosis factor-α (a pro-inflammatory cytokine) than premenopausal women, which persisted after adjustments for age and measures of fat mass (Sites et al., 2002). Larger brain volumes are typically interpreted as reflecting better cerebral health. However, it is possible that in the initial transition period to menopause, elevated systemic inflammation might lead to an increase in brain volume. Such effects have been previously demonstrated in multiple sclerosis (Cheriyan et al., 2012) and could explain the larger brain volumes detected in the

present study in postmenopausal women. One alternative interpretation for the brain volume differences is that, for unknown reasons, those with larger brain volumes might have been more likely to have menopause earlier. Although possible, this explanation is less likely given the care with which relevant covariates in our analyses were controlled for, including age, smoking history, waist circumference, diabetes, vascular/heart problems, education, physical activity, alcohol use and number of children. Furthermore, brain volumes that were unadjusted for age (and other relevant covariates), were larger in premenopausal than postmenopausal women. Matched analysis also revealed no significant differences in unadjusted head size between premenopausal and postmenopausal women, indicating that the observed results were not attributable to head size differences between groups. Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present. Another possible explanation may be that menopause confers a protective effect on brain health, which contributes to female longevity and therefore, increased dementia risk. However, the results of **Chapter 6** should be carefully interpreted and require longitudinal neuroimaging studies to investigate these possibilities further, before appropriate clinical recommendations can be provided.

7.4 Summary of recommendations

A key motivation for this thesis was to identify the contributions of menopause to brain health to better inform treatment and prevention advice that directly seeks to improve women's health. A number of robust insights/recommendations have emerged from the findings which have been discussed in detail throughout the thesis, and are summarised below:

- The misattribution of increases in total body fat and the related unfavourable lipid profile to menopause is likely to be unhelpful and disempowering for women. Instead, a more thoughtful and pro-active societal response needs to occur so women have more time and safe spaces to learn about the changes around menopause and implement appropriate lifestyle advice/recommendations. This educational advice should be provided earlier in women's lives to allow more time for the development and maintenance of a healthier lifestyle across the lifecourse. As for other complex health problems, any health policy response should not be limited to advice or education but also aim to address related systemic risk factors, such as social disadvantage, poor access to healthy foods and limited access to green or safe environments, to name a few.
- Women will have varied experiences in changing fat mass distribution depending on their age at menopause and history of HRT use. For women who do not use HRT, menopause will be more likely associated with increased central fat accumulation. For brain health, it is important for waist circumference to be consistently monitored and

ideally maintained below 80cm. This is important, given findings revealed that at least 8 out of every 10 postmenopausal women are at risk of having a waist circumference beyond this recommended threshold. Whilst the use of HRT may result in less central fat accumulation, its use should be guided by clinical advice and need and not exclusively for the purpose of managing weight gain, since its use has been shown to be associated with other health risks, such as breast cancer (see **Hormone replacement therapy** for more details).

- Given waist circumference increases by 0.51cm per year (on average for women), clinicians, policy makers and the public should give consideration to this evidence to identify appropriate lifestyle intervention responses and track the effectiveness of these strategies. Since premenopausal women have, on average, a waist circumference of 81cm at 47 years, with menopause occurring at approximately 49 years, educational programs and interventions should occur at least in the early to mid-40s, and probably before, to mitigate risks to brain health associated with central fat accumulation. These recommendations have increasing importance for women who exhibit risk factors for early age at menopause, such as a history of smoking or family history of early age at menopause (see **Age at menopause** for more details).
- Menopause nomenclature varies in the scholarly literature making synthesis and interpretation of research findings difficult. Indeed, there is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*, which may reflect a limitation of the Stages of Reproductive Aging Workshop (STRAW) criteria. Some suggestions/recommendations to address this include the transparent operationalisation of *premenopause*, which is not currently explicitly stated in STRAW or STRAW + 10. Moreover, defining regular menstruation as the number of menstrual cycles per 3 months, as a minimum requirement, which would be a practical reporting timeframe both clinically and for women to recall accurately. Additionally, it may be helpful to consider the utility of introducing normative age-ranges as a supplementary criteria for defining stages of reproductive ageing. The use of consistent terminology in research will enhance our capacity to compare results from different studies that investigate issues related to women's health and ageing.

7.5 Future research directions

The findings from the present research could be extended in a number of different directions. Firstly, whilst brain volume is a useful index of brain health, it is primarily reflective of structural, rather than functional brain health. Given ageing impacts both structure and

function, there is a need for other measures that account for these changes. One such possibility is with a multimodal brain age index (Cole, 2020; Franke et al., 2010). Brain age is calculated with statistical models that use neuroimaging data to predict chronological age. The predicted age can be compared with the actual age to determine whether the brain appears younger or older. Given the novelty of the findings from **Chapter 6**, a promising application of a brain age index would be to investigate whether it significantly differed between age-matched premenopausal and postmenopausal women. Furthermore, it would be possible to determine whether age at menopause predicts brain age. Another approach would be to determine whether the larger hippocampal volume observed in postmenopausal women compared with age-matched premenopausal women translate to functional differences in cognition, such as memory function. Moreover, inflammatory markers could also be used to index brain health. The use of a multimodal brain age index, cognitive data and inflammatory markers would allow for a better understanding of whether menopause confers protective or harmful effects for brain health.

Women who used HRT were excluded from Study 5, partly because HRT use may confound the accurate classification of women, particularly between premenopausal and postmenopausal stages. HRT use has also been shown to modulate brain volume, however, these effects vary depending on the time of initiation and duration of treatment (Boccardi et al., 2006; Erickson et al., 2005; Erickson et al., 2010; C. Lord et al., 2008; Resnick et al., 2009; Wnuk et al., 2012). Therefore, there is a need for a systematic review with meta-analysis to precisely quantify the association between HRT use and brain volume. The use of a meta-analysis will help clarify the effect of different types of HRT, duration of treatment and time of initiation on brain volume and quantify their magnitude with meta-regression analyses.

A key population of interest for future research is perimenopausal women. As noted earlier, women who were classified as perimenopausal were not included in this thesis to enable a clear comparison between groups, with premenopausal women acting as controls for any effect observed after menopause. Since this thesis has established that there is likely an association between menopause and brain health, beyond that of ageing, the study of perimenopausal women will help establish precisely when observed effects occur within the stages of reproductive ageing. The analysis of longitudinal neuroimaging data would naturally lead to the inclusion of women who were perimenopausal and would help address this question.

In this thesis, the reviews with meta-analysis that investigated changes in fat mass and lipids around menopause demonstrated a substantial amount of unexplained variance which remains to be investigated. As a result, future systematic reviews should scrutinise the role of moderators on fat mass and cholesterol changes in women as they progress through menopause,

including age at menopause onset, ethnicity, physical activity levels, genetic factors, and diet. Once identified, the extent to which potential risk factors contribute to deleterious fat mass and lipid profiles changes should be precisely quantified and ranked in order of influence/weight and potential for modification. This research will help inform the development of intervention programs, which seek to mitigate the identified risks for women and ensure that fat and lipid levels are kept in an optimal range. Additionally, more longitudinal studies that investigate changes in lipid levels as women progress from premenopausal to postmenopausal states are required to provide additional insights on changes in lipids over time and the implications this may have for brain health.

Finally, a key motivation for this thesis was to identify the contributions of menopause to brain health to better inform treatment and prevention advice that directly targets women's health. Therefore, a logical next step would be to use the robust insights/recommendations that have emerged from this thesis (see **Summary of recommendations**) to test the effectiveness of a variety of individual, clinical, environmental, cross-cultural, policy, and educational interventions with particular attention to timing and target populations.

7.6 Conclusion

Menopause is a key stage in women's lives that has not received enough attention in the scientific literature. In part, this is because of the statistical and methodological challenges associated with partitioning out effects due to ageing compared with menopause, given both co-occur. The major aims and contributions of this thesis were to investigate the associations between menopause and brain health over and beyond an effect of ageing.

The findings from this thesis have demonstrated an association between menopause and the brain, which cannot be uniquely explained by ageing. Specifically, although menopause alone was not found to be negatively associated brain health, it was associated with somewhat poorer brain health when considered concurrently with other changes around menopause. Moreover, when considering that women tend to gain abdominal fat around menopause, as well as develop an unfavourable lipid profile, and given extensive evidence in the literature that higher abdominal fat and lipid levels are associated with a greater risk of cerebro-vascular disease and dementia, hypothesising a link between menopause and poorer brain health seems warranted but will require further confirmation in future research.

As a whole, the findings from this thesis paint an optimistic picture for women's health, since the risk factors identified and linked with deleterious brain health outcomes are modifiable. If adequate support is available at a health policy, clinical and community level, these specific

risks to brain health may be reduced or prevented.

Appendix

Published manuscripts

Fat mass changes during menopause: a meta-analysis

Ambikairajah, A., Walsh, E., Tabatabaei-Jafari, H., & Cherbuin, N. (2019). Fat mass changes during menopause: a metaanalysis. *American Journal of Obstetrics & Gynecology*, *221*(5), 393-409. doi:10.1016/j.ajog.2019.04.023

Fat mass changes during menopause: a metaanalysis

Ananthan Ambikairajah, BSc, MTeach, PhDc; Erin Walsh, PhD; Hossein Tabatabaei-Jafari, MD; Nicolas Cherbuin, PhD

OBJECTIVE: Data: Fat mass has been shown to increase in aging women; however, the extent to which menopausal status mediates these changes remains unclear. The purpose of this review was to determine (1) how fat mass differs in quantity and distribution between premenopausal and postmenopausal women, (2) whether and how age and/or menopausal status moderates any observed differences, and (3) which type of fat mass measure is best suited to the detection of differences in fat mass between groups.

STUDY: This review with metaanalyses is reported according to Metaanalysis of Observational Studies in Epidemiology guidelines.

STUDY APPRAISAL AND SYNTHESIS METHODS: Studies (published up to May 2018) were identified via PubMed to provide fat mass measures in premenopausal and postmenopausal women. We included 201 cross-sectional studies in the metaanalysis, which provided a combined sample size of 1,049,919 individuals and consisted of 478,734 premenopausal women and 571,185 postmenopausal women. Eleven longitudinal studies were included in the metaanalyses, which provided a combined sample size of 2472 women who were premenopausal at baseline and postmenopausal at follow up.

RESULTS: The main findings of this review were that fat mass significantly increased between premenopausal and postmenopausal women across most measures, which included body mass index (1.14 kg/m^2; 95% confidence interval, 0.95–1.32 kg/m^2), bodyweight (1 kg; 95% confidence interval, 0.44–1.57 kg), body fat percentage (2.88%; 95% confidence interval, 2.13–3.63%), waist circumference (4.63 cm; 95% confidence interval, 3.90–5.35 cm), hip circumference (2.01 cm; 95% confidence interval, 1.36–2.65 cm), waist-hip ratio (0.04; 95% confidence interval, 0.03–0.05), visceral fat (26.90 cm^2; 95% confidence interval, 13.12–40.68), and trunk fat percentage (5.49%; 95% confidence interval, 3.91–7.06 cm^2). The exception was total leg fat percentage, which significantly decreased (–3.19%; 95% confidence interval, –5.98 to –0.41%). No interactive effects were observed between menopausal status and age across all fat mass measures.

CONCLUSION: The change in fat mass quantity between premenopausal and postmenopausal women was attributable predominantly to increasing age; menopause had no significant additional influence. However, the decrease in total leg fat percentage and increase in measures of central fat are indicative of a possible change in fat mass distribution after menopause. These changes are likely to, at least in part, be due to hormonal shifts that occur during midlife when women have a higher androgen (ie, testosterone) to estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition. Evidently, these findings suggest attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan.

Key words: adiposity, BMI, body fat percentage, DEXA, fat mass, female, menopause, premenopausal, postmenopausal, waist circumference

Overweight and obesity are major societal problems that are associated with a number of deleterious health and wellbeing outcomes that include type II diabetes mellitus,[1] dementia,[2] and cardiovascular disease (CVD)[3] and result in a significant global economic burden[4] and poorer quality of life.[5] This is of particular importance for women because CVD is the leading cause of death in women worldwide.[6] Many potential factors/mechanisms have been implicated in the accumulation of fat mass at midlife; these include aging,[7] decreased physical activity levels,[8] and sarcopenia (ie, loss of lean muscle mass), which can decrease the resting metabolic rate.[9] However, hormonal changes in middle-aged women may also be relevant particularly in moderating increases in body fat.[10,11] Given that the average age of menopause lies between 46–52 years[12] and that the average life expectancy of women in developed countries lies at approximately 81 years,[13] women will spend, on average, almost 40% of their lives in a postmenopausal state. It is therefore necessary to better understand whether and how menopause might predispose to increasing body fat to better target interventions and health policy responses.

Menopause is defined as the final menstrual period and is characterized by the progressive decline of endogenous estrogen levels.[14] Some studies have proposed that the decrease in endogenous estrogen levels may modulate body fat quantity and distribution and result in greater overall body fat and an increased amount of central fat in postmenopausal women.[10,15–17] However, there is a divide in the literature with some researchers suggesting that any observed differences in fat mass quantity or distribution in women at

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AJOG at a Glance

Why was this study conducted?

The purpose of this study was to determine how fat mass differs in quantity and distribution between premenopausal and postmenopausal women and whether age and/or menopausal status moderates any differences between the groups.

Key Findings

Fat mass increased between premenopausal and postmenopausal women across most measures (eg, waist circumference), except for total leg fat percentage, which decreased. No interactive effects were observed between menopausal status and age.

What does this add to what is known?

The change in fat mass quantity was attributable predominantly to increasing age, with menopause having no significant additional influence. However, the decrease in total leg fat percentage and increase in measures of central fat are indicative of a possible change in fat distribution after menopause. Therefore, attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan.

midlife are primarily due to aging, with menopausal status having little to no effect.[18–20] The contradictory findings could be due to a number of factors that include (1) the intertwined relationship between menopause and aging, (2) the heterogeneity in criteria that were used between studies when defining premenopausal and postmenopausal women, and (3) the heterogeneity of measures used between studies when they investigated fat mass changes in quantity and distribution.

Because of the inconsistent evidence, it is important to pool data from available studies to determine the differences in fat mass quantity and distribution between premenopausal and postmenopausal women. Moreover, confounding factors that may explain effects that currently are attributed to an altered hormonal profile in women, such as aging, have not been investigated adequately. As far as we are aware, no study to date has comprehensively reviewed the evidence and precisely estimated the results through meta-analysis. Therefore, the current study aimed to determine (1) how fat mass differs in quantity and distribution between premenopausal and postmenopausal women, (2) whether and how age and/or menopausal status moderates any observed differences, and (3) which type of fat mass measure is best suited to the detection of differences in fat mass between groups.

Methods

Reporting guidelines

This review with metaanalysis was reported according to Metaanalysis of Observational Studies in Epidemiology guidelines[21] and was registered prospectively in the PROSPERO database (CRD42018100643), which can be accessed online at the following site: (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643).

Search string

A search was conducted, limited to the PubMed database, to retrieve both cross-sectional and longitudinal studies that reported fat mass differences in quantity or distribution between premenopausal and postmenopausal women. The following search string was used: ("adipose tissue" OR "adiposity" OR "subcutaneous fat" OR "obesity" OR "overweight" OR "bodyweight" OR "body fat distribution" OR "body mass index" OR "BMI" OR "DEXA" OR "DXA" OR "dual energy x-ray absorptiometry" OR "waist to hip ratio" OR "waist-hip ratio" OR "waist circumference" OR "x-ray computed tomography" OR "computed tomography" OR "CT scan" OR "calliper" OR "skinfold" OR "skin fold" OR "abdominal MRI" OR "abdominal magnetic resonance imaging" OR "intra-abdominal fat") AND ("menarche" OR "pre-menopause" OR "premenopause" OR "pre-menopausal" OR "premenopausal" OR "reproductive" OR "menopausal transition") AND ("post-menopause" OR "postmenopause" OR "post-menopausal" OR "postmenopausal" OR "non-reproductive").

PubMed filters were used to exclude nonhuman and non-English studies. No time restrictions were applied to the literature search, which was conducted in May 2018.

Inclusion and exclusion criteria

The eligibility criteria for all included and excluded studies were predefined. Inclusion criteria were specified as (1) peer-reviewed manuscripts written in English or translated from their original language of publication to English, (2) studies that assessed human participants, and (3) studies that used continuous unadjusted measures that provide an estimate of fat mass for both healthy premenopausal and healthy postmenopausal women.

Exclusion criteria were (1) studies that exclusively investigated clinical/pathophysiological populations, (2) studies that selectively recruited women based on specific fat mass ranges or reported differences in fat mass within a narrow predetermined fat mass range (ie, only obese women), (3) studies that matched participants on a measure of fat mass, (4) cross-sectional studies with <40 participants to avoid extreme sampling bias and ensure that small studies, which are more likely to be methodologically less robust, are not included, (5) review articles, systematic reviews, and meta-analyses, (6) conference abstracts, and (7) animal studies.

Screening

Duplicate citations were removed from search results and the remaining entries were title screened by a single author (A.A.). All abstracts were then subdivided and independently double-screened by all the authors with the us of the predetermined inclusion/

exclusion criteria; any discrepancies were resolved through consensus. Finally, full-text and supplementary materials of the remaining articles were double-screened against inclusion/exclusion criteria by 3 authors (A.A., H.T.-J., and E.W.), with data extracted from relevant articles. Where data were missing, authors were contacted via email to obtain relevant information that was required for inclusion in the review. A bibliographic search of available articles and reviews was also used to identify further studies that fit the inclusion criteria.

Data extraction

All data from included articles were double extracted by 2 authors (A.A. and E.W.) to avoid transcription errors; any disagreement was resolved by consensus. Data that were extracted from each study included (1) sample size; (2) age; (3) relevant measures that provide an estimate of fat mass (Supplementary Table 1) and included body mass index (BMI), waist circumference (WC), hip circumference (HC), bodyweight (BW), total body fat percentage (BF%), trunk fat percentage (TF%), waist-to-hip ratio (WTHR), total leg fat percentage (LF%), abdominal (ASF) and suprailiac skinfold thickness (SISF), abdominal subcutaneous fat (AF), and visceral fat (VF); (4) whether information such as menopausal status, WC, and/or BMI was measured or self-reported; (5) definitions used for WC, HC, premenopausal women, and postmenopausal women; (6) whether follicle-stimulating hormone (FSH) criteria were used; (7) whether women were age matched, and (8) whether sample selection that included smoking, surgical menopause, hormone replacement therapy (HRT), CVD, and history of drug and alcohol abuse criteria were used.

Definition of premenopause and postmenopause

The precise definition for "premenopause" and "postmenopause" are known to vary substantially within the literature, which has motivated a series of attempts by international experts collaboratively to develop a comprehensive standardized set of criteria to describe the terminology that is associated with menopause.[14,22–25] The current gold standard for defining menopause nomenclature is the Stages of Reproductive Aging+10 criteria, which was established in 2012.[14] The requirement for papers to adhere to the Stages of Reproductive Aging+10 criteria would have limited the scope of the current review and prevented the inclusion of relevant studies, particular those published before 2012. Therefore, all studies that included premenopausal and postmenopausal women (as defined by the authors of those studies) were considered. Furthermore, women who were classified as perimenopausal were not included in the current meta-analysis so that a clear comparison could be made between groups, with premenopausal women acting as controls for any effect observed after menopause.

Quality assessment

The quality of included studies was assessed independently by 2 authors (A.A. and E.W.), who used an adapted version of the Newcastle-Ottawa Scale.[26] In short, the Newcastle-Ottawa Scale for cohort studies used 3 categories to evaluate individual study quality that included (1) the selection of participants, (2) the comparability of groups, and (3) the assessment/ascertainment of the outcome of interest. Notably, an item was removed from the selection and outcome sections of the Newcastle-Ottawa Scale that did not address the particular quality requirements of the present review (Appendix). Furthermore, given that all studies that included premenopausal and postmenopausal women were considered, 2 additional items were added to the comparability section to ensure that studies with better-suited designs for comparing these groups were scored accordingly. Any discrepancy in quality assessment was resolved by consensus. If consensus decisions were not possible, a third rater was used.

Multiple reports

In the cases in which multiple studies had used the same cohort and reported on the same fat mass measures, only 1 publication was used in any single analysis. Which study to include was based on the following criteria, in order of importance: (1) availability of effect sizes in study (or effect sizes provided by authors after contact), (2) sample size, (3) methods quality rating, and (4) publication date of the study (with more recent studies being prioritized). When multiple studies used the same cohort but reported on different fat mass measures, estimates from the same cohort, but with different studies, were used in separate analyses.

Statistical analysis

All statistical analyses were conducted with the open source software R (version 3.3.3)[27] running in RStudio (version 1.0.143)[28] with the use of the metafor package (version 2.0.0)[29] for the metaanalysis.

Summary measures

For both cross-sectional and longitudinal analyses, effect sizes were calculated with the use of the raw (unstandardized) mean difference (D) for fat mass between postmenopausal and premenopausal women:

$$D = \overline{X}_1 - \overline{X}_2$$

The use of raw mean differences was most appropriate, given that the outcome measure of interest (fat mass) was reported on meaningful scales that were used consistently across studies.[30] For cross-sectional studies, the variance of the effect sizes was calculated with the following formula:

$$V_{D_{cross-sectional}} = \frac{S_1^2}{n_1} + \frac{S_2^2}{n_2}$$

where S_1 and S_2 is the standard deviation for independent groups (ie, premenopausal and postmenopausal women) and n represents the number of women in each group.

For longitudinal studies, the variance of the effect sizes was calculated with the use of the following formulas:

$$V_{D_{longitudinal}} = \frac{S_{diff}^2}{n}$$

$$S_{diff} = \sqrt{S_1^2 + S_2^2 - 2 \times r \times S_2 \times S_2}$$

where r is the correlation between premenopausal and postmenopausal fat mass means.

When standard errors of the mean or 95% confidence intervals (CIs) were reported, authors were first contacted and requested to provide the unstandardized means and standard deviations. If the requested information was not provided, the standard errors of the mean and CIs were converted to standard deviations according to the method outlined in Higgins and Green.[31] Furthermore, volume measurements (cubic centimeters) for computed tomography scans were converted to surface area (square centimeters) in the following manner: thickness of slices × number of slices.

Metaanalysis

Heterogeneity was assumed because sampling and methods varied across studies and resulted in a distribution of effect sizes.[32] Therefore, a random effects model with the use of the restricted maximum likelihood estimator was used in all analyses to estimate the mean of the distribution of these effect sizes.

Heterogeneity across studies was assessed with Cochran's Q statistic (with $P<.01$ indicative of significant heterogeneity) and the I^2 statistic (values 25%, 50%, and 75% suggestive of low, moderate, and high heterogeneity, respectively).[33] To identify studies that excessively contributed to heterogeneity, sensitivity analyses were conducted according to the leave-1-out-method. Metaregression analyses that used a mixed effect model were conducted to determine the influence of moderators, such as aging. For cross-sectional studies, comparisons of fat mass differences between premenopausal and postmenopausal women were made with a test of interaction.

Reporting bias

The possible impact of publication bias was assessed by visual inspection of the funnel plots and with the Egger regression test.[34] The trim-and-fill method was also used to estimate the number of studies that may be missing from the metaanalysis and to estimate adjusted effect sizes.[35,36]

Results

The search strategy identified 2994 unique citations; bibliography searches identified an additional 11 records. After initial screening that was based on titles and abstracts, 586 publications remained for full-text assessment. After the application of inclusion and exclusion criteria, a further 300 publications were excluded (Figure 1). Of the remaining 286 studies, 210 were eligible for inclusion in the quantitative analysis, with 201 studies reporting cross-sectional data[15,18-20,35,37-232] and 11 studies reporting longitudinal data.[10,38,152,233-240]

Some studies included multiple subcohorts of premenopausal and postmenopausal women based on factors such as age,[233] ethnicity,[45,107] physical activity level,[111,213] and geographic location.[96,155,167] In these cases, the subcohorts were extracted separately and treated as discrete samples. Therefore, 217 cross-sectional (Supplementary Table 2) and 13 longitudinal samples (Supplementary Table 3) were included in the analyses.

Study quality rating

For cross-sectional studies, 101 studies were of high quality, as demonstrated by their scores that ranged from 7–9 stars on the adapted version of the Newcastle Ottawa Scale (maximum, 9 stars); 78 studies were of moderate quality (4–6 stars), and 22 studies were of poor quality (0–3 stars; Supplementary Table 4). Almost all longitudinal studies were of high quality, with the exception of 1 study,[235] which was of moderate quality with a score of 4 (Supplementary Table 5).

Summary estimates

The unstandardized mean differences (ie, estimate) of each fat mass measure for both cross-sectional and longitudinal studies are presented in Tables 1 and 2, respectively. Standardized estimates for cross-sectional and longitudinal studies are presented in Supplementary Tables 6 and 7, respectively. Cross-sectional studies compared separate premenopausal and postmenopausal groups; for longitudinal studies, all women were premenopausal at baseline and postmenopausal at follow up.

Cross-sectional metaanalysis

Cross-sectional BMI. One hundred seventy-one cross-sectional studies investigated the relationship between BMI and menopausal status. The analyses revealed that the mean BMI difference was 1.14 kg/m^2 (standard error [SE], 0.09 kg/m^2), with a yearly mean age difference of 0.07 kg/m^2 per year (Table 1).

Cross-sectional BW. One hundred nine cross-sectional studies investigated the relationship between BW and menopausal status. The analyses revealed that the mean BW difference was 1.00 kg (SE, 0.29 kg), with a yearly mean age difference of 0.07 kg per year (Table 1).

Cross-sectional WC. Seventy cross-sectional studies investigated the relationship between WC and menopausal status. The analyses revealed that the mean WC difference was 4.63 cm (SE, 0.37 cm), with a yearly mean age difference of 0.30 cm per year (Table 1).

Cross-sectional WTHR. Forty-eight cross-sectional studies investigated the relationship between WTHR and menopausal status. The analyses revealed that the mean WTHR difference was 0.0421 (SE, 0.0045), with a yearly mean age difference of 0.0026 per year (Table 1).

Cross-sectional BF%. Forty-six cross-sectional studies investigated the relationship between BF% and menopausal status. The analyses revealed that the

mean BF% difference was 2.88% (SE, 0.38%), with a yearly mean age difference of 0.21% per year (Table 1).

Cross-sectional HC. Twenty-five cross-sectional studies investigated the relationship between HC and menopausal status. The analyses revealed that the mean HC difference was 2.01 cm (SE, 0.33 cm), with a yearly mean age difference of 0.13 cm per year (Table 1).

Cross-sectional AF and VF. Ten cross-sectional studies investigated the relationship between AF/VF and menopausal status with the use of computed tomography scans. The analyses revealed that the mean AF difference was 28.73 cm^2 (SE, 10.29 cm^2), with a yearly mean age difference of 1.92 cm^2 per year; the mean VF difference was 26.90 cm^2 (SE, 7.03 cm^2), with a yearly mean age difference of 1.81 cm^2 per year (Table 1).

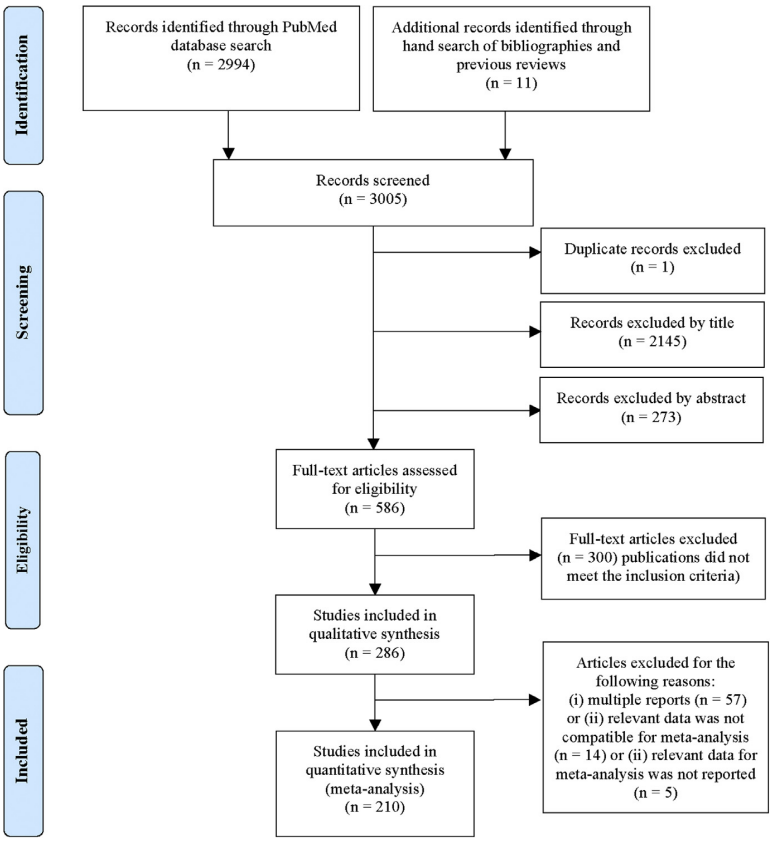
Cross-sectional SISF. Nine cross-sectional studies investigated the relationship between SISF and menopausal status. The analyses revealed that the mean SISF difference was 2.65 mm (SE, 1.12 mm), with a yearly mean age difference of 0.13 mm per year (Table 1).

Cross-sectional TF%. Seven cross-sectional studies investigated the relationship between TF% and menopausal status. The analyses revealed that the mean TF% difference was 5.49% (SE, 0.80%), with a yearly mean age difference of 0.40% per year (Table 1).

Cross-sectional ASF. Four cross-sectional studies investigated the relationship between ASF and menopausal status. The analyses revealed that the mean ASF difference was 6.46 mm (SE, 3.04 mm), with a yearly mean age difference of 0.35 mm per year (Table 1).

Cross-sectional LF%. Three cross-sectional studies investigated the relationship between LF% and menopausal status. The analyses revealed that the mean LF% difference was –3.19% (SE, 1.42%), with a yearly mean age difference of –0.17% per year (Table 1).

FIGURE 1
Flow chart



The flow chart shows the search, screening, and selection process for the studies that were included in the review and metaanalyses.

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Longitudinal metaanalysis

Longitudinal BMI. Eight longitudinal studies investigated the relationship between BMI and menopausal status. The analyses revealed that the mean BMI change was 0.93 kg/m^2 (SE, 0.34 kg/m^2), with an annual change of 0.14 kg/m^2 per year (Table 2).

Longitudinal BW. Seven longitudinal studies investigated the relationship between BW and menopausal status. The analyses revealed that the mean BW change was 2.99 kg (SE, 0.83 kg), with an annual change of 0.37 kg per year (Table 2).

Longitudinal BF%. Four longitudinal studies investigated the relationship between BF% and menopausal status. The analyses revealed that the mean BF % change was 2.18% (SE, 1.01%), with an annual change of 0.41% per year (Table 2).

Longitudinal WC. Three longitudinal studies investigated the relationship between WC and menopausal status. The analyses revealed that the mean WC change was 3.82 cm (SE, 1.51 cm), with an annual change of 0.51 cm per year (Table 2).

Longitudinal AF and VF. Three longitudinal studies investigated the relationship between AF/VF and menopausal status with the use of computed

TABLE 1
Output for cross-sectional studies

Fat mass measure	Studies, n (samples)	Total sample size, n		Mean age, y (standard deviation)[a]		Age difference	Mean fat mass (standard deviation)[a]		Unstandardized estimate (95% confidence interval)[b]	*P* value
		Premenopausal	Postmenopausal	Premenopausal	Postmenopausal		Premenopausal	Postmenopausal		
Body mass index	171 (181)	453,036	523,796	41.96 (3.69)	59.42 (3.06)	14.82 (5.36)	24.75 (1.60)	26.64 (1.25)	1.14 (0.95–1.32)	<.0001
Bodyweight	109 (122)	113,603	204,845	43.36 (4.71)	59.55 (3.27)	15.00 (5.37)	64.82 (7.91)	66.12 (9.17)	1.00 (0.44–1.57)	.0005
Waist circumference	70 (72)	214,712	326,639	42.28 (3.65)	59.07 (1.91)	16.23 (4.24)	78.58 (4.24)	83.61 (3.19)	4.63 (3.90–5.35)	<.0001
Waist-to-hip ratio	47 (50)	199,140	309,797	42.39 (3.44)	59.09 (1.42)	16.17 (3.20)	0.78 (0.03)	0.81 (0.03)	0.04 (0.03–0.05)	<.0001
Body fat percentage	46 (52)	58,605	113,226	43.81 (4.67)	59.55 (3.81)	14.83 (6.56)	32.44 (3.47)	35.69 (3.84)	2.88 (2.13–3.63)	<.0001
Hip circumference	25 (25)	185,885	297,189	42.48 (3.08)	59.15 (0.95)	16.22 (2.61)	100.30 (2.66)	102.73 (2.25)	2.01 (1.36–2.65)	<.0001
Subcutaneous abdominal fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	194.05 (23.65)	221.21 (32.09)	28.73 (8.56–48.91)	.0053
Visceral fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	15.00 (10.70)	69.22 (15.75)	104.36 (13.92)	26.90 (13.12–40.68)	.0001
Suprailiac skinfold thickness	9 (10)	1,103	745	39.76 (4.41)	61.89 (4.77)	21.46 (6.49)	22.16 (7.04)	24.55 (9.90)	2.65 (0.45–4.85)	.0181
Trunk fat percentage	7 (7)	39,335	95,756	45.28 (6.61)	59.68 (3.41)	14.32 (6.21)	31.27 (4.78)	33.74 (5.36)	5.49 (3.91–7.06)	<.0001
Abdominal skinfold thickness	4 (5)	199	359	40.64 (6.32)	62.99 (5.16)	21.04 (5.00)	26.65 (8.14)	29.43 (9.82)	6.46 (0.51–12.42)	.0335
Total leg fat percentage	3 (3)	991	524	36.96 (1.13)	55.18 (5.17)	19.41 (5.87)	36.33 (5.47)	36.00 (2.62)	−3.19 (−5.98 to −0.41)	.0246

[a] Computed as weighted means and weighted standard deviations, taking into account sample size; [b] Indicates significance at the $P<.05$ level.

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tomography scans. The analyses revealed that there was no significant mean AF difference; however, a significant difference in VF of 12.95 cm^2 (SE, 2.20 cm^2) was detected, with an annual change of 3.43 cm^2 per year (Table 2).

Sensitivity analyses

Significant heterogeneity was found in all metaanalyses performed, and the proportion of real observed variance (not related to random error) between studies (I^2) was high across all analyses (Supplementary Figures 1–17). The influence of single studies was investigated further wherever possible (ie, samples, >3) through leave-1-out analyses. The analyses predominantly demonstrated no particularly influential study and showed relative consistency in reported estimates, with a few notable exceptions. For TF% analyses, the study by Guo et al[106] was found to be influential, which could be due to the large sample size reported (Figure 2) or because bioelectrical impedance analysis was used in comparison with the other 6 studies that used dual-energy x-ray absorptiometry (DEXA) scans. When excluded from the analyses, the mean TF% difference between premenopausal and postmenopausal women increased from 5.49–6.05% (95% CI, 4.94–7.15%), with I^2 decreasing from 89.90–54.44%.

For BF% analyses (cross-sectional), the study by Sherk et al[198] was identified as influential; whereas for BMI and BW analyses (longitudinal), the study by Soreca et al[240] was identified as influential, which could be due to the relatively large mean age difference and follow-up period (41.2 years and 20 years, respectively). When removed from analyses, all estimates decreased (BF%, 2.71 [95% CI, 2.02–3.40]; BMI, 0.63 [95% CI, 0.32–0.94]; BW, 2.3 [95% CI, 1.22–3.55]), with I^2 remaining high. For AF analyses (cross-sectional), Hunter et al[118] was found to be influential. Despite being a relatively older study (published >20 years ago), metaregression analyses revealed that the year of publication had no effect on the overall estimate. When excluded from the analyses, the mean AF difference decreased from 28.73–18.81 cm^2 (95%

TABLE 2
Output for longitudinal studies

Fat mass measure	Studies, n (samples)	Total sample size, n	Mean age, y (standard deviation)[a]		Mean follow-up period, y (standard deviation)[a]	Mean fat mass (standard deviation)[a]		Unstandardized Estimate (95% confidence interval)	*P* value
			Premenopausal	Postmenopausal		Premenopausal	Postmenopausal		
Body mass index	8 (10)	2355	46.67 (2.53)	52.80 (3.71)	6.68 (2.38)	24.30 (1.97)	25.03 (2.37)	0.93 (0.26–1.59)[b]	.0061
Bodyweight	7 (7)	525	47.64 (3.06)	55.76 (5.08)	7.82 (5.35)	66.11 (3.89)	69.19 (3.71)	2.99 (1.36–4.63)[b]	.0003
Total body fat percentage	4 (4)	176	49.59 (1.24)	55.49 (3.65)	5.82 (3.25)	36.29 (4.88)	37.84 (3.33)	2.18 (0.21–4.16)[b]	.0299
Waist circumference	3 (3)	915	46.99 (2.04)	52.73 (5.17)	7.17 (1.98)	80.79 (3.62)	84.06 (2.61)	3.82 (0.87–6.77)[b]	.0111
Abdominal fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	3.90 (0.39)	215.14 (66.15)	242.28 (77.34)	18.53 (−3.64–40.69)	.1014
Visceral fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	3.90 (0.39)	78.63 (14.45)	92.23 (12.77)	12.95 (8.65–17.25)[b]	<.0001

[a] Computed as weighted means and weighted standard deviations, taking into account sample size; [b] Indicates significance at the P<.05 level.

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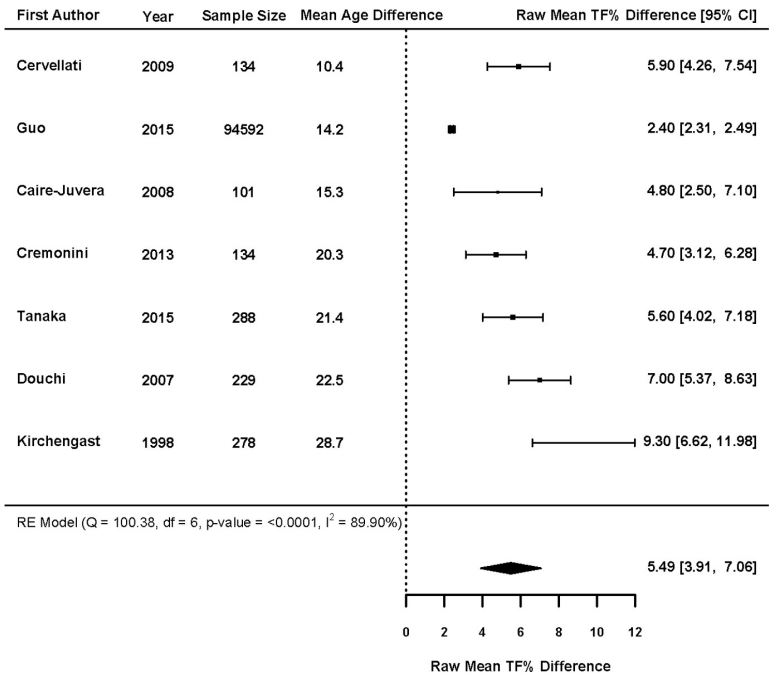
FIGURE 2
Forest plot



The forest plot shows the cross-sectional raw mean trunk fat percentage difference between premenopausal and postmenopausal women. Studies are arranged by mean age difference.

CI, confidence interval; *RE*, random effects; *TF%*, trunk fat percentage.

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CI, 3.38–34.25 cm^2), with I^2 remaining high.

One study, Franklin et al,[235] was found to be influential for BF% analyses (longitudinal), which could be, in part, for the following reasons: (1) the relatively lower quality of the study (4 stars) when compared with other studies that were included in the analyses (8 stars) or (2) the BF% was measured by 2 different methods (ie, hydrostatic weighing [at baseline] and air displacement plethysmograph [at follow up]) compared with other studies that all used DEXA at baseline and follow-up assessment or (3) the very small sample size of the study (8 participants), compared with other studies that have a mean of 56 participants (range, 48–69). When the study by Franklin et al was excluded from the analyses, there was no significant difference in mean BF%.

Publication bias

Funnel plot asymmetry diagnostics and the trim-and-fill test revealed some evidence of publication bias. Eggers regression test was significant for ASF, TF%, and LF% (cross-sectional analyses), BF% (both cross-sectional and longitudinal analyses), and VF (longitudinal analyses), which indicates some degree of asymmetry for these groups. For cross-sectional studies (Supplementary Figures 18–20), the trim-and-fill analyses identified 30 missing studies for BMI and 2 for AF, which produced larger estimates for both. For longitudinal studies (Supplementary Figures 21 and 22), however, 2 missing studies were identified for VF, which produced a smaller estimate.

Subgroup and metaregression analyses

The influence of moderators such as aging (represented as the mean age difference for cross-sectional analyses or length of follow up for longitudinal analyses) and study quality on pooled estimates was investigated by metaregression analyses that used a mixed effects model, for which a sufficient number of studies were available to assess the effect of a single predictor (ie, samples, $\geq$ 10).[31,242] Where metaregression was possible (ie, longitudinal BMI and cross-sectional BMI, BW, WC, WTHR, BF%, HC, AF, VF, and SISF), aging significantly predicted the unexplained variance (9.99–73.90%) in fat mass estimates, except for HC, AF, and SISF (Table 3). No interactive effects were observed between menopausal status and age across all fat mass measures. Furthermore, study quality had no significant effect on the overall estimate.

To examine whether the type of measure could influence the results, we performed subgroup analyses on cross-sectional studies that examined BF% to investigate the impact of DEXA scans vs other methods, such as bioelectrical impedance analysis and hydrodensitometry, on quantifying total and regional body fat percentage. Interestingly, bioelectrical impedance analysis significantly underestimated the quantity of total body fat compared with DEXA (β=–2.64%; 95% CI. –4.23 to –1.04; P=.0012), which supports previous findings.[243] Similarly, when we investigated the effects of measured vs self-reported BMI in cross-sectional studies, self-report significantly underestimated BMI (β=–0.72 kg/m^2; 95% CI, –1.34 to –0.09; P=.0240) compared with direct measurement, which aligns with previous findings.[244] After adjustment for the effect of age, however, self-report had no significant effect on the overall estimate for BMI. All longitudinal studies computed BMI based on objectively measured height and weight. For VF and AF analyses, the use of surface area estimates that were converted from volumes (which was conducted for 1 particular study[20]) had no significant effect on the overall estimate. Notably, almost all subgroup analyses that included women who were using HRT had no significant effect on estimates, except for BF% (significantly increased;

TABLE 3
Metaregression analyses after removal of the effect that is attributable to normal aging

Analyses	Samples, n	Fat mass measure	R^2[a]	Unstandardized β estimate (95% confidence interval)	*P* value
Longitudinal	10	Body mass index	73.88	0.20 (0.12–0.29)[b]	<.0001
Cross-sectional	176	Body mass index	21.61	0.06 (0.04–0.08)[b]	<.0001
	119	Bodyweight	9.99	0.10 (0.04–0.16)[b]	.0008
	71	Waist circumference	40.13	0.24 (0.16–0.32)[b]	<.0001
	51	Waist-to-hip ratio	24.87	0.0025 (0.0013–0.0037)[b]	<.0001
	50	Total body fat percentage	24.75	0.15 (0.07–0.24)[b]	.0005
	25	Hip circumference	15.74	0.09 (−0.02–0.21)	.1201
	10	Abdominal fat	9.03	1.29 (−0.70–3.28)	.2035
	10	Visceral fat	73.90	1.85 (1.04–2.67)[b]	<.0001
	10	Suprailiac skinfold thickness	0.00	0.21 (−0.19–0.60)	.3033

[a] Proportion of observed variance explained by the model; [b] Indicates significance at the $P<.05$ level; studies that did not report age were omitted from model fitting.

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β=2.46%; 95% CI, 0.16–4.76; P=.0358) and TF% (significantly decreased; β=–3.65%; 95% CI, –5.91 to –1.38; P=.0016).

Comment

This large scale, comprehensive review with metaanalyses investigated the differences in fat mass between healthy premenopausal and postmenopausal women in both cross-sectional and longitudinal studies. The main findings were that (1) there was an increase in fat mass between premenopausal and postmenopausal women across most measures, specifically BMI, BW, WC, WTHR, BF%, HC, ASF, SISF, VF, and TF %, with the exception of LF%, which decreased, and (2) the change in fat mass quantity is largely attributable to increasing age, with menopause having no detectable additional influence. These findings are important because they suggest attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan.

The relationship between menopause and aging can be difficult to disentangle because both progress concurrently. Previous research indicates that, for women who are 18–45 years old, the typical trend for BMI and BF% is an increase of 0.16 kg/m^2 per year and 0.41% per year, respectively.[245] Interestingly, the longitudinal analyses presented in this paper reflect similar annual estimates for BMI (0.14 kg/m^2 per year) and BF% (0.41% per year), which indicates that the rates of change remain the same throughout early adulthood and middle age, with menopause having no detectable additional influence above and beyond the effect of aging. Furthermore, the metaregression analyses revealed consistent, but comparatively lower, estimates for cross-sectional BMI (0.06 kg/m^2 per year) and BF% (0.15% per year). The reason for the relatively smaller estimates remains to be elucidated; however, it is possible that unmeasured and/or unreported genetic and environmental factors (eg, ethnicity, dietary changes, mood disorders and medications used in their treatment, physical activity levels, metabolic activity, and variation in sleep length and quality[8,246-248]) that varied between groups in cross-sectional studies account for this. Alternatively, this also may be explained by the well-documented differences that emerge from the less robust design of cross-sectional, compared with longitudinal, studies. As a result, the longitudinal study design is better suited to provide yearly rates of change in fat mass, which are more precise than cross-sectional estimates.

Too few longitudinal studies produced precise estimates of fat mass changes across multiple regions; however, the analysis of cross-sectional studies revealed that LF% decreased by 0.17% per year, whereas fat mass increased in abdominal indexes, such as TF% by 0.40% per year and WC (longitudinal) by 0.51 cm per year, which is indicative of a potential change in fat mass distribution after menopause. These changes, at least in part, are likely to be due to hormonal shifts that occur during midlife when women have a higher androgen (ie, testosterone)-to-estradiol ratio after menopause, which has been linked to enhanced central adiposity deposition.[249] Importantly, the increased central deposition of fat has significant clinical implications, given that a 1-cm increase in WC has been associated with a 2% increase in risk of CVD.[250] Furthermore, a higher testosterone/estradiol ratio has also been associated with deleterious health consequences in women, such as CVD.[251] Taken together, these results may help explain the fact that premenopausal women have been found to have lower

CVD incidence and mortality rates compared with men of the same age,[252] whereas postmenopausal women experience higher mortality rates because of CVD compared with men of the same age.[253] The current analyses suggests that measures that are sensitive to detecting the central deposition of adiposity, such as TF% and WC, would be preferable to BW and BMI, which are commonly used indicators of overweight and obesity. This is of particular importance because of the multifactorial changes in body composition that occur in aging women that can influence BW and/or BMI estimates, such as (1) a decrease in bone density,[254,255] (2) sarcopenia,[256] and (3) shrinking,[257] which indicate that measures that are less influenced by these changes, such as TF% and WC, would be preferable. Furthermore, when measures of fat mass were standardized (Supplementary Tables 6 and 7), cross-sectional analyses revealed that BF% had the largest magnitude of effect across estimates. However, WTHR, WC, and TF% produced comparatively more reliable estimates when we compared the precision of CIs. These results should be interpreted with caution, given that variability across measures, which include different samples, sample sizes, and measurement error, could not be accounted for.

Hormone replacement therapy and fat mass

Subgroup analyses revealed that the inclusion of women who used HRT resulted in a significant increase in BF% (β=2.46%; 95% CI, 0.16–4.76; P=.0358) and a significant decrease in TF% (β=–3.65%; 95% CI, –5.91 to –1.38; P=.0016), which is suggestive of a potential protective role of HRT in preventing/reducing trunk fat deposition, although not in preventing overall fat mass gain. These results align with a previous metaanalysis of 8 randomized control trials, which found that postmenopausal women who used HRT had less WC and TF% compared with placebo.[258] Taken together, these findings provide useful estimates for the potential protective effect of HRT on central adiposity, given that, to our knowledge, the most recent systematic review on this topic was published almost 20 years ago[259] and had insufficient studies at the time to evaluate the effect of HRT on fat mass distribution. Moreover, because HRT use has complex interactions with the body and brain, with varying benefits and disadvantages depending on the time of initiation and type and duration of treatment,[260] it is important for this topic to be investigated systematically in future with longitudinal studies.

Strengths and limitations

A key strength of the present study was that a large number of individuals were assessed for cross-sectional analyses across a wide range of measures that estimated fat mass changes in quantity and distribution between premenopausal and postmenopausal women, which resulted in a holistic understanding of body fat changes in women at midlife. Specifically, 201 cross-sectional studies were included in the metaanalysis, which provided a combined sample size of 1,049,919 individuals that consisted of 478,734 premenopausal women and 571,185 postmenopausal women.

Notable limitations included the fact that only 11 longitudinal studies were available for inclusion in the meta-analysis, which provided a combined sample size of 2472 women who were premenopausal at baseline and postmenopausal at follow up. Furthermore, it is possible that relevant studies may have been missed, given that our search was limited to the PubMed database. However, these relative weaknesses were somewhat counterbalanced by the large number of cross-sectional results that facilitated richer and comprehensive analyses that led to very consistent findings. In addition, women who were classified as perimenopausal were not included in the current metaanalysis. This was done to ensure that a clear comparison could be made between groups, with premenopausal women acting as control subjects for any effect that was observed after menopause. Moreover, the criteria that were used to identify premenopausal and postmenopausal women varied substantially among studies and may have reduced the accuracy of the reported effects.

Conclusion

To our knowledge, this is the first comprehensive review with metaanalysis of both longitudinal and cross-sectional studies to investigate changes in fat mass between premenopausal and postmenopausal women. The analyses revealed that fat mass was higher in postmenopausal, compared with premenopausal, women across most measures, with the exception of LF% (which decreased), which was indicative of a potential change in fat mass distribution after menopause. However, the change in fat mass quantity was attributable predominantly to increasing age; menopause had no significant additional influence. Given that central fat accumulation is associated with an increase in CVD risk, these results may help explain the fact that premenopausal women have been found to have lower CVD incidence and mortality rates compared with men of the same age, whereas postmenopausal women experience higher mortality rates because of CVD compared with men of the same age. An important implication of these findings is that attention should be paid to the accumulation of central fat after menopause, whereas increases in total fat mass should be monitored consistently across the lifespan. Further investigation regarding the role of other potential moderators (eg, genetics, ethnicity, dietary changes, physical activity levels, metabolic activity, mood disorders and medications used in their treatment, age of menopause onset, and variation in sleep length and quality) is required to facilitate the development of targeted and effective intervention programs and of heath policies aimed at mitigating the risk posed by increased central adiposity in women at midlife. ■

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REFERENCES

1. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and metaanalysis. BMC Public Health 2009;9:88.
2. Anstey K, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. Obes Rev 2011;12:e426–37.
3. Wilson PF, D'Agostino RB, Sullivan L, Parise H, Kannel WB. Overweight and obesity as determinants of cardiovascular risk: the Framingham experience. Arch Intern Med 2002;162:1867–72.
4. Withrow D, Alter D. The economic burden of obesity worldwide: a systematic review of the direct costs of obesity. Obes Rev 2011;12:131–41.
5. Larsson U, Karlsson J, Sullivan M. Impact of overweight and obesity on health-related quality of life: a Swedish population study. Int J Obes 2002;26:417.
6. World Health Organization. Women's Health, 2013. Available at: https://www.who.int/en/news-room/fact-sheets/detail/women-s-health. Accessed May 31, 2019.
7. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and regional fat distribution. Ageing Res Rev 2009;8:339–48.
8. Sternfeld B, Wang H, Quesenberry CP Jr, et al. Physical activity and changes in weight and waist circumference in midlife women: findings from the Study of Women's Health Across the Nation. Am J Epidemiol 2004;160:912–22.
9. Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Curr Top in Dev Bio 2005;68:123–48.
10. Razmjou S, Abdulnour J, Bastard J-P, et al. Body composition, cardiometabolic risk factors, physical activity, and inflammatory markers in premenopausal women after a 10-year follow-up: a MONET study. Menopause 2018;25:89–97.
11. Karvonen-Gutierrez C, Kim C. Association of mid-life changes in body size, body composition and obesity status with the menopausal transition healthcare. Healthcare (Basel) 2016 Jul 13;4(3). pii: E42. https://doi.org/10.3390/healthcare4030042.
12. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and metaanalyses of studies across six continents. Int J Epidemiol 2014;43:1542–62.
13. Murray CJ, Barber RM, Foreman KJ, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition. Lancet 2015;386:2145–91.
14. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab 2012;97:1159–68.
15. Tremollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. Am J Obstet Gynecol 1996;175:1594–600.
16. Park JK, Lim YH, Kim KS, et al. Body fat distribution after menopause and cardiovascular disease risk factors: Korean National Health and Nutrition Examination Survey 2010. J Womens Health 2013;22:587–94.
17. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over six years at midlife: ovarian and chronological aging. J Clin Endocrinol Metab 2007;92:895–901.
18. Soriguer F, Morcillo S, Hernando V, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause 2009;16:817–21.
19. Douchi T, Yonehara Y, Kawamura Y, Kuwahata A, Kuwahata T, Iwamoto I. Difference in segmental lean and fat mass components between pre- and postmenopausal women. Menopause 2007;14:875–8.
20. Trikudanathan S, Pedley A, Massaro JM, et al. Association of female reproductive factors with body composition: the Framingham Heart Study. J Clin Endocrinol Metab 2013;98:236–44.
21. Stroup DF, Berlin JA, Morton SC, et al. Metaanalysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000;283:2008–12.
22. World Health Organization. Research on the menopause in the 1990s: report of a WHO scientific group. 1996. Available at: https://apps.who.int/iris/handle/10665/41841. Accessed May 31, 2019.
23. World Health Organization. Research on the menopause: report of a WHO scientific group [meeting held in Geneva from 8 to 12 December 1980]. 1981. Available at: https://apps.who.int/iris/handle/10665/41526. Accessed May 31, 2019.
24. Soules MR, Sherman S, Parrott E, et al. Executive summary: stages of reproductive aging workshop (STRAW). Climacteric 2001;4:267–72.
25. Utian WH. The International Menopause menopause-related terminology definitions. Climacteric 1999;2:284–6.
26. Wells G, Shea B, O'Connell D, et al. Newcastle-Ottawa quality assessment scale cohort studies, 2014. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed May 31, 2019.
27. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016-2017.
28. RStudio Team. RStudio: integrated development for R. RStudio, Inc, Boston, MA. Available at: http://wwwrstudiocom 2015;42. Accessed February 14th, 2018.
29. Viechtbauer W. Conducting metaanalyses in R with the metafor. J Stat Software 2010;36:1–48.
30. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. Introduction to metaanalysis. West Sussex, UK: John Wiley & Sons, Ltd; 2009.
31. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1.0. The Cochrane Collaboration. Confidence intervals 2011. Available at: http://handbook-5-1.cochrane.org/. Accessed May 31, 2019.
32. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1:97–111.
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557.
34. Egger M, Smith GD, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. BMJ 1997;315:629–34.
35. Bhagat M, Mukherjee S, De P, et al. Clustering of cardiometabolic risk factors in Asian Indian women: Santiniketan women study. Menopause 2010;17:359–64.
36. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in metaanalysis. J Am Stat Assoc 2000;95:89–98.
37. Abate M, Schiavone C, Di Carlo L, Salini V. Prevalence of and risk factors for asymptomatic rotator cuff tears in postmenopausal women. Menopause 2014;21:275–80.
38. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause 2012;19:760–7.
39. Abildgaard J, Pedersen AT, Green CJ, et al. Menopause is associated with decreased whole body fat oxidation during exercise. Am J Physiol Endocrinol Metab 2013;304:E1227–36.
40. Adams-Campbell LL, Kim KS, Dunston G, Laing AE, Bonney G, Demenais F. The relationship of body mass index to reproductive factors in pre- and postmenopausal African-American women with and without breast cancer. Obes Res 1996;4:451–6.
41. Agrinier N, Cournot M, Dallongeville J, et al. Menopause and modifiable coronary heart disease risk factors: a population based study. Maturitas 2010;65:237–43.
42. Aguado F, Revilla M, Hernandez ER, Villa LF, Rico H. Behavior of bone mass measurements. Dual energy x-ray absorptiometry total body bone mineral content, ultrasound bone velocity, and computed metacarpal radiogrammetry, with age, gonadal status, and weight in healthy women. Investig Radiol 1996;31:218–22.
43. Albanese CV, Cepollaro C, de Terlizzi F, Brandi ML, Passariello R. Performance of five phalangeal QUS parameters in the evaluation of gonadal-status, age and vertebral fracture risk compared with DXA. Ultrasound Med Biol 2009;35:537–44.

44. Allali F, El Mansouri L, Abourazzak F, et al. The effect of past use of oral contraceptive on bone mineral density, bone biochemical markers and muscle strength in healthy pre and post menopausal women. BMC Womens Health 2009;9:31.
45. Aloia JF, Vaswani A, Ma R, Flaster E. To what extent is bone mass determined by fat-free or fat mass? Am J Clin Nutr 1995;61:1110–4.
46. Amankwah EK, Friedenreich CM, Magliocco AM, et al. Anthropometric measures and the risk of endometrial cancer, overall and by tumor microsatellite status and histological subtype. Am J Epidemiol 2013;177:1378–87.
47. Amarante F, Vilodre LC, Maturana MA, Spritzer PM. Women with primary ovarian insufficiency have lower bone mineral density. Brazil J Med Biol Res 2011;44:78–83.
48. Amiri P, Deihim T, Nakhoda K, Hasheminia M, Montazeri A, Azizi F. Metabolic syndrome and health-related quality of life in reproductive age and post-menopausal women: Tehran Lipid and Glucose Study. Arch Iranian Med 2014;17:423–8.
49. Angsuwathana S, Leerasiri P, Rattanachaiyanont M, et al. Health check-up program for pre/postmenopausal women at Siriraj Menopause Clinic. J Med AssocThailand 2007;90:1–8.
50. Armellini F, Zamboni M, Perdichizzi G, et al. Computed tomography visceral adipose tissue volume measurements of Italians: predictive equations. Eur J Clin Nutr 1996;50: 290–4.
51. Arthur FK, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. The prevalence of metabolic syndrome and its predominant components among pre-and post-menopausal Ghanaian women. BMC Res Notes 2013;6:446.
52. Aydin ZD. Determinants of age at natural menopause in the Isparta Menopause and Health Study: premenopausal body mass index gain rate and episodic weight loss. Menopause 2010;17:494–505.
53. Ayub N, Khan SR, Syed F. Leptin levels in pre and post menopausal Pakistani women. JPMA J Pakistan Med Assoc 2006;56:3–5.
54. Bancroft J, Cawood EH. Androgens and the menopause; a study of 40-60-year-old women. Clin Endocrinol 1996;45:577–87.
55. Bednarek-Tupikowska G, Filus A, Kuliczkowska-Plaksej J, Tupikowski K, Bohdanowicz-Pawlak A, Milewicz A. Serum leptin concentrations in pre- and postmenopausal women on sex hormone therapy. Gynecol Endocrinol 2006;22:207–12.
56. Bell RJ, Davison SL, Papalia MA, McKenzie DP, Davis SR. Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. Menopause 2007;14: 630–8.
57. Ben Ali S, Belfki-Benali H, Ahmed DB, et al. Postmenopausal hypertension, abdominal obesity, apolipoprotein and insulin resistance. Clin Exp Hypertens 2016;38:370–4.
58. Ben Ali S, Belfki-Benali H, Aounallah-Skhiri H, et al. Menopause and metabolic syndrome in tunisian women. BioMed Res Inter 2014;2014:457131.
59. Ben Ali S, Jemaa R, Ftouhi B, et al. Relationship of plasma leptin and adiponectin concentrations with menopausal status in Tunisian women. Cytokine 2011;56:338–42.
60. Berg G, Mesch V, Boero L, et al. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. Horm Metab Res 2004;36:215–20.
61. Berge LN, Bonaa KH, Nordoy A. Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. Arterioscler Thromb 1994;14:857–61.
62. Berger GM, Naidoo J, Gounden N, Gouws E. Marked hyperinsulinaemia in post-menopausal, healthy Indian (Asian) women. Diabetic Med 1995;12:788–95.
63. Berstad P, Coates RJ, Bernstein L, et al. A case-control study of body mass index and breast cancer risk in white and African-American women. Cancer Epidemiol Biomarkers Prev 2010;19:1532–44.
64. Bhurosy T, Jeewon R. Food habits, socio-economic status and body mass index among premenopausal and post-menopausal women in Mauritius. J hum nutr diet 2013;26(suppl1): 114–22.
65. Blumenthal JA, Fredrikson M, Matthews KA, et al. Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychol 1991;10:384–91.
66. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. Int J Epidemiol 1990;19: 42–8.
67. Caire-Juvera G, Arendell LA, Maskarinec G, Thomson CA, Chen Z. Associations between mammographic density and body composition in Hispanic and non-Hispanic white women by menopause status. Menopause 2008;15: 319–25.
68. Campesi I, Occhioni S, Tonolo G, et al. Ageing/menopausal status in healthy women and ageing in healthy men differently affect cardiometabolic parameters. Int J Med Sci 2016;13:124–32.
69. Carr MC, Kim KH, Zambon A, et al. Changes in LDL density across the menopausal transition. J Investig Med 2000;48:245–50.
70. Castracane VD, Kraemer RR, Franken MA, Kraemer GR, Gimpel T. Serum leptin concentration in women: effect of age, obesity, and estrogen administration. Fertil Steril 1998;70: 472–7.
71. Catsburg C, Kirsh VA, Soskolne CL, et al. Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. Breast Cancer Res Treat 2014;145:545–52.
72. Cecchini RS, Costantino JP, Cauley JA, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res 2012;5:583–92.
73. Cervellati C, Pansini FS, Bonaccorsi G, et al. Body mass index is a major determinant of abdominal fat accumulation in pre-, peri- and post-menopausal women. Gynecol Endocrinol 2009;25:413–7.
74. Chain A, Crivelli M, Faerstein E, Bezerra FF. Association between fat mass and bone mineral density among Brazilian women differs by menopausal status: the Pro-Saude Study. Nutrition 2017;33:14–9.
75. Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH. Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. Int J Obes Relat Metab Disord 2000;24:1699–704.
76. Cho GJ, Lee JH, Park HT, et al. Post-menopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause 2008;15: 524–9.
77. Cifkova R, Pitha J, Lejskova M, Lanska V, Zecova S. Blood pressure around the menopause: a population study. J Hypertens 2008;26:1976–82.
78. Copeland AL, Martin PD, Geiselman PJ, Rash CJ, Kendzor DE. Predictors of pretreatment attrition from smoking cessation among pre- and postmenopausal, weight-concerned women. Eating Behav 2006;7:243–51.
79. Cremonini E, Bonaccorsi G, Bergamini CM, et al. Metabolic transitions at menopause: in post-menopausal women the increase in serum uric acid correlates with abdominal adiposity as assessed by DXA. Maturitas 2013;75:62–6.
80. Cui LH, Shin MH, Kweon SS, et al. Relative contribution of body composition to bone mineral density at different sites in men and women of South Korea. J Bone Miner Metab 2007;25: 165–71.
81. D'Haeseleer E, Depypere H, Claeys S, Van Lierde KM. The relation between body mass index and speaking fundamental frequency in premenopausal and postmenopausal women. Menopause 2011;18:754–8.
82. Da Camara SM, Zunzunegui MV, Pirkle C, Moreira MA, Maciel AC. Menopausal status and physical performance in middle aged women: a cross-sectional community-based study in Northeast Brazil. PLoS One 2015;10: e0119480.
83. Dallongeville J, Marecaux N, Isorez D, Zylbergberg G, Fruchart JC, Amouyel P. Multiple coronary heart disease risk factors are associated with menopause and influenced by substitutive hormonal therapy in a cohort of French women. Atherosclerosis 1995;118:123–33.
84. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest 2001;120:151–5.
85. Davis CE, Pajak A, Rywik S, et al. Natural menopause and cardiovascular disease risk factors: the Poland and US Collaborative Study on Cardiovascular Disease Epidemiology. Ann Epidemiol 1994;4:445–8.

86. De Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. BMC Med 2017;15:2.
87. Den Tonkelaar I, Seidell JC, van Noord PA, Baanders-van Halewijn EA, Ouwehand IJ. Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project. Int J Obes 1990;14:753–61.
88. Dmitruk A, Czeczelewski J, Czeczelewska E, Golach J, Parnicka U. Body composition and fatty tissue distribution in women with various menstrual status. Rocz Panstw Zakl Hig 2018;69:95–101.
89. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280–5.
90. Douchi T, Oki T, Nakamura S, Ijuin H, Yamamoto S, Nagata Y. The effect of body composition on bone density in pre- and postmenopausal women. Maturitas 1997;27:55–60.
91. Douchi T, Yamamoto S, Yoshimitsu N, Andoh T, Matsuo T, Nagata Y. Relative contribution of aging and menopause to changes in lean and fat mass in segmental regions. Maturitas 2002;42:301–6.
92. Dubois EF, van den Bergh JP, Smals AG, van de Meerendonk CW, Zwinderman AH, Schweitzer DH. Comparison of quantitative ultrasound parameters with dual energy X-ray absorptiometry in pre- and postmenopausal women. Neth J Med 2001;58:62–70.
93. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K. Population-Attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol 2017;3:1228–36.
94. Ertungealp E, Seyisoglu H, Erel CT, Senturk LM, Gezer A. Changes in bone mineral density with age, menopausal status and body mass index in Turkish women. Climacteric 1999;2:45–51.
95. Feng Y, Hong X, Wilker E, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis 2008;196:590–7.
96. Formica C, Loro ML, Gilsanz V, Seeman E. Inhomogeneity in body fat distribution may result in inaccuracy in the measurement of vertebral bone mass. J Bone Miner Res 1995;10:1504–11.
97. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control 2007;18:399–413.
98. Friedenreich CM, Courneya KS, Bryant HE. Case-control study of anthropometric measures and breast cancer risk. Int J Cancer 2002;99:445–52.
99. Fu X, Ma X, Lu H, He W, Wang Z, Zhu S. Associations of fat mass and fat distribution with bone mineral density in pre- and postmenopausal Chinese women. Osteoporos Int 2011;22:113–9.
100. Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD. Quality of life and menopausal transition for middle-aged women on Kinmen island. Qual Life Res 2003;12:53–61.
101. Gambacciani M, Ciaponi M, Cappagli B, Benussi C, De Simone L, Genazzani AR. Climacteric modifications in body weight and fat tissue distribution. Climacteric 1999;2:37–44.
102. Genazzani AR, Gambacciani M. Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution. Gynecol Endocrinol 2006;22:145–50.
103. Ghosh A. Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women. Cardiovasc J S Afr 2008;19:183–7.
104. Ghosh A, Bhagat M. Anthropometric and body composition characteristics in pre- and postmenopausal Asian Indian women: Santiniketan women study. Anthropol Anz 2010;68:1–10.
105. Gram IT, Funkhouser E, Tabar L. Anthropometric indices in relation to mammographic patterns among peri-menopausal women. Int J Cancer 1997;73:323–6.
106. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Ann Epidemiol 2015;25:406–13.e6.
107. Gurka MJ, Vishnu A, Santen RJ, DeBoer MD. Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc 2016;5.
108. Hadji P, Hars O, Bock K, et al. The influence of menopause and body mass index on serum leptin concentrations. Eur J Endocrinol 2000;143:55–60.
109. Hagner W, Hagner-Derengowska M, Wiacek M, Zubrzycki IZ. Changes in level of VO2max, blood lipids, and waist circumference in the response to moderate endurance training as a function of ovarian aging. Menopause 2009;16:1009–13.
110. Han D, Nie J, Bonner MR, et al. Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. Int J Cancer 2006;119:2931–7.
111. Harting GH, Moore CE, Mitchell R, Kappus CM. Relationship of menopausal status and exercise level to HDL-cholesterol in women. Exper Aging Res 1984;10:13–8.
112. He L, Tang X, Li N, et al. Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: a population-based study. Maturitas 2012;72:132–8.
113. Hirose K, Tajima K, Hamajima N, et al. Impact of established risk factors for breast cancer in nulligravid Japanese women. Breast Cancer 2003;10:45–53.
114. Hjartaker A, Adami HO, Lund E, Weiderpass E. Body mass index and mortality in a prospectively studied cohort of Scandinavian women: the women's lifestyle and health cohort study. Eur J Epidemiol 2005;20:747–54.
115. Ho S, Wu S, Chan S, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes 2010;34:1265.
116. Hsu YH, Venners SA, Terwedow HA, et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am J Clin Nutr 2006;83:146–54.
117. Hu X, Pan X, Ma X, et al. Contribution of a first-degree family history of diabetes to increased serum adipocyte fatty acid binding protein levels independent of body fat content and distribution. Int J Obes 2016;40:1649–54.
118. Hunter G, Kekes-Szabo T, Treuth M, Williams M, Goran M, Pichon C. Intra-abdominal adipose tissue, physical activity and cardiovascular risk in pre- and post-menopausal women. Int J Obes Relat Metab Disord 1996;20:860–5.
119. Iida T, Domoto T, Takigawa A, et al. Relationships among blood leptin and adiponectin levels, fat mass, and bone mineral density in Japanese pre-and postmenopausal women. Hiroshima J Med Sci 2011;60:71–8.
120. Ilich-Ernst J, Brownbill RA, Ludemann MA, Fu R. Critical factors for bone health in women across the age span: how important is muscle mass? Medscape Womens Health 2002;7:2.
121. Ito M, Hayashi K, Uetani M, Yamada M, Ohki M, Nakamura T. Association between anthropometric measures and spinal bone mineral density. Investig Radiol 1994;29:812–6.
122. Jaff NG, Norris SA, Snyman T, Toman M, Crowther NJ. Body composition in the Study of Women Entering and in Endocrine Transition (SWEET): a perspective of African women who have a high prevalence of obesity and HIV infection. Metab Clin Exper 2015;64:1031–41.
123. Jasienska G, Ziomkiewicz A, Gorkiewicz M, Pajak A. Body mass, depressive symptoms and menopausal status: an examination of the "Jolly Fat" hypothesis. Womens Health Issues 2005;15:145–51.
124. Jeenduang N, Trongsakul R, Inhongsa P, Chaidach P. The prevalence of metabolic syndrome in premenopausal and postmenopausal women in Southern Thailand. Gynecol Endocrinol 2014;30:573–6.
125. Jeon YK, Lee JG, Kim SS, et al. Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocr J 2011;58:87–93.
126. Jurimae J, Jurimae T. Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. Am J Physiol Endocrinol Metab 2007;293:E42–7.
127. Kadam N, Chiplonkar S, Khadilkar A, Divate U, Khadilkar V. Low bone mass in urban Indian women above 40 years of age:

prevalence and risk factors. Gynecol Endocrinol 2010;26:909–17.
128. Kang EK, Park HW, Baek S, Lim JY. The association between trunk body composition and spinal bone mineral density in Korean males versus females: a Farmers' Cohort for Agricultural Work-Related Musculoskeletal Disorders (FARM) study. J Korean Med Sci 2016;31:1595–603.
129. Kaufer-Horwitz M, Pelaez-Robles K, Lazzeri-Arteaga P, Goti-Rodriguez LM, Avila-Rosas H. Hypertension, overweight and abdominal adiposity in women. An analytical perspective. Arch Med Res 2005;36:404–11.
130. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 2007;30:701–6.
131. Kim JH, Choi HJ, Kim MJ, Shin CS, Cho NH. Fat mass is negatively associated with bone mineral content in Koreans. Osteoporos Int 2012;23:2009–16.
132. Kim S, Lee JY, Im JA, et al. Association between serum osteocalcin and insulin resistance in postmenopausal, but not premenopausal, women in Korea. Menopause 2013;20:1061–6.
133. Kim YM, Kim SH, Kim S, Yoo JS, Choe EY, Won YJ. Variations in fat mass contribution to bone mineral density by gender, age, and body mass index: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008-2011. Osteoporos Int 2016;27:2543–54.
134. Kirchengast S, Gruber D, Sator M, Huber J. Impact of the age at menarche on adult body composition in healthy pre- and postmenopausal women. Am J Phys Anthropol 1998;105:9–20.
135. Kirchengast S, Hartmann B, Huber J. Serum levels of sex hormones, thyroid hormones, growth hormone, IGF I, and cortisol and their relations to body fat distribution in healthy women dependent on their menopausal status. Zeits Morphol Anthropol 1996;81:223–34.
136. Knapp KM, Blake GM, Spector TD, Fogelman I. Multisite quantitative ultrasound: precision, age- and menopause-related changes, fracture discrimination, and T-score equivalence with dual-energy X-ray absorptiometry. Osteoporos Int 2001;12:456–64.
137. Koh SJ, Hyun YJ, Choi SY, et al. Influence of age and visceral fat area on plasma adiponectin concentrations in women with normal glucose tolerance. Clin Chim Acta 2008;389:45–50.
138. Konrad T, Bär F, Schneider F, et al. Factors influencing endothelial function in healthy pre- and post-menopausal women of the EU-RISC study. Diabet Vasc Dis Res 2011;8:229–36.
139. Kontogianni MD, Dafni UG, Routsias JG, Skopouli FN. Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women. J Bone Miner Res 2004;19:546–51.
140. Konukoglu D, Serin O, Ercan M. Plasma leptin levels in obese and non-obese postmenopausal women before and after hormone replacement therapy. Maturitas 2000;36:203–7.
141. Koskova I, Petrasek R, Vondra K, et al. Weight, body composition and fat distribution of Czech women in relation with reproductive phase: a cross-sectional study. Prague Med Rep 2007;108:13–26.
142. Kotani K, Chen JT, Taniguchi N. The relationship between adiponectin and blood pressure in premenopausal and postmenopausal women. Clin Investig Med 2011;34:E125–30.
143. Kraemer RR, Synovitz LB, Gimpel T, Kraemer GR, Johnson LG, Castracane VD. Effect of estrogen on serum DHEA in younger and older women and the relationship of DHEA to adiposity and gender. Metabolism 2001;50:488–93.
144. Kuk JL, Lee S, Heymsfield SB, Ross R. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. Am J Clin Nutr 2005;81:1330–4.
145. Laitinen K, Valimaki M, Keto P. Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. Calcif Tissue Int 1991;48:224–31.
146. Lejskova M, Alusik S, Valenta Z, Adamkova S, Pitha J. Natural postmenopause is associated with an increase in combined cardiovascular risk factors. Physiol Res 2012;61:587–96.
147. Leon Guerrero RT, Novotny R, Wilkens LR, et al. Risk factors for breast cancer in the breast cancer risk model study of Guam and Saipan. Cancer Epidemiol 2017;50:221–33.
148. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clinical Nutr 1992;55:950–4.
149. Lin WY, Yang WS, Lee LT, et al. Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan. Int J Obes 2006;30:912–7.
150. Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: results from a population study of women in Goteborg, Sweden. Scand J Clin Lab Investig 1980;40:629–36.
151. Lindsay R, Cosman F, Herrington BS, Himmelstein S. Bone mass and body composition in normal women. J Bone Miner Res 1992;7:55–63.
152. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes 2008;32:949–58.
153. Lyu LC, Yeh CY, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ. Association of sex, adiposity, and diet with HDL subclasses in middle-aged Chinese. Am J Clin Nutr 2001;74:64–71.
154. Maharlouei N, Bellissimo N, Ahmadi SM, Lankarani KB. Prevalence of metabolic syndrome in pre- and postmenopausal Iranian women. Climacteric 2013;16:561–7.
155. Malacara JM, Canto de Cetina T, Bassol S, et al. Symptoms at pre- and postmenopause in rural and urban women from three States of Mexico. Maturitas 2002;43:11–9.
156. Manabe E, Aoyagi K, Tachibana H, Takemoto T. Relationship of intra-abdominal adiposity and peripheral fat distribution to lipid metabolism in an island population in western Japan: gender differences and effect of menopause. Tohoku J Exp Med 1999;188:189–202.
157. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. Eur J Cancer Prev 2001;10:33–42.
158. Mannisto S, Pietinen P, Pyy M, Palmgren J, Eskelinen M, Uusitupa M. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. Int J Cancer 1996;68:8–13.
159. Martini G, Valenti R, Giovani S, Nuti R. Age-related changes in body composition of healthy and osteoporotic women. Maturitas 1997;27:25–33.
160. Marwaha RK, Garg MK, Tandon N, Mehan N, Sastry A, Bhadra K. Relationship of body fat and its distribution with bone mineral density in Indian population. J Clin Densitom 2013;16:353–9.
161. Matsushita H, Kurabayashi T, Tomita M, Kato N, Tanaka K. Effects of uncoupling protein 1 and beta3-adrenergic receptor gene polymorphisms on body size and serum lipid concentrations in Japanese women. Maturitas 2003;45:39–45.
162. Matsuzaki M, Kulkarni B, Kuper H, et al. Association of hip bone mineral density and body composition in a rural Indian population: the Andhra Pradesh Children and Parents study (APCAPS). PLoS One 2017;12:e0167114.
163. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641–6.
164. Mesch VR, Boero LE, Siseles NO, et al. Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status. Climacteric 2006;9:40–8.
165. Meza-Munoz DE, Fajardo ME, Perez-Luque EL, Malacara JM. Factors associated with estrogen receptors-alpha (ER-alpha) and -beta (ER-beta) and progesterone receptor abundance in obese and non obese pre- and post-menopausal women. Steroids 2006;71:498–503.
166. Minatoya M, Kutomi G, Shima H, et al. Relation of serum adiponectin levels and obesity with breast cancer: a Japanese case-control study. Asian Pac J Cancer Prev 2014;15:8325–30.
167. Mo D, Hsieh P, Yu H, et al. The relationship between osteoporosis and body composition in pre- and postmenopausal women from different ethnic groups in China. Ethn Health 2017;22:295–310.

168. Muchanga Sifa MJ, Lepira FB, Longo AL, et al. Prevalence and predictors of metabolic syndrome among Congolese pre- and postmenopausal women. Climacteric 2014;17:442–8.
169. Muti P, Stanulla M, Micheli A, et al. Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: a prospective analysis of abdominal adiposity, sebum production, and hirsutism (Italy). Cancer Causes Control 2000;11:721–30.
170. Nitta J, Nojima M, Ohnishi H, et al. Weight gain and alcohol drinking associations with breast cancer risk in Japanese postmenopausal women - results from the Japan Collaborative Cohort (JACC) study. Asian Pac J Cancer Prev 2016;17:1437–43.
171. Noh HM, Song YM, Park JH, Kim BK, Choi YH. Metabolic factors and breast cancer risk in Korean women. Cancer Causes Control 2013;24:1061–8.
172. Nordin BE, Need AG, Bridges A, Horowitz M. Relative contributions of years since menopause, age, and weight to vertebral density in postmenopausal women. J Clin Endocrinol Metab 1992;74:20–3.
173. Ohta H, Kuroda T, Onoe Y, et al. Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. J Bone Miner Metab 2010;28:690–5.
174. Oldroyd B, Stewart SP, Truscott JG, Westmacott CF, Smith MA. Age related changes in body composition. Applied Rad Isot 1998;49:589–90.
175. Pacholczak R, Klimek-Piotrowska W, Kuszmiersz P. Associations of anthropometric measures on breast cancer risk in pre- and postmenopausal women–a case-control study. J Physiol Anthropol 2016;35:7.
176. Park JH, Song YM, Sung J, et al. The association between fat and lean mass and bone mineral density: the Healthy Twin Study. Bone 2012;50:1006–11.
177. Park YM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer 2017;140:2657–66.
178. Pavicic Zezelj S, Cvijanovic O, Micovic V, Bobinac D, Crncevic-Orlic Z, Malatestinic G. Effect of menopause, anthropometry, nutrition and lifestyle on bone status of women in the northern Mediterranean. West Indian Med J 2010;59:494–502.
179. Pavlica T, Mikalacki M, Matic R, et al. Relationship between BMI and skinfold thicknesses to risk factors in premenopausal and postmenopausal women. Coll Antropol 2013;37(suppl2):119–24.
180. Phillips GB, Jing T, Heymsfield SB. Does insulin resistance, visceral adiposity, or a sex hormone alteration underlie the metabolic syndrome? Studies in women. Metabolism 2008;57:838–44.
181. Polesel DN, Hirotsu C, Nozoe KT, et al. Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study. Menopause 2015;22:835–44.
182. Pollan M, Lope V, Miranda-Garcia J, et al. Adult weight gain, fat distribution and mammographic density in Spanish pre- and post-menopausal women (DDM-Spain). Breast Cancer Res Treat 2012;134:823–38.
183. Portaluppi F, Pansini F, Manfredini R, Mollica G. Relative influence of menopausal status, age, and body mass index on blood pressure. Hypertension 1997;29:976–9.
184. Priya T, Chowdhury MG, Vasanth K, et al. Assessment of serum leptin and resistin levels in association with the metabolic risk factors of pre- and post-menopausal rural women in South India. Diabet Metab Syndr 2013;7:233–7.
185. Rantalainen T, Nikander R, Heinonen A, et al. Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. Bone 2010;46:964–9.
186. Reina P, Cointry GR, Nocciolino L, et al. Analysis of the independent power of age-related, anthropometric and mechanical factors as determinants of the structure of radius and tibia in normal adults: a pQCT study. J Musculoskel Neuron Interact 2015;15:10–22.
187. Revilla M, Villa LF, Hernandez ER, Sanchez-Atrio A, Cortes J, Rico H. Influence of weight and gonadal status on total and regional bone mineral content and on weight-bearing and non-weight-bearing bones, measured by dual-energy X-ray absosorptiometry. Maturitas 1997;28:69–74.
188. Revilla M, Villa LF, Sanchez-Atrio A, Hernandez ER, Rico H. Influence of body mass index on the age-related slope of total and regional bone mineral content. Calcif Tissue Int 1997;61:134–8.
189. Rice MS, Bertrand KA, Lajous M, et al. Reproductive and lifestyle risk factors and mammographic density in Mexican women. Ann Epidemiol 2015;25:868–73.
190. Rico H, Aguado F, Arribas I, et al. Behavior of phalangeal bone ultrasound in normal women with relation to gonadal status and body mass index. Osteoporos Int 2001;12:450–5.
191. Rico H, Arribas I, Casanova FJ, Duce AM, Hernandez ER, Cortes-Prieto J. Bone mass, bone metabolism, gonadal status and body mass index. Osteoporos Int 2002;13:379–87.
192. Roelfsema F, Veldhuis JD. Growth hormone dynamics in healthy adults are related to age and sex and strongly dependent on body mass index. Neuroendocrinology 2016;103:335–44.
193. Rosenbaum M, Nicolson M, Hirsch J, et al. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J Clin Endocrinol Metab 1996;81:3424–7.
194. Salomaa V, Rasi V, Pekkanen J, et al. Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors: the FINRISK Hemostasis Study. Arterioscler Thromb Vasc Biol 1995;15:1549–55.
195. Sarrafzadegan N, Khosravi-Boroujeni H, Esmaillzadeh A, Sadeghi M, Rafieian-Kopaei M, Asgary S. The association between hypertriglyceridemic waist phenotype, menopause, and cardiovascular risk factors. Arch Iran Med 2013;16:161–6.
196. Schaberg-Lorei G, Ballard JE, McKeown BC, Zinkgraf SA. Body composition alterations consequent to an exercise program for pre and postmenopausal women. J Sports Med Phys Fitness 1990;30:426–33.
197. Schwarz S, Volzke H, Alte D, et al. Menopause and determinants of quality of life in women at midlife and beyond: the study of health in pomerania (SHIP). Menopause 2007;14:123–34.
198. Sherk VD, Malone SP, Bemben MG, Knehans AW, Palmer IJ, Bemben DA. Leptin, fat mass, and bone mineral density in healthy pre- and postmenopausal women. J Clin Densitom 2011;14:321–5.
199. Shibata H, Matsuzaki T, Hatano S. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. Am J Epidemiol 1979;109:420–4.
200. Sieminska L, Wojciechowska C, Foltyn W, et al. The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause. Endokrynol Polska 2006;57:15–22.
201. Skrzypczak M, Szwed A. Assessment of the body mass index and selected physiological parameters in pre- and post-menopausal women. Homo 2005;56:141–52.
202. Skrzypczak M, Szwed A, Pawlińska-Chmara R, Skrzypulec V. Assessment of the BMI, WHR and W/Ht in pre-and post-menopausal women. Anthropol Rev 2007;70:3–13.
203. Soderberg S, Ahren B, Eliasson M, Dinesen B, Olsson T. The association between leptin and proinsulin is lost with central obesity. J Intern Med 2002;252:140–8.
204. Son MK, Lim NK, Lim JY, et al. Difference in blood pressure between early and late menopausal transition was significant in healthy Korean women. BMC Womens Health 2015;15:64.
205. Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. J Hum Hypertens 1989;3:427–33.
206. Suarez-Ortegon MF, Arbelaez A, Mosquera M, Mendez F, Aguilar-de Plata C. C-reactive protein, waist circumference, and family history of heart attack are independent predictors of body iron stores in apparently healthy premenopausal women. Biol Trace Elem Res 2012;148:135–8.
207. Suliga E, Koziel D, Ciesla E, Rebak D, Gluszek S. Factors associated with adiposity, lipid profile disorders and the metabolic syndrome occurrence in premenopausal and postmenopausal women. PLoS One 2016;11:e0154511.
208. Sumner AE, Falkner B, Kushner H, Considine RV. Relationship of leptin

concentration to gender, menopause, age, diabetes, and fat mass in African Americans. Obes Res 1998;6:128–33.
209. Tanaka NI, Hanawa S, Murakami H, et al. Accuracy of segmental bioelectrical impedance analysis for predicting body composition in pre- and postmenopausal women. J Clin Densitom 2015;18:252–9.
210. Thomas T, Burguera B, Melton LJ 3rd, et al. Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. Metabolism 2000;49:1278–84.
211. Torng PL, Su TC, Sung FC, et al. Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women: the Chin-Shan Community Cardiovascular Cohort Study. Atherosclerosis 2000;153:413–21.
212. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Dis 2000;24:226–31.
213. Van Pelt RE, Davy KP, Stevenson ET, et al. Smaller differences in total and regional adiposity with age in women who regularly perform endurance exercise. Am J Physiol 1998;275:E626–34.
214. Veldhuis JD, Dyer RB, Trushin SA, Bondar OP, Singh RJ, Klee GG. Interleukins 6 and 8 and abdominal fat depots are distinct correlates of lipid moieties in healthy pre- and postmenopausal women. Endocrine 2016;54:671–80.
215. Wang F, Ma X, Hao Y, et al. Serum glycated albumin is inversely influenced by fat mass and visceral adipose tissue in Chinese with normal glucose tolerance. PLoS One 2012;7:e51098.
216. Wang W, Zhao LJ, Liu YZ, Recker RR, Deng HW. Genetic and environmental correlations between obesity phenotypes and age at menarche. Int J Obes 2006;30:1595–600.
217. Wang WS, Wahlqvist ML, Hsu CC, Chang HY, Chang WC, Chen CC. Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in Taiwan. BMC Public Health 2012;12:111.
218. Wee J, Sng BY, Shen L, Lim CT, Singh G, Das De S. The relationship between body mass index and physical activity levels in relation to bone mineral density in premenopausal and postmenopausal women. Arch Osteoporos 2013;8:162.
219. Williams PT, Krauss RM. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. Arterioscler Thromb Vasc Biol 1997;17:1082–90.
220. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. Arch Intern Med 1991;151:97–102.
221. Xu L, Nicholson P, Wang QJ, Wang Q, Alen M, Cheng S. Fat mass accumulation compromises bone adaptation to load in Finnish women: a cross-sectional study spanning three generations. J Bone Miner Res 2010;25:2341–9.
222. Yamatani H, Takahashi K, Yoshida T, Takata K, Kurachi H. Association of estrogen with glucocorticoid levels in visceral fat in postmenopausal women. Menopause 2013;20:437–42.
223. Yannakoulia M, Melistas L, Solomou E, Yiannakouris N. Association of eating frequency with body fatness in pre- and postmenopausal women. Obesity 2007;15:100–6.
224. Yoldemir T, Erenus M. The prevalence of metabolic syndrome in pre- and postmenopausal women attending a tertiary clinic in Turkey. Eur J Obstet Gynecol Reprod Biol 2012;164:172–5.
225. Yoo HJ, Park MS, Yang SJ, et al. The differential relationship between fat mass and bone mineral density by gender and menopausal status. J Bone Miner Metab 2012;30:47–53.
226. Yoo KY, Kim H, Shin HR, et al. Female sex hormones and body mass in adolescent and postmenopausal Korean women. J Korean Med Sci 1998;13:241–6.
227. Yoshimoto N, Nishiyama T, Toyama T, et al. Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. Cancer Sci 2011;102:2065–72.
228. Zhong N, Wu XP, Xu ZR, et al. Relationship of serum leptin with age, body weight, body mass index, and bone mineral density in healthy mainland Chinese women. Clin Chim Acta 2005;351:161–8.
229. Zhou JL, Lin SQ, Shen Y, Chen Y, Zhang Y, Chen FL. Serum lipid profile changes during the menopausal transition in Chinese women: a community-based cohort study. Menopause 2010;17:997–1003.
230. Zhou Y, Zhou X, Guo X, et al. Prevalence and risk factors of hypertension among pre- and post-menopausal women: a cross-sectional study in a rural area of northeast China. Maturitas 2015;80:282–7.
231. Zivkovic TB, Vuksanovic M, Jelic MA, et al. Obesity and metabolic syndrome during the menopause transition in Serbian women. Climacteric 2011;14:643–8.
232. Shakir YA, Samsioe G, Nyberg P, Lidfeldt J, Nerbrand C. Cardiovascular risk factors in middle-aged women and the association with use of hormone therapy: results from a population-based study of Swedish women: he Women's Health in the Lund Area (WHILA) Study. Climacteric 2004;7:274–83.
233. Akahoshi M, Soda M, Nakashima E, et al. Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. Atherosclerosis 2001;156:157–63.
234. Ford K, Sowers M, Crutchfield M, Wilson A, Jannausch M. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. Menopause 2005;12:308–17.
235. Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution with menopause. Metabolism 2009;58:311–5.
236. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med 2008;168:1568–75.
237. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab 2009;94:1104–10.
238. Liu-Ambrose T, Kravetsky L, Bailey D, et al. Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: a 12-year observational study. Calcif Tissue Int 2006;79:145–51.
239. Macdonald HM, New SA, Campbell MK, Reid DM. Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. Osteoporos Int 2005;16:163–71.
240. Soreca I, Rosano C, Jennings JR, et al. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. Psychosom Med 2009;71:485–90.
241. Williams MJ, Hunter GR, Kekes-Szabo T, et al. Intra-abdominal adipose tissue cut-points related to elevated cardiovascular risk in women. Int J Obes Related Metab Disord 1996;20:613–7.
242. Field A, Miles J, Field Z. Discovering statistics using R. London, UK: Sage publications; 2012.
243. Bolanowski M, Nilsson BE. Assessment of human body composition using dual-energy x-ray absorptiometry and bioelectrical impedance analysis. Med Sc Monit 2001;7:1029–33.
244. Ng SP, Korda R, Clements M, et al. Validity of self-reported height and weight and derived body mass index in middle-aged and elderly individuals in Australia. Aust N Z J Public Health 2011;35:557–63.
245. Siervogel RM, Wisemandle W, Maynard LM, et al. Serial changes in body composition throughout adulthood and their relationships to changes in lipid and lipoprotein levels: The Fels Longitudinal Study. Arterioscler Thromb Vasc Biol 1998;18:1759–64.
246. Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB. Association between reduced sleep and weight gain in women. Am J Epidemiol 2006;164:947–54.
247. Davis SR, Castelo-Branco C, Chedraui P, et al. Understanding weight gain at menopause. Climacteric 2012;15:419–29.
248. Demerath EW, Rogers NL, Reed D, et al. Significant associations of age, menopausal status and lifestyle factors with visceral adiposity in African-American and European-American women. Ann Hum Biol 2011;38:247–56.

249. Janssen I, Powell LH, Jasielec MS, Kazlauskaite R. Covariation of change in bioavailable testosterone and adiposity in midlife women. Obesity 2015;23:488–94.
250. De Koning L, Merchant AT, Pogue J, Anand SS. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur Heart J 2007;28:850–6.
251. Zhao D, Guallar E, Ouyang P, et al. Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. J Am Coll Cardiol 2018;71:2555–66.
252. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. PloS One 2013;8:e63347.
253. McAloon CJ, Boylan LM, Hamborg T, et al. The changing face of cardiovascular disease 2000–2012: an analysis of the world health organisation global health estimates data. Int J Cardiol 2016;224:256–64.
254. Steiger P, Cummings SR, Black DM, Spencer NE, Genant HK. Age-related decrements in bone mineral density in women over 65. J Bone Miner Res 1992;7:625–32.
255. Douchi T, Kosha S, Uto H, et al. Precedence of bone loss over changes in body composition and body fat distribution within a few years after menopause. Maturitas 2003;46:133–8.
256. Shafiee G, Keshtkar A, Soltani A, Ahadi Z, Larijani B, Heshmat R. Prevalence of sarcopenia in the world: a systematic review and meta-analysis of general population studies. J Diabet Metab Disord 2017;16:21.
257. Perissinotto E, Pisent C, Sergi G, Grigoletto F, Enzi G, Group IW. Anthropometric measurements in the elderly: age and gender differences. Br J Nutr 2002;87:177–86.
258. Salpeter S, Walsh J, Ormiston T, et al. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. Diabetes Obes Metab 2006;8:538–54.
259. Kongnyuy EJ, Norman RJ, Flight IH, Rees MC. Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution. Cochrane Database Syst Rev 2000;(2):CD001018.
260. Nelson HD, Humphrey LL, Nygren P, Teutsch SM, Allan JD. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002;288:872–81.

Appendix
Adapted Newcastle-Ottawa Quality Assessment Form for Cohort Studies

Selection of premenopausal and postmenopausal women

1. Representativeness of the postmenopausal cohort
   A. Truly representative of the average postmenopausal woman in the community
   B. Somewhat representative of the average postmenopausal woman in the community
   C. Selected group of users eg nurses, volunteers
   D. No description of the derivation of the cohort
2. Selection of the premenopausal cohort
   A. Drawn from the same or similar community as the postmenopausal cohort
   B. Drawn from a different source
   C. No description of the derivation of the premenopausal cohort
3. Ascertainment of menopausal status
   A. Secure record (eg, surgical records)
   B. Structured interview
   C. Written self report
   D. No description
   E. Other

Comparability of premenopausal and postmenopausal women

4. Comparability of premenopausal and postmenopausal women on the basis of the study design
   A. Lifestyle/demographic characteristics of premenopausal and postmenopausal women recorded and reported, with age as a minimum.
   B. The mean difference in age between premenopausal and postmenopausal women enables a reasonable comparison which is not highly confounded by age (ie, approximately $\leq$10 years for cross-sectional studies). Note: For longitudinal studies, an appropriate follow-up period is required (ie, premenopausal at baseline and postmenopausal at follow up).
5. Was a clear definition used to describe premenopausal women?
   A. Yes
   B. No
6. Was a clear definition used to describe postmenopausal women?
   A. Yes
   B. No

Outcome

7. Assessment of fat mass
   A. Measured
   B. Self report
   C. No description
8. Was the same method of measurement of fat mass conducted for both premenopausal and postmenopausal women?
   A. Yes
   B. No
   C. No description

SELECTION	/3
COMPARABILITY	/4
OUTCOME	/2
TOTAL	/9
Rater #1 Initials:	
SELECTION	/3
COMPARABILITY	/4
OUTCOME	/2
TOTAL	/9
Rater #2 Initials:	

Note: A study can be given a maximum of 1 star for each numbered item within the Selection and Outcome categories. The exception to this is for the Comparability section.

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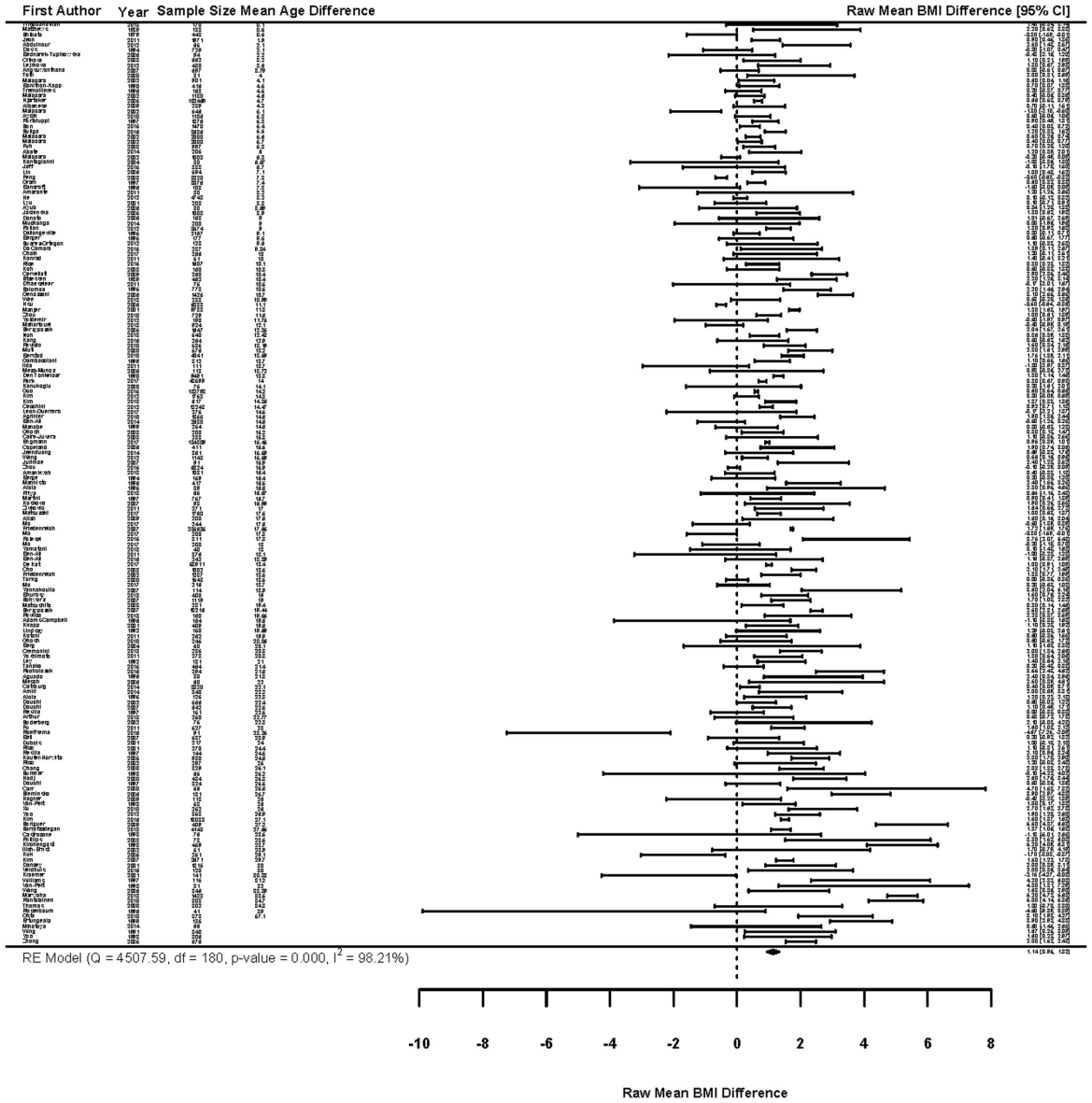
SUPPLEMENTARY FIGURE 1

Forest plot of the cross-sectional raw mean body mass index difference between premenopausal and postmenopausal women



Studies are arranged by mean age difference.

BMI, body mass index; *CI*, confidence interval; *RE*, random effects.

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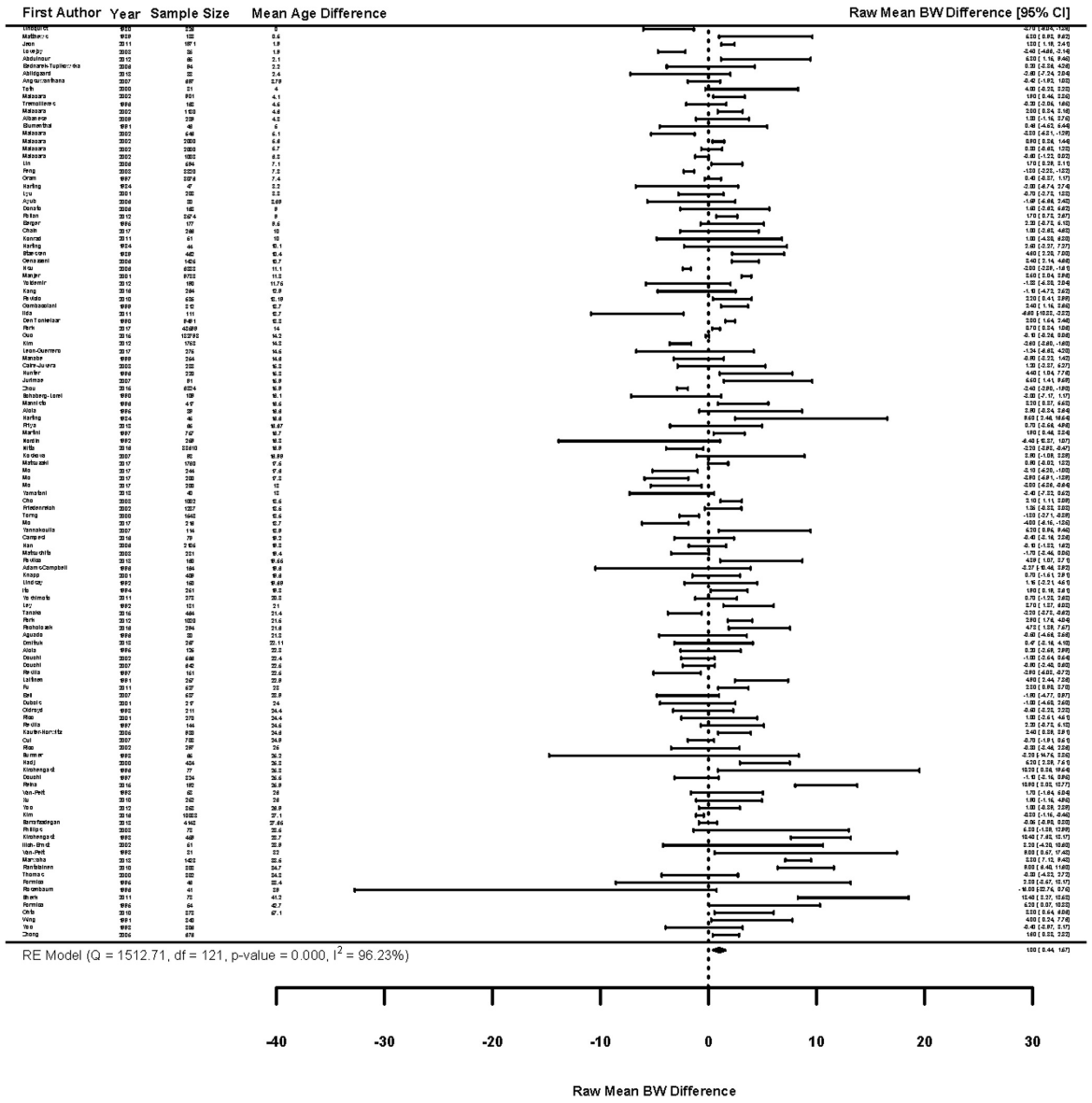
SUPPLEMENTARY FIGURE 2

Forest plot of the cross-sectional raw mean bodyweight difference between premenopausal and postmenopausal women



Studies are arranged by mean age difference.

BW, bodyweight; *CI*, confidence interval; *RE*, random effects.

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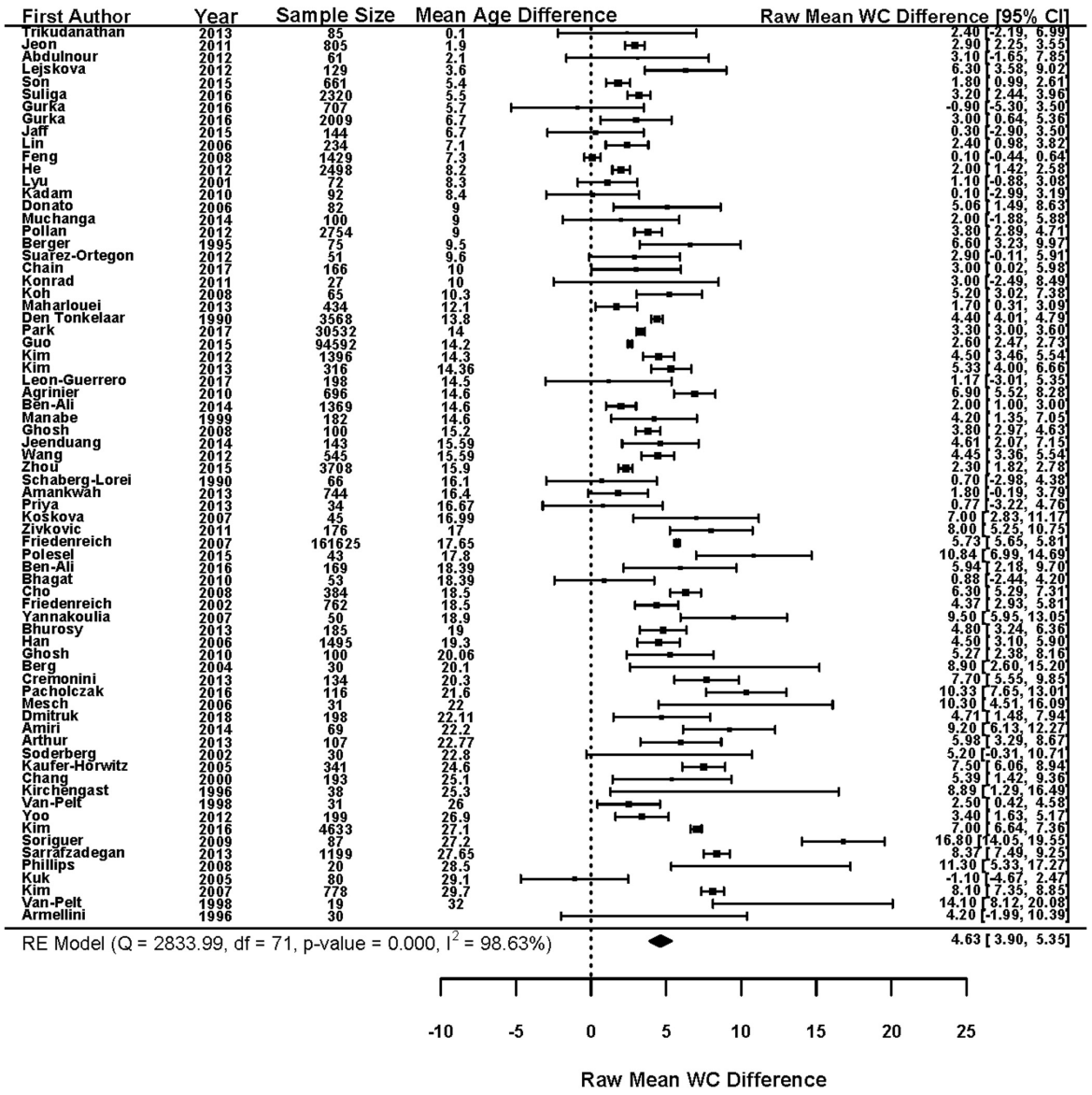
SUPPLEMENTARY FIGURE 3

Forest plot of the cross-sectional raw mean waist circumference difference between premenopausal and postmenopausal women



Studies are arranged by mean age difference.

CI, confidence interval; *RE*, random effects; *WC*, waist circumference.

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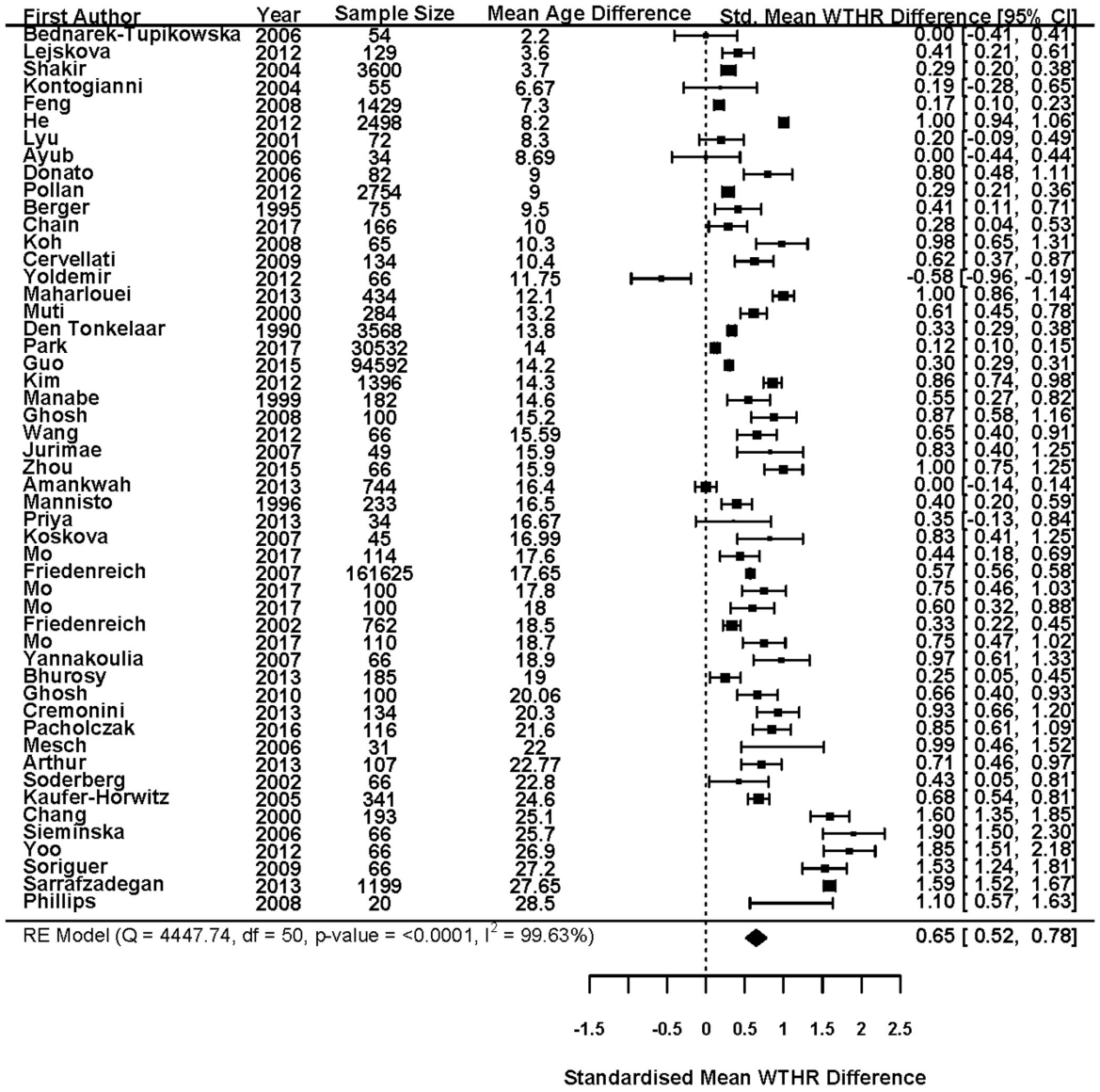
SUPPLEMENTARY FIGURE 4
Forest plot of the cross-sectional standardized mean waist-to-hip ratio difference between premenopausal and postmenopausal women

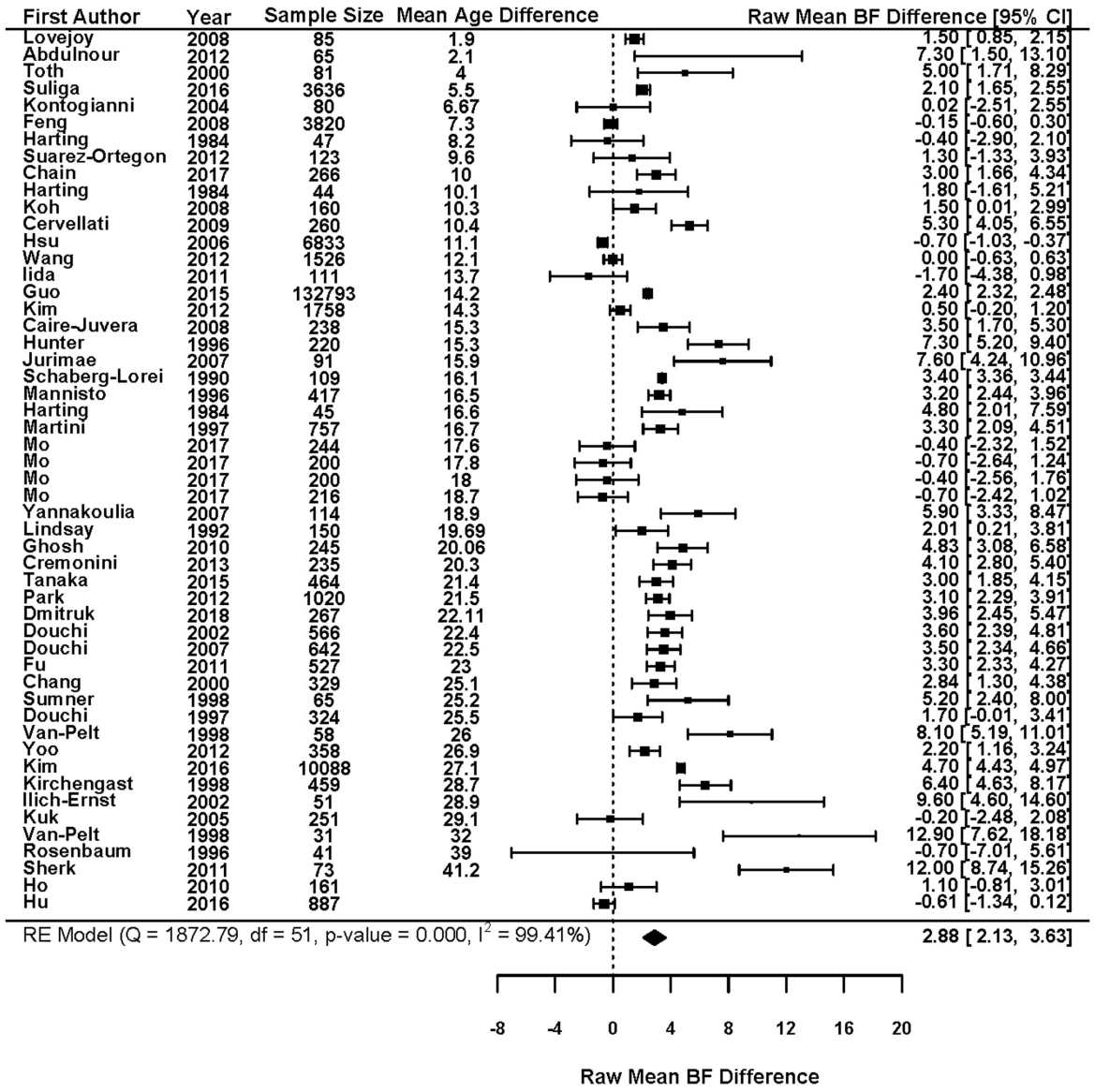


Studies are arranged by mean age difference. Standardized units have been used because of the amount of (residual) heterogeneity with nonpositive sampling variances.

CI, confidence interval; *RE*, random effects; *Std*, standardized; *WTHR*, waist-to-hip ratio.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 5
Forest plot of the cross-sectional raw mean body fat percentage difference between premenopausal and postmenopausal women

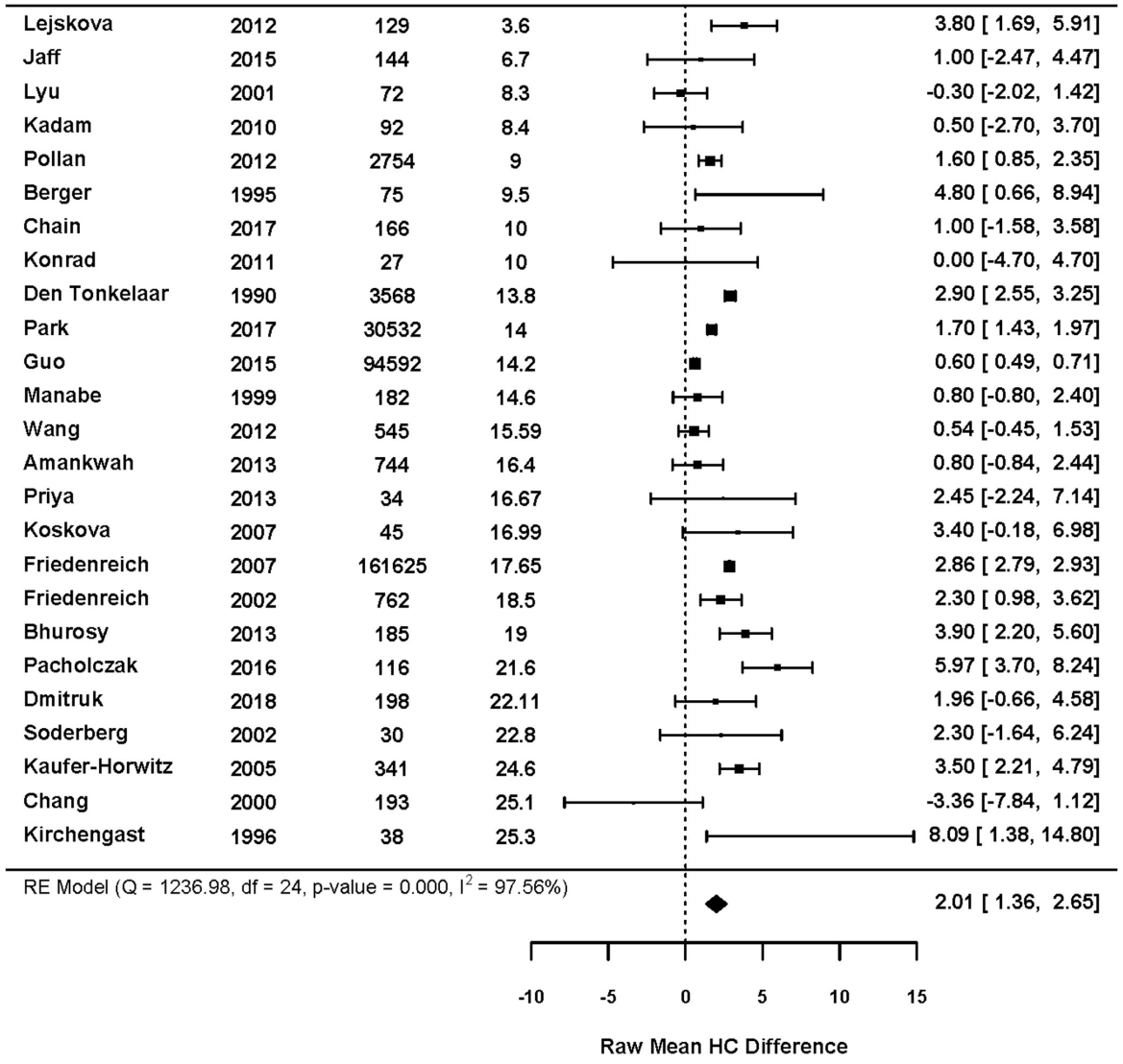


Studies are arranged by mean age difference.

BF, body fat; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 6
Forest plot of the cross-sectional raw mean hip circumference difference between premenopausal and postmenopausal women

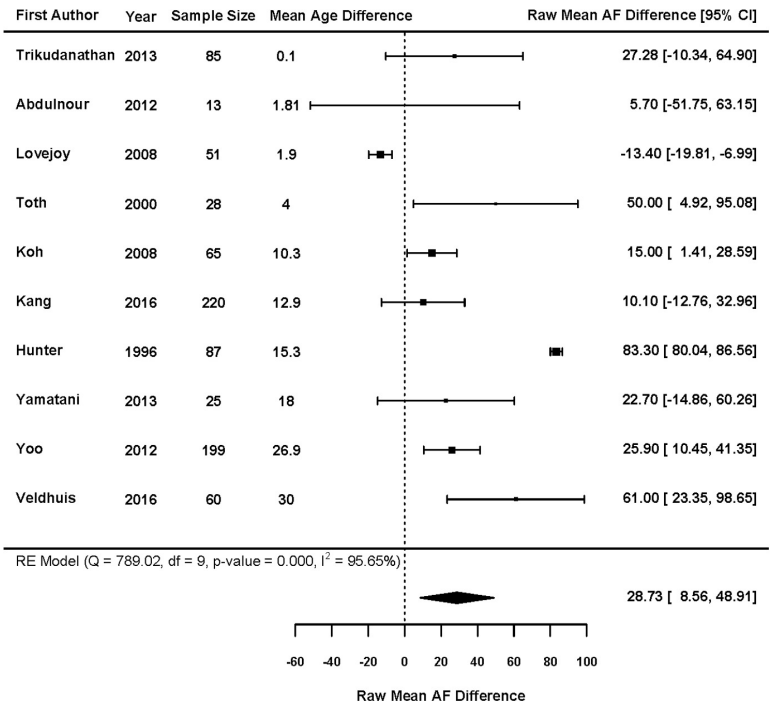


Studies are arranged by mean age difference.

CI, confidence interval; *HC*, hip circumference; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 7
Forest plot of the cross-sectional raw mean abdominal fat difference between premenopausal and postmenopausal women

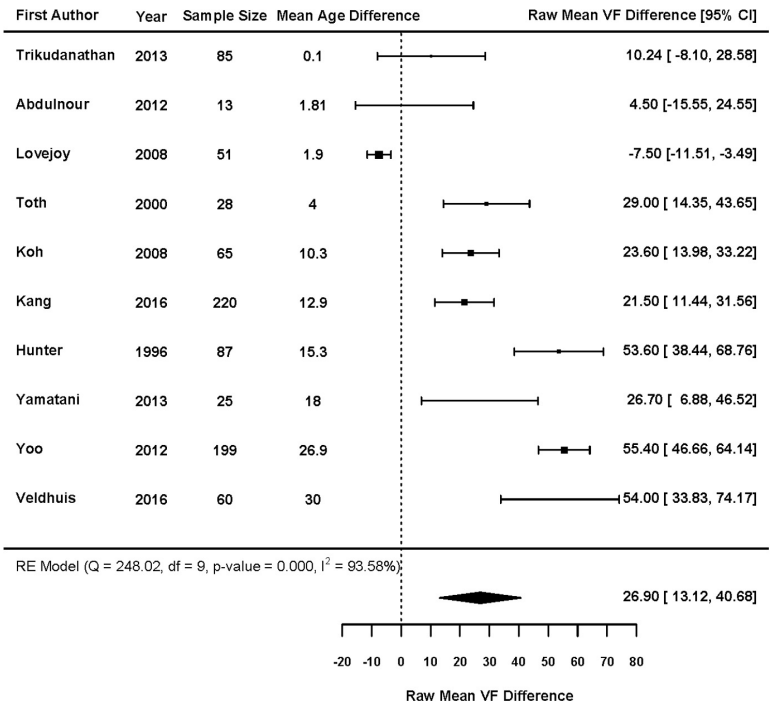


Studies are arranged by mean age difference.

AF, abdominal fat; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 8
Forest plot of the cross-sectional raw mean visceral fat difference between premenopausal and postmenopausal women

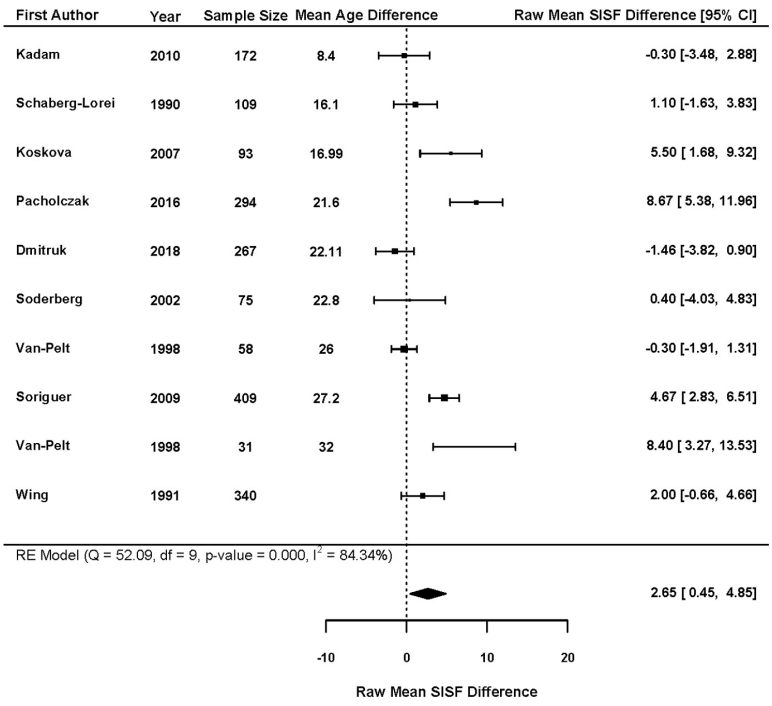


Studies are arranged by mean age difference.

CI, confidence interval; *RE*, random effects; *VF*, visceral fat.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 9
Forest plot of the cross-sectional raw mean suprailiac skinfold thickness difference between premenopausal and postmenopausal women

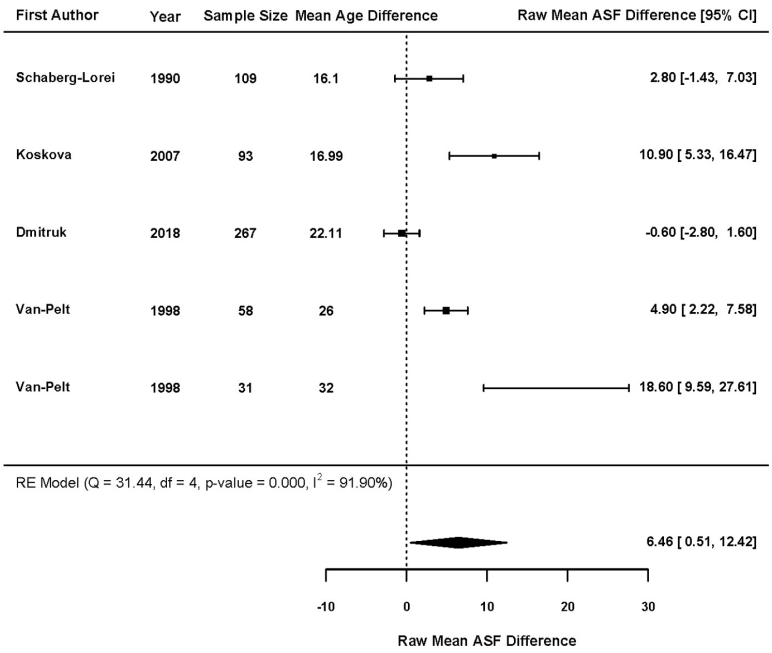


Studies are arranged by mean age difference.

CI, confidence interval; *RE*, random effects; *SISF*, suprailiac skinfold thickness.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 10
Forest plot of the cross-sectional raw mean abdominal skinfold thickness difference between premenopausal and postmenopausal women

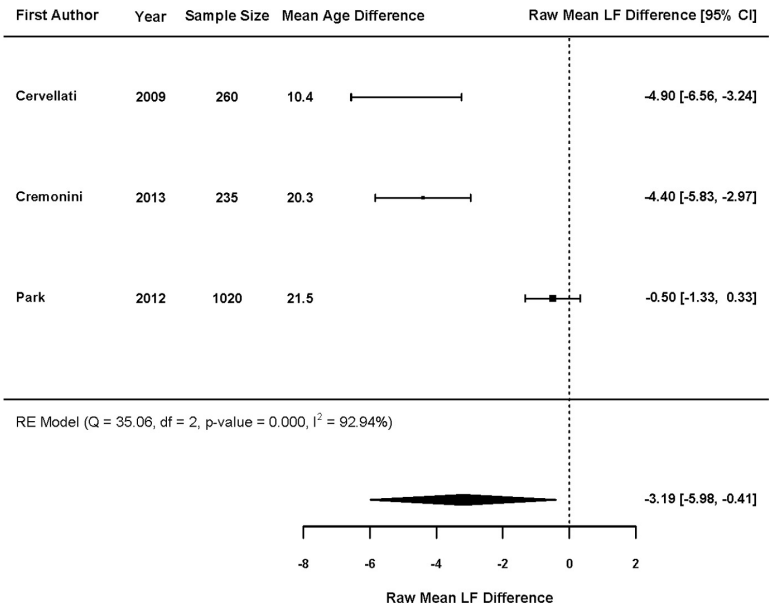


Studies are arranged by mean age difference.

ASF, abdominal skinfold thickness; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 11
Forest plot of the cross-sectional raw mean leg fat percentage difference between premenopausal and postmenopausal women

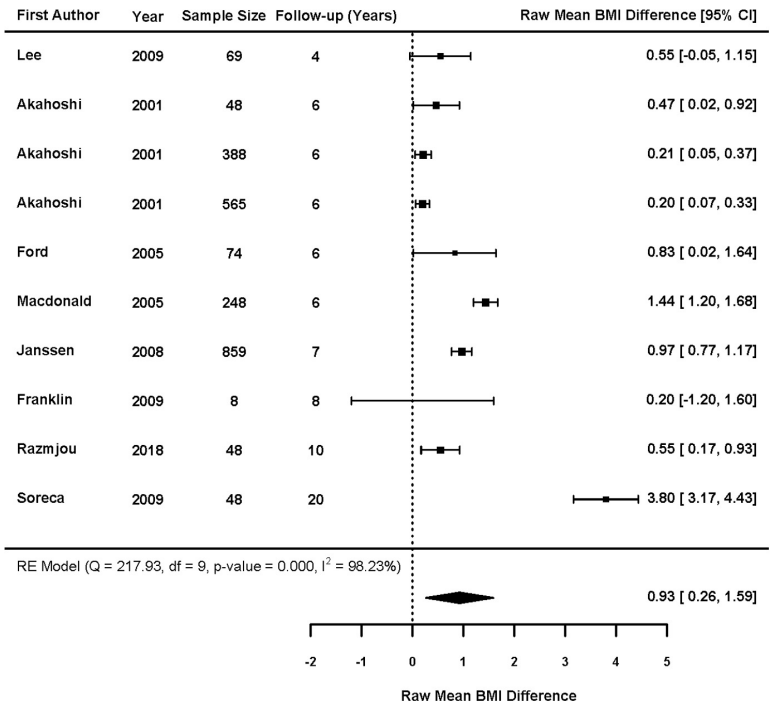


Studies are arranged by mean age difference.

CI, confidence interval; *LF*, leg fat; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 12
Forest plot of the longitudinal body mass index change for postmenopausal women who were premenopausal at baseline

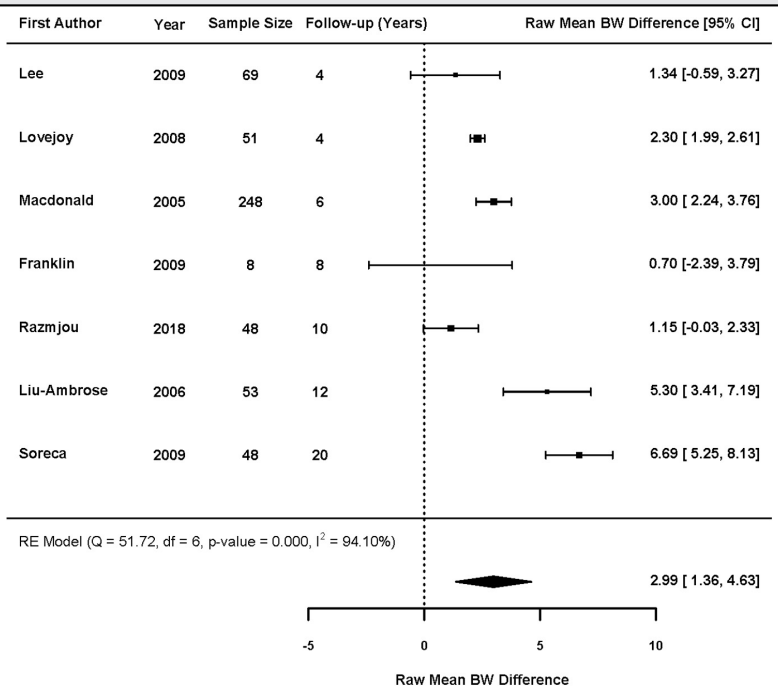


Studies are arranged by follow-up period.

BMI, body mass index; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 13
Forest plot of the longitudinal bodyweight change for postmenopausal women who were premenopausal at baseline

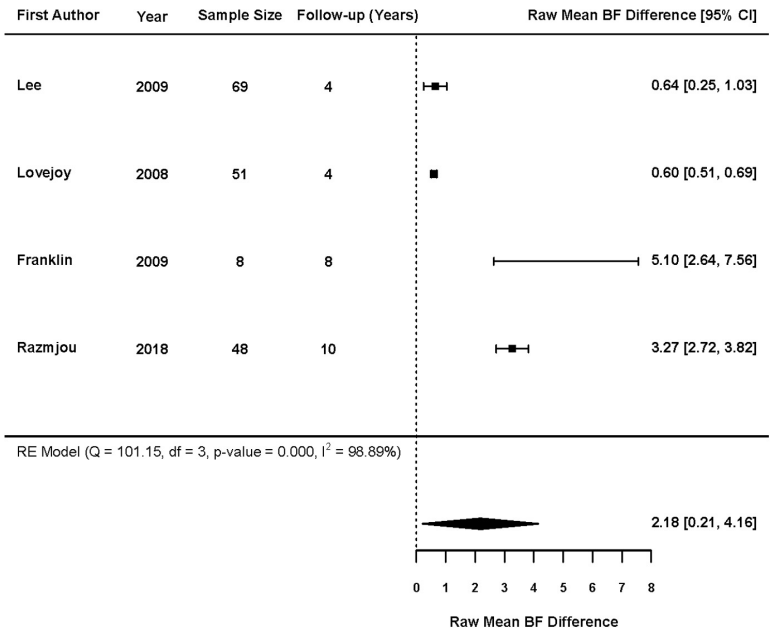


Studies are arranged by follow-up period.

BW, bodyweight; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 14
Forest plot of the longitudinal body fat percentage change for postmenopausal women who were premenopausal at baseline

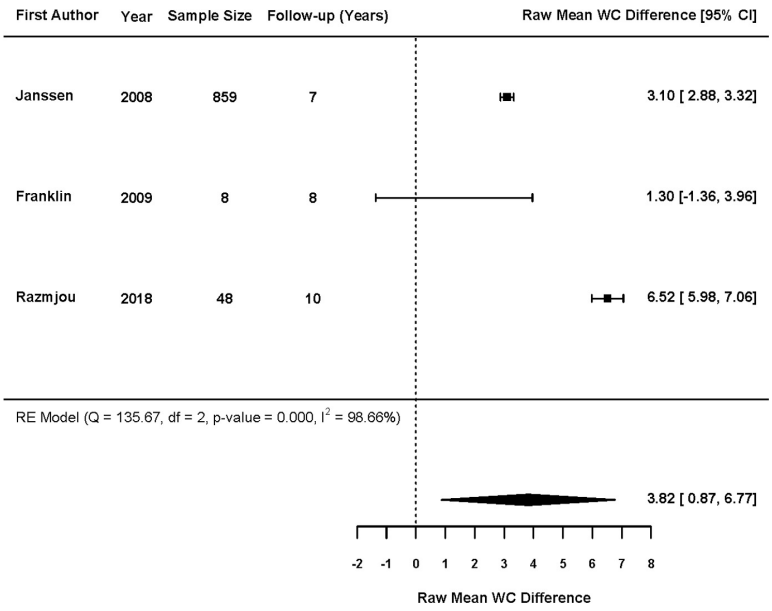


Studies are arranged by follow-up period.

BF, body fat; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 15
Forest plot of the longitudinal waist circumference change for postmenopausal women who were premenopausal at baseline

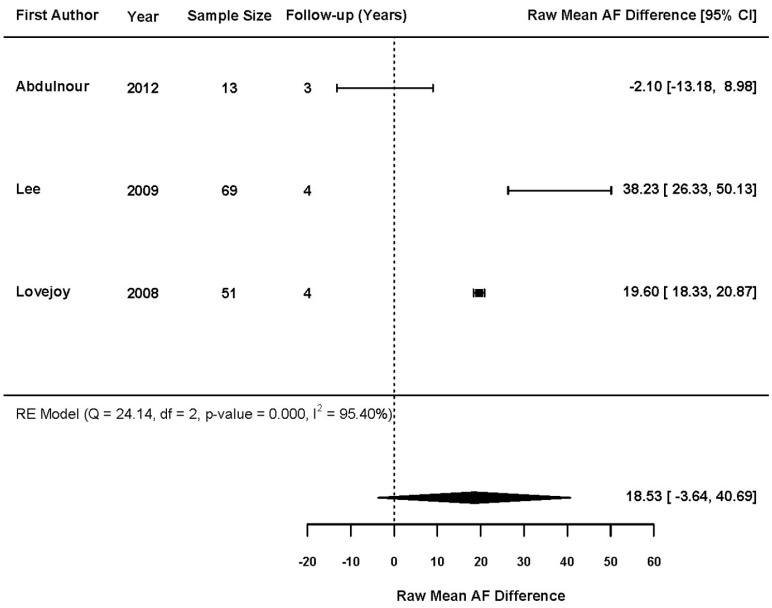


Studies are arranged by follow-up period.

CI, confidence interval; *RE*, random effects; *WC*, waist circumference.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 16
Forest plot of the longitudinal abdominal fat change for postmenopausal women who were premenopausal at baseline

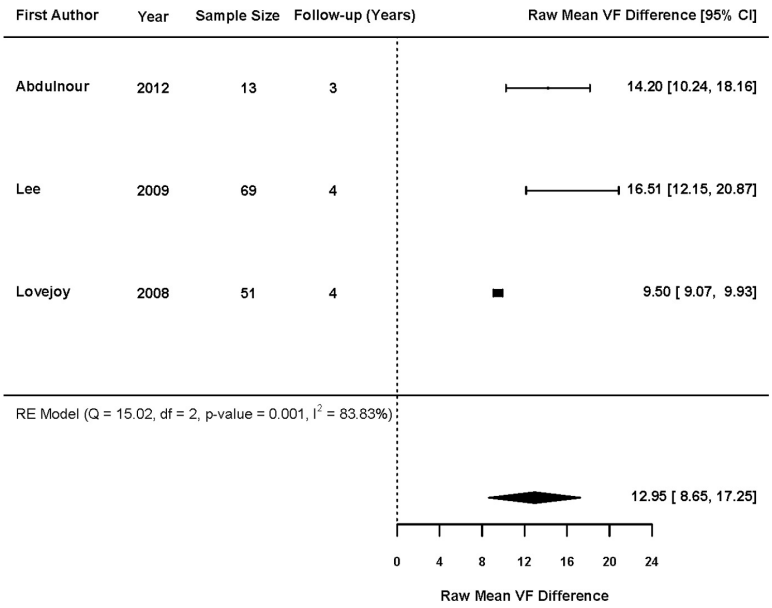


Studies are arranged by follow-up period.

AF, abdominal fat; *CI*, confidence interval; *RE*, random effects.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 17
Forest plot of the longitudinal visceral fat change for postmenopausal women who were premenopausal at baseline

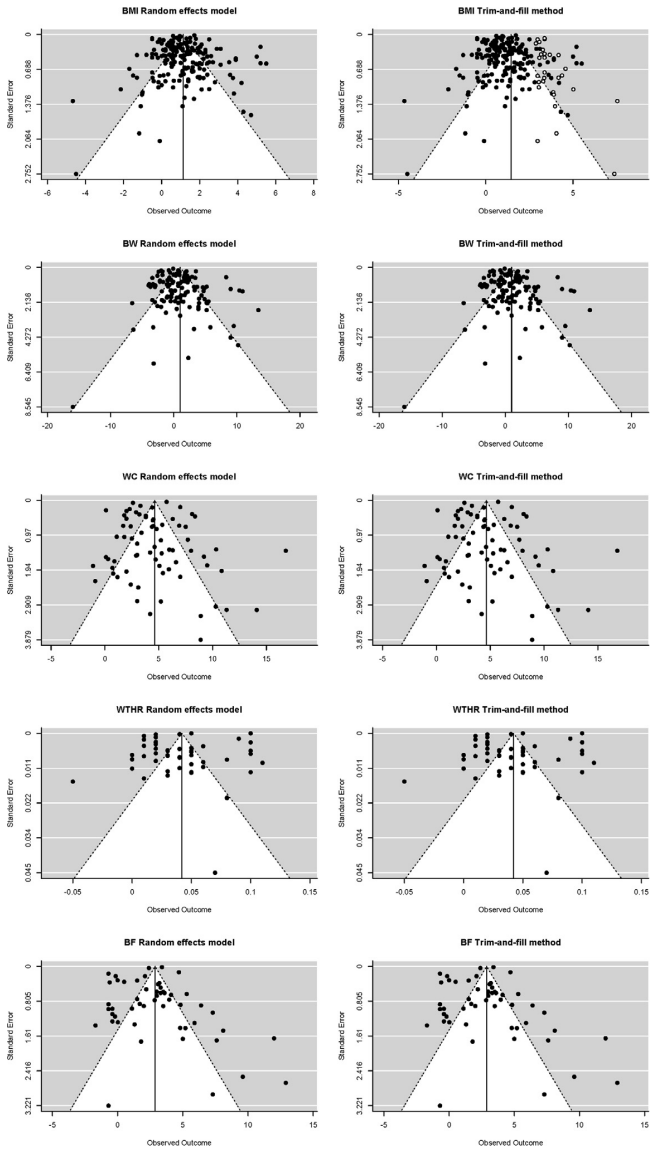


Studies are arranged by follow-up period.

CI, confidence interval; *RE*, random effects; *VF*, visceral fat.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 18
Funnel plots for cross-sectional studies with the use of a random effects model and the trim and fill method

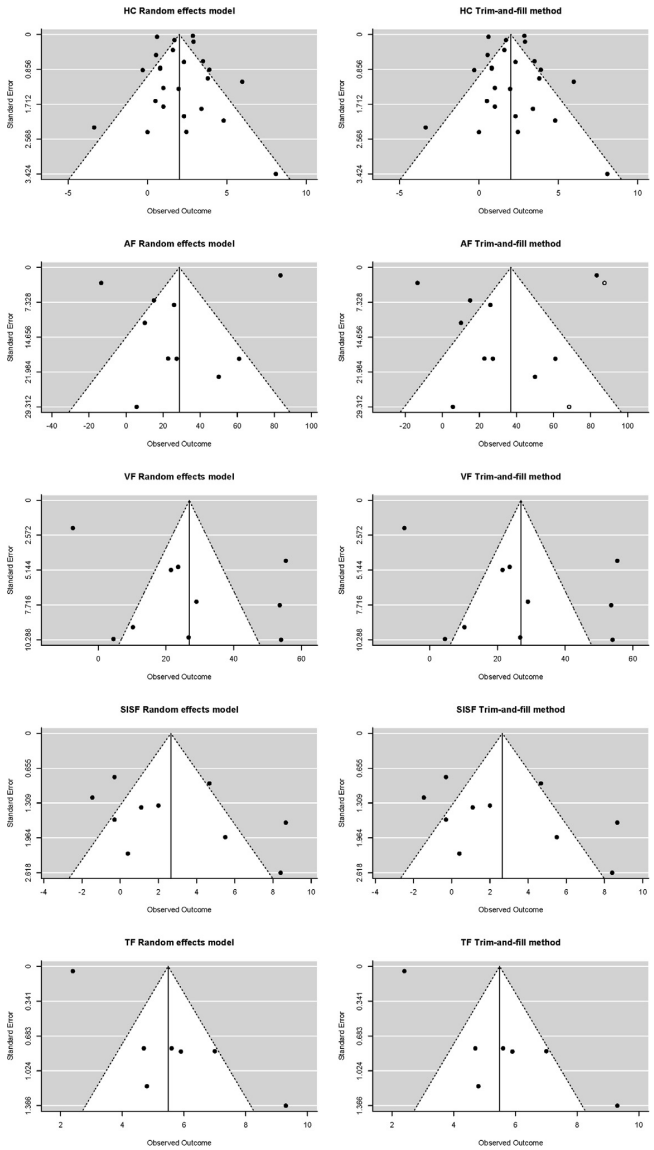


Left column, random effects model; **right column**, trim and fill method. *Filled circles* represent studies that were included in the metaanalyses; *open circles* represent possible missing studies.

BF, body fat; *BMI*, body mass index; *BW*, bodyweight; *WC*, waist circumference; *WTHR*, waist-to-hip ratio.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 19
Funnel plots for cross-sectional studies with the use of a random effects model and the trim and fill method

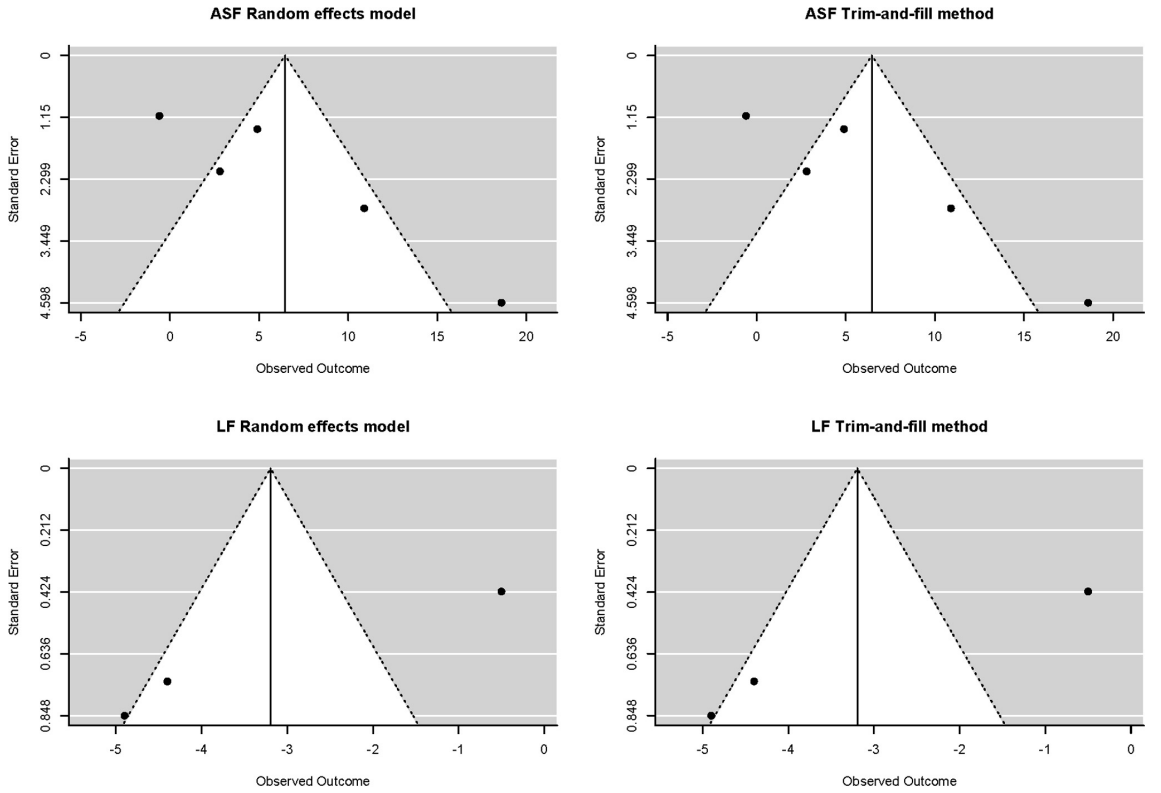


Left column, random effects model; **right column**, trim and fill method. *Filled circles* represent studies that were included in the metaanalyses; *open circles* represent possible missing studies.

AF, abdominal fat; *HC*, hip circumference; *SISF*, suprailiac skinfold thickness; *TF*, trunk fat; *VF*, visceral fat.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 20
Funnel plots for cross-sectional studies with the use of a random effects model and the trim and fill method

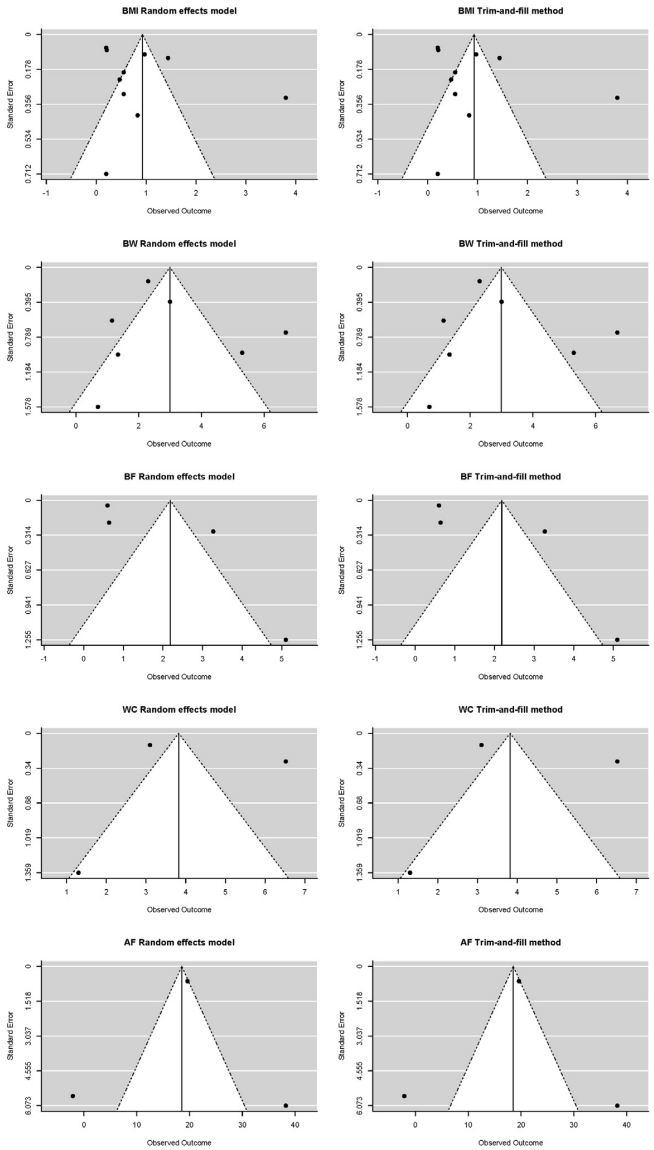


Left column, random effects model; **right column**, trim and fill method. *Filled circles* represent studies that were included in the metaanalyses; *open circles* represent possible missing studies.

ASF, abdominal skinfold thickness; *LF*, leg fat.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 21
Funnel plots for longitudinal studies with the use of a random effects model and the trim and fill method

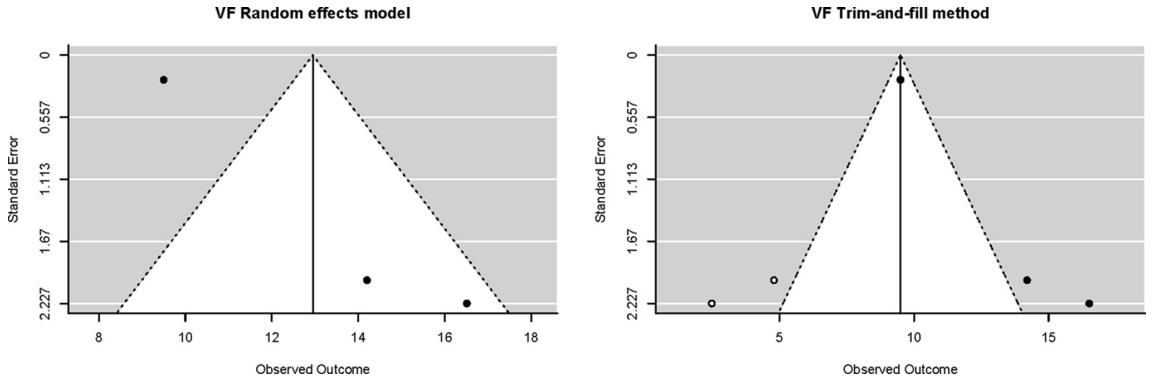


Left column, random effects model; **right column**, trim and fill method. *Filled circles* represent studies that were included in the metaanalyses; *open circles* represent possible missing studies.

AF, abdominal fat; *BF*, body fat; *BMI*, body mass index; *BW*, bodyweight; *WC*, waist circumference.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY FIGURE 22
Funnel plot for a longitudinal study with the use of a random effects model and the trim and fill method



Left column, random effects model; **right column**, trim and fill method. *Filled circles* represent studies that were included in the metaanalyses; *open circles* represent possible missing studies.

VF, visceral fat.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY TABLE 1
Definition of data elements

Data element name	Abbreviation	Unit of measurement	Type/method of measurement
Body mass index	BMI	Weight in kilograms divided by height in meters squared (kg/m^2)	Measured directly or with self-reported weight and height
Bodyweight	BW	Weight in kilograms (kg)	Measured directly or with self-report weight
Waist circumference	WC	Centimeters (cm)	According to the World Health Organization, measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest
Hip circumference	HC	Centimeters (cm)	According to the World Health Organization, measured around the widest portion of the buttocks
Waist-to-hip ratio	WTHR	A ratio of waist circumference to hip circumference	Divide waist circumference by hip circumference
Body fat percentage	BF%	Percentage (%)	Dual energy x-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA) or hydrodensitometry or near infrared interactance or skinfold estimates
Trunk fat percentage	TF%	Percentage (%)	Dual energy x-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA)
Total leg fat percentage	LF%	Percentage (%)	Dual energy x-ray absorptiometry (DEXA) or bioelectrical impedance analysis (BIA)
Subcutaneous abdominal fat	AF	Centimeters cubed (cm^3)	Computed tomography (CT) scan
Visceral fat	VF	Centimeters cubed (cm^3)	Computed tomography (CT) scan
Suprailiac skinfold thickness	SISF	Millimeters (mm)	Measure the thickness of skin at the suprailiac, with the use of calipers
Abdominal skinfold thickness	ASF	Millimeters (mm)	Measure the thickness of skin at the suprailiac, with the use of calipers

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Abate et al[1]	2014	205	46.7	1.9	52.7	3.4	*	—	—	—	—	—	—	—	—	—	—	—
Abdulnour et al[2]	2012	65	52.3	0.5	54.4	2	*	*	*	—	*	—	—	—	—	—	—	—
	2012	31	50.95	1.31	52.76	2.16	*	*	*	—	*	—	*	*	—	—	—	—
Abildgaard et al[3]	2013	33	49.6	1.8	52	2	—	*	—	—	—	—	—	—	—	—	—	—
Adams-Campbell et al[4]	1996	164	39.3	6.9	58.9	10.1	*	*	—	—	—	—	—	—	—	—	—	—
Agrinier et al[5]	2010	1355	42.8	4.4	57.4	5.4	*	—	*	—	—	—	—	—	—	—	—	—
Aguado et al[6]	1996	80	38.8	8.4	60.6	9.6	*	*	—	—	—	—	—	—	—	—	—	—
Albanese et al[7]	2009	289	48.8	3.8	53.6	3.7	*	*	—	—	—	—	—	—	—	—	—	—
Allali et al[8]	2009	200	43.9	6.3	61.5	8.8	*	—	—	—	—	—	—	—	—	—	—	—
Aloia et al[9]	1995	39	37.5	5.82	54.1	7.96	*	*	—	—	—	—	—	—	—	—	—	—
	1995	125	40.2	7.2	62.5	7.81	*	*	—	—	—	—	—	—	—	—	—	—
Amankwah et al[10]	2013	1,031	46.3	6.5	62.7	7.2	*	—	*	*	—	*	—	—	—	—	—	—
Amarante et al[11]	2011	80	43.96	7.08	52.16	3.65	*	—	—	—	—	—	—	—	—	—	—	—
Amiri et al[12]	2014	340	36.8	11.52	59	7.48	*	—	*	—	—	—	—	—	—	—	—	—
Angsuwanthana et al[13]	2007	697	49.4	3.39	53.19	5.94	*	*	—	—	—	—	—	—	—	—	—	—
Armellini et al[14]	1996	72	NA		NA		—	—	*	—	—	—	—	—	—	—	—	—
Arthur et al[15]	2013	250	34.48	8.85	57.25	8.28	*	—	*	*	—	—	—	—	—	—	—	—
Aydin et al[16]	2010	1,106	48.7	2.6	54	3.4	*	—	—	—	—	—	—	—	—	—	—	—
Ayub et al[17]	2006	80	42.46	7.3	51.15	7.71	*	*	—	*	—	—	—	—	—	—	—	—
Bancroft and Cawood[18]	1996	103	47.6	3.7	55.4	3.05	*	—	—	—	—	—	—	—	—	—	—	—
Bednarek-Tupikowska et al[19]	2006	94	48.3	2.3	50.5	3	*	*	—	*	—	—	—	—	—	—	—	—
Bell et al[20]	2007	587	38.9	7.9	62.8	8.3	*	*	—	—	—	—	—	—	—	—	—	—
Ben-Ali et al[21]	2016	242	39.48	7.79	57.87	7.65	*	—	*	—	—	—	—	—	—	—	—	—
Ben-Ali et al[22]	2014	2,680	42.9	5	57.5	7.3	*	—	*	—	—	—	—	—	—	—	—	—
Ben-Ali et al[23]	2011	376	35.3	7.6	53.4	6.2	*	—	—	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Berg et al[24]	2004	50	36.9	4.1	57	5.3	*	—	*	—	—	—	—	—	—	—	—	—
Berge et al[25]	1994	159	38.9	7.2	55.3	6.1	*	—	—	—	—	—	—	—	—	—	—	—
Berger et al[26]	1995	177	38.2	5	47.7	3.8	*	*	*	*	—	*	—	—	—	—	—	—
Berstad et al[27]	2010	4,041	42.83	5.1	56.42	5.46	*	—	—	—	—	—	—	—	—	—	—	—
Bhagat et al[28]	2010	214	33.77	6.57	52.16	6.27	—	—	*	—	—	—	—	—	—	—	—	—
Bhurosy and Jeewon[29]	2013	400	34	NA	53	NA	*	—	*	*	—	*	—	—	—	—	—	—
Blumenthal et al[30]	1991	46	47	2	52	3	—	*	—	—	—	—	—	—	—	—	—	—
Bonithon-Kopp et al[31]	1990	416	47.8	2.2	52.3	1.8	*	—	—	—	—	—	—	—	—	—	—	—
Caire-Juvera et al[32]	2008	238	44.8	2.39	60.1	3.59	*	*	—	—	*	—	—	—	—	*	—	—
Campesi et al[33]	2016	79	36.2	7.6	55.4	5.1	—	*	—	—	—	—	—	—	—	—	—	—
Carr et al[34]	2000	56	35.4	8.6	61	4.1	*	—	—	—	—	—	—	—	—	—	—	—
Castracane et al[35]	1998	76	27.3	0.63	55.8	0.85	*	—	—	—	—	—	—	—	—	—	—	—
Catsburg et al[36]	2014	3,320	45.8	8.9	67.9	11.2	*	—	—	—	—	—	—	—	—	—	—	—
Cecchini et al[37]	2012	12,243	46.34	4.28	60.81	7.51	*	—	—	—	—	—	—	—	—	—	—	—
Cervellati et al[38]	2009	260	38.1	6.73	48.5	6.95	*	—	—	*	*	—	—	—	—	*	—	*
Chain et al[39]	2017	266	47	5	57	7	*	*	*	*	*	*	—	—	—	—	—	—
Chang et al[40]	2000	329	36.1	6.5	61.2	6.2	*	—	*	*	*	*	—	—	—	—	—	—
Cho et al[41]	2008	1,002	40.5	7.8	59	6.6	*	*	*	—	—	—	—	—	—	—	—	—
Cifkova et al[42]	2008	662	48.9	2.39	52.1	1.92	*	—	—	—	—	—	—	—	—	—	—	—
Copeland et al[43]	2006	411	36	8.5	51.5	7.7	*	—	—	—	—	—	—	—	—	—	—	—
Cremonini et al[44]	2013	235	35.2	10.7	55.5	4.8	*	—	*	*	*	—	—	—	—	*	—	*
Cui et al[45]	2007	703	38.4	8.6	63.3	6.5	—	*	—	—	—	—	—	—	—	—	—	—
D'haeseleer et al[46]	2011	75	48.3	2.3	58.8	5.4	*	—	—	—	—	—	—	—	—	—	—	—
Da Camara et al[47]	2015	237	44.63	3.36	54.47	5.24	*	—	—	—	—	—	—	—	—	—	—	—
Dallongeville et al[48]	1995	2,167	48.3	3.4	57.4	3.9	*	—	—	—	—	—	—	—	—	—	—	—
Dancey et al[49]	2001	1,315	35	5.65	65	6.83	*	—	—	—	—	—	—	—	—	—	—	—
Davis et al[50]	1994	729	48.1	1.7	50.2	1.7	*	—	—	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
De Kat et al[51]	2017	53,911	36.9	8.1	55.3	7.4	*	—	—	—	—	—	—	—	—	—	—	—
Den Tonkelaar et al[52]	1990	9,491	44	3.6	57.8	7.4	*	*	*	*	—	*	—	—	—	—	—	—
Dmitruk et al[53]	2018	267	44.48	2.22	66.59	6.69	—	*	*	—	*	*	—	—	*	—	*	—
Donato et al[54]	2006	168	44.3	3.6	53.3	3.8	*	*	*	*	—	—	—	—	—	—	—	—
Douchi et al[55]	1997	324	36.6	9.4	62.1	7.7	*	*	—	—	*	—	—	—	—	—	—	—
Douchi et al[56]	2002	566	39.1	9.1	61.5	7.2	*	*	—	—	*	—	—	—	—	—	—	—
Douchi et al[57]	2007	642	39	9	61.5	7.4	*	*	—	—	*	—	—	—	—	*	—	—
Dubois et al[58]	2001	217	39	9	63	8	*	*	—	—	—	—	—	—	—	—	—	—
Engmann et al[59]	2017	184,309	46.27	3.75	61.72	7.2	*	—	—	—	—	—	—	—	—	—	—	—
Ertungealp et al[60]	1999	185	NA		NA		*	—	—	—	—	—	—	—	—	—	—	—
Feng et al[61]	2008	3,820	43.7	3	51	2.6	*	*	*	*	*	—	—	—	—	—	—	—
Formica et al[62]	1995	54	26.3	3.64	69	4.68	—	*	—	—	—	—	—	—	—	—	—	—
	1995	46	26.5	3.82	64.9	4.23	—	*	—	—	—	—	—	—	—	—	—	—
Friedenreich et al[63]	2007	285,685	41.11	6.9	58.76	6.25	*	—	*	*	—	*	—	—	—	—	—	—
Friedenreich et al[64]	2002	1,237	44.3	5.9	62.8	9	*	*	*	*	—	*	—	—	—	—	—	—
Fu et al[65]	2011	527	38	8.6	61	7.2	*	*	—	—	*	—	—	—	—	—	—	—
Fuh et al[66]	2003	997	43.6	2.9	49.4	3.8	*	—	—	—	—	—	—	—	—	—	—	—
Gambacciani et al[67]	1999	812	41.3	7.8	55	4.16	*	*	—	—	—	—	—	—	—	—	—	—
Genazzani and Gambacciani[68]	2006	1,425	42.3	9.3	53	5.95	*	*	—	—	—	—	—	—	—	—	—	—
Ghosh[69]	2008	200	40.2	6.5	55.4	5.2	*	—	*	*	—	—	—	—	—	—	—	—
Ghosh and Bhagat[70]	2010	245	32.66	5.75	52.72	5.62	*	—	*	*	*	—	—	—	—	—	—	—
Gram et al[71]	1997	3,076	44.3	3.5	51.7	3.6	*	*	—	—	—	—	—	—	—	—	—	—
Guo et al[72]	2015	132,793	45.5	3.4	59.7	5.5	*	*	*	*	*	*	—	—	—	*	—	—
Gurka et al[73]	2016	2,177	47.6	3.4	54.3	3.6	—	—	*	—	—	—	—	—	—	—	—	—
	2016	779	47.4	2.1	53.1	4.1	—	—	*	—	—	—	—	—	—	—	—	—
Hadji et al[74]	2000	434	36.5	10.4	61.8	8.9	*	*	—	—	—	—	—	—	—	—	—	—
Hagner et al[75]	2009	118	36.5	5.17	62.5	5.43	*	—	—	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Han et al[76]	2006	2,105	44.1	4.6	63.4	8.9	—	*	*	—	—	—	—	—	—	—	—	—
Harting et al[77]	1984	45	33.8	8.2	50.4	3.8	—	*	—	—	*	—	—	—	—	—	—	—
	1984	47	37.9	8.2	46.1	8.2	—	*	—	—	*	—	—	—	—	—	—	—
	1984	44	36.9	8.1	47	7.3	—	*	—	—	*	—	—	—	—	—	—	—
He et al[78]	2012	4,743	45.8	3.6	54	3.6	*	—	*	*	—	—	—	—	—	—	—	—
Hirose et al[79]	2003	16,132	42.2	NA	60	NA	*	*	—	—	—	—	—	—	—	—	—	—
	2003	1,716	38	NA	61.4	NA	*	*	—	—	—	—	—	—	—	—	—	—
Hjartaker et al[80]	2005	102,469	40.7	5	45.4	4.1	*	—	—	—	—	—	—	—	—	—	—	—
Ho et al[81]	2010	161	NA		NA		—	—	—	—	*	—	—	—	—	—	—	—
Hsu et al[82]	2006	6,833	41.5	5.3	52.6	4.7	*	*	—	—	*	—	—	—	—	—	—	—
Hu et al[83]	2016	887	NA		NA		—	—	—	—	*	—	—	—	—	—	—	—
Hunter et al[84]	1996	220	36.2	9	51.5	10.2	—	*	—	—	*	—	*	*	—	—	—	—
Iida et al[85]	2011	111	47.6	3.8	61.3	6.6	*	*	—	—	*	—	—	—	—	—	—	—
Ilich-Ernst et al[86]	2002	51	33	9.2	61.9	3.3	*	*	—	—	*	—	—	—	—	—	—	—
Ito et al[87]	1994	251	38.8	10	58.6	5.8	—	*	—	—	—	—	—	—	—	—	—	—
Jaff et al[88]	2015	338	45.1	3.3	51.8	3.86	*	—	*	—	—	*	—	—	—	—	—	—
Jasienska et al[89]	2005	1,003	48.5	2.81	57.4	4.41	*	—	—	—	—	—	—	—	—	—	—	—
Jeenduang et al[90]	2014	361	42.58	6.62	58.17	9.65	*	—	*	—	—	—	—	—	—	—	—	—
Jeon et al[91]	2011	1971	49.3	8.5	51.2	9	*	*	*	—	—	—	—	—	—	—	—	—
Jurimae and Jurimae[92]	2007	91	40.8	5.7	56.7	3.6	*	*	—	*	*	—	—	—	—	—	—	—
Kadam et al[93]	2010	172	45.6	4.8	54	7.1	—	—	*	—	—	*	—	—	*	—	—	—
Kang et al[94]	2016	264	47.9	3.3	60.8	6	*	*	—	—	—	—	*	*	—	—	—	—
Kaufer-Horwitz et al[95]	2005	980	33.7	8.4	58.3	6.9	*	*	*	*	—	*	—	—	—	—	—	—
Kim et al[96]	2007	2,671	35.4	8.1	65.1	9.3	*	—	*	—	—	—	—	—	—	—	—	—
Kim et al[97]	2012	1,758	50.7	2.8	65	7.4	*	*	*	*	*	—	—	—	—	—	—	—
Kim et al[98]	2013	617	42.12	6.22	56.48	6.55	*	—	*	—	—	—	—	—	—	—	—	—
Kim et al[99]	2016	10,088	36.9	8.7	64	9.7	*	*	*	—	*	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Kirchengast et al[100]	1998	77	27.1	NA	55.8	NA	*	*	—	—	*	—	—	—	—	*	—	—
Kirchengast et al[101]	1996	459	26.8	NA	52.1	NA	—	*	*	—	—	*	—	—	—	—	—	—
Knapp et al[102]	2001	409	40.3	9.5	59.9	7.5	*	*	—	—	—	—	—	—	—	—	—	—
Koh et al[103]	2008	160	44.2	2.92	54.5	4.35	*	—	*	*	*	—	*	*	—	—	—	—
Konrad et al[104]	2011	51	43	5	53	4	*	*	*	—	—	*	—	—	—	—	—	—
Kontogianni et al[105]	2004	80	47.8	3.14	54.47	5.36	*	—	—	*	*	—	—	—	—	—	—	—
Konukoglu et al[106]	2000	75	35.4	8.3	49.5	4.7	*	—	—	—	—	—	—	—	—	—	—	—
Koskova et al[107]	2007	93	42.54	2.5	59.53	2.71	*	*	*	*	—	*	—	—	*	—	*	—
Kotani et al[108]	2011	262	44.7	4.9	64.6	4.4	*	—	—	—	—	—	—	—	—	—	—	—
Kraemer et al[109]	2001	141	26.8	4.9	57.63	7.47	*	—	—	—	—	—	—	—	—	—	—	—
Kuk et al[110]	2005	251	37.6	8.6	66.7	8	*	—	*	—	*	—	—	—	—	—	—	—
Laitinen et al[111]	1991	257	36.7	9	59.6	6.4	—	*	—	—	—	—	—	—	—	—	—	—
Lejskova et al[112]	2012	480	48.6	2.4	52.2	2	*	—	*	*	—	*	—	—	—	—	—	—
Leon-Guerrero et al[113]	2017	275	43.94	6.63	58.44	8.69	*	*	*	—	—	—	—	—	—	—	—	—
Ley et al[114]	1992	131	32	6	53	5	*	*	—	—	—	—	—	—	—	—	—	—
Lin et al[115]	2006	594	46	3.6	53.1	4.4	*	*	*	—	—	—	—	—	—	—	—	—
Lindquist and Bengtsson[116]	1980	326	50	NA	50	NA	—	*	—	—	—	—	—	—	—	—	—	—
Lindsay et al[117]	1992	150	39.65	9.98	59.34	8.37	*	*	—	—	*	—	—	—	—	—	—	—
Lovejoy et al[118]	2008	85	50.2	0.3	52.1	0.3	—	*	—	—	*	—	*	*	—	—	—	—
Lyu et al[119]	2001	203	45.1	3.4	53.4	5	*	*	*	*	—	*	—	—	—	—	—	—
Maharlouei et al[120]	2013	924	46.5	5	58.6	6.7	*	—	*	*	—	—	—	—	—	—	—	—
Malacara et al[121]	2002	901	46.8	3.1	50.9	4.4	*	*	—	—	—	—	—	—	—	—	—	—
	2002	1,180	45.2	2.9	49.8	3.28	*	*	—	—	—	—	—	—	—	—	—	—
	2002	546	44.8	3.6	49.9	4.2	*	*	—	—	—	—	—	—	—	—	—	—
	2002	2,000	45.1	3.4	50.8	3.4	*	*	—	—	—	—	—	—	—	—	—	—
	2002	1,008	44.3	2.4	50.6	2.6	*	*	—	—	—	—	—	—	—	—	—	—
	2002	2,000	45.4	2.6	51	2.4	*	*	—	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Manabe et al[122]	1999	254	45.7	4.2	60.3	5.5	*	*	*	*	—	*	—	—	—	—	—	—
Manjer et al[123]	2001	9,738	42.8	7.9	54.1	3	*	*	—	—	—	—	—	—	—	—	—	—
Mannisto et al[124]	1996	417	43.3	6	59.8	7.7	*	*	—	*	*	—	—	—	—	—	—	—
Martini et al[125]	1997	757	43.2	6.7	59.9	8.1	*	*	—	—	*	—	—	—	—	—	—	—
Marwaha et al[126]	2013	1,423	31	8.6	64.5	7.4	*	*	—	—	—	—	—	—	—	—	—	—
Matsushita et al[127]	2003	281	43	6.3	62.4	7.9	*	*	—	—	—	—	—	—	—	—	—	—
Matsuzaki et al[128]	2017	1,760	29.3	9.9	46.8	6.9	*	*	—	—	—	—	—	—	—	—	—	—
Matthews et al[129]	1989	138	47.3	1.5	47.8	1.6	*	*	—	—	—	—	—	—	—	—	—	—
Mesch et al[130]	2006	60	33	5.6	55	5.6	*	—	*	*	—	—	—	—	—	—	—	—
Meza-Munoz et al[131]	2006	113	40.03	7.16	53.75	4.28	*	—	—	—	—	—	—	—	—	—	—	—
Minatoya et al[132]	2014	66	NA		NA		*	—	—	—	—	—	—	—	—	—	—	—
Mo et al[133]	2017	200	41.7	6.3	59.7	6.8	*	*	—	*	*	—	—	—	—	—	—	—
	2017	200	42	5.4	59.8	7	*	*	—	*	*	—	—	—	—	—	—	—
	2017	216	42.1	6.4	60.8	8.1	*	*	—	*	*	—	—	—	—	—	—	—
	2017	244	43.2	7	60.8	7.6	*	*	—	*	*	—	—	—	—	—	—	—
Muchanga et al[134]	2014	200	44	3	53	4	*	—	*	—	—	—	—	—	—	—	—	—
Muti et al[135]	2000	576	44.5	4.8	57.7	5.1	*	—	—	*	—	—	—	—	—	—	—	—
Nitta et al[136]	2016	38,610	45.5	3.8	62.4	7.8	—	*	—	—	—	—	—	—	—	—	—	—
Noh et al[137]	2013	540	46.92	4.7	59.34	5.82	*	—	—	—	—	—	—	—	—	—	—	—
Nordin et al[138]	1992	259	43.1	7.5	59.9	8.5	—	*	—	—	—	—	—	—	—	—	—	—
Ohta et al[139]	2010	373	14.8	1.7	71.9	4.5	*	*	—	—	—	—	—	—	—	—	—	—
Oldroyd et al[140]	1998	211	37.2	8.8	61.6	7.9	—	*	—	—	—	—	—	—	—	—	—	—
Pacholczak et al[141]	2016	294	41.8	6.1	63.4	10.2	*	*	*	*	—	*	—	—	*	—	—	—
Park et al[142]	2012	1,020	37	7.25	58.5	7.7	—	*	—	—	*	—	—	—	—	—	—	*
Park et al[143]	2017	43,599	45.6	5	59.6	6.8	*	*	*	*	—	*	—	—	—	—	—	—
Pavicic Zezelj et al[144]	2010	535	45.6	6	58.79	8.2	*	*	—	—	—	—	—	—	—	—	—	—
Pavlica et al[145]	2013	160	38.87	9.81	58.42	1.01	*	*	—	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Phillips et al[146]	2008	78	32.9	9.14	61.4	10.73	*	*	*	*	—	—	—	—	—	—	—	—
Polesel et al[147]	2015	311	34.83	8.4	52.63	5.72	*	—	*	—	—	—	—	—	—	—	—	—
Pollan et al[148]	2012	3,574	49	2.9	58	4.5	*	*	*	*	—	*	—	—	—	—	—	—
Portaluppi et al[149]	1997	1,376	48	3.1	53.3	4.2	*	—	—	—	—	—	—	—	—	—	—	—
Priya et al[150]	2013	65	38.65	6.21	55.32	6.32	*	*	*	*	—	*	—	—	—	—	—	—
Rantalainen et al[151]	2010	303	23	4.7	57.7	4.2	*	*	—	—	—	—	—	—	—	—	—	—
Reina et al[152]	2015	192	33	11	58.9	8.9	—	*	—	—	—	—	—	—	—	—	—	—
Revilla et al[153]	1997	151	37.4	7.2	59.9	9.7	*	*	—	—	—	—	—	—	—	—	—	—
Revilla et al[154]	1997	144	36.1	6.9	60.6	10.5	*	*	—	—	—	—	—	—	—	—	—	—
Rice et al[155]	2015	1,607	43.3	4.1	53.4	5.3	*	—	—	—	—	—	—	—	—	—	—	—
Rico et al[156]	2001	270	35.1	7.7	59.5	9.8	*	*	—	—	—	—	—	—	—	—	—	—
Rico et al[157]	2002	297	34	7	59	9	*	*	—	—	—	—	—	—	—	—	—	—
Roelfsema et al[158]	2016	91	35.83	6.84	59.08	6.81	*	—	—	—	—	—	—	—	—	—	—	—
Rosenbaum et al[159]	1996	41	27	8.94	66	9.17	*	*	—	—	*	—	—	—	—	—	—	—
Salomaa et al[160]	1995	778	47.4	2.4	57.9	4.9	*	—	—	—	—	—	—	—	—	—	—	—
Sarrafzadegan et al[161]	2013	4,143	32.15	9.22	59.8	10.39	*	*	*	*	—	—	—	—	—	—	—	—
Schaberg-Lorei et al[162]	1990	109	42.3	4.8	58.4	5.1	—	*	*	—	*	—	—	—	*	—	*	—
Schwarz et al[163]	2007	1,119	45.6	4.2	64.6	8	*	—	—	—	—	—	—	—	—	—	—	—
Shakir et al[164]	2004	4,092	53.2	1.6	56.9	2.9	—	—	—	*	—	—	—	—	—	—	—	—
Sherk et al[165]	2011	73	22.8	2.74	64	3.93	—	*	—	—	*	—	—	—	—	—	—	—
Shibata et al[166]	1979	448	46.9	1.4	47.4	1.4	*	—	—	—	—	—	—	—	—	—	—	—
Sieminska et al[167]	2006	131	28.2	4.1	53.9	3.2	*	—	—	*	—	—	—	—	—	—	—	—
Skrzypczak and Szwed[168]	2005	1,647	43.66	4.07	56.01	7.08	*	—	—	—	—	—	—	—	—	—	—	—
Skrzypczak et al[169]	2007	10,216	43.43	4.93	62.87	8.53	*	—	—	—	—	—	—	—	—	—	—	—
Soderberg et al[170]	2002	75	37.9	7.9	60.7	6.1	*	—	*	*	—	*	—	—	*	—	—	—
Son et al[171]	2015	1,470	46.8	2.5	52.2	3.1	*	—	*	—	—	—	—	—	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Soriguer et al[172]	2009	409	36.9	7.5	64.1	5.2	*	—	*	*	—	—	—	—	*	—	—	—
Staessen et al[173]	1989	462	42.6	5.1	53	5	*	*	—	—	*	—	—	—	—	—	—	—
Suarez-Ortegon et al[174]	2012	123	42.2	5.6	51.8	6.8	*	—	*	—	*	—	—	—	—	—	—	—
Suliga et al[175]	2016	3,636	49.7	3.1	55.2	3	*	—	*	—	*	—	—	—	—	—	—	—
Sumner et al[176]	1998	65	32.6	3.7	57.8	5.9	*	*	—	—	*	—	—	—	—	—	—	—
Tanaka et al[177]	2015	464	41.4	6.5	62.8	6.8	*	*	—	—	*	—	—	—	—	*	—	—
Thomas et al[178]	2000	302	35	8.6	69.8	13.1	*	*	—	—	—	—	—	—	—	—	—	—
Torng et al[179]	2000	1,543	42.7	5.8	61.2	9.5	*	*	—	—	—	—	—	—	—	—	—	—
Toth et al[180]	2000	81	47	3	51	4	*	*	—	—	*	—	*	*	—	—	—	—
Tremollieres et al[181]	1996	168	49.3	3.2	53.8	3.1	*	*	—	—	—	—	—	—	—	—	—	—
Trikudanathan et al[182]	2013	170	49.3	3	49.4	3	*	—	*	—	—	—	*	*	—	—	—	—
Van-Pelt et al[183]	1998	31	29	4.12	61	4.36	*	*	*	—	*	—	—	—	*	—	*	—
	1998	58	30	5.48	56	5.57	*	*	*	—	*	—	—	—	*	—	*	—
Veldhuis et al[184]	2016	120	34	9.3	64	8.52	*	—	—	—	—	—	*	*	—	—	—	—
Wang et al[185]	2012	1,526	44.2	6.6	56.3	4.6	—	—	—	—	*	—	—	—	—	—	—	—
Wang et al[186]	2006	346	33.36	9.2	66.75	10.75	*	—	—	—	—	—	—	—	—	—	—	—
Wang et al[187]	2012	1,143	49.13	2.72	64.72	7.61	*	—	*	*	—	*	—	—	—	—	—	—
Wee et al[188]	2013	283	45.81	1.12	56.8	1.84	*	—	—	—	—	—	—	—	—	—	—	—
Williams et al[189]	1997	115	32.7	10.9	63.9	11.6	*	—	—	—	—	—	—	—	—	—	—	—
Wing et al[190]	1991	340	NA		NA		*	*	—	—	—	—	—	—	*	—	—	—
Xu et al[191]	2010	252	44.7	4.1	70.7	6.3	*	*	—	—	—	—	—	—	—	—	—	—
Yamatani et al[192]	2013	40	42.6	7.35	60.6	7.5	*	*	—	—	—	—	*	*	—	—	—	—
Yannakoulia et al[193]	2007	114	38.6	7.7	57.5	6.2	*	*	*	*	*	—	—	—	—	—	—	—
Yoldemir and Erenus[194]	2012	190	45.27	2.93	57.02	6.15	*	*	—	*	—	—	—	—	—	—	—	—
Yoo et al[195]	2012	358	34.2	9.7	61.1	7.7	*	*	*	*	*	—	*	*	—	—	—	—

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 2

Table of study characteristics for cross-sectional studies *(continued)*

Study	Year	Sample size, n	Premenopausal women: Mean age, y	Premenopausal women: Standard deviation	Postmenopausal women: Mean age, y	Postmenopausal women: Standard deviation	Body mass index	Body-weight	Waist circumference	Waist-to-hip ratio	Total body fat percentage	Hip circumference	Subcutaneous abdominal fat	Visceral fat	Suprailiac skinfold thickness	Trunk fat percentage	Abdominal skinfold thickness	Leg fat percentage
Yoo et al[196]	1998	306	NA		NA		*	*	—	—	—	—	—	—	—	—	—	—
Yoshimoto et al[197]	2011	278	41.8	6.2	62.1	8.2	*	*	—	—	—	—	—	—	—	—	—	—
Zhong et al[198]	2005	676	NA		NA		*	*	—	—	—	—	—	—	—	—	—	—
Zhou et al[199]	2010	729	42.2	3.8	53.8	2.8	*	—	—	—	—	—	—	—	—	—	—	—
Zhou et al[200]	2015	6,324	44.1	4.8	60	7.8	*	*	*	*	—	—	—	—	—	—	—	—
Zivkovic et al[201]	2011	271	37	5.3	54	4.5	*	—	*	—	—	—	—	—	—	—	—	—

NA, not available. The *asterisk* indicates inclusion of the measure.

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SUPPLEMENTARY TABLE 3
Table of study characteristics for longitudinal studies

Study	Year	Sample Size	Mean age, y (standard deviation)		Body mass index	Bodyweight	Waist circumference	Total body fat percentage	Subcutaneous abdominal fat	Visceral fat
			Premenopausal	Postmenopausal						
Abdulnour et al[2]	2012	13	50.65 (2.26)	52.76 (2.16)	—	—	—	—	*	*
Akahoshi et al[202]	2001	48	39.40 (1.60)	45.30 (1.50)	*	—	—	—	—	—
	2001	388	44.20 (1.60)	50.10 (1.50)	*	—	—	—	—	—
	2001	565	48.30 (1.70)	54.20 (1.70)	*	—	—	—	—	—
Ford et al[203]	2005	74	40.07 (4.43)	45.77 (4.62)	*	—	—	—	—	—
Franklin et al[204]	2009	8	49.30 (1.70)	57.00 (2.26)	*	*	*	*	—	—
Janssen et al[205]	2008	859	46.81 (2.52)	52.29 (2.86)	*	—	*	—	—	—
Lee et al[206]	2009	69	50.60 (2.60)	54.70 (2.60)	*	*	—	*	*	*
Liu-Ambrose et al[207]	2006	53	40.50 (4.70)	53.20 (4.70)	—	*	—	—	—	—
Lovejoy et al[118]	2008	51	48.10 (0.30)	52.10 (0.30)	—	*	—	*	*	*
Macdonald et al[208]	2005	248	47.72 (1.40)	54.13 (1.52)	*	*	—	—	—	—
Razmjou et al[209]	2018	48	49.77 (1.80)	59.97 (1.78)	*	*	*	*	—	—
Soreca et al[210]	2009	48	47.98 (1.32)	67.98 (1.32)	*	*	—	—	—	—

The *asterisk* indicates inclusion of the measure.

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	(out of 9)
Abate et al[1]	2014	—	*	—	*	*	*	*	*	*	7
Abdulnour et al[2]	2012	*	*	—	*	*	*	*	*	*	8
Abildgaard et al[3]	2013	*	*	—	*	*	*	*	*	*	8
Adams-Campbell et al[4]	1996	*	*	*	*	—	—	—	—	*	5
Agrinier et al[5]	2010	*	*	*	*	—	*	*	*	*	8
Aguado et al[6]	1996	—	*	—	*	—	—	—	*	*	4
Albanese et al[7]	2009	*	*	—	*	*	*	*	*	*	8
Allali et al[8]	2009	*	*	—	*	—	—	—	—	—	3
Aloia et al[9]	1995	*	*	—	*	—	—	—	—	—	3
Amankwah et al[10]	2013	*	*	*	*	—	*	*	*	*	8
Amarante et al[11]	2011	—	—	—	*	*	—	*	—	*	4
Amiri et al[12]	2014	*	*	*	*	—	—	*	*	*	7
Angsuwanthana et al[13]	2007	*	*	*	*	*	*	*	*	*	9
Armellini et al[14]	1996	*	*	—	—	—	—	—	*	*	4
Arthur et al[15]	2013	*	*	—	*	—	*	*	*	*	7
Aydin et al[16]	2010	*	*	*	*	*	*	*	*	*	9
Ayub et al[17]	2006	—	—	—	*	*	—	—	*	*	4
Bancroft et al[18]	1996	*	*	*	*	*	*	*	*	*	9
Bednarek-Tupikowska et al[19]	2006	—	—	—	*	*	—	—	*	*	4
Bell et al[20]	2007	*	*	—	*	—	*	*	*	*	7
Ben-Ali et al[21]	2016	*	*	—	*	—	—	*	*	*	6
Ben-Ali et al[22]	2014	*	*	—	*	—	—	*	*	*	6
Ben-Ali et al[23]	2011	*	*	—	*	—	*	*	*	*	7
Berg et al[24]	2004	—	—	—	*	—	*	*	*	*	5
Berge et al[25]	1994	*	*	*	*	—	*	*	—	—	6
Berger et al[26]	1995	—	*	—	*	*	*	*	*	*	7
Berstad et al[27]	2010	*	*	*	*	—	*	*	—	*	7

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	(out of 9)
Bhagat et al[28]	2010	*	*	—	*	—	*	*	*	*	7
Bhurosy et al[29]	2013	*	*	—	*	—	*	*	*	*	7
Blumenthal et al[30]	1991	*	*	*	*	*	*	*	—	—	7
Bonithon-Kopp et al[31]	1990	*	*	—	*	*	*	*	—	—	6
Caire-Juvera et al[32]	2008	*	*	—	*	—	*	*	*	*	7
Campesi et al[33]	2016	—	—	—	*	—	*	*	—	—	3
Carr et al[34]	2000	*	*	—	*	—	*	*	—	—	5
Castracane et al[35]	1998	—	—	—	*	—	*	—	—	—	2
Catsburg et al[36]	2014	*	*	—	*	—	—	—	—	*	4
Cecchini et al[37]	2012	*	*	—	—	—	*	*	*	*	6
Cervellati et al[38]	2009	—	—	—	*	—	*	*	*	*	5
Chain et al[39]	2017	*	*	—	*	*	—	*	*	*	7
Chang et al[40]	2000	*	*	—	*	—	*	*	*	*	7
Cho et al[41]	2008	*	*	—	*	—	—	*	*	*	6
Cifkova et al[42]	2008	*	*	—	*	*	*	*	*	*	8
Copeland et al[43]	2006	*	*	—	*	—	*	*	*	*	7
Cremonini et al[44]	2013	*	*	—	*	—	*	*	*	*	7
Cui et al[45]	2007	*	*	—	*	—	*	*	*	*	7
D'haeseleer et al[46]	2011	—	—	*	*	*	*	*	—	*	6
Da Camara et al[47]	2015	*	*	*	*	*	*	*	*	*	9
Dallongeville et al[48]	1995	*	*	—	*	*	—	*	*	*	7
Dancey et al[49]	2001	*	*	—	*	—	*	*	—	—	5
Davis et al[50]	1994	*	*	—	*	*	*	*	—	—	6
De Kat et al[51]	2017	*	*	—	*	—	*	*	*	*	7
Den Tonkelaar et al[52]	1990	*	*	—	*	—	—	*	*	*	6
Dmitruk et al[53]	2018	*	*	—	*	—	*	*	*	*	7
Donato et al[54]	2006	*	*	*	*	*	*	*	*	*	9

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 4
Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	(out of 9)
Douchi et al[55]	1997	*	*	—	*	—	*	—	*	*	6
Douchi et al[56]	2002	*	*	—	*	—	*	*	*	*	7
Douchi et al[57]	2007	*	*	—	*	—	—	*	*	*	6
Dubois et al[58]	2001	—	*	—	*	—	*	*	—	—	4
Engmann et al[59]	2017	*	*	—	*	—	*	*	—	*	6
Ertungealp et al[60]	1999	*	—	—	—	—	—	—	—	—	1
Feng et al[61]	2008	*	*	*	*	—	*	*	*	*	8
Formica et al[62]	1995	*	*	—	*	—	—	—	—	—	3
Friedenreich et al[63]	2007	*	*	—	*	—	*	*	*	*	7
Friedenreich et al[64]	2002	*	*	*	*	—	*	*	*	*	8
Fu et al[65]	2011	*	*	—	*	—	*	*	*	*	7
Fuh et al[66]	2003	*	*	—	*	*	*	*	*	*	8
Gambacciani et al[67]	1999	*	*	—	*	—	*	*	*	*	7
Genazzani et al[68]	2006	*	*	—	*	—	*	*	*	*	7
Ghosh et al[69]	2008	*	*	—	*	—	*	*	*	*	7
Ghosh et al[70]	2010	*	*	—	*	—	*	*	*	*	7
Gram et al[71]	1997	*	*	—	*	*	—	*	*	*	7
Guo et al[72]	2015	*	*	—	*	—	*	*	*	*	7
Gurka et al[73]	2016	*	*	*	*	*	*	*	—	—	7
Hadji et al[74]	2000	*	*	—	*	—	*	*	*	*	7
Hagner et al[75]	2009	*	*	—	*	—	*	*	*	*	7
Han et al[76]	2006	*	*	—	*	—	—	*	*	*	6
Harting et al[77]	1984	*	*	—	*	—	*	—	—	—	4
He et al[78]	2012	*	*	—	*	*	*	*	*	*	8
Hirose et al[79]	2003	*	*	—	*	—	—	—	—	*	4
Hjartaker et al[80]	2005	*	*	—	*	*	*	*	—	*	7
Ho et al[81]	2010	*	*	*	—	—	*	*	*	*	7

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019.

(continued)

SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score (out of 9)
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	
Hsu et al[82]	2006	*	*	—	*	—	—	—	*	*	5
Hu et al[83]	2016	*	*	—	—	—	—	—	*	*	4
Hunter et al[84]	1996	*	*	—	*	—	—	*	*	*	6
Iida et al[85]	2011	*	*	—	*	—	—	—	*	*	5
Ilich-Ernst et al[86]	2002	—	—	—	*	—	—	—	*	*	3
Ito et al[87]	1994	—	—	—	*	—	*	*	—	—	3
Jaff et al[88]	2015	*	*	—	*	*	*	*	*	*	8
Jasienska et al[89]	2005	*	*	—	*	*	—	—	*	*	6
Jeenduang et al[90]	2014	*	*	—	*	—	—	*	*	*	6
Jeon et al[91]	2011	*	*	—	*	*	*	*	*	*	8
Jurimae et al[92]	2007	—	—	—	*	—	*	*	*	*	5
Kadam et al[93]	2010	*	*	—	*	*	*	*	*	*	8
Kang et al[94]	2016	*	*	—	*	—	—	—	*	*	5
Kaufer-Horwitz et al[95]	2005	*	*	—	*	—	*	*	*	*	7
Kim et al[96]	2007	*	*	—	*	—	—	*	*	*	6
Kim et al[97]	2012	*	*	—	*	—	—	—	*	*	5
Kim et al[98]	2013	*	*	*	*	—	—	*	*	*	7
Kim et al[99]	2016	*	*	—	*	—	—	—	*	*	5
Kirchengast et al[100]	1996	*	*	*	*	—	*	*	*	*	8
Kirchengast et al[101]	1998	*	*	*	*	—	*	*	*	*	8
Knapp et al[102]	2001	*	—	—	*	—	—	—	—	—	2
Koh et al[103]	2008	*	*	—	*	—	*	*	*	*	7
Konrad et al[104]	2011	*	*	—	*	*	—	*	*	*	7
Kontogianni et al[105]	2004	*	*	*	*	*	—	*	*	*	8
Konukoglu et al[106]	2000	—	—	*	*	—	—	*	—	—	3
Koskova et al[107]	2007	*	*	*	*	—	*	*	*	*	8
Kotani et al[108]	2011	—	—	—	*	—	—	*	*	*	4

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	(out of 9)
Kraemer et al[109]	2001	*	*	—	*	—	—	—	—	—	3
Kuk et al[110]	2005	*	*	—	*	—	—	—	*	*	5
Laitinen et al[111]	1991	*	*	—	*	—	—	—	—	—	3
Lejskova et al[112]	2012	*	*	—	*	*	*	*	*	*	8
Leon-Guerrero et al[113]	2017	*	*	—	*	—	*	*	*	*	7
Ley et al[114]	1992	*	*	—	*	—	*	*	*	*	7
Lin et al[115]	2006	*	*	—	*	*	—	*	*	*	7
Lindquist et al[116]	1980	*	*	*	*	*	*	*	*	*	9
Lindsay et al[117]	1992	*	*	—	*	—	—	—	*	*	5
Lovejoy et al[118]	2008	*	*	*	*	*	—	*	*	*	8
Lyu et al[119]	2001	*	*	—	*	*	—	*	*	*	7
Maharlouei et al[120]	2013	*	*	—	*	—	*	*	*	*	7
Malacara et al[121]	2002	*	*	*	*	*	*	*	—	*	8
Manabe et al[122]	1999	—	*	—	*	—	—	—	*	*	4
Manjer et al[123]	2001	*	*	—	*	—	*	*	*	*	7
Mannisto et al[124]	1996	*	*	*	*	—	—	—	*	*	6
Martini et al[125]	1997	*	*	—	*	—	—	*	*	*	6
Marwaha et al[126]	2013	*	*	—	*	—	*	*	*	*	7
Matsushita et al[127]	2003	*	*	—	*	—	*	—	*	*	6
Matsuzaki et al[128]	2017	*	*	—	*	—	—	—	*	*	5
Matthews et al[129]	1989	*	*	*	*	*	*	*	—	—	7
Mesch et al[130]	2006	—	—	—	*	—	*	*	*	*	5
Meza-Munoz et al[131]	2006	*	*	—	*	—	*	*	*	*	7
Minatoya et al[132]	2014	*	*	—	—	—	—	—	—	—	2
Mo et al[133]	2017	*	*	—	*	—	—	—	*	*	5
Muchanga et al[134]	2014	*	*	*	*	*	*	*	*	*	9
Muti et al[135]	2000	*	*	—	*	—	—	*	*	*	6

Ambikairajah. Fat mass changes during menopause. Am J Obstet Gynecol 2019. *(continued)*

SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score (out of 9)
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	
Nitta et al[136]	2016	*	*	—	*	—	—	—	—	—	3
Noh et al[137]	2013	*	*	*	*	—	*	*	*	*	8
Nordin et al[138]	1992	—	—	—	*	—	—	—	—	—	1
Ohta et al[139]	2010	*	*	*	*	—	—	—	*	*	6
Oldroyd et al[140]	1998	—	—	—	*	—	—	—	—	—	1
Pacholczak et al[141]	2016	*	*	—	*	—	—	*	*	*	6
Park et al[142]	2012	*	*	—	*	—	—	—	*	*	5
Park et al[143]	2017	*	*	—	*	—	*	*	—	*	6
Pavicic et al[144]	2010	*	*	—	*	—	*	*	*	*	7
Pavlica et al[145]	2013	*	*	—	*	—	—	—	*	*	5
Phillips et al[146]	2008	*	*	—	*	—	—	*	*	*	6
Polesel et al[147]	2015	*	*	*	*	—	*	*	*	*	8
Pollan et al[148]	2012	*	*	—	*	*	*	*	*	*	8
Portaluppi et al[149]	1997	—	*	*	*	*	*	*	*	*	8
Priya et al[150]	2013	*	*	—	*	—	—	*	*	*	6
Rantalainen et al[151]	2010	—	—	—	*	—	*	—	*	*	4
Reina et al[152]	2015	—	*	—	*	—	—	—	—	—	2
Revilla et al[153]	1997	*	—	—	*	—	*	*	*	*	6
Revilla et al[154]	1997	*	*	—	*	—	*	*	*	*	7
Rice et al[155]	2015	*	*	—	*	—	*	*	—	*	6
Rico et al[156]	2001	*	—	*	*	—	*	*	*	*	7
Rico et al[157]	2002	*	—	*	*	—	*	*	*	*	7
Roelfsema et al[158]	2016	*	—	—	*	—	*	*	*	*	6
Rosenbaum et al[159]	1996	—	—	—	*	—	*	*	*	*	5
Salomaa et al[160]	1995	*	*	—	*	—	*	*	*	*	7
Sarrafzadegan et al[161]	2013	*	*	—	*	—	—	—	*	*	5
Schaberg-Lorei et al[162]	1990	—	—	—	*	—	—	—	*	*	3

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SUPPLEMENTARY TABLE 4
Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	(out of 9)
Schwarz et al[163]	2007	*	*	—	*	—	*	*	*	*	7
Shakir et al[164]	2004	*	*	*	*	*	*	*	*	*	9
Sherk et al[165]	2011	—	—	—	*	—	—	—	*	*	3
Shibata et al[166]	1979	—	*	—	*	*	—	—	—	—	3
Sieminska et al[167]	2006	—	—	—	*	—	*	*	—	—	3
Skrzypczak et al[168]	2005	*	*	—	*	—	*	*	*	*	7
Skrzypczak et al[169]	2007	*	*	—	*	—	*	*	*	*	7
Soderberg et al[170]	2002	*	*	—	*	—	*	*	*	*	7
Son et al[171]	2015	*	*	—	*	*	*	*	*	*	8
Soriguer et al[172]	2009	*	*	—	*	—	—	*	*	*	6
Staessen et al[173]	1989	—	—	—	*	—	—	*	*	*	4
Suarez-Ortegon et al[174]	2012	—	—	—	*	*	—	—	*	*	4
Suliga et al[175]	2016	*	*	—	*	*	—	*	*	*	7
Sumner et al[176]	1998	—	—	—	*	—	—	*	*	*	4
Tanaka et al[177]	2015	—	—	—	*	—	*	*	*	*	5
Thomas et al[178]	2000	*	*	—	*	—	—	*	*	*	6
Torng et al[179]	2000	*	*	—	*	—	—	*	*	*	6
Toth et al[180]	2000	—	*	*	*	*	*	*	*	*	8
Tremollieres et al[181]	1996	*	*	*	*	*	—	*	*	*	8
Trikudanathan et al[182]	2013	*	*	*	*	*	—	*	*	*	8
Van-Pelt et al[183]	1998	—	—	*	*	—	*	*	*	*	6
Veldhuis et al[184]	2016	*	*	*	*	—	—	*	*	*	7
Wang et al[185]	2012	*	*	—	*	—	—	—	*	*	5
Wang et al[186]	2006	*	*	—	*	—	—	*	*	*	6
Wang et al[187]	2012	*	*	—	*	—	*	*	—	*	6
Wee et al[188]	2013	—	*	—	*	—	*	*	*	*	6
Williams et al[189]	1997	*	*	—	*	—	*	*	*	*	7

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SUPPLEMENTARY TABLE 4

Quality assessment of individual cross-sectional studies *(continued)*

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		Total score (out of 9)
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	
Wing et al[190]	1991	*	*	—	—	—	*	*	*	*	6
Xu et al[191]	2010	*	*	*	*	—	*	*	*	*	8
Yamatani et al[192]	2013	*	*	*	*	—	—	*	*	*	7
Yannakoulia et al[193]	2007	*	*	*	*	—	*	*	*	*	8
Yoldemir et al[194]	2012	*	*	*	*	—	*	*	*	*	8
Yoo et al[195]	2012	*	*	*	*	—	—	*	*	*	7
Yoo et al[196]	1998	*	*	*	—	—	*	*	*	*	7
Yoshimoto et al[197]	2011	*	*	—	*	—	—	—	—	—	3
Zhong et al[198]	2005	*	*	—	—	—	—	—	*	*	4
Zhou et al[199]	2010	*	*	*	*	—	*	*	*	*	8
Zhou et al[200]	2015	*	*	—	*	—	—	*	*	*	6
Zivkovic et al[201]	2011	*	*	—	*	—	—	*	*	*	6

The *asterisk* indicates inclusion of the measure.

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SUPPLEMENTARY TABLE 5

Quality assessment of individual longitudinal studies

		Newcastle-Ottawa quality assessment scale (adapted)									
		Selection			Comparability				Outcome		
Study	Year	Question 1	Question 2	Question 3	Question 4a	Question 4b	Question 5	Question 6	Question 7	Question 8	Total score (of 9)
Abdulnour et al[2]	2012	*	*	—	*	*	*	*	*	*	8
Akahoshi et al[202]	2001	*	*	*	*	*	*	*	*	*	9
Ford et al[203]	2005	*	—	*	*	*	*	*	*	*	8
Franklin et al[204]	2009	—	—	—	*	*	—	*	*	—	4
Janssen et al[205]	2008	*	*	—	*	*	*	*	*	*	8
Lee et al[206]	2009	*	*	—	*	*	*	*	*	*	8
Liu-Ambrose et al[207]	2006	*	*	—	*	*	*	*	*	*	8
Lovejoy et al[118]	2008	*	*	*	*	*	—	*	*	*	8
Macdonald et al[208]	2005	*	*	—	*	*	*	*	*	*	8
Razmjou et al[209]	2018	*	*	—	*	*	*	*	*	*	8
Soreca et al[210]	2009	*	*	—	*	*	*	—	*	*	7

The *asterisk* indicates the study met the criterion for the question.

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SUPPLEMENTARY TABLE 6

Output for cross-sectional studies

Data element name	Studies, n (samples)	Total sample size, n		Mean age, y (standard deviation)[a]		Mean fat mass, •••• (standard deviation)[a]		Estimate, •••• (95% confidence interval)			
		Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Unstandardized	*P* value	Standardized	*P* value
Body mass index	171 (181)	453,036	523,796	41.96 (3.69)	59.42 (3.06)	24.75 (1.60)	26.64 (1.25)	1.14 (0.95−1.32)[b]	<.0001	0.28 (0.23−0.33)[b]	<.0001
Bodyweight	109 (122)	113,603	204,845	43.36 (4.71)	59.55 (3.27)	64.82 (7.91)	66.12 (9.17)	1.00 (0.44−1.57)[b]	.0005	0.08 (0.03−0.14)[b]	.0040
Waist circumference	70 (72)	214,712	326,639	42.28 (3.65)	59.07 (1.91)	78.58 (4.24)	83.61 (3.19)	4.63 (3.90−5.35)[b]	<.0001	0.45 (0.37−0.52)[b]	<.0001
Waist-to-hip ratio	47 (50)	199,140	309,797	42.39 (3.44)	59.09 (1.42)	0.78 (0.03)	0.81 (0.03)	0.04 (0.03−0.05)[b]	<.0001	0.65 (0.52−0.77)[b]	<.0001
Total body fat percentage	46 (52)	58,605	113,226	43.81 (4.67)	59.55 (3.81)	32.44 (3.47)	35.69 (3.84)	2.88 (2.13−3.63)[b]	<.0001	0.90 (0.09−1.71)[b]	.0292
Hip circumference	25 (25)	185,885	297,189	42.48 (3.08)	59.15 (0.95)	100.30 (2.66)	102.73 (2.25)	2.01 (1.36−2.65)[b]	<.0001	0.20 (0.13−0.27)[b]	<.0001
Subcutaneous abdominal fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	194.05 (23.65)	221.21 (32.09)	28.73 (8.56−48.91)[b]	.0053	0.85 (−0.50−2.21)	.2176
Visceral fat	10 (10)	696	833	41.01 (6.96)	57.48 (5.36)	69.22 (15.75)	104.36 (13.92)	26.90 (13.12−40.68)[b]	.0001	0.59 (0.20−0.98)[b]	.0028
Suprailiac skinfold thickness	9 (10)	1,103	745	39.76 (4.41)	61.89 (4.77)	22.16 (7.04)	24.55 (9.90)	2.65 (0.45−4.85)[b]	.0181	0.28 (0.05−0.50)[b]	.0149
Trunk fat percentage	7 (7)	39,335	95,756	45.28 (6.61)	59.68 (3.41)	31.27 (4.78)	33.74 (5.36)	5.49 (3.91−7.06)[b]	<.0001	0.68 (0.52−0.83)[b]	<.0001
Abdominal skinfold thickness	4 (5)	199	359	40.64 (6.32)	62.99 (5.16)	26.65 (8.14)	29.43 (9.82)	6.46 (0.51−12.42)[b]	.0335	0.61 (0.05−1.18)[b]	.0338
Total leg fat percentage	3 (3)	991	524	36.96 (1.13)	55.18 (5.17)	36.33 (5.47)	36.00 (2.62)	−3.19 (−5.98 to −0.41)[b]	.0246	−0.51 (−0.95 to −0.07)[b]	.0227

[a] Computed as weighted means and weighted standard deviations, taking into account sample size; [b] Indicates significance at the $P<.05$ level.

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SUPPLEMENTARY TABLE 7
Output for longitudinal studies

Data element name	Studies, n (samples)	Total sample size, n	Mean age, y (standard deviation)[a]		Mean fat mass, •••• (standard deviation)[a]		Estimate, •••• (95% confidence interval)			
			Premenopausal	Postmenopausal	Premenopausal	Postmenopausal	Unstandardized	*P* value	Standardized	*P* value
Body mass index	8 (10)	2355	46.67 (2.53)	52.80 (3.71)	24.30 (1.97)	25.03 (2.37)	0.93 (0.26−1.59)[b]	.0061	0.21 (0.07−0.35)[b]	.0036
Bodyweight	7 (7)	525	47.64 (3.06)	55.76 (5.08)	66.11 (3.89)	69.19 (3.71)	2.99 (1.36−4.63)[b]	.0003	0.39 (0.12−0.66)[b]	.0049
Total body fat percentage	4 (4)	176	49.59 (1.24)	55.49 (3.65)	36.29 (4.88)	37.84 (3.33)	2.18 (0.21−4.16)[b]	.0299	0.28 (0.13−0.42)[b]	.0001
Waist circumference	3 (3)	915	46.99 (2.04)	52.73 (5.17)	80.79 (3.62)	84.06 (2.61)	3.82 (0.87−6.77)[b]	.0111	0.38 (−0.07−0.84)	.1004
Subcutaneous abdominal fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	215.14 (66.15)	242.28 (77.34)	18.53 (−3.64−40.69)	.1014	0.52 (−0.31−1.35)	.2168
Visceral fat	3 (3)	133	49.65 (1.61)	53.51 (1.64)	78.63 (14.45)	92.23 (12.77)	12.95 (8.65−17.25)[b]	<.0001	0.49 (−0.03−1.01)	.0629

[a] Computed as weighted means and weighted standard deviations, taking into account sample size; [b] Indicates significance at the $P<.05$ level.

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SUPPLEMENTARY REFERENCES (TABLES 2–5)

1. Abate M, Schiavone C, Di Carlo L, Salini V. Prevalence of and risk factors for asymptomatic rotator cuff tears in postmenopausal women. Menopause 2014;21:275–80.

2. Abdulnour J, Doucet E, Brochu M, et al. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal-Ottawa New Emerging Team group study. Menopause 2012;19:760–7.

3. Abildgaard J, Pedersen AT, Green CJ, et al. Menopause is associated with decreased whole body fat oxidation during exercise. Am J Physiol Endocrinol Metab 2013;304:E1227–36.

4. Adams-Campbell LL, Kim KS, Dunston G, Laing AE, Bonney G, Demenais F. The relationship of body mass index to reproductive factors in pre- and postmenopausal African-American women with and without breast cancer. Obes Res 1996;4:451–6.

5. Agrinier N, Cournot M, Dallongeville J, et al. Menopause and modifiable coronary heart disease risk factors: a population based study. Maturitas 2010;65:237–43.

6. Aguado F, Revilla M, Hernandez ER, Villa LF, Rico H. Behavior of bone mass measurements: dual energy x-ray absorptiometry total body bone mineral content, ultrasound bone velocity, and computed metacarpal radiogrammetry, with age, gonadal status, and weight in healthy women. Invest Radiol 1996;31:218–22.

7. Albanese CV, Cepollaro C, de Terlizzi F, Brandi ML, Passariello R. Performance of five phalangeal QUS parameters in the evaluation of gonadal-status, age and vertebral fracture risk compared with DXA. Ultrasound Med Biol 2009;35:537–44.

8. Allali F, El Mansouri L, Abourazzak F, et al. The effect of past use of oral contraceptive on bone mineral density, bone biochemical markers and muscle strength in healthy pre and post menopausal women. BMC Womens Health 2009;9:31.

9. Aloia JF, Vaswani A, Ma R, Flaster E. To what extent is bone mass determined by fat-free or fat mass? Am J Clin Nutr 1995;61:1110–4.

10. Amankwah EK, Friedenreich CM, Magliocco AM, et al. Anthropometric measures and the risk of endometrial cancer, overall and by tumor microsatellite status and histological subtype. Am J Epidemiol 2013;177:1378–87.

11. Amarante F, Vilodre LC, Maturana MA, Spritzer PM. Women with primary ovarian insufficiency have lower bone mineral density. Braz J Med Biol Res 2011;44:78–83.

12. Amiri P, Deihim T, Nakhoda K, Hasheminia M, Montazeri A, Azizi F. Metabolic syndrome and health-related quality of life in reproductive age and post-menopausal women: Tehran Lipid and Glucose Study. Arch Iran Med 2014;17:423–8.

13. Angsuwathana S, Leerasiri P, Rattanachaiyanont M, et al. Health check-up program for pre/postmenopausal women at Siriraj Menopause Clinic. J Med Assoc Thai 2007;90:1–8.

14. Armellini F, Zamboni M, Perdichizzi G, et al. Computed tomography visceral adipose tissue volume measurements of Italians: predictive equations. Eur J Clin Nutr 1996;50:290–4.

15. Arthur FK, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. The prevalence of metabolic syndrome and its predominant components among pre-and post-menopausal Ghanaian women. BMC Res Notes 2013;6:446.

16. Aydin ZD. Determinants of age at natural menopause in the Isparta Menopause and Health Study: premenopausal body mass index gain rate and episodic weight loss. Menopause 2010;17:494–505.

17. Ayub N, Khan SR, Syed F. Leptin levels in pre and post menopausal Pakistani women. J Pak Med Assoc 2006;56:3–5.

18. Bancroft J, Cawood EH. Androgens and the menopause; a study of 40-60-year-old women. Clin Endocrinol 1996;45:577–87.

19. Bednarek-Tupikowska G, Filus A, Kuliczkowska-Plaksej J, Tupikowski K, Bohdanowicz-Pawlak A, Milewicz A. Serum leptin concentrations in pre- and postmenopausal women on sex hormone therapy. Gynecol Endocrinol 2006;22:207–12.

20. Bell RJ, Davison SL, Papalia MA, McKenzie DP, Davis SR. Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. Menopause 2007;14:630–8.

21. Ben Ali S, Belfki-Benali H, Ahmed DB, et al. Postmenopausal hypertension, abdominal obesity, apolipoprotein and insulin resistance. Clin Exper Hypertens 2016;38:370–4.

22. Ben Ali S, Belfki-Benali H, Aounallah-Skhiri H, et al. Menopause and metabolic syndrome in tunisian women. BioMed Res Int 2014;2014:457131.

23. Ben Ali S, Jemaa R, Ftouhi B, et al. Relationship of plasma leptin and adiponectin concentrations with menopausal status in Tunisian women. Cytokine 2011;56:338–42.

24. Berg G, Mesch V, Boero L, et al. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. Horm Metab Res 2004;36:215–20.

25. Berge LN, Bonaa KH, Nordoy A. Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. Arteriosclero Thromb 1994;14:857–61.

26. Berger GM, Naidoo J, Gounden N, Gouws E. Marked hyperinsulinaemia in postmenopausal, healthy Indian (Asian) women. Diabet Med 1995;12:788–95.

27. Berstad P, Coates RJ, Bernstein L, et al. A case-control study of body mass index and breast cancer risk in white and African-American women. Cancer Epidemiol Biomarkers Prev 2010;19:1532–44.

28. Bhagat M, Mukherjee S, De P, et al. Clustering of cardiometabolic risk factors in Asian Indian women: Santiniketan women study. Menopause 2010;17:359–64.

29. Bhurosy T, Jeewon R. Food habits, socioeconomic status and body mass index among premenopausal and post-menopausal women in Mauritius. J Hum Nutr Diet 2013;26(suppl1):114–22.

30. Blumenthal JA, Fredrikson M, Matthews KA, et al. Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychol 1991;10:384–91.

31. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. Int J Epidemiol 1990;19:42–8.

32. Caire-Juvera G, Arendell LA, Maskarinec G, Thomson CA, Chen Z. Associations between mammographic density and body composition in Hispanic and non-Hispanic white women by menopause status. Menopause 2008;15:319–25.

33. Campesi I, Occhioni S, Tonolo G, et al. Ageing/menopausal status in healthy women and ageing in healthy men differently affect cardiometabolic parameters. Int J Med Sci 2016;13:124–32.

34. Carr MC, Kim KH, Zambon A, et al. Changes in LDL density across the menopausal transition. J Investig Med 2000;48:245–50.

35. Castracane VD, Kraemer RR, Franken MA, Kraemer GR, Gimpel T. Serum leptin concentration in women: effect of age, obesity, and estrogen administration. Fertil Steril 1998;70:472–7.

36. Catsburg C, Kirsh VA, Soskolne CL, et al. Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. Breast Cancer Res Treat 2014;145:545–52.

37. Cecchini RS, Costantino JP, Cauley JA, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res 2012;5:583–92.

38. Cervellati C, Pansini FS, Bonaccorsi G, et al. Body mass index is a major determinant of abdominal fat accumulation in pre-, peri- and post-menopausal women. Gynecol Endocrinol 2009;25:413–7.

39. Chain A, Crivelli M, Faerstein E, Bezerra FF. Association between fat mass and bone mineral density among Brazilian women differs by menopausal status: The Pro-Saude Study. Nutrition 2017;33:14–9.

40. Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH. Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. Int J Obes Relat Metab Disord 2000;24:1699–704.

41. Cho GJ, Lee JH, Park HT, et al. Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause 2008;15:524–9.

42. Cifkova R, Pitha J, Lejskova M, Lanska V, Zecova S. Blood pressure around the menopause: a population study. J Hyperten 2008;26:1976–82.

43. Copeland AL, Martin PD, Geiselman PJ, Rash CJ, Kendzor DE. Predictors of

pretreatment attrition from smoking cessation among pre- and postmenopausal, weight-concerned women. Eating Behav 2006;7:243–51.
44. Cremonini E, Bonaccorsi G, Bergamini CM, et al. Metabolic transitions at menopause: in post-menopausal women the increase in serum uric acid correlates with abdominal adiposity as assessed by DXA. Maturitas 2013;75:62–6.
45. Cui LH, Shin MH, Kweon SS, et al. Relative contribution of body composition to bone mineral density at different sites in men and women of South Korea. J Bone Miner Metab 2007;25:165–71.
46. D'Haeseleer E, Depypere H, Claeys S, Van Lierde KM. The relation between body mass index and speaking fundamental frequency in premenopausal and postmenopausal women. Menopause 2011;18:754–8.
47. Da Camara SM, Zunzunegui MV, Pirkle C, Moreira MA, Maciel AC. Menopausal status and physical performance in middle aged women: a cross-sectional community-based study in Northeast Brazil. PLoS One 2015;10:e0119480.
48. Dallongeville J, Marecaux N, Isorez D, Zylbergberg G, Fruchart JC, Amouyel P. Multiple coronary heart disease risk factors are associated with menopause and influenced by substitutive hormonal therapy in a cohort of French women. Atherosclerosis 1995;118:123–33.
49. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest 2001;120:151–5.
50. Davis CE, Pajak A, Rywik S, et al. Natural menopause and cardiovascular disease risk factors:the Poland and US Collaborative Study on Cardiovascular Disease Epidemiology. Ann Epidemiol 1994;4:445–8.
51. De Kat AC, Dam V, Onland-Moret NC, Eijkemans MJ, Broekmans FJ, van der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. BMC Med 2017;15:2.
52. Den Tonkelaar I, Seidell JC, van Noord PA, Baanders-van Halewijn EA, Ouwehand IJ. Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project. Int J Obes 1990;14:753–61.
53. Dmitruk A, Czeczelewski J, Czeczelewska E, Golach J, Parnicka U. Body composition and fatty tissue distribution in women with various menstrual status. Rocz Panstw Zakl Hig 2018;69:95–101.
54. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause 2006;13:280–5.
55. Douchi T, Oki T, Nakamura S, Ijuin H, Yamamoto S, Nagata Y. The effect of body composition on bone density in pre- and postmenopausal women. Maturitas 1997;27:55–60.
56. Douchi T, Yamamoto S, Yoshimitsu N, Andoh T, Matsuo T, Nagata Y. Relative contribution of aging and menopause to changes in lean and fat mass in segmental regions. Maturitas 2002;42:301–6.
57. Douchi T, Yonehara Y, Kawamura Y, Kuwahata A, Kuwahata T, Iwamoto I. Difference in segmental lean and fat mass components between pre- and postmenopausal women. Menopause 2007;14:875–8.
58. Dubois EF, van den Bergh JP, Smals AG, van de Meerendonk CW, Zwinderman AH, Schweitzer DH. Comparison of quantitative ultrasound parameters with dual energy X-ray absorptiometry in pre- and postmenopausal women. Neth J Med 2001;58:62–70.
59. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K. Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol 2017;3:1228–36.
60. Ertungealp E, Seyisoglu H, Erel CT, Senturk LM, Gezer A. Changes in bone mineral density with age, menopausal status and body mass index in Turkish women. Climacteric 1999;2:45–51.
61. Feng Y, Hong X, Wilker E, et al. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis 2008;196:590–7.
62. Formica C, Loro ML, Gilsanz V, Seeman E. Inhomogeneity in body fat distribution may result in inaccuracy in the measurement of vertebral bone mass. J Bone Miner Res 1995;10:1504–11.
63. Friedenreich C, Cust A, Lahmann PH, et al. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control 2007;18:399–413.
64. Friedenreich CM, Courneya KS, Bryant HE. Case-control study of anthropometric measures and breast cancer risk. Int J Cancer 2002;99:445–52.
65. Fu X, Ma X, Lu H, He W, Wang Z, Zhu S. Associations of fat mass and fat distribution with bone mineral density in pre- and postmenopausal Chinese women. Osteoporos Int 2011;22:113–9.
66. Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD. Quality of life and menopausal transition for middle-aged women on Kinmen island. Quality Life Res 2003;12:53–61.
67. Gambacciani M, Ciaponi M, Cappagli B, Benussi C, De Simone L, Genazzani AR. Climacteric modifications in body weight and fat tissue distribution. Climacteric 1999;2:37–44.
68. Genazzani AR, Gambacciani M. Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution. Gynecol Endocrinol 2006;22:145–50.
69. Ghosh A. Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women. Cardiovasc J S Afr 2008;19:183–7.
70. Ghosh A, Bhagat M. Anthropometric and body composition characteristics in pre- and postmenopausal Asian Indian women: Santiniketan women study. Anthropol Anz 2010;68:1–10.
71. Gram IT, Funkhouser E, Tabar L. Anthropometric indices in relation to mammographic patterns among peri-menopausal women. Int J Cancer 1997;73:323–6.
72. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Ann Epidemiol 2015;25:406–13.e6.
73. Gurka MJ, Vishnu A, Santen RJ, DeBoer MD. Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc 2016;5.
74. Hadji P, Hars O, Bock K, et al. The influence of menopause and body mass index on serum leptin concentrations. Eur J Endocrinol 2000;143:55–60.
75. Hagner W, Hagner-Derengowska M, Wiacek M, Zubrzycki IZ. Changes in level of VO2max, blood lipids, and waist circumference in the response to moderate endurance training as a function of ovarian aging. Menopause 2009;16:1009–13.
76. Han D, Nie J, Bonner MR, et al. Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. Int J Cancer 2006;119:2931–7.
77. Harting GH, Moore CE, Mitchell R, Kappus CM. Relationship of menopausal status and exercise level to HDL-cholesterol in women. Exp Aging Res 1984;10:13–8.
78. He L, Tang X, Li N, et al. Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: a population-based study. Maturitas 2012;72:132–8.
79. Hirose K, Tajima K, Hamajima N, et al. Impact of established risk factors for breast cancer in nulligravid Japanese women. Breast Cancer 2003;10:45–53.
80. Hjartaker A, Adami HO, Lund E, Weiderpass E. Body mass index and mortality in a prospectively studied cohort of Scandinavian women: the women's lifestyle and health cohort study. Eur J Epidemiol 2005;20:747–54.
81. Ho S, Wu S, Chan S, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes 2010;34:1265.
82. Hsu YH, Venners SA, Terwedow HA, et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am J Clin Nutr 2006;83:146–54.
83. Hu X, Pan X, Ma X, et al. Contribution of a first-degree family history of diabetes to increased serum adipocyte fatty acid binding protein levels independent of body fat content and distribution. Int J Obes 2016;40:1649–54.
84. Hunter G, Kekes-Szabo T, Treuth M, Williams M, Goran M, Pichon C. Intra-abdominal adipose tissue, physical activity and cardiovascular risk in pre-and post-menopausal women. Int J Obes Relat Metab Dis 1996;20:860–5.

85. Iida T, Domoto T, Takigawa A, et al. Relationships among blood leptin and adiponectin levels, fat mass, and bone mineral density in Japanese pre-and postmenopausal women. Hiroshima J Med Sci 2011;60:71–8.
86. Ilich-Ernst J, Brownbill RA, Ludemann MA, Fu R. Critical factors for bone health in women across the age span: how important is muscle mass? Medscape Womens Health 2002;7:2.
87. Ito M, Hayashi K, Uetani M, Yamada M, Ohki M, Nakamura T. Association between anthropometric measures and spinal bone mineral density. Investig Radiol 1994;29:812–6.
88. Jaff NG, Norris SA, Snyman T, Toman M, Crowther NJ. Body composition in the Study of Women Entering and in Endocrine Transition (SWEET): A perspective of African women who have a high prevalence of obesity and HIV infection. Metabolism 2015;64:1031–41.
89. Jasienska G, Ziomkiewicz A, Gorkiewicz M, Pajak A. Body mass, depressive symptoms and menopausal status: an examination of the "Jolly Fat" hypothesis. Womens Health Issues 2005;15:145–51.
90. Jeenduang N, Trongsakul R, Inhongsa P, Chaidach P. The prevalence of metabolic syndrome in premenopausal and postmenopausal women in Southern Thailand. Gynecol Endocrinol 2014;30:573–6.
91. Jeon YK, Lee JG, Kim SS, et al. Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocrine J 2011;58:87–93.
92. Jurimae J, Jurimae T. Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. Am J Physiol Endocrinol Metab 2007;293:E42–7.
93. Kadam N, Chiplonkar S, Khadilkar A, Divate U, Khadilkar V. Low bone mass in urban Indian women above 40 years of age: prevalence and risk factors. Gynecol Endocrinol 2010;26:909–17.
94. Kang EK, Park HW, Baek S, Lim JY. The association between trunk body composition and spinal bone mineral density in Korean males versus females: a Farmers' Cohort for Agricultural Work-Related Musculoskeletal Disorders (FARM) study. J Korean Med Sci 2016;31:1595–603.
95. Kaufer-Horwitz M, Pelaez-Robles K, Lazzeri-Arteaga P, Goti-Rodriguez LM, Avila-Rosas H. Hypertension, overweight and abdominal adiposity in women: an analytical perspective. Arch Med Res 2005;36:404–11.
96. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care 2007;30:701–6.
97. Kim JH, Choi HJ, Kim MJ, Shin CS, Cho NH. Fat mass is negatively associated with bone mineral content in Koreans. Osteoporos Int 2012;23:2009–16.
98. Kim S, Lee JY, Im JA, et al. Association between serum osteocalcin and insulin resistance in postmenopausal, but not premenopausal, women in Korea. Menopause 2013;20:1061–6.
99. Kim YM, Kim SH, Kim S, Yoo JS, Choe EY, Won YJ. Variations in fat mass contribution to bone mineral density by gender, age, and body mass index: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008-2011. Osteoporos Int 2016;27:2543–54.
100. Kirchengast S, Gruber D, Sator M, Huber J. Impact of the age at menarche on adult body composition in healthy pre- and postmenopausal women. Am J Phys Anthropol 1998;105:9–20.
101. Kirchengast S, Hartmann B, Huber J. Serum levels of sex hormones, thyroid hormones, growth hormone, IGF I, and cortisol and their relations to body fat distribution in healthy women dependent on their menopausal status. Zeit Morphol Anthropol 1996;81:223–34.
102. Knapp KM, Blake GM, Spector TD, Fogelman I. Multisite quantitative ultrasound: precision, age- and menopause-related changes, fracture discrimination, and T-score equivalence with dual-energy X-ray absorptiometry. Osteoporos Int 2001;12:456–64.
103. Koh SJ, Hyun YJ, Choi SY, et al. Influence of age and visceral fat area on plasma adiponectin concentrations in women with normal glucose tolerance. Clin Chim Acta 2008;389:45–50.
104. Konrad T, Bär F, Schneider F, et al. Factors influencing endothelial function in healthy pre- and post-menopausal women of the EU-RISC study. Diabet Vasc Dis Res 2011;8:229–36.
105. Kontogianni MD, Dafni UG, Routsias JG, Skopouli FN. Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women. J Bone Miner Res 2004;19:546–51.
106. Konukoglu D, Serin O, Ercan M. Plasma leptin levels in obese and non-obese postmenopausal women before and after hormone replacement therapy. Maturitas 2000;36:203–7.
107. Koskova I, Petrasek R, Vondra K, et al. Weight, body composition and fat distribution of Czech women in relation with reproductive phase: a cross-sectional study. Prague Med Rep 2007;108:13–26.
108. Kotani K, Chen JT, Taniguchi N. The relationship between adiponectin and blood pressure in premenopausal and postmenopausal women. Clin Investig Med 2011;34:E125–30.
109. Kraemer RR, Synovitz LB, Gimpel T, Kraemer GR, Johnson LG, Castracane VD. Effect of estrogen on serum DHEA in younger and older women and the relationship of DHEA to adiposity and gender. Metabolism 2001;50:488–93.
110. Kuk JL, Lee S, Heymsfield SB, Ross R. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. Am J Clin Nutr 2005;81:1330–4.
111. Laitinen K, Valimaki M, Keto P. Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. Calcif Tissue Int 1991;48:224–31.
112. Lejskova M, Alusik S, Valenta Z, Adamkova S, Pitha J. Natural postmenopause is associated with an increase in combined cardiovascular risk factors. Physiol Res 2012;61:587–96.
113. Leon Guerrero RT, Novotny R, Wilkens LR, et al. Risk factors for breast cancer in the breast cancer risk model study of Guam and Saipan. Cancer Epidemiol 2017;50:221–33.
114. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr 1992;55:950–4.
115. Lin WY, Yang WS, Lee LT, et al. Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan. Int J Obes 2006;30:912–7.
116. Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: results from a population study of women in Goteborg, Sweden. Scand J Clin Lab Investig 1980;40:629–36.
117. Lindsay R, Cosman F, Herrington BS, Himmelstein S. Bone mass and body composition in normal women. J Bone Miner Res 1992;7:55–63.
118. Lovejoy JC, Champagne CM, de Jonge L, Xie H, Smith SR. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes 2008;32:949–58.
119. Lyu LC, Yeh CY, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ. Association of sex, adiposity, and diet with HDL subclasses in middle-aged Chinese. Am J Clin Nutr 2001;74:64–71.
120. Maharlouei N, Bellissimo N, Ahmadi SM, Lankarani KB. Prevalence of metabolic syndrome in pre- and postmenopausal Iranian women. Climacteric 2013;16:561–7.
121. Malacara JM, Canto de Cetina T, Bassol S, et al. Symptoms at pre- and postmenopause in rural and urban women from three states of Mexico. Maturitas 2002;43:11–9.
122. Manabe E, Aoyagi K, Tachibana H, Takemoto T. Relationship of intra-abdominal adiposity and peripheral fat distribution to lipid metabolism in an island population in western Japan: gender differences and effect of menopause. Tohoku J Exp Med 1999;188:189–202.
123. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. Eur J Cancer Prev 2001;10:33–42.
124. Mannisto S, Pietinen P, Pyy M, Palmgren J, Eskelinen M, Uusitupa M. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. Int J Cancer 1996;68:8–13.
125. Martini G, Valenti R, Giovani S, Nuti R. Age-related changes in body composition of healthy and osteoporotic women. Maturitas 1997;27:25–33.

126. Marwaha RK, Garg MK, Tandon N, Mehan N, Sastry A, Bhadra K. Relationship of body fat and its distribution with bone mineral density in Indian population. J Clin Densitom 2013;16:353–9.
127. Matsushita H, Kurabayashi T, Tomita M, Kato N, Tanaka K. Effects of uncoupling protein 1 and beta3-adrenergic receptor gene polymorphisms on body size and serum lipid concentrations in Japanese women. Maturitas 2003;45:39–45.
128. Matsuzaki M, Kulkarni B, Kuper H, et al. Association of Hip Bone Mineral Density and Body Composition in a Rural Indian Population: The Andhra Pradesh Children and Parents Study (APCAPS). PLoS One 2017;12: e0167114.
129. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med 1989;321:641–6.
130. Mesch VR, Boero LE, Siseles NO, et al. Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status. Climacteric 2006;9:40–8.
131. Meza-Munoz DE, Fajardo ME, Perez-Luque EL, Malacara JM. Factors associated with estrogen receptors-alpha (ER-alpha) and -beta (ER-beta) and progesterone receptor abundance in obese and non obese pre- and post-menopausal women. Steroids 2006;71: 498–503.
132. Minatoya M, Kutomi G, Shima H, et al. Relation of serum adiponectin levels and obesity with breast cancer: a Japanese case-control study. Asian Pac J Cancer Prev 2014;15: 8325–30.
133. Mo D, Hsieh P, Yu H, et al. The relationship between osteoporosis and body composition in pre- and postmenopausal women from different ethnic groups in China. Ethn Health 2017;22: 295–310.
134. Muchanga Sifa MJ, Lepira FB, Longo AL, et al. Prevalence and predictors of metabolic syndrome among Congolese pre- and postmenopausal women. Climacteric 2014;17: 442–8.
135. Muti P, Stanulla M, Micheli A, et al. Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: a prospective analysis of abdominal adiposity, sebum production, and hirsutism (Italy). Cancer Causes Control 2000;11: 721–30.
136. Nitta J, Nojima M, Ohnishi H, et al. Weight gain and alcohol drinking associations with breast cancer risk in Japanese postmenopausal women: results from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev 2016;17:1437–43.
137. Noh HM, Song YM, Park JH, Kim BK, Choi YH. Metabolic factors and breast cancer risk in Korean women. Cancer Causes Control 2013;24:1061–8.
138. Nordin BE, Need AG, Bridges A, Horowitz M. Relative contributions of years since menopause, age, and weight to vertebral density in postmenopausal women. J Clin Endocrinol Metab 1992;74:20–3.
139. Ohta H, Kuroda T, Onoe Y, et al. Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. J Bone Miner Metab 2010;28:690–5.
140. Oldroyd B, Stewart SP, Truscott JG, Westmacott CF, Smith MA. Age related changes in body composition. Applied Radiat Isot 1998;49:589–90.
141. Pacholczak R, Klimek-Piotrowska W, Kuszmiersz P. Associations of anthropometric measures on breast cancer risk in pre- and postmenopausal women: a case-control study. J Physiol Anthropol 2016;35:7.
142. Park JH, Song YM, Sung J, et al. The association between fat and lean mass and bone mineral density: the Healthy Twin Study. Bone 2012;50:1006–11.
143. Park YM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer 2017;140:2657–66.
144. Pavicic Zezelj S, Cvijanovic O, Micovic V, Bobinac D, Crncevic-Orlic Z, Malatestinic G. Effect of menopause, anthropometry, nutrition and lifestyle on bone status of women in the northern Mediterranean. West Indian Med J 2010;59:494–502.
145. Pavlica T, Mikalacki M, Matic R, et al. Relationship between BMI and skinfold thicknesses to risk factors in premenopausal and postmenopausal women. Coll Antropol 2013;37(suppl2):119–24.
146. Phillips GB, Jing T, Heymsfield SB. Does insulin resistance, visceral adiposity, or a sex hormone alteration underlie the metabolic syndrome? Studies in women. Metabolism 2008;57:838–44.
147. Polesel DN, Hirotsu C, Nozoe KT, et al. Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study. Menopause 2015;22:835–44.
148. Pollan M, Lope V, Miranda-Garcia J, et al. Adult weight gain, fat distribution and mammographic density in Spanish pre- and postmenopausal women (DDM-Spain). Breast Cancer Res Treat 2012;134:823–38.
149. Portaluppi F, Pansini F, Manfredini R, Mollica G. Relative influence of menopausal status, age, and body mass index on blood pressure. Hypertension 1997;29:976–9.
150. Priya T, Chowdhury MG, Vasanth K, et al. Assessment of serum leptin and resistin levels in association with the metabolic risk factors of pre- and post-menopausal rural women in South India. Diabet Metab Synd 2013;7:233–7.
151. Rantalainen T, Nikander R, Heinonen A, et al. Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. Bone 2010;46:964–9.
152. Reina P, Cointry GR, Nocciolino L, et al. Analysis of the independent power of age-related, anthropometric and mechanical factors as determinants of the structure of radius and tibia in normal adults: a pQCT study. J Musculoskelet Neuronal Interact 2015;15: 10–22.
153. Revilla M, Villa LF, Hernandez ER, Sanchez-Atrio A, Cortes J, Rico H. Influence of weight and gonadal status on total and regional bone mineral content and on weight-bearing and non-weight-bearing bones, measured by dual-energy X-ray absosorptiometry. Maturitas 1997;28:69–74.
154. Revilla M, Villa LF, Sanchez-Atrio A, Hernandez ER, Rico H. Influence of body mass index on the age-related slope of total and regional bone mineral content. Calcif Tissue Int 1997;61:134–8.
155. Rice MS, Bertrand KA, Lajous M, et al. Reproductive and lifestyle risk factors and mammographic density in Mexican women. Ann Epidemiol 2015;25:868–73.
156. Rico H, Aguado F, Arribas I, et al. Behavior of phalangeal bone ultrasound in normal women with relation to gonadal status and body mass index. Osteoporos Int 2001;12:450–5.
157. Rico H, Arribas I, Casanova FJ, Duce AM, Hernandez ER, Cortes-Prieto J. Bone mass, bone metabolism, gonadal status and body mass index. Osteoporos Int 2002;13:379–87.
158. Roelfsema F, Veldhuis JD. Growth hormone dynamics in healthy adults are related to age and sex and strongly dependent on body mass index. Neuroendocrinology 2016;103: 335–44.
159. Rosenbaum M, Nicolson M, Hirsch J, et al. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J Clinical Endocrinol Metab 1996;81: 3424–7.
160. Salomaa V, Rasi V, Pekkanen J, et al. Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors. The FINRISK Hemostasis Study. Arterioscler Thromb Vasc Biol 1995;15:1549–55.
161. Sarrafzadegan N, Khosravi-Boroujeni H, Esmaillzadeh A, Sadeghi M, Rafieian-Kopaei M, Asgary S. The association between hypertriglyceridemic waist phenotype, menopause, and cardiovascular risk factors. Arch Iran Med 2013;16:161–6.
162. Schaberg-Lorei G, Ballard JE, McKeown BC, Zinkgraf SA. Body composition alterations consequent to an exercise program for pre and postmenopausal women. J Sports Med Phys Fit 1990;30:426–33.
163. Schwarz S, Volzke H, Alte D, et al. Menopause and determinants of quality of life in women at midlife and beyond: the study of health in pomerania (SHIP). Menopause 2007;14:123–34.
164. Shakir YA, Samsioe G, Nyberg P, Lidfeldt J, Nerbrand C. Cardiovascular risk factors in middle-aged women and the association with use of hormone therapy: results from a population-based study of Swedish women. The Women's Health in the Lund Area (WHILA) Study. Climacteric 2004;7:274–83.

165. Sherk VD, Malone SP, Bemben MG, Knehans AW, Palmer IJ, Bemben DA. Leptin, fat mass, and bone mineral density in healthy pre- and postmenopausal women. J Clin Densitom 2011;14:321–5.
166. Shibata H, Matsuzaki T, Hatano S. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. Am J Epidemiol 1979;109:420–4.
167. Sieminska L, Wojciechowska C, Foltyn W, et al. The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause. Endokrynol Polska 2006;57:15–22.
168. Skrzypczak M, Szwed A. Assessment of the body mass index and selected physiological parameters in pre- and post-menopausal women. Homo 2005;56:141–52.
169. Skrzypczak M, Szwed A, Pawlińska-Chmara R, Skrzypulec V. Assessment of the BMI, WHR and W/Ht in pre-and post-menopausal women. Anthropol Rev 2007;70:3–13.
170. Soderberg S, Ahren B, Eliasson M, Dinesen B, Olsson T. The association between leptin and proinsulin is lost with central obesity. J Intern Med 2002;252:140–8.
171. Son MK, Lim NK, Lim JY, et al. Difference in blood pressure between early and late menopausal transition was significant in healthy Korean women. BMC Womens Health 2015;15:64.
172. Soriguer F, Morcillo S, Hernando V, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause 2009;16:817–21.
173. Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. J Hum Hypertens 1989;3:427–33.
174. Suarez-Ortegon MF, Arbelaez A, Mosquera M, Mendez F, Aguilar-de Plata C. C-reactive protein, waist circumference, and family history of heart attack are independent predictors of body iron stores in apparently healthy premenopausal women. Biol Trace Elem Res 2012;148:135–8.
175. Suliga E, Koziel D, Ciesla E, Rebak D, Gluszek S. Factors associated with adiposity, lipid profile disorders and the metabolic syndrome occurrence in premenopausal and postmenopausal women. PLoS One 2016;11:e0154511.
176. Sumner AE, Falkner B, Kushner H, Considine RV. Relationship of leptin concentration to gender, menopause, age, diabetes, and fat mass in African Americans. Obes Res 1998;6:128–33.
177. Tanaka NI, Hanawa S, Murakami H, et al. Accuracy of segmental bioelectrical impedance analysis for predicting body composition in pre- and postmenopausal women. J Clin Densitom 2015;18:252–9.
178. Thomas T, Burguera B, Melton LJ 3rd, et al. Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. Metabolism 2000;49:1278–84.
179. Torng PL, Su TC, Sung FC, et al. Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women: the Chin-Shan Community Cardiovascular Cohort Study. Atherosclerosis 2000;153:413–21.
180. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Dis 2000;24:226–31.
181. Tremollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. Am J Obstet Gynecol 1996;175:1594–600.
182. Trikudanathan S, Pedley A, Massaro JM, et al. Association of female reproductive factors with body composition: the Framingham Heart Study. J Clin Endocrinol Metab 2013;98:236–44.
183. Van Pelt RE, Davy KP, Stevenson ET, et al. Smaller differences in total and regional adiposity with age in women who regularly perform endurance exercise. Am J Physiol 1998;275:E626–34.
184. Veldhuis JD, Dyer RB, Trushin SA, Bondar OP, Singh RJ, Klee GG. Interleukins 6 and 8 and abdominal fat depots are distinct correlates of lipid moieties in healthy pre- and postmenopausal women. Endocrine 2016;54:671–80.
185. Wang F, Ma X, Hao Y, et al. Serum glycated albumin is inversely influenced by fat mass and visceral adipose tissue in Chinese with normal glucose tolerance. PLoS One 2012;7:e51098.
186. Wang W, Zhao LJ, Liu YZ, Recker RR, Deng HW. Genetic and environmental correlations between obesity phenotypes and age at menarche. Int J Obes 2006;30:1595–600.
187. Wang WS, Wahlqvist ML, Hsu CC, Chang HY, Chang WC, Chen CC. Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in Taiwan. BMC Public Health 2012;12:111.
188. Wee J, Sng BY, Shen L, Lim CT, Singh G, Das De S. The relationship between body mass index and physical activity levels in relation to bone mineral density in premenopausal and postmenopausal women. Arch Osteoporos 2013;8:162.
189. Williams PT, Krauss RM. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. Arterioscler Thromb Vasc Biol 1997;17:1082–90.
190. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. Arch Intern Med 1991;151:97–102.
191. Xu L, Nicholson P, Wang QJ, Wang Q, Alen M, Cheng S. Fat mass accumulation compromises bone adaptation to load in Finnish women: a cross-sectional study spanning three generations. J Bone Miner Res 2010;25:2341–9.
192. Yamatani H, Takahashi K, Yoshida T, Takata K, Kurachi H. Association of estrogen with glucocorticoid levels in visceral fat in postmenopausal women. Menopause 2013;20:437–42.
193. Yannakoulia M, Melistas L, Solomou E, Yiannakouris N. Association of eating frequency with body fatness in pre- and postmenopausal women. Obesity 2007;15:100–6.
194. Yoldemir T, Erenus M. The prevalence of metabolic syndrome in pre- and postmenopausal women attending a tertiary clinic in Turkey. Eur J Obstet Gynecol Reprod Biol 2012;164:172–5.
195. Yoo HJ, Park MS, Yang SJ, et al. The differential relationship between fat mass and bone mineral density by gender and menopausal status. J Bone Miner Metab 2012;30:47–53.
196. Yoo KY, Kim H, Shin HR, et al. Female sex hormones and body mass in adolescent and postmenopausal Korean women. J Korean Med Sci 1998;13:241–6.
197. Yoshimoto N, Nishiyama T, Toyama T, et al. Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. Cancer Sci 2011;102:2065–72.
198. Zhong N, Wu XP, Xu ZR, et al. Relationship of serum leptin with age, body weight, body mass index, and bone mineral density in healthy mainland Chinese women. Clin Chim Acta 2005;351:161–8.
199. Zhou JL, Lin SQ, Shen Y, Chen Y, Zhang Y, Chen FL. Serum lipid profile changes during the menopausal transition in Chinese women: a community-based cohort study. Menopause 2010;17:997–1003.
200. Zhou Y, Zhou X, Guo X, et al. Prevalence and risk factors of hypertension among pre- and post-menopausal women: a cross-sectional study in a rural area of northeast China. Maturitas 2015;80:282–7.
201. Zivkovic TB, Vuksanovic M, Jelic MA, et al. Obesity and metabolic syndrome during the menopause transition in Serbian women. Climacteric 2011;14:643–8.
202. Akahoshi M, Soda M, Nakashima E, et al. Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. Atherosclerosis 2001;156:157–63.
203. Ford K, Sowers M, Crutchfield M, Wilson A, Jannausch M. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. Menopause 2005;12:308–17.
204. Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution with menopause. Metabolism 2009;58:311–5.
205. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation. Arch Intern Med 2008;168:1568–75.

206. Lee CG, Carr MC, Murdoch SJ, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab 2009;94:1104–10.
207. Liu-Ambrose T, Kravetsky L, Bailey D, et al. Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: a 12-year observational study. Calcif Tissue Int 2006;79:145–51.
208. Macdonald HM, New SA, Campbell MK, Reid DM. Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. Osteoporos Int 2005;16:163–71.
209. Razmjou S, Abdulnour J, Bastard J-P, et al. Body composition, cardiometabolic risk factors, physical activity, and inflammatory markers in premenopausal women after a 10-year follow-up: a MONET study. Menopause 2018;25:89–97.
210. Soreca I, Rosano C, Jennings JR, et al. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. Psychosom Med 2009;71:485–90.

Lipid profile differences during menopause: a review with meta-analysis

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REVIEW ARTICLE

Lipid profile differences during menopause: a review with meta-analysis

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Abstract

Objectives: The aim of the study was to determine lipid profile differences between premenopausal and postmenopausal women.

Methods: The present review used a meta-analytic approach. Sixty-six studies were included, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal.

Results: The main findings were that (1) lipoproteins were significantly higher in postmenopausal women compared to premenopausal women including triglycerides (0.27 mmol/L, 95% confidence interval, 0.22-0.31), total cholesterol (0.58, 0.50-0.65), low-density lipoprotein (0.45, 0.38-0.53), and total cholesterol to high-density lipoprotein levels (0.39, 0.16-0.62); (2) there was no difference in high-density lipoprotein levels between premenopausal and postmenopausal women (0.02, −0.00-0.04); and (3) the differences in lipid levels was partly attributable to the mean age difference between premenopausal and postmenopausal women.

Conclusions: These findings are important as they provide precise estimates of lipid differences in women around menopause. Furthermore the results suggest that the unfavorable lipid profile that develops in postmenopausal women puts them at higher risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

Key Words: Cholesterol – Female – Lipoproteins – Postmenopausal – Premenopausal.

Menopause is characterized by the progressive decline of endogenous estrogen levels and is defined as the final menstrual period.[1] As women progress from a premenopausal to postmenopausal state, deleterious changes in serum lipid profiles have been shown to occur, as demonstrated by the increased levels of low-density lipoprotein (LDL), total cholesterol (TC), and triglycerides (TG).[2,3] Previous narrative reviews that have discussed lipid changes in women around menopause have been limited by a paucity of quantitative estimates,[4-6] which are typically made available through a systematic review of the literature with meta-analyses. This has not yet been done for serum lipids, perhaps because the extant literature on this topic may be too large to systematically review. We have recently conducted a meta-analysis on fat mass differences between premenopausal and postmenopausal women[7] and in this process we have also extracted relevant lipid profile data. Given that lipid profiles are highly related to fat mass, particularly central obesity,[8] the data extracted from our previous review provide a useful representation of lipid changes in women around menopause. It is therefore within this context that we are reviewing data and reporting precise quantitative estimates on lipid profile differences between premenopausal and postmenopausal women to address this gap in the literature. This review will provide important information to clinicians and critical evidence on lipid differences, which can guide the development of targeted interventions to facilitate positive health outcomes for postmenopausal women.

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METHODS

The methodology of the initial meta-analyses is reported elsewhere in detail[7] and was registered prospectively in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643). Briefly the PubMed database was searched (to May 2018) with filters applied to

exclude both non-human and non-English studies. In addition, the criteria and methods described in the following sections were used.

Inclusion and exclusion criteria

Both longitudinal and cross-sectional studies that investigated both healthy premenopausal and healthy postmenopausal women were included, whereas studies that exclusively investigated clinical/pathophysiological populations or had fewer than 40 participants were excluded. The sample size cutoff was established to avoid extreme sampling bias and ensure that small studies, which are more likely to be methodologically less robust, are not included.

Data extraction

Available lipid data that were extracted from each study included high-density lipoprotein (HDL), LDL, TC, TGs, and TC to HDL ratio. The International System of Units (SI) mmol/L was used to express lipid levels. Articles that reported lipids as mg/dL were converted to mmol/L by multiplying the values by 0.02586 (for HDL, LDL, and TC) or by 0.01129 (for TG). Two authors (A.A. and E.W.) double extracted all data from included articles to avoid transcription errors with any disagreement resolved by consensus.

Statistics

R (version 3.3.3)[9] operating within RStudio (version 1.0.143)[10] was used to conduct all statistical analysis. The metafor package (version 2.0.0)[11] was used for the meta-analysis.

Meta-analysis

Because the sampling of populations and methodology varied across studies, heterogeneity was assumed, which resulted in a distribution of effect sizes.[12] Therefore, all analyses used a random effects model (using the restricted maximum likelihood estimator) to estimate the mean of the distribution of these effect sizes.

Cochran's Q statistic (with $P < 0.01$ indicative of significant heterogeneity) and the I^2 statistic (values 25%, 50%, and 75% suggestive of low, moderate, and high heterogeneity, respectively) were used to assess heterogeneity across studies.[13] Sensitivity analyses using the leave-one-out-method were conducted to identify studies that excessively contributed to heterogeneity. Meta-regression analyses using a mixed effect model were conducted to determine the influence of moderators, such as aging.

Bias

Funnel plots and Egger regression test were used to investigate the possible impact of publication bias.[14] The trim and fill method was also used to estimate the number of studies that may be missing from the meta-analysis and to estimate adjusted effect sizes.[15,16]

RESULTS

Effect sizes

The unstandardized raw mean differences (ie, estimate) for each lipid measure between postmenopausal and premenopausal women are presented in Table 1. Some studies included multiple subcohorts of premenopausal and postmenopausal women. In these cases, subcohorts were extracted separately and treated as discrete samples. Three longitudinal studies were identified; however, such studies did not report compatible measures and therefore were not suitable for meta-analysis. Sixty-six cross-sectional studies reporting on 67 sample populations were included in the analyses (see Table, Supplemental Digital Content 1, http://links.lww.com/MENO/A452, which includes study characteristics).

Meta-analysis results

High-density lipoprotein

Fifty-seven studies examined the association between HDL and menopausal status. There were no significant mean HDL differences between premenopausal and postmenopausal women (Table 1 and Fig. 1).

Triglycerides

Fifty-seven studies examined the association between TG and menopausal status. The mean TG change was 0.27 mmol/L (SE = 0.02; Table 1 and see Figure, Supplemental Digital Content 2, http://links.lww.com/MENO/A455), which illustrates a forest plot for TG with an annual difference of 0.02 mmol/L/yr.

TABLE 1. *Output for cross-sectional studies*

No	Lipid measure	*k* (Samples)	Total preM sample size	Total postM sample size	PreM mean age (SD)	PostM mean age (SD)	Age mean difference (SD)	PreM mean lipid level (SD)	PostM mean lipid level (SD)	Estimate (95% CI)	*P*
1	HDL	58 (59)	64,330	42,650	38.98 (5.74)	56.41 (3.58)	15.74 (7.62)	1.53 (0.18)	1.55 (0.20)	0.02 (–0.00, 0.04)	0.0973
2	TG	57 (58)	24,365	25,642	42.36 (6.00)	57.14 (4.04)	13.71 (8.35)	1.28 (0.29)	1.57 (0.34)	**0.27 (0.22, 0.31)**	<0.0001
3	TC	56 (56)	66,062	41,940	39.19 (5.69)	56.57 (3.50)	15.71 (7.37)	4.77 (0.35)	5.57 (0.46)	**0.58 (0.50, 0.65)**	<0.0001
4	LDL	49 (49)	63,246	39,176	38.90 (5.71)	56.55 (3.65)	16.01 (7.63)	2.90 (0.25)	3.46 (0.32)	**0.45 (0.38, 0.53)**	<0.0001
5	TC:HDL	10 (10)	1,982	1,803	43.05 (4.67)	58.39 (4.43)	14.85 (7.82)	3.74 (0.24)	4.27 (0.51)	**0.39 (0.16, 0.62)**	0.0008

Bolded estimates indicate significance at the $P < 0.05$ level. Means and standard deviations are computed as weighted means and weighted standard deviations, taking into account sample size. For HDL, TC, and LDL, to convert values from SI units (mmol/L) to mg/dL, multiply by 38.67, however, for TG, multiply by 88.57.

HDL, high-density lipoprotein; *k*, number of studies; LDL, low-density lipoprotein; postM, postmenopausal; preM, premenopausal; SD, standard deviation; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

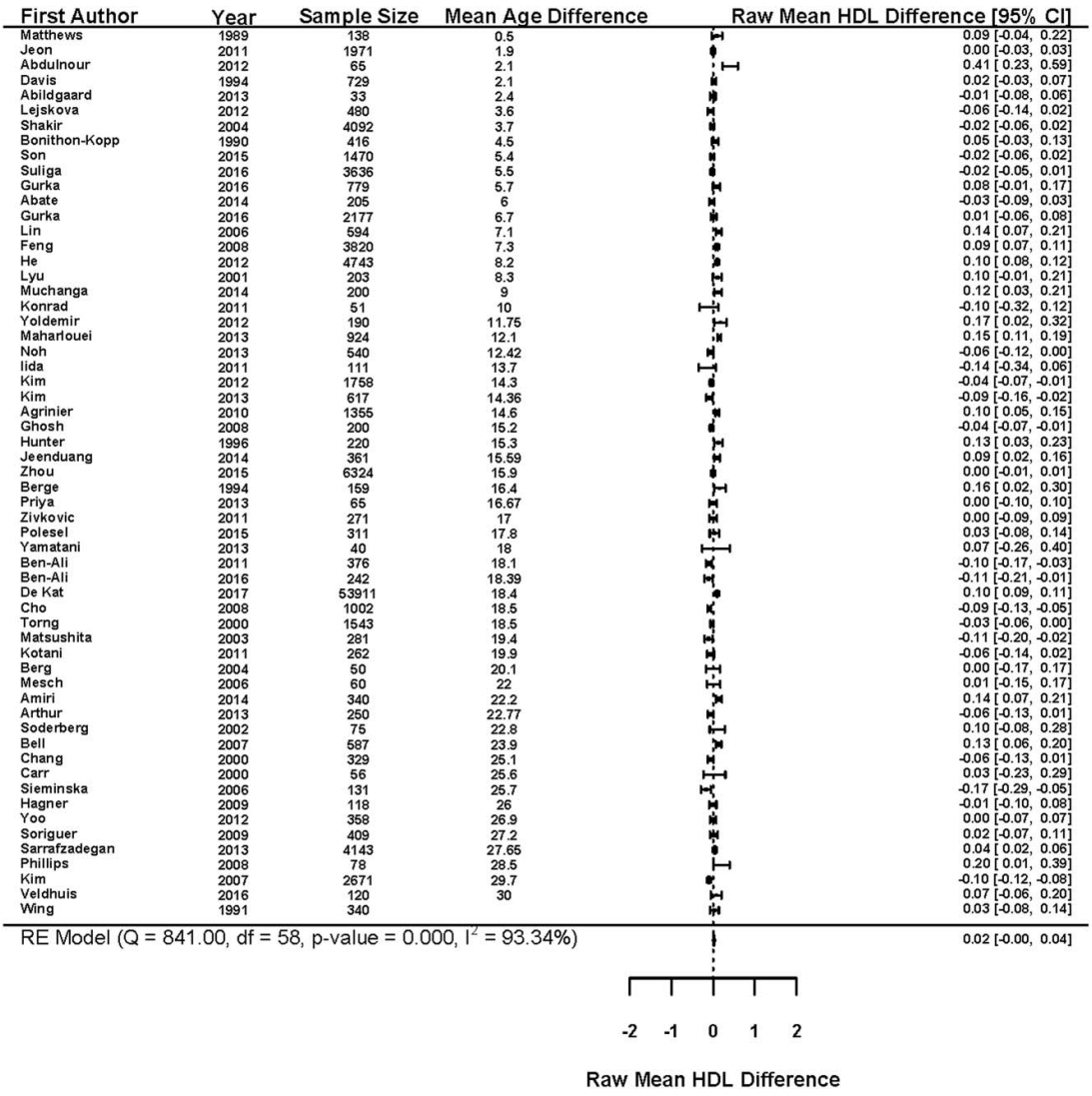

FIG. 1. Forest plot of the raw mean high-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. HDL, high-density lipoprotein; RE model, random effects model.

Total cholesterol

Fifty-five studies examined the association between TC and menopausal status. The mean TC change was 0.58 mmol/L (SE = 0.04; Table 1 and see Figure, Supplemental Digital Content 3, http://links.lww.com/MENO/A456, which illustrates a forest plot for TC), with an annual difference of 0.04 mmol/L/yr.

Low-density lipoprotein

Forty-eight studies examined the association between LDL and menopausal status. The mean LDL change was 0.46 mmol/L (SE = 0.04; Table 1 and Fig. 2), with an annual difference of 0.03 mmol/L/yr.

Total cholesterol to high-density lipoprotein ratio

Ten studies examined the association between TC to HDL ratio and menopausal status. The mean TC to HDL change was 0.39 mmol/L (SE = 0.12; Table 1 and see Figure, Supplemental Digital Content 4, http://links.lww.com/MENO/A457, which illustrates a forest plot for TC to HDL ratio), with an annual difference of 0.03 mmol/L/yr.

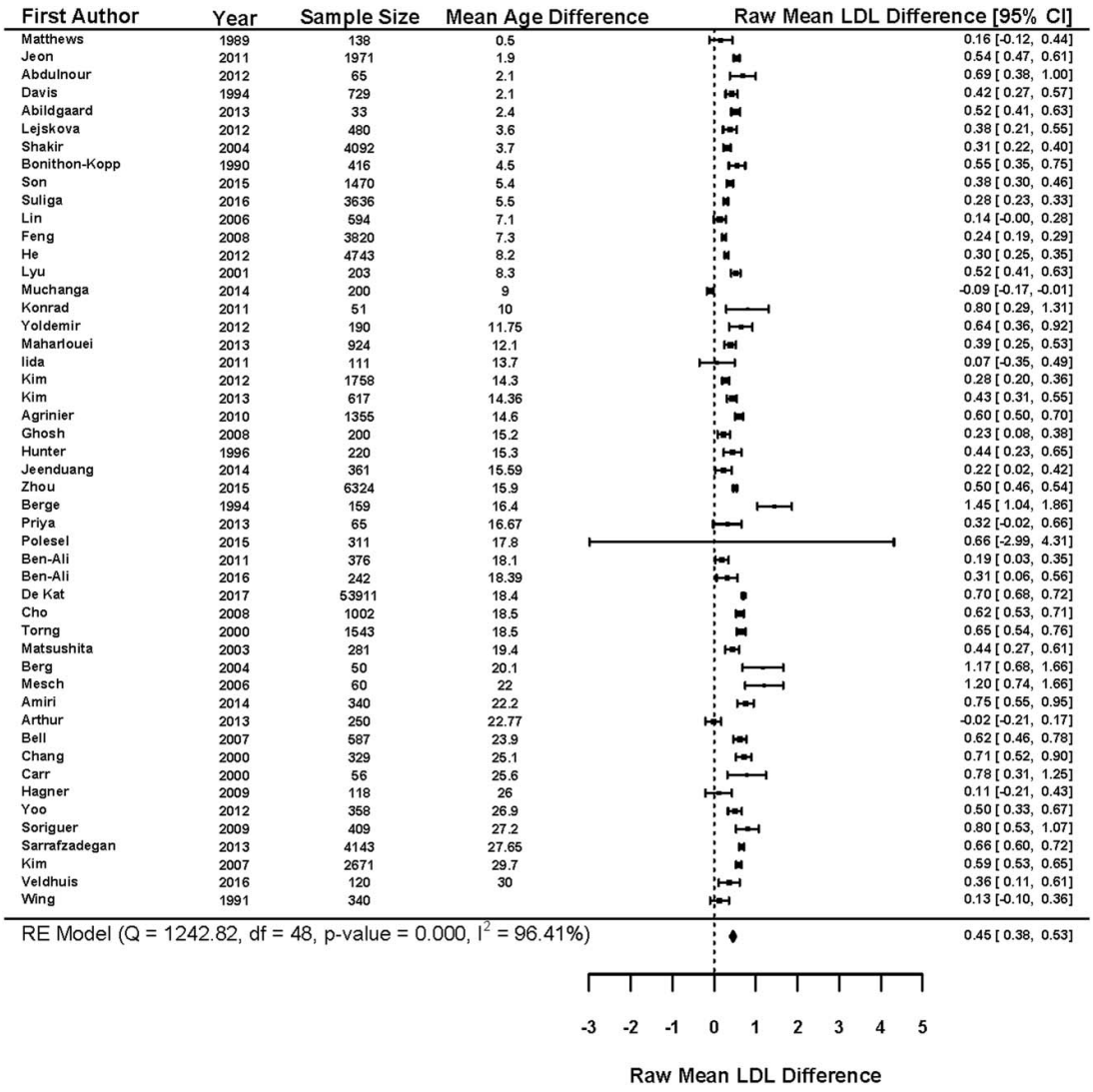

FIG. 2. Forest plot of the raw mean low-density lipoprotein difference between premenopausal and postmenopausal women. Studies are ordered by mean age difference. LDL, low-density lipoprotein; RE model, random effects model.

Sensitivity analyses

In all meta-analyses performed, significant heterogeneity was found and the proportion of real variance that was not related to random error between studies (I^2) was high for all analyses. Leave-one-out-analyses revealed no particularly influential study and showed relative consistency in reported estimates.

Publication bias

The trim and fill test and funnel plot diagnostics revealed some evidence of publication bias. Eggers regression test was significant for TC and LDL analyses, indicating some asymmetry. The trim and fill analyses identified one missing study for HDL and five for LDL (Fig. 3). Although these results suggest that some publication bias is likely to be present, the differences between actual and reported estimates were generally quite small. The inclusion of missing studies did not change the relationship or significance of the results.

Metaregression and subgroup analyses

Aging (ie, the mean age difference between premenopausal and postmenopausal women) significantly predicted the unexplained variance (9.71%-40.08%) in lipid estimates (Table 2). More specifically, the meta-regression (which

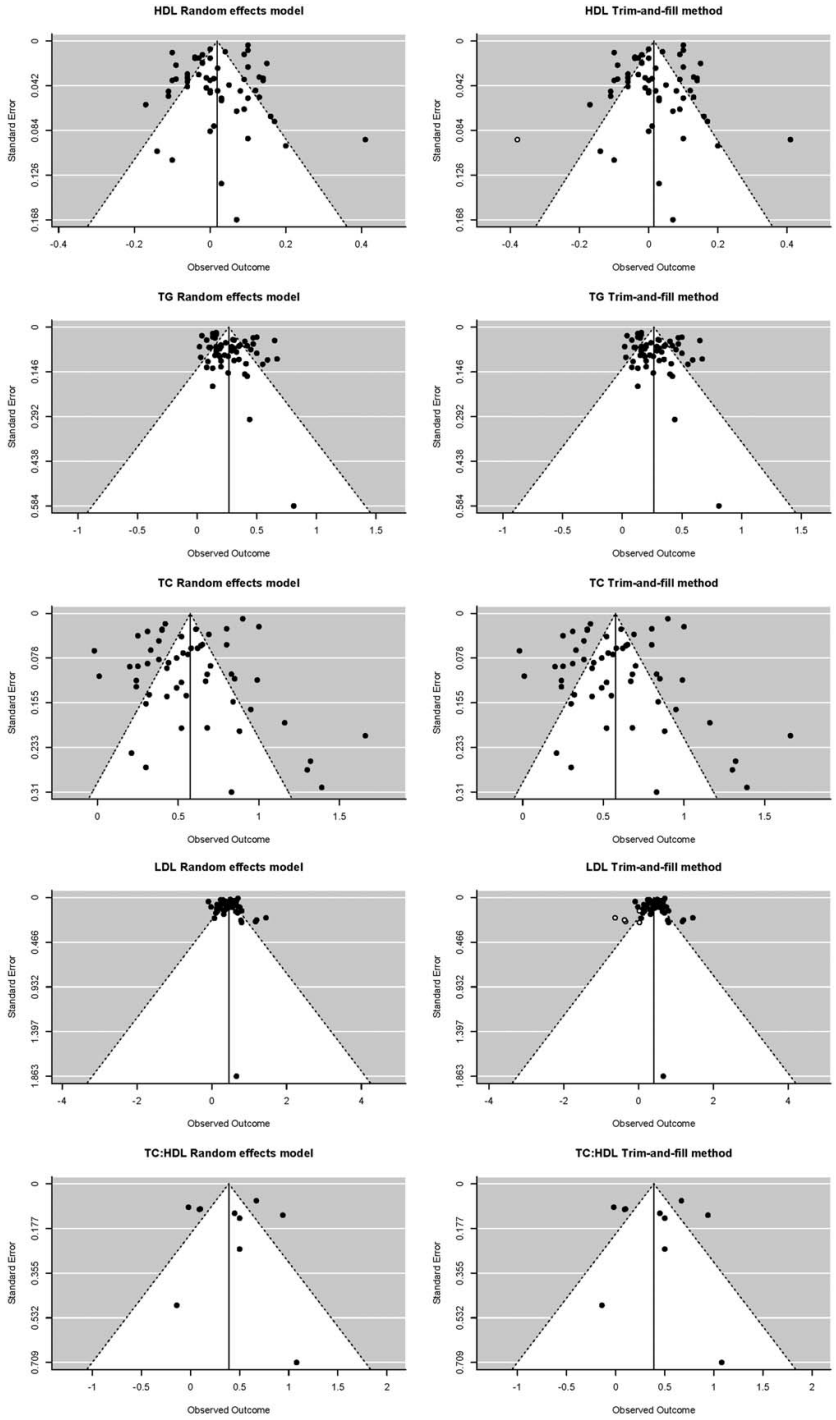

FIG. 3. Funnel plots using a random effects model (left column) and the trim and fill method (right column). Filled circles represent included studies in the meta-analyses and open circles represent possible missing studies. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

TABLE 2. *Metaregression analyses after removing the effect attributable to normal aging*

Lipid measure	Samples	R^2	Unstandardized β estimate (95% CI)	*P*
TG	57	36.61	**0.0103 (0.0059, 0.0147)**	<0.0001
TC	55	9.71	**0.0113 (0.0021, 0.0205)**	0.0164
LDL	48	10.13	**0.0088 (0.0006, 0.0171)**	0.0351
TC:HDL	10	40.08	**0.0243 (0.0025, 0.0462)**	0.0289

The unstandardized estimates reflect increases in lipid levels for every year of difference between premenopausal and postmenopausal women. Bolded estimates indicate significance at the $P < 0.05$ level. Studies that did not report age were omitted from model fitting. For TC and LDL, to convert values from SI units (mmol/L) to mg/dL, multiply by 38.67, however, for TG, multiply by 88.57.
LDL, low-density lipoprotein; R^2, proportion of observed variance explained by the model; TC, total cholesterol; TC:HDL, total cholesterol to high-density lipoprotein ratio; TG, triglyceride.

used a mixed effects model) indicated that for every year difference between premenopausal and postmenopausal women, there was a 0.01 mmol/L increase in TG, TC, and LDL and a 0.02 mmol/L increase in TC to HDL ratio (Table 2). The inclusion of women using hormone therapy had no significant effect on the overall estimates.

Subgroup analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women (compared to studies with a mean age difference of >5 years) revealed no significant differences for HDL, LDL, TC, and TC to HDL ratio. Studies that, however, had a mean age difference greater than 5 years had a 0.1295 mmol/L increase in TG (SE 0.06, 95% CI from 0.02 to 0.24). Notably, I^2 remained high across all subgroup analyses. Furthermore, subset analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women revealed no difference in the direction or significance of effects compared to initial estimates. The magnitude of estimates for most measures was also very similar (see Table, Supplemental Digital Content 5, http://links.lww.com/MENO/A453, which illustrates subset analyses). Notably, however, the magnitude of effect decreased for TGs (initial estimate: 0.27 mmol/L, 95% confidence interval 0.22-0.31; <5 years mean difference estimate: 0.14, 0.09-0.19) and could not be investigated in the TC to HDL levels due to insufficient studies available for subset analyses. Furthermore, the heterogeneity remained high (ie, >75%) across all analyses (see Table, Supplemental Digital Content 6, http://links.lww.com/MENO/A454, which illustrates heterogeneity for subset analyses), except for TGs (88.68%-55.28%) and LDL (96.41%-69.73%).

DISCUSSION

The current review investigated the differences in lipid levels between healthy premenopausal and postmenopausal women. The main findings of this review were that (1) TG, TC, LDL, and TC to HDL ratio levels were significantly higher in postmenopausal women compared to premenopausal women; (2) there was no difference in HDL levels between premenopausal and postmenopausal women; and (3) the differences in lipid levels were partly attributable to the mean age difference between premenopausal and postmenopausal women.

It is important to determine why an unfavorable lipid profile develops in postmenopausal women comparatively to premenopausal women. Although both aging and menopause are potentially implicated, it can be difficult to delineate the individual influence of each because both progress concurrently. Previous research indicates that for women aged 18 to 45 years the typical trends for TG, TC, and LDL is 0.070, 0.010, and 0.003 mmol/yr, respectively.[17] The analyses presented in this article reflect consistent but comparatively smaller annual estimates for TG (0.02 mmol/yr), yet larger annual estimates for TC (0.04 mmol/yr) and LDL (0.03 mmol/yr), which would suggest that the annual difference in lipid estimates does not remain the same throughout early adulthood and middle age. Although the current study has, however, identified aging as a key predictor of the difference in lipid levels between premenopausal and postmenopausal women, which explains a portion of the variance (9.71%-40.08%), there are other possible genetic and environmental factors that may account for the remaining variance and inconsistencies between estimates. For example, a longitudinal study revealed that lipid profiles fluctuated in premenopausal women depending on the stage of their menstrual cycle, with the follicular phase (indicative of high endogenous estrogen levels), associated with decreased TC, LDL, and TG.[18] Furthermore, the use of estrogen alone hormone therapy has been linked with raised HDL and lowered LDL and TC levels.[19] Taken together, these findings suggest that the decline in estrogen levels that accompany menopause may have a harmful effect on the overall lipid profile of postmenopausal women. Our previous meta-analysis, however, demonstrated that increases in fat mass between premenopausal and postmenopausal women were largely attributable to aging.[7] Therefore, it is also possible that the age-related differences in lipid profiles are linked with similar factors as those associated with increased fat mass including poor diet and low levels of physical activity. Further insights regarding the precise influence of these modifiable lifestyle factors on overall lipid changes in women around menopause will result in the development of focused and effective holistic intervention programs that seek to mitigate the identified risks for women.

Although the recommended cholesterol ranges and thresholds vary as a function of individual risk for developing lipid-related disorders, the recommended LDL levels are less than 3.36 mmol/L for individuals with moderate coronary heart disease (CHD) risk (ie, a clustering of two lifestyle risk factors including obesity, physical inactivity, elevated TG, low HDL cholesterol, or metabolic syndrome).[20] In this study, it is important to note that the mean LDL cholesterol

level for premenopausal women is 2.90 mmol/L, whereas postmenopausal women are above the recommended levels (3.46 mmol/L) for individuals with moderate CHD risk. This suggests that postmenopausal women who have a clustering of risk factors for CHD should be especially observant to differences in cholesterol after menopause, given that an unfavorable lipid profile develops at this time. Interestingly, although some studies report that HDL levels decrease after menopause onset,[2] the current review aligns with studies that suggest that HDL levels remain unchanged.[21,22]

Strengths and limitations

A key strength of the present study was that a large number of individuals were included in the analyses, resulting in a comprehensive assessment of lipid profile differences between premenopausal and postmenopausal women. Specifically, 66 cross-sectional studies were included in the meta-analyses, which provided a total sample of 114,655 women consisting of 68,394 that were premenopausal and 46,261 that were postmenopausal. Furthermore, as far as we are aware, this review is the first to provide precise quantitative estimates about lipid profile differences between premenopausal and postmenopausal women.

Notable limitations included the fact that there were insufficient longitudinal studies available for meta-analyses. Furthermore, the literature was not systematically reviewed before conducting the meta-analyses, which increased the possibility of publication bias in reported findings. Publication bias analyses were, however, conducted and revealed only small differences between actual and reported estimates, which did not change the relationship or significance of the results.

Future directions

Given the heterogeneity of findings and that a large amount of unexplained variance remains to be investigated, future systematic reviews should investigate the role of moderators on cholesterol changes in women, including age of menopause onset, ethnicity, physical activity levels, genetic factors, diet, obesity, and hormone therapy use. Once identified, the extent to which potential risk factors contribute to deleterious lipid profile changes should be precisely quantified and ranked in order of influence/weight and potential for modification, such that informed intervention programs, which seek to mitigate the identified risks for women and ensure that lipid levels are kept in the normal range, can be effectively developed. In addition, more longitudinal studies that investigate changes in lipid levels as women progress from premenopausal to postmenopausal states are required so that additional insights can be provided regarding changes that occur during perimenopause.

CONCLUSIONS

The current analyses revealed that postmenopausal women develop an unfavorable lipid profile compared to premenopausal women, which is partly attributed to mean age differences between these groups. These findings are important as they provide precise estimates of lipid changes in women around menopause. Furthermore the results suggest that particular attention should be paid to differences in lipid levels after menopause due to the development of an unfavorable lipid profile that can increase the risk of cardiovascular disease such as heart disease and stroke if appropriate lifestyle/pharmacological interventions are not implemented.

REFERENCES

1. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97:1159-1168.
2. Jensen J, Nilas L, Christiansen C. Influence of menopause on serum lipids and lipoproteins. *Maturitas* 1990;12:321-331.
3. Derby CA, Crawford SL, Pasternak RC, Sowers M, Sternfeld B, Matthews KA. Lipid changes during the menopause transition in relation to age and weight the study of women's health across the nation. *Am J Epidemiol* 2009;169:1352-1361.
4. Gaspard UJ, Gottal J-M, Van den Brûle FA. Postmenopausal changes of lipid and glucose metabolism: a review of their main aspects. *Maturitas* 1995;21:171-178.
5. Carr MC. The emergence of the metabolic syndrome with menopause. *J Clin Endocrinol Metab* 2003;88:2404-2411.
6. Kolovou GD, Bilianou HG. Influence of aging and menopause on lipids and lipoproteins in women. *Angiology* 2008;59 (2_suppl):54S-57S.
7. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a meta-analysis. *Am J Obstet Gynecol* 2019; pii: S0002-9378(19)30588-5. doi: 10.1016/j.ajog.2019.04.023.
8. Hodson L, Banerjee R, Rial B, et al. Menopausal status and abdominal obesity are significant determinants of hepatic lipid metabolism in women. *J Am Heart Assoc* 2015;4:e002258.
9. R Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria: R Foundation for Statistical Computing. 2017.
10. RStudio Team. RStudio: Integrated Development for R. Boston, MA: RStudio, Inc; 2015; 42. Available at: http://wwwrstudiocom. Accessed February 14, 2018.
11. Viechtbauer W. Conducting meta-analyses in R with the metafor. *J Stat Softw* 2010;36:1-48.
12. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010;1:97-111.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
14. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.
15. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 2000;56:455-463.
16. Duval S, Tweedie R. A nonparametric ''trim and fill'' method of accounting for publication bias in meta-analysis. *J Am Stat Assoc* 2000;95:89-98.
17. Siervogel RM, Wisemandle W, Maynard LM, et al. Serial changes in body composition throughout adulthood and their relationships to changes in lipid and lipoprotein levels: The Fels Longitudinal Study. *Arter Thromb Vasc Biol* 1998;18:1759-1764.
18. Gaskins AJ, Zhang C, Perkins NJ, et al. A longitudinal study of serum lipoproteins in relation to endogenous reproductive hormones during the menstrual cycle: findings from the BioCycle study. *J Clin Endocrinol Metab* 2010;95:E80-E85.
19. Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974-2000. *Fertil Steril* 2001;75:898-915.
20. Grundy SM, Cleeman JI, Bairey Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol* 2004;44:720-732.
21. Zhou J-L, Lin S-Q, Shen Y, Chen Y, Zhang Y, Chen F-L. Serum lipid profile changes during the menopausal transition in Chinese women: a community-based cohort study. *Menopause* 2010;17:997-1003.
22. Fukami K, Koike K, Hirota K, Yoshikawa H, Miyake A. Perimenopausal changes in serum lipids and lipoproteins: a 7-year longitudinal study. *Maturitas* 1995;22:193-197.

A review of menopause nomenclature

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REVIEW Open Access

A review of menopause nomenclature

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Abstract

Menopause nomenclature varies in the scholarly literature making synthesis and interpretation of research findings difficult. Therefore, the present study aimed to review and discuss critical developments in menopause nomenclature; determine the level of heterogeneity amongst menopause definitions and compare them with the Stages of Reproductive Aging Workshop criteria. Definitions/criteria used to characterise premenopausal and postmenopausal status were extracted from 210 studies and 128 of these studies were included in the final analyses. The main findings were that 39.84% of included studies were consistent with STRAW classification of *premenopause*, whereas 70.31% were consistent with STRAW classification of *postmenopause*. Surprisingly, major inconsistencies relating to premenopause definition were due to a total lack of reporting of any definitions/criteria for premenopause (39.84% of studies). In contrast, only 20.31% did not report definitions/criteria for postmenopause. The present findings indicate that there is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. We propose three key suggestions/recommendations, which can be distilled from these findings. Firstly, premenopause should be transparently operationalised and reported. Secondly, as a minimum requirement, regular menstruation should be defined as the number of menstrual cycles in a period of at least 3 months. Finally, the utility of introducing normative age-ranges as supplementary criterion for defining stages of reproductive ageing should be considered. The use of consistent terminology in research will enhance our capacity to compare results from different studies and more effectively investigate issues related to women's health and ageing.

Plain Language Summary

The meaning of *menopause* is widely understood, but often imprecisely defined in research. The present findings revealed that there is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. Three key suggestions/recommendations can be distilled from these findings. Firstly, premenopause should be transparently operationalised and reported. Secondly, as a minimum requirement, regular menstruation should be defined as the number of menstrual cycles in a period of at least 3 months. Finally, the utility of introducing normative age-ranges as supplementary criterion for defining stages of reproductive ageing should be considered. The use of consistent terminology in research will enhance our capacity to compare results from different studies and more effectively investigate issues related to women's health and ageing.

Keywords: Menopause, Nomenclature, STRAW, WHO

Introduction

Menopause is a critical stage of female reproductive ageing and health, with important implications relating to fat mass and its distribution [1], dyslipidemia [2] and neurodegeneration [3, 4]. In this context, it is likely that some of the biological changes co-occurring with menopause, contribute to the well-documented higher risk of

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dementia in women [5], as well as the observed increase in cardiovascular disease whose pattern becomes more similar to that of men at older ages despite its lower prevalence at younger ages [6, 7]. However, the contributions of menopause to health have been historically understudied in the context of ageing [8]. For example, over a period of 23 years (1995–2017), peer-reviewed neuroimaging articles which focused on menopause only accounted for approximately 2% of the ageing literature [8]. There are many possible explanations (including sex biases in research), however, a critical challenge for menopause research has been the operationalisation of menopause nomenclature.

The meaning of *menopause* is widely understood, but often imprecisely defined in research. The standards for defining menopause nomenclature, such as *premenopause* and *postmenopause* vary substantially across publications. Although, the precise extent of this heterogeneity remains to be established—perhaps because the extant literature on this topic may be too large to systematically review—it is clear that such variability across studies makes the synthesis and comparison of findings difficult. In recognition of this issue, there have been a number of attempts by international experts to collaboratively develop a comprehensive standardised set of criteria to describe terminology associated with menopause [9–14]. Whilst promising developments have been made in recent decades, a follow-up investigation regarding the frequency and consistency of uptake and use of the proposed criteria have not been adequately investigated. Therefore, the degree to which standardised criteria have been successfully implemented in publications relating to menopause research remains unknown.

To address this gap we have leveraged on our recent systematic review with meta-analysis focused on fat mass differences between premenopausal and postmenopausal women, which included 210 studies consisting of 1,052,391 women, by extracting definitions used to characterise premenopausal and postmenopausal status in a broad cross-section of peer-reviewed literature [1]. The present study aims to first review and discuss critical developments in menopause nomenclature, with a particular emphasis placed on the implications that current criteria have for menopause research. Then, to assess the level of heterogeneity in menopause nomenclature identified through our previous systematic review [7]. Finally, to contrast the extracted definitions against the Stages of Reproductive Aging Workshop (STRAW) criteria [11, 13, 14].

WHO (1981–1999)

According to the more recently established guidelines by a World Health Organization (WHO) "Scientific Group on Research in the Menopause", natural menopause is defined as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity [9, 10]. Furthermore, natural menopause is deemed to have occurred after 12 consecutive months of amenorrhea, for which no other obvious pathological or physiological causes could be determined. As seen in Fig. 1, menopause occurs at the final menstrual period (FMP), which can only be known with certainty retrospectively, a year or more after the event. Induced menopause, however, is defined as the cessation of menstruation following either surgical removal of both ovaries (i.e. oophorectomy), or iatrogenic ablation of ovarian function (i.e. chemotherapy or irradiation).

The WHO (1996) highlighted that *premenopause* was often used ambiguously by researchers, either to refer to the 1 or 2 years immediately before menopause or alternatively, to encompass the entire reproductive period up to the FMP, which was the recommended use of the term. Other critical stages defined by the WHO included *postmenopause* (i.e. the period following the FMP regardless of whether menopause was induced or spontaneous); perimenopause (i.e. the period immediately prior to the FMP when endocrinological, biological and clinical features of approaching menopause commence, as well as the first year after menopause); and the menopausal transition (i.e. the period of time before FMP, when variability

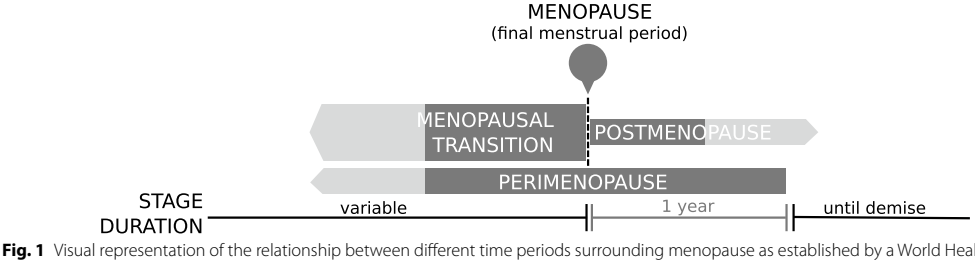

Fig. 1 Visual representation of the relationship between different time periods surrounding menopause as established by a World Health Organization Scientific Group on Research in the Menopause. Figure is a modification of work found in World Health Organization [9]

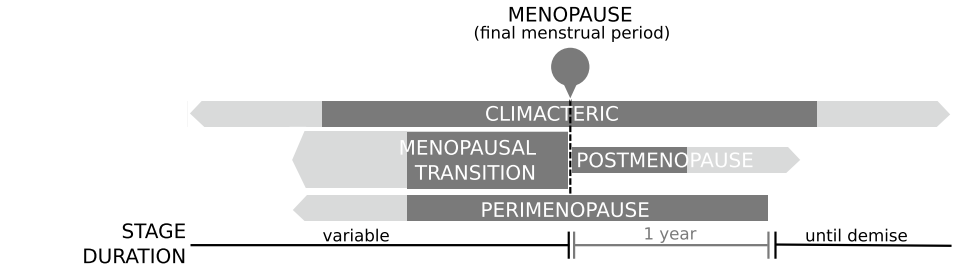

Fig. 2 Updated visual representation of the relationship between different time periods surrounding menopause, which includes the term *Climacteric* as defined by The Council of Affiliated Menopause Societies. Figure is a modification of work found in Utian [13]

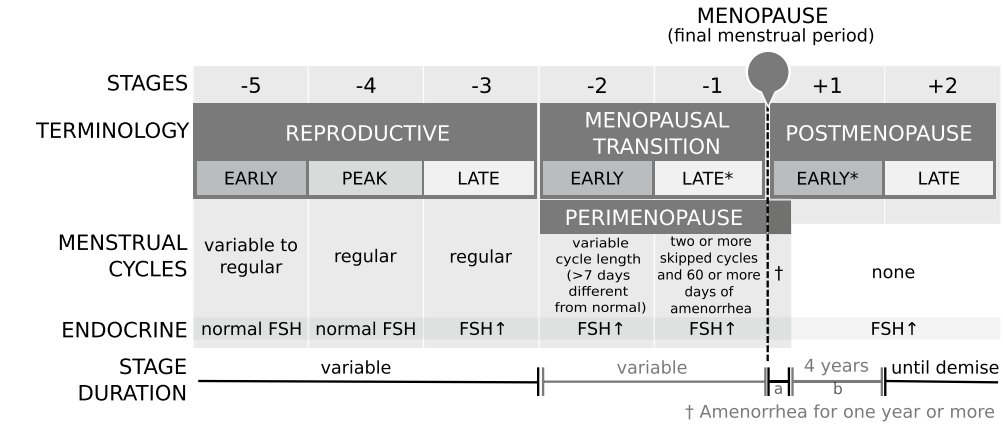

Fig. 3 STRAW staging system. *Stages most likely to be characterised by vasomotor symptoms; FSH, follicle stimulating hormone; ↑, elevated. Figure is a modification of work found in Soules et al. [14]

in the menstrual cycle is usually increased). Finally, it was strongly recommended that the term *climacteric*, which was previously used interchangeably with *perimenopause*, should be abandoned to avoid confusion. However, due to widespread popularity and the prevailing use of the word, *climacteric* was reinstated by The Council of Affiliated Menopause Societies (CAMS) in 1999 and was defined as a phase which incorporates perimenopause, but extends for a longer variable period before and after perimenopause and marks the transition from the reproductive to non-reproductive states (Fig. 2) [13].

STRAW (2001)

The nomenclature established thus far facilitated a scientific consensus for describing female reproductive ageing, however, there were still limitations that needed to be addressed. For example, the WHO and CAMS definitions had vague starting points and used terms such as premenopause, perimenopause, menopausal transition and climacteric which, to some extent, had overlapping time periods. This lack of clear, objective criteria to describe the stages of female reproductive ageing led to the Stages of Reproductive Ageing Workshop (STRAW) in 2001. The ensuing STRAW criteria separated the stages of female reproductive ageing into seven distinct segments (Fig. 3), with a particular focus on healthy women undergoing natural menopause. Furthermore, menstrual cycles, endocrine/biochemical factors, signs/symptoms in other organ systems, and uterine/ovarian anatomy were used to define the stages of female reproductive ageing.

Within the STRAW criteria, menopause is central to the staging system and was labelled as point zero (0). There are five stages preceding the FMP (−5 to −1) and two following it (+1 to+2). Stages −5 to −3 encompassed the Reproductive Interval; −2 to −1 reflected

the Menopausal Transition; and +1 to +2 defined Postmenopause [14]. The menopausal transition (−2 to −1) began with a variation in menstrual cycle length and rise in follicle stimulating hormone (FSH) and ended with the FMP. Early postmenopause (+1) was defined as within 5 years since the FMP and was further subdivided into segments 'a'; the first 12 months after the FMP and 'b'; the following 4 years. Whereas late postmenopause (+2) was defined as having a variable duration since it ended with a woman's death. Finally, the STRAW criteria defined perimenopause (−2 to +1a) as ending 12 months after the FMP. Furthermore, it was suggested that the terms perimenopause and climacteric should be synonymous in meaning and used with patients or the public, but not in scientific papers, in accordance with the WHO recommendations.

Importantly, the validity and reliability of the STRAW recommendations has been evaluated and was broadly supported by the ReSTAGE Collaboration, which conducted empirical analyses on four cohort studies including the TREMIN study, the Seattle Midlife Women's Health Study, the Study of Women's Health Across the Nation (SWAN) and the Melbourne Women's Midlife Health Project [12, 15, 16]. However, particular limitations have also been noted and modifications to the STRAW criteria were suggested by the ReSTAGE collaboration. In particular, when the STRAW criteria were first established, there was a lack of multiethnic cohort studies available, which limited the generalisability of the staging system to diverse populations [11]. Furthermore, the initial STRAW criteria only considered FSH as a biomarker, with relatively little clarification about the precise timing of change in FSH levels or quantitative criteria for FSH, due to insufficient data [11]. As a result, the initial STRAW criteria focused primarily on menstrual bleeding patterns and qualitative FSH levels. Other important limitations of the original STRAW criteria included their exclusive applicability to healthy women, with explicit recommendations against applying the criteria to women who either (i) smoked, (ii) had a BMI greater than 30 kg/m^2 or less than 18 kg/m^2, (iii) engaged in heavy exercise (greater than 10 h per week of aerobic exercise), (iv) had chronic menstrual cycle irregularity, (v) had a prior hysterectomy, (vi) had abnormal uterine anatomy (e.g. fibroids) or (vii) had abnormal ovarian anatomy (e.g. endometrioma).

STRAW + 10 (2011)

In 2011, the STRAW + 10 criteria [11] were established to reflect significant advances in the field of female reproductive ageing and to provide updated recommendations that addressed certain limitations present in the initial staging criteria.

The STRAW + 10 staging system suggested that the late reproductive stage (−3) should be subdivided into two stages (−3b and −3a) based on menstrual cycle characteristics and FSH levels (Fig. 4). This was done to recognise subtle changes in menstrual cycle flow and also shorter cycle lengths in stage −3a, in addition to an increased variability in FSH levels [11]. Secondly, the new recommendations incorporated the suggestions provided by the ReSTAGE Collaboration, which proposed that more precise menstrual cycle criteria should be used to describe the early (−2) and late (−1) menopausal transition, in addition to the quantification of FSH levels in late menopausal transition [4]. Specifically, the early menopausal transition (−2) was discernible from the late reproductive stage (−3a) due to an increased variability in menstrual cycle length (defined as a difference of 7 days or more in length of a menstrual cycle that is persistent i.e. reoccurs within 10 cycles of the first variable length cycle). Furthermore, late menopausal transition (−1) was marked by an interval of amenorrhea greater or equal to 60 days, in addition to an increased FSH level greater than 25 IU/L [11, 12]. Finally, early postmenopause (+1) was further subdivided into three stages (+1a, +1b, +1c) to account for the continual increase in FSH and decrease in estradiol for 2 years after FMP, whereby +1a corresponded with 12 months after FMP i.e. end of perimenopause and +1b referred to the year prior to the stabilisation of high FSH and low estradiol levels (+1c).

The STRAW + 10 staging system has been found to be applicable to most women regardless of age, demographic, body mass index (BMI) or lifestyle characteristics [11]. However there are still significant areas of scientific research that need to be prioritised to strengthen future criteria including (i) the use of standardised assays for key biomarkers (e.g. Anti-Mullerian hormone), (ii) further empirical analysis across multiple cohorts to specify menstrual cycle criteria for the late reproductive stage, and (iii) further research aimed at better understanding reproductive ageing in women who have had either the removal of a single ovary and/or a hysterectomy, chronic illness such as HIV infection, cancer treatment, polycystic ovary syndrome or premature ovarian failure [11]. Another critical limitation of the STRAW + 10 criteria is that they do not apply to women who are using exogenous hormones, such as hormone replacement therapy (HRT). Likely because HRT use may confound the accurate classification of women into distinct reproductive stages. This is a key consideration that needs to be appropriately accounted for in studies that are interested in investigating varying outcomes in women at different stages of reproductive ageing.

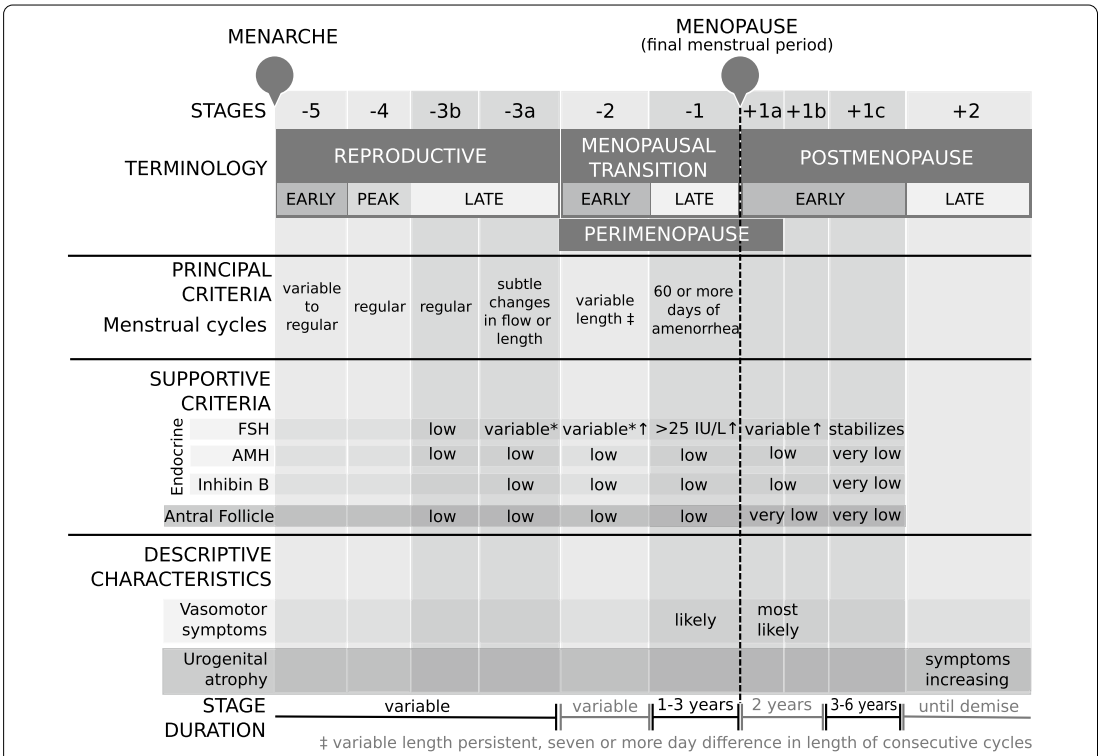

Fig. 4 STRAW + 10 staging system. *, blood drawn on cycle days 2–5; FSH, follicle stimulating hormone; AMH, anti-mullerian hormone; ↑, elevated. Figure is a modification of work found in Harlow et al. [11]

Despite these limitations, the STRAW criteria has significantly advanced our understanding of women's health and is widely considered the current gold standard for defining terms related to female reproductive ageing. However, the uptake and use of the STRAW criteria in publications relating to menopause research remains unknown and is addressed next.

Methods

The definitions of premenopausal and postmenopausal women were extracted from the 210 studies (Additional file 1: Table 1, Additional file 2: Table 2) [17–134, 134–168, 168–225, 236] that were eligible for inclusion in the meta-analysis from a previous systematic review, which aimed to identify all peer-reviewed articles reporting on changes in fat mass around menopause [1]. Given that the focus of the present study is the relationship between definitions used in the current literature and the STRAW criteria, only studies published 4 years after the establishment of the STRAW criteria in 2001 (i.e. 2005 onwards) have been included in the analysis. The 4-year lag time was implemented to conservatively account for the 'study inception to publication' timeframe, which may have limited the ability for certain studies published between 2001 and 2005 to effectively implement the STRAW criteria. Similarly, longitudinal studies, which had baseline assessments prior to 2005, were excluded. Therefore, 128 studies were included in the final analyses.

Protocol and registration

The methodology of the initial meta-analyses is reported elsewhere in detail [1] and was pre-registered in the PROSPERO database (CRD42018100643), which can be accessed online (http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018100643).

Search string

The PubMed database was used to conduct a systematic search and retrieve all studies that reported fat mass differences in quantity or distribution between premenopausal and postmenopausal women. The following search string was used: ("adipose tissue" OR "adiposity"

OR "subcutaneous fat" OR "obesity" OR "overweight" OR "body weight" OR "body fat distribution" OR "body mass index" OR "BMI" OR "DEXA" OR "DXA" OR "dual energy x-ray absorptiometry" OR "waist to hip ratio" OR "waist-hip ratio" OR "waist circumference" OR "x-ray computed tomography" OR "computed tomography" OR "CT scan" OR "caliper" OR "skinfold" OR "skin fold" OR "abdominal MRI" OR "abdominal magnetic resonance imaging" OR "intra-abdominal fat") AND ("menarche" OR "pre-menopause" OR "premenopause" OR "pre-menopausal" OR "premenopausal" OR "reproductive" OR "menopausal transition") AND ("post-menopause" OR "postmenopause" OR "post-menopausal" OR "postmenopausal" OR "non-reproductive"). PubMed filters were used to exclude non-human and non-English studies. No time restrictions were applied to the literature search, which was conducted in May 2018.

Inclusion and exclusion criteria

Studies that investigated both healthy premenopausal and healthy postmenopausal women were included, whereas studies that (i) exclusively investigated clinical/pathophysiological populations or (ii) had fewer than 40 participants were excluded.

Data extraction

Available definitions/criteria used to describe premenopausal and postmenopausal women were extracted from each study. Where data was missing or unclear, authors were contacted via email to obtain relevant information. All data from included articles was double extracted by two authors (AA and EW) to avoid transcription errors with any disagreement resolved by consensus.

Quality assessment

The quality of included studies was independently assessed by two authors (AA and EW), using an adapted version of the Newcastle–Ottawa Scale (NOS) [226]. More information on the quality of included studies can be found in our recent systematic review with meta-analysis [1]. In short, the NOS for cohort studies utilised three categories to evaluate individual study quality including (1) the selection of participants, (2) the comparability of groups and (3) the assessment/ascertainment of the outcome of interest. Notably, a clear definition of premenopausal and postmenopausal women was included as a criterion when assessing study quality, specifically for the comparability of groups. Any discrepancy in quality assessment was resolved by consensus. If consensus decisions were not possible a third rater was used.

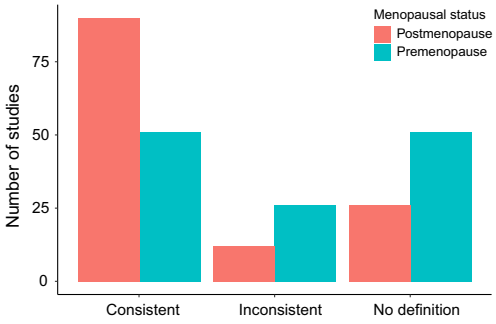

Fig. 5 Consistency of definitions with STRAW criteria

Results

The raw extracted definitions for studies are presented in Additional file 1: Table 1 and Additional file 2: Table 2. The consistency of definitions with STRAW criteria for included studies is presented in Fig. 5.

Premenopausal women

Cycle regularity

A total of 41 studies included the criterion *regular menstruation*, three included *regular menstruation in the last 5 years*, 1 included *regular menstruation in the past 2 years* and 1 included *regular menstruation in the past year*. Therefore, 46 studies (35.94%) were consistent with STRAW classification of premenopause, based on menstrual cycles.

Two studies used *still cycling*, 2 used *no increase in cycle irregularity* and 2 used *no change in flow* when characterising premenopausal women. Cycle regularity was further quantified by the use of cycles per month(s) or cycles per year(s). Three studies included the criteria *one menstruation in the past 33 days*, 2 included *two menstruations in the last 3 months*, 1 included *at least one menstruation in the last 3 months*, 1 included *11–13 cycles per year*, 1 included *8 menses in the last year*, 2 included *one menstrual cycle in the last 12 months* and 1 included *one menstrual cycle in the last 2 years*. One study identified premenopause as *the whole reproductive period up until menopause*.

Hormone levels

Six studies 4.69% used FSH levels as one of the criteria, consistent with STRAW classification of premenopause, based on hormone levels. Of these 6 studies, 1 used *regular menstruation* as an additional criterion, whereas the other 5 attempted to quantify cycle regularity. The threshold for FSH levels ranged from less than 20 IU/L to less than 40 IU/L.

Age

Four studies included women over a specific age ranging from 40 to 44. However all 4 studies also included other subcategories such as *regular menstruation*. Two studies used age brackets that included *25–45*, and *45–55*. Ten studies included women who were less than a specific age, which ranged from 35 to 55 years. Of these 3 studies used *age* as the only criterion to define premenopause. One study included *age* as a subcategory of their definition, however, did not define it precisely.

Not postmenopausal or pregnant

Five studies included *no criteria for postmenopause*, 4 included *no symptoms of menopause*, 4 included *no climacteric complaints*, 3 included *no HRT use* and 3 included *no hysterectomy or ovaries removed* as criteria for categorising premenopause. One study used pregnancy as a criterion for defining premenopause.

No definition

Of the 128 studies included, 51 (39.84%) did not report definitions/criteria for premenopause.

Postmenopausal women

Amenorrhea or the final menstrual period (FMP)

Eighty studies included the criterion *at least 12 months of amenorrhea*, 1 included *less than 2 years from the FMP*, 1 included *1–5 years since the FMP*, 1 included *0–6 years after the FMP*, 1 included *greater than 1 but less than 7 years of amenorrhea*, 1 included *greater than 2 but less than 7 years amenorrhea* and 2 included *2 years after the FMP*. Therefore, 87 studies (67.97%) were consistent with STRAW classification of postmenopause, based on menstrual cycles.

Two studies included *at least 6 months of amenorrhea* and 1 included *at least 11 months of amenorrhea*. Three studies included the term *no menstrual cycles or periods or no menstrual bleeding* however, further detail regarding the duration of amenorrhea was not provided.

Hormone levels

Fourteen studies (10.94%) used FSH levels as a criterion, consistent with STRAW classification of postmenopause, based on hormone levels. Of these 11 studies used menstrual criteria consistent with STRAW, 2 used hormonal criterion alone and 1 included *no menstrual bleeding*. For hormone thresholds, of the 14 studies, 8 used the threshold for FSH levels *as greater than 30 IU/L* and 2 used *greater than 40 IU/L*. One study did not report FSH thresholds, whereas the remaining 3 studies had FSH levels that included *greater than 20 IU/L, greater than 55 IU/L* and *between 22 to 138 IU/L*. Two studies used estradiol levels with thresholds ranging from *less than 20 pg/mL* to *less than 50 pg/mL*. One study also used Luteinizing Hormone (LH) levels *greater than 30 IU/L*.

Natural or surgical menopause

Twelve studies specifically stated *natural menopause*, 3 stated *no surgical removal of ovaries and/or uterus* and 2 stated *not due to surgery or any other biological or physiological causes*. Twelve studies included the criteria *bilateral oophorectomy*, 2 included *hysterectomy* and 1 included *cessation of menses induced by surgery*.

Age

Twelve studies included women over a specific age, ranging from *40 to 55*. Of these 2 studies used age as the only criterion to define postmenopausal women.

Hormone replacement therapy (HRT)

Five studies included *women not taking HRT*, whereas 4 studies included *women taking HRT*, and 1 study included *women taking ovarian suppressing drugs or contraception eliminating menstruation*.

No definition

Of the 128 studies included, 26 (20.31%) did not report any definitions/criteria for postmenopause.

Discussion

To our knowledge, this review is the first to assess the uptake and use of the STRAW criteria by extracting definitions used to characterise premenopausal and postmenopausal status in a broad cross-section of peer-reviewed literature from our recent systematic review with meta-analysis [1]. The main findings were that 39.84% of included studies were consistent with STRAW classification of *premenopause*, whereas 70.31% were consistent with STRAW classification of *postmenopause* (Fig. 5). Furthermore, 39.84% did not report definitions/criteria for premenopausal women, whereas, 20.31% did not report definitions/criteria for postmenopausal women.

For menstrual cycle variability, 35.94% of studies were consistent with STRAW classification of *premenopause* and 67.97% for *postmenopause*. Notably, STRAW + 10 later distinguished menstrual cycle variability as the most important criteria for the reproductive staging system [11], which is reflective of its use in the literature. For *postmenopause*, the current results reflect a conceptualisation consistent with the STRAW criteria, which require the relationship between the FMP and start of *postmenopause* to be explicitly defined. However, this same level of consistency was not observed for *premenopause*. One possible explanation relates to the term *premenopause* not having been explicitly used in the STRAW criteria

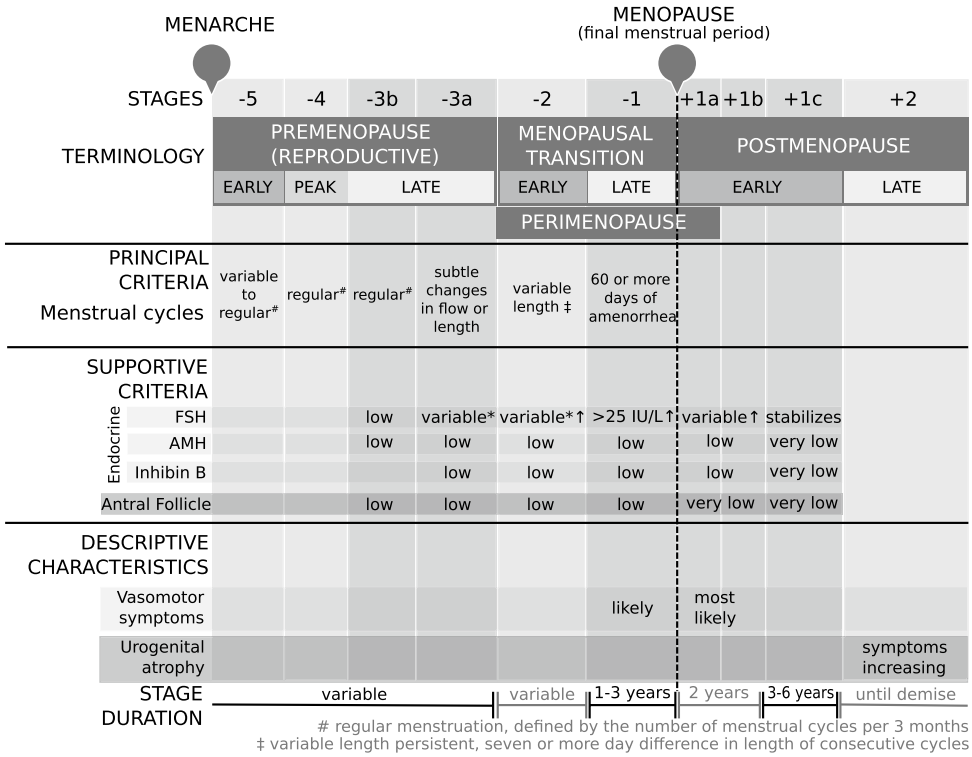

Fig. 6 Recommended revision to the STRAW + 10 staging system to include the transparent operationalisation of *premenopause* and define *regular menstruation* as the number of menstrual cycles per 3 months, as a minimum requirement, which would be a practical reporting timeframe both clinically and for women to recall accurately. *, blood drawn on cycle days 2–5; FSH, follicle stimulating hormone; AMH, anti-mullerian hormone; ↑, elevated. Figure is a modification of work found in Harlow et al. [11]

[11, 14]. Instead, it is inferred to be synonymous with *reproductive stage*. Given its wide clinical and scientific use, our recommendation is that the transparent operationalisation of *premenopause* may improve the consistency and application of the STRAW criteria (Fig. 6). Another possibility is the degree of uncertainty regarding the precise meaning of *regular menstruation*. Specifically, 14.29% of studies that defined *premenopause* attempted to quantify regular menstruation as the number of menstrual cycles per days, month(s) or year(s). This uncertainty may reflect a key limitation of the STRAW [14] and more recent STRAW + 10 [11] criteria, which principally describe the reproductive period as having *regular menstrual cycles*, with no guidelines provided regarding the interpretation of *regular*. Moreover, previous research has demonstrated the lack of clear clinical definitions for reproductive stages can significantly decrease the accuracy of participant's self-report [227]. Since menstrual cycles can be skipped due to reasons unrelated to menopause including extreme exercise, pregnancy, weight fluctuations or illness it would be highly preferable if *regular menstruation* was specifically and consistently defined for a defined period. We recommend that defining regular menstruation as the number of menstrual cycles per 3 months, as a minimum requirement, would be a practical reporting timeframe both clinically and for women to recall accurately (Fig. 6).

For hormone levels, 4.69% of studies were consistent with STRAW classification of premenopause and 10.94% for postmenopause. STRAW + 10 later distinguished hormone levels as a supportive criterion for the reproductive staging system given the lack of international standardisation of biomarker assays as well as their cost and/or invasiveness and inequity across low-socioeconomic countries [11]. Notably, Anti-Mullerian hormone (AMH) has emerged as a primary candidate for developing an international standard biomarker since it is detectable in peripheral circulation [228] and does

not change in response to an acute endogenous rise in hormones such as FSH and estrogen [229–231]. Whilst promising, insights about staging reproductive ageing can also be drawn from research that aims to predict age of menopause. Unsurprisingly, age is a useful predictor of menopausal status [232], given ageing and menopause co-occur [233]. However, evidence suggests that the combination of hormones, such as AMH and age does not provide a statistically significant improvement to predictions of time to menopause than age alone (Age C-statistic = 84%, 95% CI 83–86%; Age + AMH C-statistic = 86%, 95% CI 85–87%) [232]. These findings indicate that there is utility in introducing normative age-ranges as a supplementary criterion for defining stages of reproductive ageing. Compared with the establishment of standardised biomarker assays, the use of normative age-ranges can be done relatively quickly and reliably, using available evidence from multiple large population studies, such as the UK Biobank study [234]. This need is recognised by the number of studies in this review with a definition that has attempted to use age to further clarify menopausal status (Premenopause: 19.48%; Postmenopause: 11.76%). Moreover, the use of age as an additional component of the supportive criteria for determining reproductive stage becomes further evident when women who use HRT or suffer from chronic illness are considered. For example, a systematic review with meta-analysis of randomised controlled trials showed that the incidence of chemotherapy induced amenorrhea is 61% (95% CI 51–68%) for women with breast cancer [235]. For these women, the current use of principal criteria, which relies solely on menstrual cycles, is inadequate. This emphasises the urgent need to expand the supportive criteria to ensure STRAW + 10 can be utilised by women using HRT or suffering from chronic illness that impacts menstrual cycles.

Altogether, 33.77% of studies that defined premenopause and 11.76% of studies that defined postmenopause used criteria inconsistent with STRAW criteria. The disproportionate use of additional criteria for defining *premenopause* compared with *postmenopause* is further indication that the term *premenopause* is not precisely and systematically defined by the STRAW criteria. This has prompted researchers to use additional/alternative criteria to achieve clarity. Unfortunately, the consequence of non-standardised criteria is increased heterogeneity, which can lead to the synthesis of imprecise estimates. Moreover, of the 128 included studies, 39.84% did not report definitions/criteria for premenopausal women, whereas, only 20.31% did not report definitions/criteria for postmenopausal women. This difference may reflect a belief that the definition/criteria for premenopausal women is widely understood, with no need for further clarification by authors. However, in the context of the findings presented in this review, it is more likely these trends reflect a poor understanding of the term *premenopause* compared with *postmenopause*.

Conclusion

There is a significant amount of heterogeneity associated with the definition of *premenopause*, compared with *postmenopause*. We propose three key suggestions/recommendations, which can be distilled from these findings. Firstly, premenopause, which is not currently explicitly stated in STRAW or STRAW + 10, should be transparently operationalised and reported. Secondly, as a minimum requirement, regular menstruation should be defined as the number of menstrual cycles in a period of at least 3 months. Finally, the utility of introducing normative age-ranges as supplementary criterion for defining stages of reproductive ageing should be considered. The use of consistent terminology in research will enhance our capacity to compare results from different studies and more effectively investigate issues related to women's health and ageing.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-022-01336-7.

Additional file 1: Table 1. Premenopause definition.

Additional file 2: Table 2. Postmenopause definition.

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Author contributions
AA contributed to the design of the study, data screening and extraction and managed all aspects of manuscript preparation and submission. EW contributed to data screening, data extraction and editing of the manuscript. NC contributed to the design of the study, data screening, provided methodological input, theoretical expertise and contributed to the editing of the manuscript. All authors meet the criteria for authorship. AA is the guarantor for this study. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publications
Not applicable.

Competing interests
All authors report no competing interests.

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References

1. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. Am J Obstet Gynecol. 2019;221:393-409.e50.
2. Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis. Menopause. 2019. https://doi.org/10.1097/GME.0000000000001403.
3. Ambikairajah A, Tabatabaei-Jafari H, Walsh E, Hornberger M, Cherbuin N. Longitudinal changes in fat mass and the hippocampus. Obesity. 2020;28:1263–9.
4. Ambikairajah A, Tabatabaei-Jafari H, Hornberger M, Cherbuin N. Age, menstruation history, and the brain. Menopause. 2021;28:167–74.
5. GBD 2019 Collaborators. Global mortality from dementia: application of a new method and results from the Global Burden of Disease Study 2019. Alzheimer's Dement. 2021;7:e12200.
6. Mikkola TS, Gissler M, Merikukka M, Tuomikoski P, Ylikorkala O. Sex differences in age-related cardiovascular mortality. PLoS ONE. 2013;8:e63347.
7. McAloon CJ, Boylan LM, Hamborg T. The changing face of cardiovascular disease 2000: an analysis of the world health organisation global health estimates data. Int J Cardiol. 2016;224:256–64.
8. Taylor CM, Pritschet L, Yu S, Jacobs EG. Applying a women's health lens to the study of the aging brain. Front Hum Neurosci. 2019. https://doi.org/10.3389/fnhum.2019.00224.
9. World Health Organization. Research on the menopause in the 1990s: report of a WHO scientific group. Geneva: World Health Organization; 1996.
10. World Health Organization. Research on the menopause: report of a WHO scientific group [meeting held in Geneva from 8 to 12]. Geneva: World Health Organization; 1980.
11. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J Clin Endocrinol Metab. 2012;97:1159–68.
12. Harlow SD, Crawford S, Dennerstein L, Burger HG, Mitchell ES, Sowers M-F, et al. Recommendations from a multi-study evaluation of proposed criteria for staging reproductive aging. Climacteric. 2007;10:112–9.
13. Utian WH. The international menopause menopause-related terminology definitions. Climacteric. 1999;2:284–6.
14. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: stages of reproductive aging workshop (STRAW). Climacteric. 2001;4:267–72.
15. Harlow SD, Cain K, Crawford S, Dennerstein L, Little R, Mitchell ES, et al. Evaluation of four proposed bleeding criteria for the onset of late menopausal transition. J Clin Endocrinol Metab. 2006;91:3432–8.
16. Harlow SD, Mitchell ES, Crawford S, Nan B, Little R, Taffe J. The ReSTAGE Collaboration: defining optimal bleeding criteria for onset of early menopausal transition. Fertil Steril. 2008;89:129–40.
17. Abate M, Schiavone C, Di Carlo L, Salini V. Prevalence of and risk factors for asymptomatic rotator cuff tears in postmenopausal women. Menopause. 2014;21:275–80.
18. Abdulnour J, Doucet E, Brochu M. The effect of the menopausal transition on body composition and cardiometabolic risk factors: a Montreal–Ottawa New Emerging Team group study. Menopause. 2012. https://doi.org/10.1097/gme.0b013e318240f6f3.
19. Abildgaard J, Pedersen AT, Green CJ. Menopause is associated with decreased whole body fat oxidation during exercise. Am J Physiol Endocrinol Metab. 2013;304:E1227–36.
20. Adams-Campbell LL, Kim KS, Dunston G, Laing AE, Bonney G, Demenais F. The relationship of body mass index to reproductive factors in pre- and postmenopausal African-American women with and without breast cancer. Obes Res. 1996;4:451–6.
21. Agrinier N, Cournot M, Dallongeville J. Menopause and modifiable coronary heart disease risk factors: a population based study. Maturitas. 2010;65:237–43.
22. Aguado F, Revilla M, Hernandez ER, Villa LF, Rico H. Behavior of bone mass measurements. Dual energy x-ray absorptiometry total body bone mineral content, ultrasound bone velocity, and computed metacarpal radiogrammetry, with age, gonadal status, and weight in healthy women. Invest Radiol. 1996;31:218–22.
23. Albanese CV, Cepollaro C, Terlizzi F, Brandi ML, Passariello R. Performance of five phalangeal QUS parameters in the evaluation of gonadal-status, age and vertebral fracture risk compared with DXA. Ultrasound Med Biol. 2009;35:537–44.
24. Allali F, El Mansouri L, Abourazzak F. The effect of past use of oral contraceptive on bone mineral density, bone biochemical markers and muscle strength in healthy pre and post menopausal women. BMC Women's Health. 2009. https://doi.org/10.1186/1472-6874-9-31.
25. Aloia JF, Vaswani A, Ma R, Flaster E. To what extent is bone mass determined by fat-free or fat mass? Am J Clin Nutr. 1995;61:1110–4.
26. Amankwah EK, Friedenreich CM, Magliocco AM. Anthropometric measures and the risk of endometrial cancer, overall and by tumor microsatellite status and histological subtype. Am J Epidemiol. 2013;177:1378–87.
27. Amarante F, Vilodre LC, Maturana MA, Spritzer PM. Women with primary ovarian insufficiency have lower bone mineral density. Braz J Med Biol Res. 2011;44:78–83.
28. Amiri P, Deihim T, Nakhoda K, Hasheminia M, Montazeri A, Azizi F. Metabolic syndrome and health-related quality of life in reproductive age and post-menopausal women: Tehran Lipid and Glucose Study. Arch Iran Med. 2014;17:423–8.
29. Angsuwathana S, Leerasiri P, Rattanachaiyanont M. Health check-up program for pre/postmenopausal women at Siriraj Menopause Clinic. J Med Assoc Thai. 2007;90:1–8.
30. Armellini F, Zamboni M, Perdichizzi G. Computed tomography visceral adipose tissue volume measurements of Italians. Predictive equations. Eur J Clin Nutr. 1996;50:290–4.
31. Arthur FK, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. The prevalence of metabolic syndrome and its predominant components among pre-and postmenopausal Ghanaian women. BMC Res Notes. 2013. https://doi.org/10.1186/1756-0500-6-446.
32. Aydin ZD. Determinants of age at natural menopause in the Isparta Menopause and Health Study: premenopausal body mass index gain rate and episodic weight loss. Menopause. 2010. https://doi.org/10.1097/gme.0b013e3181c73093.
33. Ayub N, Khan SR, Syed F. Leptin levels in pre and post menopausal Pakistani women. JPMA. 2006;56:3–5.
34. Bancroft J, Cawood EH. Androgens and the menopause; a study of 40–60-year-old women. Clin Endocrinol. 1996;45:577–87.
35. Bednarek-Tupikowska G, Filus A, Kuliczkowska-Plaksej J, Tupikowski K, Bohdanowicz-Pawlak A, Milewicz A. Serum leptin concentrations in pre- and postmenopausal women on sex hormone therapy. Gynecol Endocrinol. 2006;22:207–12.
36. Bell RJ, Davison SL, Papalia M-A, McKenzie DP, Davis SR. Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. Menopause. 2007;14:630–8.
37. Ben Ali S, Jemaa R, Ftouhi B, Kallel A, Feki M, Slimene H, et al. Relationship of plasma leptin and adiponectin concentrations with menopausal status in Tunisian women. Cytokine. 2011;56:338–42.
38. Ben Ali S, Belfki-Benali H, Aounallah-Skhiri H, Traissac P, Maire B, Delpeuch F, et al. Menopause and metabolic syndrome in Tunisian women. BioMed Res Int. 2014;2014:e457131.
39. Ben Ali S, Belfki-Benali H, Ahmed DB, Haddad N, Jmal A, Abdennebi M, et al. Postmenopausal hypertension, abdominal obesity, apolipoprotein and insulin resistance. Clin Exp Hypertens. 2016;38:370–4.
40. Berg G, Mesch V, Boero L. Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. Horm Metab Res. 2004;36:215–20.
41. Berge LN, Bonaa KH, Nordoy A. Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. Arterioscler Thromb. 1994;14:857–61.

42. Berger GM, Naidoo J, Gounden N, Gouws E. Marked hyperinsulinaemia in postmenopausal, healthy Indian (Asian) women. Diabet Med. 1995;12:788–95.
43. Berstad P, Coates RJ, Bernstein L. A case-control study of body mass index and breast cancer risk in white and African-American women. Cancer Epidemiol Biomark Prev. 2010;19:1532–44.
44. Bhagat M, Mukherjee S, De P. Clustering of cardiometabolic risk factors in Asian Indian women: Santiniketan women study. Menopause. 2010. https://doi.org/10.1097/gme.0b013e3181bfac28.
45. Bhurosy T, Jeewon R. Food habits, socioeconomic status and body mass index among premenopausal and post-menopausal women in Mauritius. J Hum Nutr Diet. 2013;1:114–22.
46. Blumenthal JA, Fredrikson M, Matthews KA. Stress reactivity and exercise training in premenopausal and postmenopausal women. Health Psychol. 1991;10:384–91.
47. Bonithon-Kopp C, Scarabin PY, Darne B, Malmejac A, Guize L. Menopause-related changes in lipoproteins and some other cardiovascular risk factors. Int J Epidemiol. 1990;19:42–8.
48. Caire-Juvera G, Arendell LA, Maskarinec G, Thomson CA, Chen Z. Associations between mammographic density and body composition in Hispanic and non-Hispanic white women by menopause status. Menopause. 2008. https://doi.org/10.1097/gme.0b013e3181405b8a.
49. Campesi I, Occhioni S, Tonolo G. Ageing/menopausal status in healthy women and ageing in healthy men differently affect cardiometabolic parameters. Int J Med Sci. 2016;13:124–32.
50. Carr MC, Kim KH, Zambon A. Changes in LDL density across the menopausal transition. J Invest Med. 2000;48:245–50.
51. Castracane VD, Kraemer RR, Franken MA, Kraemer GR, Gimpel T. Serum leptin concentration in women: effect of age, obesity, and estrogen administration. Fertil Steril. 1998;70:472–7.
52. Catsburg C, Kirsh VA, Soskolne CL. Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. Breast Cancer Res Treat. 2014;145:545–52.
53. Cecchini RS, Costantino JP, Cauley JA. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. Cancer Prev Res (Philadelphia, Pa). 2012;5:583–92.
54. Cervellati C, Pansini FS, Bonaccorsi G. Body mass index is a major determinant of abdominal fat accumulation in pre-, peri- and postmenopausal women. Gynecol Endocrinol. 2009;25:413–7.
55. Chain A, Crivelli M, Faerstein E, Bezerra FF. Association between fat mass and bone mineral density among Brazilian women differs by menopausal status: the Pro-Saude Study. Nutrition. 2017;33:14–9.
56. Chang CJ, Wu CH, Yao WJ, Yang YC, Wu JS, Lu FH. Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. Int J Obes Relat Metab Disord. 2000;24:1699–704.
57. Cho GJ, Lee JH, Park HT. Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. Menopause. 2008. https://doi.org/10.1097/gme.0b013e3181559860.
58. Cifkova R, Pitha J, Lejskova M, Lanska V, Zecova S. Blood pressure around the menopause: a population study. J Hypertens. 2008;26:1976–82.
59. Copeland AL, Martin PD, Geiselman PJ, Rash CJ, Kendzor DE. Predictors of pretreatment attrition from smoking cessation among pre- and postmenopausal, weight-concerned women. Eat Behav. 2006;7:243–51.
60. Cremonini E, Bonaccorsi G, Bergamini CM. Metabolic transitions at menopause: in post-menopausal women the increase in serum uric acid correlates with abdominal adiposity as assessed by DXA. Maturitas. 2013;75:62–6.
61. Cui LH, Shin MH, Kweon SS. Relative contribution of body composition to bone mineral density at different sites in men and women of South Korea. J Bone Miner Metab. 2007;25:165–71.
62. da Câmara SM, Zunzunegui MV, Pirkle C, Moreira MA, Maciel ÁC. Menopausal status and physical performance in middle aged women: a cross-sectional community-based study in Northeast Brazil. PLoS ONE. 2015;10:e0119480.
63. Dallongeville J, Marecaux N, Isorez D, Zylbergberg G, Fruchart JC, Amouyel P. Multiple coronary heart disease risk factors are associated with menopause and influenced by substitutive hormonal therapy in a cohort of French women. Atherosclerosis. 1995;118:123–33.
64. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea. Chest. 2001;120:151–5.
65. Davis CE, Pajak A, Rywik S. Natural menopause and cardiovascular disease risk factors. The Poland and US Collaborative Study on Cardiovascular Disease Epidemiology. Ann Epidemiol. 1994;4:445–8.
66. De Kat AC, Dam V, Onland-Moret NC, Eijkemans MJC, Broekmans FJM, Van Der Schouw YT. Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. BMC Med. 2017;15:2.
67. den Tonkelaar I, Seidell JC, van Noord PA, Baanders-van Halewijn EA, Ouwehand IJ. Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: a cross-sectional study in 11,825 Dutch women participating in the DOM-project. Int J Obes. 1990;14:753–61.
68. D'Haeseleer E, Depypere H, Claeys S, Van Lierde KM. The relation between body mass index and speaking fundamental frequency in premenopausal and postmenopausal women. Menopause. 2011. https://doi.org/10.1097/gme.0b013e31820612d5.
69. Dmitruk A, Czeczelewski J, Czeczelewska E, Golach J, Parnicka U. Body composition and fatty tissue distribution in women with various menstrual status. Roczniki Panstwowego Zakladu Higieny. 2018;69:95–101.
70. Donato GB, Fuchs SC, Oppermann K, Bastos C, Spritzer PM. Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause. 2006. https://doi.org/10.1097/01.gme.0000177907.32634.ae.
71. Douchi T, Oki T, Nakamura S, Ijuin H, Yamamoto S, Nagata Y. The effect of body composition on bone density in pre- and postmenopausal women. Maturitas. 1997;27:55–60.
72. Douchi T, Yamamoto S, Yoshimitsu N, Andoh T, Matsuo T, Nagata Y. Relative contribution of aging and menopause to changes in lean and fat mass in segmental regions. Maturitas. 2002;42:301–6.
73. Douchi T, Yonehara Y, Kawamura Y, Kuwahata A, Kuwahata T, Iwamoto I. Difference in segmental lean and fat mass components between pre- and postmenopausal women. Menopause. 2007;14:875–8.
74. Dubois EF, Bergh JP, Smals AG, Meerendonk CW, Zwinderman AH, Schweitzer DH. Comparison of quantitative ultrasound parameters with dual energy X-ray absorptiometry in pre- and postmenopausal women. Neth J Med. 2001;58:62–70.
75. Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K. Population-attributable risk proportion of clinical risk factors for breast cancer. JAMA Oncol. 2017;3:1228–36.
76. Ertungealp E, Seyisoglu H, Erel CT, Senturk LM, Gezer A. Changes in bone mineral density with age, menopausal status and body mass index in Turkish women. Climacteric. 1999;2:45–51.
77. Feng Y, Hong X, Wilker E. Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. Atherosclerosis. 2008;196:590–7.
78. Formica C, Loro ML, Gilsanz V, Seeman E. Inhomogeneity in body fat distribution may result in inaccuracy in the measurement of vertebral bone mass. J Bone Miner Res. 1995;10:1504–11.
79. Friedenreich CM, Courneya KS, Bryant HE. Case–control study of anthropometric measures and breast cancer risk. Int J Cancer. 2002;99:445–52.
80. Friedenreich C, Cust A, Lahmann PH. Anthropometric factors and risk of endometrial cancer: the European prospective investigation into cancer and nutrition. Cancer Causes Control. 2007;18:399–413.
81. Fu X, Ma X, Lu H, He W, Wang Z, Zhu S. Associations of fat mass and fat distribution with bone mineral density in pre- and postmenopausal Chinese women. Osteoporosis Int. 2011;22:113–9.
82. Fuh J-L, Wang S-J, Lee S-J, Lu S-R, Juang K-D. Quality of life and menopausal transition for middle-aged women on Kinmen island. Qual Life Res. 2003;12:53–61.
83. Gambacciani M, Ciaponi M, Cappagli B, Benussi C, De Simone L, Genazzani AR. Climacteric modifications in body weight and fat tissue distribution. Climacteric. 1999;2:37–44.
84. Genazzani AR, Gambacciani M. Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution. Gynecol Endocrinol. 2006;22:145–50.

85. Ghosh A. Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women. Cardiovasc J Afr. 2008;19:183–7.
86. Ghosh A, Bhagat M. Anthropometric and body composition characteristics in pre- and postmenopausal Asian Indian women: Santiniketan women study. Anthropologischer Anzeiger. 2010;68:1–10.
87. Gram IT, Funkhouser E, Tabar L. Anthropometric indices in relation to mammographic patterns among peri-menopausal women. Int J Cancer. 1997;73:323–6.
88. Guerrero RTL, Novotny R, Wilkens LR, Chong M, White KK, Shvetsov YB, et al. Risk factors for breast cancer in the breast cancer risk model study of Guam and Saipan. Cancer Epidemiol. 2017;50:221–33.
89. Guo W, Bradbury KE, Reeves GK, Key TJ. Physical activity in relation to body size and composition in women in UK Biobank. Ann Epidemiol. 2015;25:406-413.e6.
90. Gurka MJ, Vishnu A, Santen RJ, DeBoer MD. Progression of metabolic syndrome severity during the menopausal transition. J Am Heart Assoc. 2016. https://doi.org/10.1161/JAHA.116.003609.
91. Hadji P, Hars O, Bock K. The influence of menopause and body mass index on serum leptin concentrations. Eur J Endocrinol. 2000;143:55–60.
92. Hagner W, Hagner-Derengowska M, Wiacek M, Zubrzycki IZ. Changes in level of V O_{2max}, blood lipids, and waist circumference in the response to moderate endurance training as a function of ovarian aging. Menopause. 2009;16:1009–13.
93. Han D, Nie J, Bonner MR. Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. Int J Cancer. 2006;119:2931–7.
94. Harting GH, Moore CE, Mitchell R, Kappus CM. Relationship of menopausal status and exercise level to HDL-cholesterol in women. Exp Aging Res. 1984;10:13–8.
95. He L, Tang X, Li N. Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: a population-based study. Maturitas. 2012;72:132–8.
96. Hirose K, Tajima K, Hamajima N, Takezaki T, Inoue M, Kuroishi T, et al. Impact of established risk factors for breast cancer in nulligravid Japanese women. Breast Cancer. 2003;10:45.
97. Hjartaker A, Adami HO, Lund E, Weiderpass E. Body mass index and mortality in a prospectively studied cohort of Scandinavian women: the women's lifestyle and health cohort study. Eur J Epidemiol. 2005;20:747–54.
98. Ho S, Wu S, Chan S, Sham A. Menopausal transition and changes of body composition: a prospective study in Chinese perimenopausal women. Int J Obes. 2010;34(8):1265–74.
99. Hsu Y-H, Venners SA, Terwedow HA, Feng Y, Niu T, Li Z, et al. Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. Am J Clin Nutr. 2006;83:146–54.
100. Hu X, Pan X, Ma X. Contribution of a first-degree family history of diabetes to increased serum adipocyte fatty acid binding protein levels independent of body fat content and distribution. Int J Obes. 2005;40:1649–54.
101. Hunter G, Kekes-Szabo T, Treuth M, Williams M, Goran M, Pichon C. Intra-abdominal adipose tissue, physical activity and cardiovascular risk in pre- and post-menopausal women. Int J Obes Relat Metab Disord. 1996;20:860–5.
102. Iida T, Domoto T, Takigawa A. Relationships among blood leptin and adiponectin levels, fat mass, and bone mineral density in Japanese pre- and postmenopausal women. Hiroshima J Med Sci. 2011;60:71–8.
103. Ilich-Ernst J, Brownbill RA, Ludemann MA, Fu R. Critical factors for bone health in women across the age span: how important is muscle mass? Medscape Women's Health. 2002;7(3):2.
104. Ito M, Hayashi K, Uetani M, Yamada M, Ohki M, Nakamura T. Association between anthropometric measures and spinal bone mineral density. Invest Radiol. 1994;29:812–6.
105. Jaff NG, Norris SA, Snyman T, Toman M, Crowther NJ. Body composition in the Study of Women Entering and in Endocrine Transition (SWEET): a perspective of African women who have a high prevalence of obesity and HIV infection. Metabolism. 2015;64:1031–41.
106. Jasienska G, Ziomkiewicz A, Gorkiewicz M, Pajak A. Body mass, depressive symptoms and menopausal status: an examination of the "Jolly Fat" hypothesis. Women's Health Issues. 2005;15:145–51.
107. Jeenduang N, Trongsakul R, Inhongsa P, Chaidach P. The prevalence of metabolic syndrome in premenopausal and postmenopausal women in Southern Thailand. Gynecol Endocrinol. 2014;30:573–6.
108. Jeon YK, Lee JG, Kim SS. Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. Endocr J. 2011;58:87–93.
109. Jurimae J, Jurimae T. Plasma adiponectin concentration in healthy pre- and postmenopausal women: relationship with body composition, bone mineral, and metabolic variables. Am J Physiol Endocrinol Metab. 2007;293:E42–7.
110. Kadam N, Chiplonkar S, Khadilkar A, Divate U, Khadilkar V. Low bone mass in urban Indian women above 40 years of age: prevalence and risk factors. Gynecol Endocrinol. 2010;26:909–17.
111. Kang EK, Park HW, Baek S, Lim JY. The association between trunk body composition and spinal bone mineral density in Korean males versus females: a farmers' cohort for agricultural work-related musculoskeletal disorders (FARM) study. J Korean Med Sci. 2016;31:1595–603.
112. Kaufer-Horwitz M, Pelaez-Robles K, Lazzeri-Arteaga P, Goti-Rodriguez LM, Avila-Rosas H. Hypertension, overweight and abdominal adiposity in women. An analytical perspective. Arch Med Res. 2005;36:404–11.
113. Kim HM, Park J, Ryu SY, Kim J. The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001. Diabetes Care. 2007;30:701–6.
114. Kim JH, Choi HJ, Kim MJ, Shin CS, Cho NH. Fat mass is negatively associated with bone mineral content in Koreans. Osteoporos Int. 2012;23:2009–16.
115. Kim S, Lee JY, Im JA. Association between serum osteocalcin and insulin resistance in postmenopausal, but not premenopausal, women in Korea. Menopause. 2013;20:1061–6.
116. Kim YM, Kim SH, Kim S, Yoo JS, Choe EY, Won YJ. Variations in fat mass contribution to bone mineral density by gender, age, and body mass index: the Korea National Health and Nutrition Examination Survey (KNHANES) 2008. Osteoporos Int. 2016;27:2543–54.
117. Kirchengast S, Hartmann B, Huber J. Serum levels of sex hormones, thyroid hormones, growth hormone, IGF I, and cortisol and their relations to body fat distribution in healthy women dependent on their menopausal status. Z Morphol Anthropol. 1996;81:223–34.
118. Kirchengast S, Gruber D, Sator M, Huber J. Impact of the age at menarche on adult body composition in healthy pre- and postmenopausal women. Am J Phys Anthropol. 1998;105:9–20.
119. Knapp KM, Blake GM, Spector TD, Fogelman I. Multisite quantitative ultrasound: precision, age-and menopause-related changes, fracture discrimination, and T-score equivalence with dual-energy X-ray absorptiometry. Osteoporos Int. 2001;12:456–64.
120. Koh SJ, Hyun YJ, Choi SY. Influence of age and visceral fat area on plasma adiponectin concentrations in women with normal glucose tolerance. Clin Chim Acta. 2008;389:45–50.
121. Konrad T, Bär F, Schneider F. Factors influencing endothelial function in healthy pre- and post-menopausal women of the EU-RISC study. Diab Vasc Dis Res. 2011;8:229–36.
122. Kontogianni MD, Dafni UG, Routsias JG, Skopouli FN. Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women. J Bone Miner Res. 2004;19:546–51.
123. Konukoglu D, Serin O, Ercan M. Plasma leptin levels in obese and non-obese postmenopausal women before and after hormone replacement therapy. Maturitas. 2000;36:203–7.
124. Koskova I, Petrasek R, Vondra K. Weight, body composition and fat distribution of Czech women in relation with reproductive phase: a cross-sectional study. Prague Med Rep. 2007;108:13–26.
125. Kotani K, Chen JT, Taniguchi N. The relationship between adiponectin and blood pressure in premenopausal and postmenopausal women. Clin Invest Med. 2011;34:E125–30.
126. Kraemer RR, Synovitz LB, Gimpel T, Kraemer GR, Johnson LG, Castracane VD. Effect of estrogen on serum DHEA in younger and older women and the relationship of DHEA to adiposity and gender. Metabolism. 2001;50:488–93.

127. Kuk JL, Lee S, Heymsfield SB, Ross R. Waist circumference and abdominal adipose tissue distribution: influence of age and sex. Am J Clin Nutr. 2005;81:1330–4.
128. Laitinen K, Valimaki M, Keto P. Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. Calcif Tissue Int. 1991;48:224–31.
129. Lejskova M, Alusik S, Valenta Z, Adamkova S, Pitha J. Natural postmenopause is associated with an increase in combined cardiovascular risk factors. Physiol Res. 2012;61:587–96.
130. Ley CJ, Lees B, Stevenson JC. Sex- and menopause-associated changes in body-fat distribution. Am J Clin Nutr. 1992;55:950–4.
131. Lin WY, Yang WS, Lee LT. Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan. Int J Obes. 2005;30:912–7.
132. Lindquist O, Bengtsson C. Serum lipids, arterial blood pressure and body weight in relation to the menopause: results from a population study of women in Goteborg, Sweden. Scand J Clin Lab Invest. 1980;40:629–36.
133. Lindsay R, Cosman F, Herrington BS, Himmelstein S. Bone mass and body composition in normal women. J Bone Miner Res. 1992;7:55–63.
134. Lovejoy JC, Champagne CM, Jonge L, Xie H, Smith S. Increased visceral fat and decreased energy expenditure during the menopausal transition. Int J Obes. 2005;32:949–58.
135. Lyu LC, Yeh CY, Lichtenstein AH, Li Z, Ordovas JM, Schaefer EJ. Association of sex, adiposity, and diet with HDL subclasses in middle-aged Chinese. Am J Clin Nutr. 2001;74:64–71.
136. Maharlouei N, Bellissimo N, Ahmadi SM, Lankarani KB. Prevalence of metabolic syndrome in pre- and postmenopausal Iranian women. Climacteric. 2013;16:561–7.
137. Malacara JM, Cetina T, Bassol S. Symptoms at pre- and postmenopause in rural and urban women from three States of Mexico. Maturitas. 2002;43:11–9.
138. Manabe E, Aoyagi K, Tachibana H, Takemoto T. Relationship of intra-abdominal adiposity and peripheral fat distribution to lipid metabolism in an island population in western Japan: gender differences and effect of menopause. Tohoku J Exp Med. 1999;188:189–202.
139. Manjer J, Kaaks R, Riboli E, Berglund G. Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: a prospective study within the Malmo Preventive Project. Eur J Cancer Prev. 2001;10:33–42.
140. Mannisto S, Pietinen P, Pyy M, Palmgren J, Eskelinen M, Uusitupa M. Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. Int J Cancer. 1996;68:8–13.
141. Martini G, Valenti R, Giovani S, Nuti R. Age-related changes in body composition of healthy and osteoporotic women. Maturitas. 1997;27:25–33.
142. Marwaha RK, Garg MK, Tandon N, Mehan N, Sastry A, Bhadra K. Relationship of body fat and its distribution with bone mineral density in Indian population. J Clin Densitom. 2013;16:353–9.
143. Matsushita H, Kurabayashi T, Tomita M, Kato N, Tanaka K. Effects of uncoupling protein 1 and Beta3-adrenergic receptor gene polymorphisms on body size and serum lipid concentrations in Japanese women. Maturitas. 2003;45:39–45.
144. Matsuzaki M, Kulkarni B, Kuper H. Association of hip bone mineral density and body composition in a rural Indian population: the Andhra Pradesh children and parents study (APCAPS). PLoS ONE. 2017;12:e0167114.
145. Matthews KA, Meilahn E, Kuller LH, Kelsey SF, Caggiula AW, Wing RR. Menopause and risk factors for coronary heart disease. N Engl J Med. 1989;321:641–6.
146. Mesch VR, Boero LE, Siseles NO. Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status. Climacteric. 2006;9:40–8.
147. Meza-Munoz DE, Fajardo ME, Perez-Luque EL, Malacara JM. Factors associated with estrogen receptors-alpha (ER-alpha) and -beta (ER-beta) and progesterone receptor abundance in obese and non obese pre- and post-menopausal women. Steroids. 2006;71:498–503.
148. Minatoya M, Kutomi G, Shima H. Relation of serum adiponectin levels and obesity with breast cancer: a Japanese case–control study. Asian Pac J Cancer Prev. 2014;15:8325–30.
149. Mo D, Hsieh P, Yu H. The relationship between osteoporosis and body composition in pre- and postmenopausal women from different ethnic groups in China. Ethn Health. 2017;22:295–310.
150. Muchanga Sifa MJ, Lepira FB, Longo AL, Sumaili EK, Makulo JR, Mbelambela EP, et al. Prevalence and predictors of metabolic syndrome among Congolese pre- and postmenopausal women. Climacteric. 2014;17:442–8.
151. Muti P, Stanulla M, Micheli A. Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: a prospective analysis of abdominal adiposity, sebum production, and hirsutism (Italy). Cancer Causes Control. 2000;11:721–30.
152. Nitta J, Nojima M, Ohnishi H. Weight gain and alcohol drinking associations with breast cancer risk in Japanese postmenopausal women—results from the Japan Collaborative Cohort (JACC) Study. Asian Pac J Cancer Prev. 2016;17:1437–43.
153. Noh HM, Song YM, Park JH, Kim BK, Choi YH. Metabolic factors and breast cancer risk in Korean women. Cancer Causes Control. 2013;24:1061–8.
154. Nordin BE, Need AG, Bridges A, Horowitz M. Relative contributions of years since menopause, age, and weight to vertebral density in postmenopausal women. J Clin Endocrinol Metab. 1992;74:20–3.
155. Ohta H, Kuroda T, Onoe Y. Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. J Bone Miner Metab. 2010;28:690–5.
156. Oldroyd B, Stewart SP, Truscott JG, Westmacott CF, Smith MA. Age related changes in body composition. Appl Radiat Isot. 1998;49:589.
157. Pacholczak R, Klimek-Piotrowska W, Kuszmiersz P. Associations of anthropometric measures on breast cancer risk in pre- and postmenopausal womena case–control study. J Physiol Anthropol. 2016. https://doi.org/10.1186/s40101-016-0090-x.
158. Park J-H, Song Y-M, Sung J, Lee K, Kim YS, Kim T, et al. The association between fat and lean mass and bone mineral density: the Healthy Twin Study. Bone. 2012;50:1006–11.
159. Park YM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. Int J Cancer. 2017;140:2657–66.
160. Pavlica T, Mikalacki M, Matic R. Relationship between BMI and skinfold thicknesses to risk factors in premenopausal and postmenopausal women. Coll Antropol. 2013;2:119–24.
161. Phillips GB, Jing T, Heymsfield SB. Does insulin resistance, visceral adiposity, or a sex hormone alteration underlie the metabolic syndrome? Studies in women. Metabolism. 2008;57:838–44.
162. Polesel DN, Hirotsu C, Nozoe KT, Boin AC, Bittencourt L, Tufik S, et al. Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: a cross-sectional population-based study. Menopause. 2015;22:835–44.
163. Pollan M, Lope V, Miranda-Garcia J. Adult weight gain, fat distribution and mammographic density in Spanish pre- and post-menopausal women (DDM-Spain). Breast Cancer Res Treat. 2012;134:823–38.
164. Portaluppi F, Pansini F, Manfredini R, Mollica G. Relative influence of menopausal status, age, and body mass index on blood pressure. Hypertension. 1997;29:976–9.
165. Priya T, Chowdhury MG, Vasanth K. Assessment of serum leptin and resistin levels in association with the metabolic risk factors of pre- and post-menopausal rural women in South India. Diabetes Metab Syndr. 2013;7:233–7.
166. Rantalainen T, Nikander R, Heinonen A. Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. Bone. 2010;46:964–9.
167. Reina P, Cointry GR, Nocciolino L. Analysis of the independent power of age-related, anthropometric and mechanical factors as determinants of the structure of radius and tibia in normal adults. A pQCT study. J Musculoskelet Neuronal Interact. 2015;15:10–22.
168. Revilla M, Villa LF, Hernandez ER, Sanchez-Atrio A, Cortes J, Rico H. Influence of weight and gonadal status on total and regional bone mineral content and on weight-bearing and non-weight-bearing bones, measured by dual-energy X-ray absosorptiometry. Maturitas. 1997;28:69–74.
169. Rice MS, Bertrand KA, Lajous M. Reproductive and lifestyle risk factors and mammographic density in Mexican women. Ann Epidemiol. 2015;25:868–73.

170. Rico H, Aguado F, Arribas I, Hernandez ER, Villa LF, Seco C, et al. Behavior of phalangeal bone ultrasound in normal women with relation to gonadal status and body mass index. Osteoporos Int. 2001;12:450–5.
171. Rico H, Arribas I, Casanova FJ, Duce AM, Herna ER, Cortes-Prieto J. Bone mass, bone metabolism, gonadal status and body mass index. Osteoporos Int. 2002;13:379–87.
172. Roelfsema F, Veldhuis JD. Growth hormone dynamics in healthy adults are related to age and sex and strongly dependent on body mass index. Neuroendocrinology. 2016;103:335–44.
173. Rosenbaum M, Nicolson M, Hirsch J. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J Clin Endocrinol Metab. 1996;81:3424–7.
174. Salomaa V, Rasi V, Pekkanen J. Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors. The FINRISK Hemostasis Study. Arterioscler Thromb Vasc Biol. 1995;15:1549–55.
175. Sarrafzadegan N, Khosravi-Boroujeni H, Esmaillzadeh A, Sadeghi M, Rafieian-Kopaei M, Asgary S. The association between hypertriglyceridemic waist phenotype, menopause, and cardiovascular risk factors. Arch Iran Med. 2013;16:161–6.
176. Schaberg-Lorei G, Ballard JE, McKeown BC, Zinkgraf SA. Body composition alterations consequent to an exercise program for pre and postmenopausal women. J Sports Med Phys Fit. 1990;30:426–33.
177. Schwarz S, Völzke H, Alte D, Schwahn C, Grabe HJ, Hoffmann W, et al. Menopause and determinants of quality of life in women at midlife and beyond: the study of health in Pomerania (SHIP). Menopause. 2007;14:123–34.
178. Shakir YA, Samsioe G, Nyberg P, Lidfeldt J, Nerbrand C. Cardiovascular risk factors in middle-aged women and the association with use of hormone therapy: results from a population-based study of Swedish women. The Women's Health in the Lund Area (WHILA) Study. Climacteric. 2004;7:274–83.
179. Sherk VD, Malone SP, Bemben MG, Knehans AW, Palmer IJ, Bemben DA. Leptin, fat mass, and bone mineral density in healthy pre- and postmenopausal women. J Clin Densitom. 2011;14:321–5.
180. Shibata H, Matsuzaki T, Hatano S. Relationship of relevant factors of atherosclerosis to menopause in Japanese women. Am J Epidemiol. 1979;109:420–4.
181. Sieminska L, Wojciechowska C, Foltyn W. The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause. Endokrynol Pol. 2006;57:15–22.
182. Skrzypczak M, Szwed A. Assessment of the body mass index and selected physiological parameters in pre- and post-menopausal women. HOMO. 2005;56:141–52.
183. Skrzypczak M, Szwed A, Pawlińska-Chmara R, Skrzypulec V. Assessment of the BMI, WHR and W/Ht in pre-and postmenopausal women. Anthropol Rev. 2007;70:3–13.
184. Soderberg S, Ahren B, Eliasson M, Dinesen B, Olsson T. The association between leptin and proinsulin is lost with central obesity. J Intern Med. 2002;252:140–8.
185. Son MK, Lim NK, Lim JY. Difference in blood pressure between early and late menopausal transition was significant in healthy Korean women. BMC Women's Health. 2015. https://doi.org/10.1186/s12905-015-0219-9.
186. Soriguer F, Morcillo S, Hernando V, Valdés S, de Adana MSR, Olveira G, et al. Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: longitudinal study. Menopause. 2009;16:817–21.
187. Staessen J, Bulpitt CJ, Fagard R, Lijnen P, Amery A. The influence of menopause on blood pressure. J Hum Hypertens. 1989;3:427–33.
188. Suarez-Ortegon MF, Arbelaez A, Mosquera M, Mendez F, Aguilar-de PC. C-reactive protein, waist circumference, and family history of heart attack are independent predictors of body iron stores in apparently healthy premenopausal women. Biol Trace Elem Res. 2012;148:135–8.
189. Suliga E, Koziel D, Ciesla E, Rebak D, Gluszek S. Factors associated with adiposity, lipid profile disorders and the metabolic syndrome occurrence in premenopausal and postmenopausal women. PLoS ONE. 2016;11:e0154511.
190. Sumner AE, Falkner B, Kushner H, Considine RV. Relationship of leptin concentration to gender, menopause, age, diabetes, and fat mass in African Americans. Obes Res. 1998;6:128–33.
191. Tanaka NI, Hanawa S, Murakami H. Accuracy of segmental bioelectrical impedance analysis for predicting body composition in pre- and postmenopausal women. J Clin Densitom. 2015;18:252–9.
192. Thomas T, Burguera B, Melton LJ III, Atkinson EJ, O'Fallon WM, Riggs BL, et al. Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. Metabolism. 2000;49:1278–84.
193. Torng PL, Su TC, Sung FC. Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women: the Chin-Shan Community Cardiovascular Cohort Study. Atherosclerosis. 2000;153:413–21.
194. Toth MJ, Tchernof A, Sites CK, Poehlman ET. Effect of menopausal status on body composition and abdominal fat distribution. Int J Obes Relat Metab Disord. 2000;24:226–31.
195. Tremollieres FA, Pouilles JM, Ribot CA. Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. Am J Obstet Gynecol. 1996;175:1594–600.
196. Trikudanathan S, Pedley A, Massaro JM. Association of female reproductive factors with body composition: the Framingham Heart Study. J Clin Endocrinol Metab. 2013;98:236–44.
197. Van Pelt RE, Davy KP, Stevenson ET, Wilson TM, Jones PP, Desouza CA, et al. Smaller differences in total and regional adiposity with age in women who regularly perform endurance exercise. Am J Physiol Endocrinol Metab. 1998;275:E626–34.
198. Veldhuis JD, Dyer RB, Trushin SA, Bondar OP, Singh RJ, Klee GG. Interleukins 6 and 8 and abdominal fat depots are distinct correlates of lipid moieties in healthy pre- and postmenopausal women. Endocrine. 2016;54:671–80.
199. Wang W, Zhao LJ, Liu YZ, Recker RR, Deng HW. Genetic and environmental correlations between obesity phenotypes and age at menarche. Int J Obes. 2005;30:1595–600.
200. Wang WS, Wahlqvist ML, Hsu CC, Chang HY, Chang WC, Chen CC. Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in Taiwan. BMC Public Health. 2012. https://doi.org/10.1186/1471-2458-12-111.
201. Wang F, Ma X, Hao Y. Serum glycated albumin is inversely influenced by fat mass and visceral adipose tissue in Chinese with normal glucose tolerance. PLoS ONE. 2012;7:e51098.
202. Wee J, Sng BY, Shen L, Lim CT, Singh G, Das De S. The relationship between body mass index and physical activity levels in relation to bone mineral density in premenopausal and postmenopausal women. Arch Osteoporos. 2013. https://doi.org/10.1007/s11657-013-0162-z.
203. Williams PT, Krauss RM. Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. Arterioscler Thromb Vasc Biol. 1997;17:1082–90.
204. Wing RR, Matthews KA, Kuller LH, Meilahn EN, Plantinga PL. Weight gain at the time of menopause. Arch Intern Med. 1991;151:97–102.
205. Xu L, Nicholson P, Wang QJ, Wang Q, Alen M, Cheng S. Fat mass accumulation compromises bone adaptation to load in Finnish women: a cross-sectional study spanning three generations. J Bone Miner Res. 2010;25:2341–9.
206. Yamatani H, Takahashi K, Yoshida T, Takata K, Kurachi H. Association of estrogen with glucocorticoid levels in visceral fat in postmenopausal women. Menopause. 2013. https://doi.org/10.1097/gme.0b013e318271a640.
207. Yannakoulia M, Melistas L, Solomou E, Yiannakouris N. Association of eating frequency with body fatness in pre- and postmenopausal women. Obesity. 2007;15:100–6.
208. Yoldemir T, Erenus M. The prevalence of metabolic syndrome in pre- and post-menopausal women attending a tertiary clinic in Turkey. Eur J Obstet Gynecol Reprod Biol. 2012;164:172–5.
209. Yoo KY, Kim H, Shin HR. Female sex hormones and body mass in adolescent and postmenopausal Korean women. J Korean Med Sci. 1998;13:241–6.
210. Yoo HJ, Park MS, Yang SJ. The differential relationship between fat mass and bone mineral density by gender and menopausal status. J Bone Miner Metab. 2012;30:47–53.
211. Yoshimoto N, Nishiyama T, Toyama T. Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. Cancer Sci. 2011;102:2065–72.

212. Žeželj SP, Cvijanović O, Mičović V, Bobinac D, Crnčević-Orlić Ž, Malatestinić G. Effect of menopause, anthropometry, nutrition and lifestyle on bone status of women in the northern Mediterranean. West Indian Med J. 2010;59:494.
213. Zhong N, Wu XP, Xu ZR. Relationship of serum leptin with age, body weight, body mass index, and bone mineral density in healthy mainland Chinese women. Clin Chim Acta. 2005;351:161–8.
214. Zhou J-L, Lin S-Q, Shen Y, Chen Y, Zhang Y, Chen F-L. Serum lipid profile changes during the menopausal transition in Chinese women: a community-based cohort study. Menopause. 2010;17:997–1003.
215. Zhou Y, Zhou X, Guo X. Prevalence and risk factors of hypertension among pre- and post-menopausal women: a cross-sectional study in a rural area of northeast China. Maturitas. 2015;80:282–7.
216. Zivkovic TB, Vuksanovic M, Jelic MA. Obesity and metabolic syndrome during the menopause transition in Serbian women. Climacteric. 2011;14:643–8.
217. Akahoshi M, Soda M, Nakashima E. Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. Atherosclerosis. 2001;156:157–63.
218. Ford K, Sowers M, Crutchfield M, Wilson A, Jannausch M. A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. Menopause. 2005;12:308–17.
219. Franklin RM, Ploutz-Snyder L, Kanaley JA. Longitudinal changes in abdominal fat distribution with menopause. Metabolism. 2009;58:311–5.
220. Janssen I, Powell LH, Crawford S, Lasley B, Sutton-Tyrrell K. Menopause and the metabolic syndrome: the study of women's health across the nation. Arch Intern Med. 2008;168:1568–75.
221. Lee CG, Carr MC, Murdoch SJ. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab. 2009;94:1104–10.
222. Liu-Ambrose T, Kravetsky L, Bailey D, Sherar L, Mundt C, Baxter-Jones A, et al. Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: a 12-year observational study. Calcif Tissue Int. 2006;79:145–51.
223. Macdonald HM, New SA, Campbell MK, Reid DM. Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. Osteoporos Int. 2005;16:163–71.
224. Razmjou S, Abdulnour J, Bastard J-P, Fellahi S, Doucet É, Brochu M, et al. Body composition, cardiometabolic risk factors, physical activity, and inflammatory markers in premenopausal women after a 10-year follow-up: a MONET study. Menopause. 2018;25:89–97.
225. Soreca I, Rosano C, Jennings JR, Sheu LK, Kuller LH, Matthews KA, et al. Gain in adiposity across 15 years is associated with reduced gray matter volume in healthy women. Psychosom Med. 2009;71:485–90.
226. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle–Ottawa quality assessment scale cohort studies. Ottawa: University of Ottawa; 2014.
227. Smith-DiJulio K, Mitchell ES, Woods NF. Concordance of retrospective and prospective reporting of menstrual irregularity by women in the menopausal transition. Climacteric. 2005;8:390–7.
228. Kevenaar ME, Meerasahib MF, Kramer P, van de Lang-Born BMN, de Jong FH, Groome NP, et al. Serum anti-Müllerian hormone levels reflect the size of the primordial follicle pool in mice. Endocrinology. 2006;147:3228–34.
229. de Vet A, Laven JSE, de Jong FH, Themmen APN, Fauser BCJM. Antimüllerian hormone serum levels: a putative marker for ovarian aging. Fertil Steril. 2002;77:357–62.
230. Feyereisen E, Lozano DHM, Taieb J, Hesters L, Frydman R, Fanchin R. Anti-Müllerian hormone: clinical insights into a promising biomarker of ovarian follicular status. Reprod Biomed Online. 2006;12:695–703.
231. van Rooij IAJ. Serum anti-Mullerian hormone levels: a novel measure of ovarian reserve. Hum Reprod. 2002;17:3065–71.
232. Depmann M, Eijkemans MJC, Broer SL, Tehrani FR, Solaymani-Dodaran M, Azizi F, et al. Does AMH relate to timing of menopause? Results of an individual patient data meta-analysis. J Clin Endocrinol Metab. 2018;103:3593–600.
233. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. Int J Epidemiol. 2014;43:1542–62.
234. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
235. Zavos A, Valachis A. Risk of chemotherapy-induced amenorrhea in patients with breast cancer: a systematic review and meta-analysis. Acta Oncol. 2016;55:664–70.
236. Revilla M, Villa LF, Sanchez-Atrio A, Hernandez ER, Rico H. Influence of body mass index on the age-related slope of total and regional bone mineral content. Calcif Tissue Int. 1997. https://doi.org/10.1007/s002239900310.

Publisher's Note

Longitudinal changes in fat mass and the hippocampus

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Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Longitudinal Changes in Fat Mass and the Hippocampus

Ananthan Ambikairajah [1], *Hossein Tabatabaei-Jafari* [1], *Erin Walsh* [1], *Michael Hornberger* [2], *and Nicolas Cherbuin* [1]

Objective: This study aimed to investigate cross-sectional and longitudinal associations between fat mass (i.e., body mass index [BMI], waist circumference [WC], and waist to hip ratio [WTHR]) and hippocampal volumes.

Methods: UK Biobank participants ($N = 20,395$) aged 40 to 70 years (mean follow-up = 7.66 years), were included and categorized into one of four groups, which represented their baseline fat mass status and trajectory of change by follow-up assessment: normal weight to overweight/obesity, overweight/obesity to normal weight (ON), normal weight stable (NS), or overweight/obesity stable (OS). Regression models used NS (WC < 80 cm in women and < 94 cm in men; WTHR < 0.85 in women and < 0.90 in men; BMI < 25 kg/m^2 in women and men) as the reference group. Hippocampal volumes were automatically segmented using the FMRIB Software Library.

Results: Compared with NS, OS (BMI: $B = -62.23$ [SE = 16.76]; WC: $B = -145.56$ [SE = 16.97]; WTHR: $B = -101.26$ [SE = 19.54]) and ON (BMI: $B = -61.1$ [SE = 30.3]; WC: $B = -93.77$ [SE = 24.96]; WTHR: $B = -69.92$ [SE = 26.22]) had significantly lower hippocampal volumes.

Conclusions: The detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

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Study Importance

What is already known?

- In addition to being associated with deleterious health and well-being outcomes, including type 2 diabetes mellitus, cancer, and cardiovascular disease, overweight BMI in midlife confers a 35% increased risk of developing Alzheimer disease compared with normal BMI.

What does this study add?

- Our findings indicate that the detrimental effects of overweight/obesity on the neurological health of individuals may extend beyond the duration of overweight/obesity itself.

How might these results change the focus of clinical practice?

- The clinical translation of our research findings is important to ensure that possible populations at risk for poor neurological health are not overlooked and that, instead, targeted intervention programs are developed to mitigate identified risks.

Introduction

The prevalence of overweight and obesity has accelerated in recent decades, with current global estimates indicating that the proportion of adults with body mass index (BMI) greater than 25 kg/m^2 (i.e., overweight) is one in three (1,2). These findings are of particular importance within the context of our globally aging population given that previous research has demonstrated that, in addition to being associated with several unfavorable health and well-being outcomes (including type 2 diabetes mellitus, cancer, and cardiovascular disease) (3), overweight BMI in midlife confers a 35% increased risk of developing Alzheimer disease compared with normal BMI (4).

The hippocampus is a brain region that is sensitive to changes, particularly in the early stages of neurodegeneration (5-7). Notably, the accumulation of fat tissue, particularly visceral fat (which is often prevalent in individuals with overweight/obesity), is known to be closely linked with elevated levels of proinflammatory cytokines (8-10), which are associated with smaller hippocampal volumes (11). In animal models, obesity in aging is associated with a heightened state of systemic inflammation, which exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus (12). These pathophysiological consequences of overweight/obesity have been closely linked with impaired hippocampal integrity in humans (11,13). Interestingly, a postmortem study of nondemented elderly individuals revealed that those with obesity had neuropathological hallmarks of Alzheimer disease, such as higher levels of hippocampal amyloid-β peptides, amyloid precursor protein, and hyperphosphorylated tau protein, compared with those without obesity (14). However, neuroimaging studies have revealed that the association between fat mass and hippocampal volume in adults of middle to early-old age has been less consistent, with studies reporting negative (15-18), positive (19), or no association (20-22). The heterogeneous results may be explained by

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the typical use of BMI, which does not precisely index changes in visceral fat and is inherently biased by the aging process (23). Therefore, other cost-effective, feasible, and useful clinical measures, including waist circumference (WC) and/or waist to hip ratio (WTHR), may be better suited for representing changes in visceral fat. Critically, objectively measured longitudinal changes in WC and WTHR have not been adequately investigated in previous studies examining the relationship between fat mass and hippocampal volume (12,16-17,24).

In the current study, we aimed to rectify these shortcomings by investigating the associations of fat mass (i.e., BMI, WC, and WTHR) and changes in fat mass over time with hippocampal volumes in women and men of middle to early-old age. Secondary aims were to (1) determine whether these associations differed between measures of fat mass and (2) determine which measures of fat mass were most strongly associated with total body fat and visceral fat, as measured by the gold standard tool, dual-energy x-ray absorptiometry (DXA). It was hypothesized that any observed associations between fat mass and the hippocampus would be dependent on (1) baseline fat mass status (i.e., normal weight, overweight, or obesity), (2) the trajectory of change, and (3) the measure of fat mass used. It was predicted that individuals who were classified as having chronic overweight/obesity (and who thereby experience chronic, low-grade, systemic inflammation as well as other comorbidities) would have lower hippocampal volumes than those who progressed from normal weight to overweight/obesity categories or maintained their weight within the normal range. Furthermore, it was hypothesized that these results would be best represented by the fat mass measure that was most suited for indexing changes in visceral fat.

Methods

Participants

A total of 502,536 participants aged 37 to 73 years at baseline (2006-2010) from the UK Biobank study (25) were considered for inclusion. Participants were recruited from the National Health Service central registers. Of those considered, as a minimum requirement, only those who had completed a structural magnetic resonance imaging (MRI) scan ($n = 21{,}390$) and who had a measure for BMI, WC, and hip circumference (HC) at baseline and the follow-up assessment (2014+) were included ($n = 20{,}849$). After we excluded participants with neurological disorders (including stroke; $n = 256$), those who were underweight (BMI < 18.5; $n = 179$), and those with extreme obesity (BMI > 50; $n = 20$), 20,395 participants remained for analysis in the present study. None of the included participants had dementia. UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (reference: 11/NW/0382). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Fat mass measures

BMI, WC, and WTHR were measured at baseline, the first follow-up assessment, and the second follow-up assessment (Figure 1). Trained staff used standardized procedures to obtain body size measurements. Participants were asked to remove shoes, socks, and heavy outer clothing before body weight was measured with the Tanita BC-418MA body composition analyzer and standing height was measured using a Seca 202 height measure. BMI was calculated as weight (in kilograms)/height (in meters squared). WC was measured with a Wessex non-stretchable sprung tape measure at the level of the umbilicus, whereas HC was measured at the widest point. WTHR was computed as WC (in centimeters)/HC (in centimeters). Total body fat and visceral fat were measured (for 4,482 and 4,431 participants, respectively) using a DXA device, specifically the GE Lunar iDXA.

Of the 20,395 participants included in the study, 5,080 had an additional follow-up measure of fat mass (Figure 1). For these participants, annual changes in fat mass were calculated with the formula:

$$y = B_0 + B_1 \text{follow up (years)},$$

where B_0 is the fat mass at each time point and B_1 is the annual change in fat mass.

For each measure of fat mass, participants were then categorized into one of four groups, which represented their baseline fat mass status and their trajectory of change by follow-up assessment: normal weight to overweight/obesity (NO), overweight/obesity to normal weight (ON), normal weight stable (NS), or overweight/obesity stable (OS). Standardized criteria from the International Diabetes Federation (26) and the World Health Organization (27,28) were used to classify normal and overweight/obesity groups. Specifically, BMI was ≥ 25 kg/m^2 for men and women with overweight/obesity and < 25 kg/m^2 for men and women with normal weight; WC was ≥ 80 cm and ≥ 94 cm for women and men with overweight/obesity, respectively, and < 80 cm and < 94 cm for women and men with normal weight, respectively; and WTHR was ≥ 0.85 and ≥ 0.90 for women and men with overweight/obesity, respectively, and < 0.85 and < 0.90 for women and men with normal weight, respectively.

Covariates

Covariates included sex, follow-up period, self-reported age, educational attainment, vascular/heart problems (i.e., heart attack, angina, or hypertension), and diabetes diagnosed by a doctor. Participants were classified as having hypertension if they were using blood pressure medication and were classified as having diabetes if they were using oral antidiabetic medication or insulin. Further covariates included self-reported physical activity (i.e., number of days per week spent doing at least 10 minutes of continuous vigorous activity), smoking status (i.e., ever or never), and frequency of alcohol intake.

Image acquisition

MRI scans were acquired at the second follow-up assessment (Figure 1). All participants were imaged across three imaging centers with identical scanners (3T Siemens Skyra, running VD13A SP4) using a 32-channel head coil (29). T1-weighted images were acquired in the sagittal orientation using a three-dimensional magnetization-prepared rapid acquisition gradient echo sequence over a duration of 5 minutes (resolution = 1 × 1 × 1 mm; field of view = 208 × 256 × 256 matrix) (29).

Segmentation and image analysis

Images were processed and analyzed by the UK Biobank imaging team using FMRIB Software Library version 6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard MRI analysis protocols has been reported elsewhere (29,30); however, we have included an overview of key steps. The UK Biobank processing pipeline included a linear and then a nonlinear registration to a 1-mm-resolution version of the MNI152 template. Automated tissue segmentation was conducted, and subcortical structures, such as the hippocampus, were modeled.

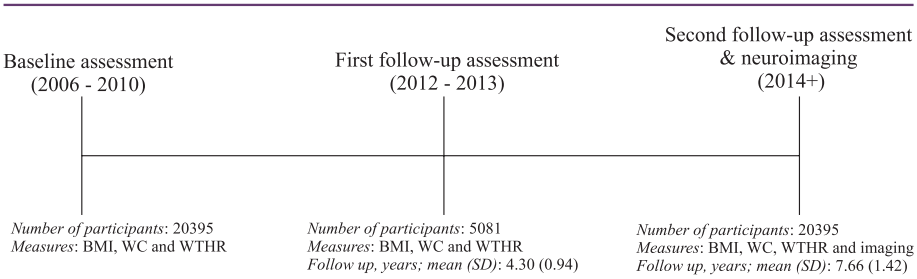

Figure 1 Timeline of UK Biobank study. WC, waist circumference; WTHR, waist to hip ratio.

Raw hippocampal volumes were multiplied by the overall volumetric head-size scaling factor to obtain normalized volumes, which were subsequently used for all analyses.

Statistical methods

All statistical analyses were conducted using R (version 3.6.1; R Foundation for Statistical Computing), in RStudio (version 1.1.419). Pearson correlation coefficients were used to measure the strength of the associations between BMI, WC, and WTHR and DXA measurements of total body fat and visceral fat. Multiple linear hierarchical regression models were then computed to quantify the association between fat mass and changes in fat mass and hippocampal volumes, controlling for age and sex (model 1). Model 2 further controlled for education, vascular/heart problems, diabetes, physical activity, smoking status, and alcohol use. Analyses investigating the associations between fat mass categories (i.e., NO, ON, NS, and OS) and the hippocampus also adjusted for length of follow-up (years). Within each fat mass category, longitudinal changes in fat mass and the hippocampus were assessed. Because the fat mass thresholds for categorization differed between men and women (particularly for WC and WTHR), these analyses were repeated separately. Both unstandardized beta coefficients and annual percentage change in fat mass were used in the reporting and interpretation of results, when appropriate. Annual percentage change was calculated by dividing the annual change in fat mass by the baseline fat mass and multiplying by 100. The α level was set at <0.05. Nonlinear associations were explored by fitting a squared term for fat mass. Assumptions of linearity, including homoscedasticity and normality of residuals, were examined.

Results

The participants' demographic and health characteristics are presented in Table 1. Differences between those who were included and excluded are reported in Supporting Information Table S1. For those included, participants were, on average, 54.86 years old (SD = 7.48 years) at baseline and had a mean follow-up time of 7.66 years (SD = 1.42 years). The average total hippocampal volume was 7,709.73 mm^3 (SD = 867.92 mm^3). On average, participants lost 68.6 g/y over the follow-up period. Box plots of fat mass change over the follow-up period between NS, NO, OS, and ON groups are presented in Figure 2. Demographic information for NS, NO, OS, and ON groups for each fat mass measure is presented in Supporting Information Tables S2-S4.

TABLE 1 Demographic and health characteristics

	Value
Sample size, *N*	20,395
Age, mean (SD), y	54.86 (7.48)
Follow-up period, mean (SD), y	7.66 (1.42)
Female sex, *n* (%)	10,658 (52.26)
BMI, mean (SD)	26.67 (4.16)
Waist circumference, mean (SD), cm	88.12 (12.44)
Waist to hip ratio, mean (SD)	0.86 (0.087)
Education (college degree), *n* (%)	9,491 (46.54)
Hypertension, *n* (%)	4,240 (20.79)
Diabetes, *n* (%)	544 (2.67)
Ever smoker, *n* (%)	11,623 (56.99)
Total hippocampal volume, mean (SD), mm^3	7,709.73 (867.92)

There were 109 (0.53%) participants missing data for education, 147 (0.72%) participants missing data for hypertension, 4 (0.02%) participants missing data for diabetes, and 44 (0.22%) participants missing data for smoking status.

Cross-sectional analyses revealed that after adjustment for all covariates, higher BMI, WC, and WTHR were each individually associated with lower hippocampal volumes (Supporting Information Table S5) (BMI: $B = -9.61$ [SE = 1.77]; WC: $B = -6.74$ [SE = 0.69]; WTHR: $B = -690.78$ [SE = 119.13]).

Overall, longitudinal changes in continuous BMI, WC, or WTHR were not significantly associated with lower hippocampal volumes (Supporting Information Table S6); however, compared with participants with NS, for BMI, WC, or WTHR, participants classified as OS (BMI: $B = -62.23$ [SE = 16.76]; WC: $B = -145.56$ [SE = 16.97]; WTHR: $B = -101.26$ [SE = 19.54]) or ON (BMI: $B = -61.1$ [SE = 30.3]; WC: $B = -93.77$ [SE = 24.96]; WTHR: $B = -69.92$ [SE = 26.22]) had significantly lower hippocampal volumes across all three measures of fat mass (Table 2). For WC or WTHR, participants with NO also had significantly lower hippocampal volumes than those with NS (WC: $B = -74.39$ [SE = 25.51]; WTHR: $B = -62.09$ [SE = 22.52]). However, for BMI, participants with NO had no significant difference in hippocampal volume compared with those with NS.

Analyses were repeated separately for women and men (Supporting Information Tables S7-S8). For men, OS (BMI: $B = -92.17$ [SE = 26.55];

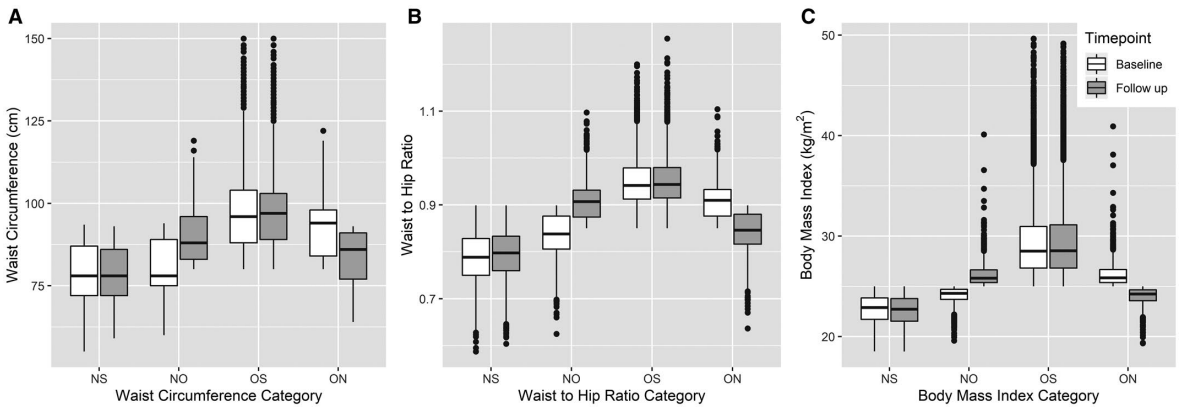

Figure 2 Fat mass change over follow-up for each group. (**A**) Waist circumference groups. (**B**) Waist to hip ratio groups. (**C**) BMI category groups. NO, normal weight to overweight/obesity; NS, normal weight stable; ON, overweight/obesity to normal weight; OS, overweight/obesity stable.

TABLE 2 Longitudinal categorical analysis results for total hippocampus

Measure	Predictors	Estimate	SE	95% CI	*P*	R^2
BMI	NO	−45.95	32.24	−109.14 to 17.25	0.154	0.155
	OS	−62.23	16.76	−95.07 to −29.38	**<0.001**	…
	ON	−61.10	30.30	−120.50 to −1.71	**0.044**	…
WC	NO	−74.39	25.51	−124.39 to −24.40	**0.004**	0.157
	OS	−145.56	16.97	−178.83 to −112.29	**<0.001**	…
	ON	−93.77	24.96	−142.69 to −44.85	**<0.001**	…
WTHR	NO	−62.09	22.52	−106.24 to −17.95	**0.006**	0.155
	OS	−101.26	19.54	−139.57 to −62.95	**<0.001**	…
	ON	−69.92	26.22	−121.32 to −18.53	**0.008**	…

Model adjusted for age, sex, follow-up (years), education, vascular/heart problems, diabetes, physical activity, smoking, and alcohol use. All estimates unstandardized for hippocampus (measured in cubic millimeters). $P < 0.05$ considered significant and presented in bold text.
NO, normal weight to overweight/obesity; ON, overweight/obesity to normal weight; OS, overweight/obesity stable; WC, waist circumference; WTHR, waist to hip ratio.

WC: $B = -206.02$ [SE = 25.69]; WTHR: $B = -114.98$ [SE = 29.08]) and ON (BMI: $B = -97.79$ [SE = 45.76]; WC: $B = -91.18$ [SE = 34.5]; WTHR: $B = -96.29$ [SE = 40.49]) groups were consistently associated with lower hippocampal volumes compared with the NS group across all measures of fat mass. However, no significant differences in hippocampal volumes were consistently found between the NO and NS groups. For women, the OS group had consistently lower hippocampal volumes than the NS group across all measures of fat mass (BMI: $B = -45.19$ [SE = 21.52]; WC: $B = -101.73$ [SE = 22.5]; WTHR: $B = -70.54$ [SE = 28.67]). For WC and WTHR, the NO group had lower hippocampal volumes than the NS group (WC: $B = -84$ [SE = 32.43]; WTHR: $B = -103.79$ [SE = 28.43]); however, these differences were not found for BMI. Participants with ON had significantly lower hippocampal volumes compared with the NS group for WC ($B = -113.16$ [SE = 36.51]); however, this difference was not observed for WTHR or BMI.

For each individual subgroup (NS, NO, OS, and ON), annual change in BMI, WC, or WTHR had no significant association with hippocampal volume (Supporting Information Table S9). This was consistently observed between women and men (Supporting Information Tables S10-S11).

As seen in Table 3, WC was most correlated with visceral fat ($r = 0.83$) compared with WTHR ($r = 0.73$) and BMI ($r = 0.69$). However, BMI was most correlated with total body fat ($r = 0.90$) compared with WC ($r = 0.72$) and WTHR ($r = 0.29$).

Discussion

In this study, we aimed to investigate the association of fat mass and longitudinal changes in fat mass with hippocampal volumes in women and men of middle to early-old age. To better understand these relationships, in the current study, we also aimed to determine whether observed associations differed between measures of fat mass and identify which measures of fat mass were most strongly associated with total body fat and visceral fat, as indicated by DXA. The key findings were

TABLE 3 Simple Pearson correlation analysis results between WC, WTHR, and BMI and DXA measures of TBF and VF

	TBF	95% CI	*P*	VF	95% CI	*P*
BMI	0.897	0.891-0.903	**<0.001**	0.688	0.672-0.703	**<0.001**
WC	0.719	0.706-0.734	**<0.001**	0.827	0.817-0.836	**<0.001**
WTHR	0.291	0.264-0.318	**<0.001**	0.728	0.714-0.742	**<0.001**

TBF and VF measured for 4,482 and 4,431 participants, respectively, using DXA. $P < 0.05$ considered significant and presented in bold text.
DXA, dual-energy x-ray absorptiometry; TBF, total body fat; VF, visceral fat; WC, waist circumference; WTHR, waist to hip ratio.

that (1) WC was most strongly correlated with visceral fat ($r=0.83$) compared with WTHR ($r=0.73$) and BMI ($r=0.69$), (2) individuals with chronic overweight/obesity had significantly lower hippocampal volumes (WC: 1.13% smaller; WTHR: 0.79% smaller; BMI: 0.49% smaller [after adjustment for all covariates]) compared with those who maintained a normal level of fat mass (WC < 80 cm in women and < 94 cm in men; WTHR < 0.85 in women and < 0.90 in men; BMI < 25 kg/m^2 in women and men) at baseline and follow-up (average follow-up = 7.66 years), and (3) individuals who were within a normal range of fat mass at the follow-up assessment, yet were previously classified as having overweight/obesity at baseline, had lower hippocampal volumes than those who remained at normal weight (WC: 0.73% smaller; WTHR: 0.55% smaller; BMI: 0.48% smaller [after adjustment for all covariates]). Notably, the significant cross-sectional association between fat mass and hippocampal volume was not previously detected in a study on the same cohort (18). In that particular study, the sample was half the size of the present study, and depression was also considered as a covariate. Our analysis did not include depression as a covariate, partly because of the significant degree of missingness present. The current findings emphasize the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.

Overweight/obesity is a complex condition that has multifactorial components (including genetic, environmental, and socioeconomic factors) that underlie its etiology. The current findings further highlight the complexity of overweight/obesity by emphasizing the long-term impact the condition may have on the neurological health of individuals. There are several possible biological mechanisms that may explain the consistent finding that those with OS or ON had lower hippocampal volumes than those with NS across all measures of fat mass. For example, previous studies have demonstrated that the accumulation of fat tissue, particularly visceral fat, is closely linked with elevated levels of proinflammatory cytokines (19-21), which have been associated with smaller hippocampal volumes (22). This is of particular importance because the current results revealed that (1) WC was most strongly associated with visceral fat and (2) the largest effect was consistently found for WC, as those with OS and ON had 1.13% and 0.73% smaller hippocampal volumes, respectively, than those with NS for WC compared with WTHR (OS: 0.79% smaller hippocampus; ON: 0.55% smaller hippocampus) and BMI (OS: 0.49% smaller hippocampus; ON: 0.48% smaller hippocampus). Notably, no statistical differences between NS and NO groups were found for BMI, which was lowly correlated with visceral fat levels compared with WC but was most highly correlated with total body fat; however, for both WC and WTHR, the NO group had significantly lower hippocampal volumes than the NS group (0.58% and 0.49% smaller, respectively).

Taken together, the current findings seem to suggest that an accumulated burden of pathology may have developed in those with OS, ON, and NO, compared with NS, perhaps as a result of chronic, low-grade systemic inflammation that persists, which is common in individuals with overweight/obesity (because of an accumulation of visceral fat tissue), or other pathological mechanisms, resulting in lower hippocampal volumes. This is consistent with the literature, which has shown that chronic obesity is associated with a cascade of potentially harmful physiological processes (including oxidative stress, inflammation, and insulin resistance) implicated in the deterioration of metabolic homeostasis (31) and that chronic obesity has been linked with accelerated neurodegeneration (32). Furthermore, previous research has demonstrated that individuals who gained weight, lost weight, or maintained obesity had an increased risk of mortality compared with those who maintained normal amounts of body fat (33). Therefore, these results appear to indicate that it is the chronicity of overweight/obesity that is associated with lower hippocampal volumes. However, an alternative explanation is that, for reasons not well understood, those with ON or OS had lower hippocampal volumes at baseline. Although possible, this explanation is less likely given the substantial amount of evidence in the literature that has demonstrated the link between obesity and neurodegeneration (4,34,35), which also aligns with experimental data in animals showing that obesity in mice can lead to decreased neurogenesis and accelerated neurodegeneration, resulting in dementia pathology (36,37). Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present, and future research should investigate this further.

The use of BMI, WC, and WTHR enabled the comparison of results across three commonly used clinical measures/indices of fat mass. Although more precise technology for measuring fat mass exists, such as DXA and MRI (38), these tools require relatively large investments of time, money, and resources, compared with BMI, WC, and WTHR. Furthermore, longitudinal measures of fat mass, by using DXA or MRI, are currently not available in the UK Biobank data set. As a result, an important question is raised by these findings: which clinical measure (BMI, WC, or WTHR) best represents the association between fat mass and the hippocampus and which may, therefore, be a better predictor of future neurodegeneration? First, as previously noted, a correlation analysis indicated that WC was most strongly associated with visceral fat ($r=0.83$) compared with WTHR ($r=0.73$) and BMI ($r=0.69$). This may provide a theoretical rationale for its use as a clinical measure to assess the association between fat mass and the hippocampus. Furthermore, a subgroup analysis in women revealed statistically significant differences for WC between NO, OS, and ON groups and those with NS; however, these differences were not consistently found for WTHR and BMI (Supporting Information Table S7). Several possible reasons may account for these findings. For example, previous research has demonstrated that women tend to accumulate central fat (specifically visceral

fat) during midlife (39), which may explain the observed associations given that WC was most strongly correlated with visceral fat, which has been previously linked to neurodegeneration through the elevation of proinflammatory cytokines (22). Another possibility is that the individuals who were in each fat mass group (NS, NO, OS, and ON) varied to a certain degree between measures because of the differences in the standardized cutoff points used for categorization. Therefore, the observed differences in results may reflect the sensitivity of the fat mass thresholds for each category (NS, NO, OS, and ON) to better capture individuals who had healthier hippocampal volumes than others. To assess this, a post hoc analysis was conducted, in which a fifth group included individuals (n = 3,998) who consistently had NS for BMI, WC, and WTHR (henceforth consistent NS [CNS]). Interestingly, for WC, no difference was found between those with NS or CNS. Furthermore, the magnitude and significance of effects remained consistent between NS and NO, OS, and ON groups, with and without the inclusion of the CNS group (Supporting Information Table S12). Alternatively, for WTHR and BMI, the CNS group had significantly larger hippocampal volumes than those with NS. Furthermore, the differences between ON and OS groups and the NS group for BMI were no longer detected once the CNS group was included. A similar result was observed for the ON and NO groups for WTHR. Therefore, the CNS group was likely capturing the individuals with larger hippocampal volumes for BMI and WTHR but not WC. This may be because BMI and WTHR measures reflect body size and on-average head size, which is itself associated with hippocampal volume. These findings seem to further demonstrate the robustness and sensitivity of WC for assessing the relationship between visceral fat and hippocampal volume. Taken together, these results align with and extend on previous studies that have noted that WC is a more sensitive indicator for determining the adverse effects of overweight and obesity on brain health than BMI, particularly in women (40).

Key strengths of the current study include (1) the large cohort of adults of middle to early-old age (20,395 individuals) that included both men and women, (2) the use of longitudinal changes in fat mass, and (3) the use of multiple commonly used clinical measures/indices of fat mass (including BMI, WC, and WTHR) to address the questions of interest. Furthermore, because of the large sample size, a large number of relevant covariates could be adjusted for (including age, sex, follow-up period, educational attainment, vascular/heart problems [i.e., heart attack, angina, or hypertension], diabetes, physical activity, smoking status, and alcohol intake), which ensured that observed associations were unlikely driven by common comorbid conditions that are often associated with obesity, such as diabetes, hypertension, and physical activity levels. Notably, previous studies that have examined the association of longitudinal changes in fat mass with hippocampal volumes in adults of middle to early-old age have been limited by sample size (12,16,17). Two of the three studies used BMI as their only measure of fat mass (16,17); one was focused on a sample consisting only of men (16), whereas the other used self-reported BMI (12). The third estimated BMI and WC in participants aged 50 years (17). Given this, the current study is unique in its ability to directly measure, assess, and discuss the temporal association of longitudinal changes in BMI, WC, and WTHR with the hippocampus within a large cohort of both men and women.

A limitation of the current study is that imaging data were available only at one time point (Figure 1). Therefore, it is difficult to determine whether other age-related factors could be responsible for the observed differences or, as previously discussed, whether these differences were already present at baseline. For example, if smaller hippocampal volumes were observed at baseline and were associated with longitudinal increases in adiposity, then these findings may highlight a predisposed vulnerability to external food cues driving eating behavior. Furthermore, clear standardized thresholds for WC and WTHR that separate overweight and obesity groups do not currently exist. This limited the ability to identify possible differences that may exist between participants with overweight and obesity for WC and WTHR. Additionally, healthy participation bias for the UK Biobank cohort indicates that these findings may not be completely representative of the broader population and that they require replication in other data sets (41). Our study was limited to the association between changes in fat mass and the brain; however, future studies would benefit from investigating whether the observed results translate to differences in cognitive performance, particularly in domains related to the hippocampus such as learning and memory.

Conclusion

The current findings emphasize the importance of maintaining normal weight for neurological health and also suggest that the detrimental effects of overweight/obesity may extend beyond the duration of overweight/obesity itself.O

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Supporting information: Additional Supporting Information may be found in the online version of this article.

References

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014;384:766-781.
2. Stevens GA, Singh GM, Lu Y, et al; Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). National, regional, and global trends in adult overweight and obesity prevalences. *Popul Health Metr* 2012;10:22. doi:10.1186/1478-7954-10-22
3. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of comorbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 2009;9:88. doi:10.1186/1471-2458-9-88
4. Anstey KJ, Cherbuin N, Budge M, Young J. Body mass index in midlife and late-life as a risk factor for dementia: a meta-analysis of prospective studies. *Obes Rev* 2011;12:e426-e437. doi:10.1111/j.1467-789X.2010.00825.x
5. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239-259.
6. Karas GB, Scheltens P, Rombouts SA, et al. Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *Neuroimage* 2004;23:708-716.
7. Zakzanis KK, Graham SJ, Campbell Z. A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. *Neuropsychol Rev* 2003;13:1-18.
8. Fontana L, Eagon JC, Trujillo ME, Scherer PE, Klein S. Visceral fat adipokine secretion is associated with systemic inflammation in obese humans. *Diabetes* 2007;56:1010-1013.
9. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. *Annu Rev Immunol* 2011;29:415-445.
10. Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun* 2014;42:10-21.
11. Sudheimer KD, O'Hara R, Spiegel D, et al. Cortisol, cytokines, and hippocampal volume interactions in the elderly. *Front Aging Neurosci* 2014;6:153. doi:10.3389/fnagi.2014.00153
12. Tucsek Z, Toth P, Sosnowska D, et al. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects

on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci* 2014;69:1212-1226.
13. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron* 2015;85:296-302.
14. Mrak RE. Alzheimer-type neuropathological changes in morbidly obese elderly individuals. *Clin Neuropathol* 2009;28:40-45.
15. Bruehl H, Wolf OT, Sweat V, Tirsi A, Richardson S, Convit A. Modifiers of cognitive function and brain structure in middle-aged and elderly individuals with type 2 diabetes mellitus. *Brain Res* 2009;1280:186-194.
16. Cherbuin N, Sargent-Cox K, Fraser M, Sachdev P, Anstey KJ. Being overweight is associated with hippocampal atrophy: the PATH Through Life Study. *Int J Obes (Lond)* 2015;39:1509-1514.
17. Jagust W, Harvey D, Mungas D, Haan M. Central obesity and the aging brain. *Arch Neurol* 2005;62:1545-1548.
18. Raji CA, Ho AJ, Parikshak NN, et al. Brain structure and obesity. *Hum Brain Mapp* 2010;31:353-364.
19. Widya RL, de Roos A, Trompet S, et al; PROSPER Study Group. Increased amygdalar and hippocampal volumes in elderly obese individuals with or at risk of cardiovascular disease. *Am J Clin Nutr* 2011;93:1190-1195.
20. Bobb JF, Schwartz BS, Davatzikos C, Caffo B. Cross-sectional and longitudinal association of body mass index and brain volume. *Hum Brain Mapp* 2014;35:75-88.
21. Driscoll I, Beydoun MA, An Y, et al. Midlife obesity and trajectories of brain volume changes in older adults. *Hum Brain Mapp* 2012;33:2204-2210.
22. Hamer M, Batty GD. Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. *Neurology* 2019;92:e594-e600. doi:10.1212/WNL.0000000000006879
23. Romero-Corral A, Somers VK, Sierra-Johnson J, et al. Accuracy of body mass index in diagnosing obesity in the adult general population. *Int J Obes (Lond)* 2008;32:959-966.
24. Croll PH, Bos D, Ikram MA, Rivadeneira F, Voortman T, Vernooij MW. Body composition is not related to structural or vascular brain changes. *Front Neurol* 2019;10:559. doi:10.3389/fneur.2019.00559
25. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med* 2015;12:e1001779. doi:10.1371/journal.pmed.1001779
26. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome--a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006;23:469-480.
27. World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. Geneva, Switzerland: World Health Organization; 2000.
28. World Health Organization. *Waist Circumference and Waist-Hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008*. Geneva, Switzerland: World Health Organization; 2011.
29. Miller KL, Alfaro-Almagro F, Bangerter NK, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nat Neurosci* 2016;19:1523-1536.
30. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. *Neuroimage* 2018;166:400-424.
31. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediators Inflamm* 2010;2010:289645. doi:10.1155/2010/289645
32. Glass CK, Saijo K, Winner B, Marchetto MC, Gage FH. Mechanisms underlying inflammation in neurodegeneration. *Cell* 2010;140:918-934.
33. Chen C, Ye Y, Zhang Y, Pan XF, Pan A. Weight change across adulthood in relation to all cause and cause specific mortality: prospective cohort study. *BMJ* 2019;367:l5584. doi:10.1136/bmj.l5584
34. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes Rev* 2008;9:204-218.
35. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. *Lancet* 2017;390:2673-2734.
36. Cai D. Neuroinflammation and neurodegeneration in overnutrition-induced diseases. *Trends Endocrinol Metab* 2013;24:40-47.
37. Julien C, Tremblay C, Phivilay A, et al. High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiol Aging* 2010;31:1516-1531.
38. Borga M, West J, Bell JD, et al. Advanced body composition assessment: from body mass index to body composition profiling. *J Investig Med* 2018;66:1-9. doi:10.1136/jim-2018-000722
39. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. *Am J Obstet Gynecol* 2019;221:393-409.e50.
40. Kurth F, Levitt JG, Phillips OR, et al. Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Hum Brain Mapp* 2013;34:1737-1746.
41. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026-1034.

Age, menstruation history, and the brain

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ORIGINAL STUDY

Age, menstruation history, and the brain

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Abstract

Objectives: To investigate the cross-sectional association between measures of menstruation history (including menopausal status, age of menopause, age of menarche, and duration of reproductive stage) and brain volume.

Methods: Women (aged 45 to 79 years) from the UK Biobank were included ($n = 5{,}072$) after excluding those who had (1) hysterectomy or bilateral oophorectomy, (2) ever used menopausal hormone therapy, (3) ever had a stroke, or (4) were perimenopausal. Multiple linear hierarchical regression models were computed to quantify the cross-sectional association between measures of menstruation history and brain volume. Sensitivity analysis based on propensity matching for age (and other demographic/health covariates) were applied to estimate differences in brain volumes between matched premenopausal and postmenopausal women.

Results: Postmenopausal women had 1.06% (95% confidence interval [CI]; 1.05-1.06) and 2.17% (95% CI, 2.12-2.22) larger total brain volume (TBV) and hippocampal volumes (HV), respectively, than premenopausal women. Sensitivity analysis with age matched samples produced consistent results (TBV: 0.82%, 95% CI, 0.25-1.38; HV: 1.33%, 95% CI, 0.01-2.63). For every year increase in age above 45 years, postmenopausal women experienced 0.23% greater reduction in TBV than premenopausal women (95% CI, −0.60 to −0.14), which was not observed for HV. Moreover, every 1 year delayed onset of menopause after 45 was associated with 0.32% (95% CI, −0.35 to −0.28) and 0.31% (95% CI, −0.40 to −0.22) smaller TBV and HV, respectively. Every additional year in age of menarche was associated with 0.10% (95% CI, 0.04-0.16) larger TBV, which was not detected for HV. Similarly, every 1 year increase in duration of reproductive stage was associated with 0.09% smaller TBV (95% CI, −0.15 to −0.03), which was not detected for HV.

Conclusions: Menopause may contribute to brain volume beyond typical aging effects. Furthermore, early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume. Further research is required to determine whether the negative association between age of menopause and HV is potentially an indicator of future vulnerability for dementia.

Key Words: Menopause – Neuroimaging – Postmenopausal – Premenopausal – UK biobank.

Age-standardized global prevalence for dementia is 17% higher in women than men, indicating that the higher prevalence in women may not be solely due to age.[1] Results from the Framingham Study revealed that the remaining lifetime risk of Alzheimers disease (AD), the most common form of dementia, was almost twice as high for a 65 year old woman (12%) than a 65 year old man (6.3%).[2] The longer life span observed in women does not fully explain the sex bias for AD, but increases the overall prevalence of all-cause dementia in women among the oldest old.[3] Moreover,

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menstruation history may also be particularly relevant, given that it is unique to female aging.

The association between menstruation history (including menopausal status, age of menopause, age of menarche, and duration of reproductive stage) and dementia is currently unclear. Some evidence indicates that younger age at menopause, later age at menarche and shorter reproductive spans are associated with elevated risk of developing dementia.[4] For example, women with reproductive spans less than 20 years and between 21 and 34 years had a 55% and 26% increased risk of dementia, respectively, compared to those with a reproductive span of 34 years or higher.[4] However, there is considerable heterogeneity in findings which do not support a consistent association between early menopause or a shorter reproductive period and increased dementia risk.[5]

Considering that AD pathology begins decades before the presentation of clinical symptoms, the effect of menstruation history on brain health may be reflected in brain volume.[6-8] Notably, brain volume loss within the hippocampus has been reliably associated with the early stages of AD[7] and is also predictive of conversion to AD from mild cognitive impairment.[9-11] Moreover, the hippocampus is particularly vulnerable to the impact of aging in healthy individuals.[12] However, the association between menopausal status and the hippocampus has been inconsistent. Some research has demonstrated that postmenopausal women experience greater decreases in hippocampal volume compared to premenopausal women,[13,14] whereas others report no significant differences.[15,16] This may be because previous studies did not precisely match premenopausal and postmenopausal women for age, which may have confounded a possible effect of menopause with that of typical aging. Furthermore, the association between other measures of menstruation history (including age of menopause, menarche, and duration of reproductive stage) and brain volume remains unclear.

Therefore, this study aimed to investigate the associations between measures of menstruation history (including menopausal status, age of menopause, age of menarche, and duration of reproductive stage) and brain volume.

METHODS

Participants

The UK Biobank study is a large population-based cohort, which consists of 502,506 participants aged 37 to 73 years at baseline who were recruited from the National Health Service central registers.[17] Of those participants, 11,243 women underwent a structural magnetic resonance imaging scan and were considered for inclusion. Of those, 1,960 were excluded because of missing data for menopausal status, giving a sample of 9,283 women. The Stages of Reproductive Aging Workshop criteria defines menopause as 1 year of amenorrhea after the final menstrual period.[18,19] Women who may have been classified as perimenopausal (ie, were not premenopausal and had reported an age of menopause less than 1 year ago), were excluded from the analyses ($n = 116$). This was done to ensure that a clear comparison could be made between groups, with premenopausal women acting as control participants for any effect that was observed after menopause. Furthermore, two women who had self-reported premenopausal status after the age of 70 years were excluded from analyses. Of those considered, after excluding participants who had reported (1) had a hysterectomy or bilateral oophorectomy ($n = 1045$), (2) ever used menopausal hormone therapy ($n = 3,441$), or (3) ever had a stroke ($n = 76$), 5,072 women meeting the inclusion criteria were available for analysis (premenopausal = 735 and postmenopausal = 4,337). Differences between those who were included and excluded have been reported in Supplemental Table 1, http://links.lww.com/MENO/A680. A flowchart describing sample selection is presented in Figure 1.

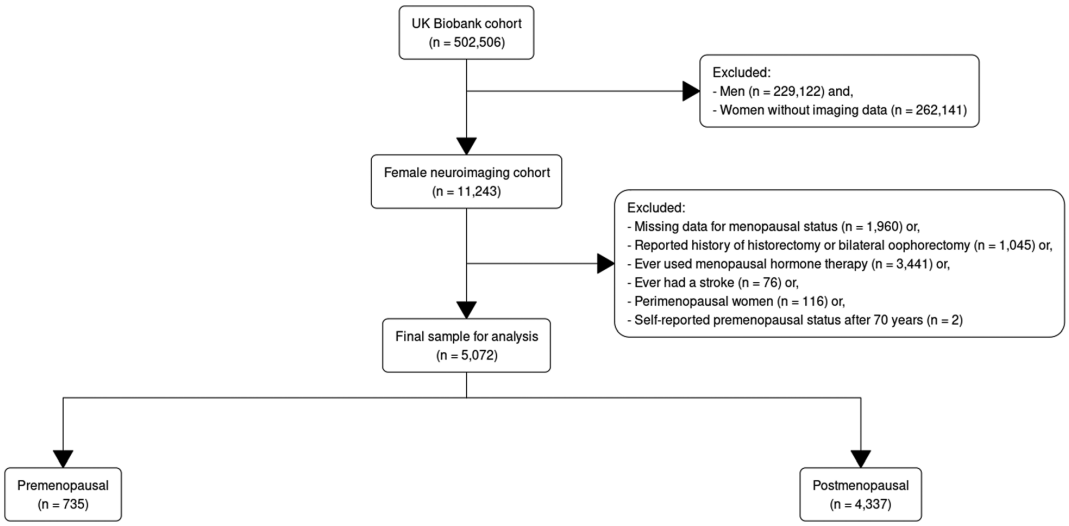

FIG. 1. Flowchart describing sample selection.

Ethical approval

UK Biobank received ethical approval from the North West Multi-center Research Ethics Committee (REC reference: 11/NW/0382). All participants gave written informed consent before enrollment in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Measures

Menstruation history

Measures of menstruation history included menopausal status, age of menopause, age of menarche, and duration of reproductive stage. Participants self-reported menopausal status, age of menopause and age of menarche at baseline assessment, first follow up and second follow up assessment (ie, imaging visit). The first instance of self-reported age of menopause and age of menarche were used for all analyses. Years since menopause was computed by subtracting age of menopause from age at imaging visit. Duration of reproductive stage was calculated by subtracting age of menarche from age of menopause.

Neuroimaging

Image acquisition

All participants were imaged across three imaging centers with identical scanners (3T Siemens Skyra running VD13A SP4) using a 32-channel head coil.[20] T1-weighted images were acquired in the sagittal orientation using a 3D magnetization-prepared rapid acquisition gradient echo (MPRAGE) sequence over a duration of 5 minutes; resolution = 1 × 1 × 1 mm; field of view = 208 × 256 × 256 matrix.[20]

Segmentation and image analysis

Images were processed and analyzed by the UK Biobank imaging team using the FMRIB Software Library (FSL) v6.0 (http://fsl.fmrib.ox.ac.uk/fsl). More detailed information on the standard magnetic resonance imaging analysis protocols have been reported elsewhere.[20,21] Briefly, the UK Biobank processing pipeline included a linear and nonlinear registration to the MNI152 template using FLIRT and FNIRT, respectively. Brain extraction was achieved by using the inverse of the MNI152 alignment warp with a standard-space brain mask transformed into the native space and applied to the image. Automated tissue segmentation was conducted with FAST to segment the brain tissue into gray matter, white matter, and cerebrospinal fluid. As part of the segmentation, intensity bias was estimated, which generated a fully bias-field corrected version of the brain-extracted image. The external surface of the skull was then estimated from the T1-weighted image and used to normalize brain tissue volumes for head size, compared with the MNI152 template. Subcortical structures (including total hippocampal volume - ie, left and right hippocampi combined) were derived using FIRST. Notably, all brain volumes used in subsequent analyses were normalized for head size.

Covariates

Covariates included self-reported age, smoking history (ie, ever or never), waist circumference, educational attainment, physical activity (ie, number of days per week spent doing at least 10 min of continuous vigorous activity), frequency of alcohol intake (ie, daily or almost daily, 3-4 times/wk, 1-2 times/wk, 1-3 times/mo, special occasions only, never or prefer not to answer), and number of children. Further covariates included self-reported vascular/heart problems (including heart attack, angina, or hypertension) and diabetes, diagnosed by doctor. Additionally, participants were also classified as hypertensive if they were using blood pressure medication and/or as diabetic if they were using oral antidiabetic medication or insulin.

Statistical methods

All statistical analyses were conducted using R (version 4.0.0), in RStudio (version 1.3.952). Descriptive analyses were conducted using *t* tests to compare premenopausal and postmenopausal women on continuous variables and chi square tests for categorical data.

Multiple linear hierarchical regression models were computed to quantify the association between menopausal status and brain volume (ie, total brain volume and hippocampal volume), while controlling for age (centered on 45 years, the youngest reported age at imaging assessment), smoking history, waist circumference and diabetes history (Model 1). Model 2 further controlled for vascular/heart problems, education, physical activity, alcohol use, and number of children. Interactions between menopausal status and age were also tested (Model 3). Since the age range for postmenopausal women exceeded that for premenopausal women, these analyses were repeated in an age restricted sample of 1,431 women aged 45 to 55 years (premenopausal = 720; postmenopausal = 711). To further delineate the effects of aging and menopause, sensitivity analyses using propensity matching was conducted to compare closely matched premenopausal and postmenopausal women (1:1 ratio). Exact matching was conducted for age and nearest neighbor matching for smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems, and diabetes (using package *MatchIt*, version 3.0.2). A linear regression model was then computed to estimate differences in total brain volume and hippocampal volume between the matched groups.

In addition, multiple linear hierarchical regression models were computed to determine the association between age, age of menopause, age of menarche, duration of reproductive stage, and brain volume. Premenopausal women were excluded from analyses of age of menopause and duration of reproductive stage. For analysis concerning age of menopause, to improve interpretability, age of menopause was centered at 45 years and years since menopause was used to account for current age. For duration of reproductive stage, in addition to age, age at menopause (centered on 45 y) was adjusted to account for similar duration of reproductive stage

lengths between women with varying ages at menopause. Due to the large sample size in this study, it was possible to resolve partial effects, even among predictors that were highly correlated. After accounting for age, Model 1 also controlled for smoking history, waist circumference and diabetes history. Model 2 further controlled for vascular/heart problems, education, physical activity, alcohol use, and number of children.

The alpha level was set at < 0.05. Unstandardised beta-coefficients and proportional percentage differences in brain volume were reported. These proportions were computed by using the baseline brain volumes (ie, when $x = 0$) and the beta-coefficients. Nonlinear associations were explored by fitting a quadratic term for age. Assumptions of linearity, including homoscedasticity and normality of residuals were examined.

RESULTS

The participants' demographic and health characteristics are presented in Table 1. Included participants were on average 60.32 years (standard deviation [SD] = 7.11, range = 45 to 79). On average, every year increase in age after 45 years was associated with 0.34% (95% confidence interval [CI], −0.35 to −0.32) lower total brain volume and 0.26% (95% CI, −0.30 to −0.23) lower hippocampal volume, after adjusting for all covariates (Supplemental Table 2, http://links.lww.com/MENO/A681). A scatterplot showing the distribution of total brain volume and hippocampal volume across time for premenopausal and postmenopausal women is presented in Figure 2.

Menopausal status and brain volume

After adjusting for all covariates, a significant effect of menopausal status was detected, with postmenopausal women having 1.06% (95% CI, 1.05-1.07) larger total brain volume and 2.17% (95% CI, 2.12-2.22) larger hippocampal volume than premenopausal women (Table 2). For total brain volume, there was a significant interaction between age and menopausal status, indicating that for every 1 year increase in age above 45, postmenopausal women experienced 0.23% greater reduction in total brain volume than premenopausal women (95% CI, −0.60 to −0.14). Similar interactive effects were not found in the hippocampus (Table 2). These findings were consistent in an age restricted sample of 1,431 women (premenopausal = 720; postmenopausal = 711), aged 45 to 55 years (Supplemental Table 3, http://links.lww.com/MENO/A682). Specifically, after adjusting for all covariates, postmenopausal women had 2.46% (95% CI, 2.29-2.62) larger total brain volume and 1.23% (95% CI, 1.17-2.29) larger hippocampal volume than premenopausal women (Supplemental Table 3, http://links.lww.com/MENO/A682). For total brain volume, there was a significant interaction between age and menopausal status, indicating that for every 1 year increase in age above 45 years, postmenopausal women experienced 0.27% greater reduction in total brain volume than premenopausal women (95% CI, −0.71 to −0.06). Similar interactive effects were not found in the hippocampus (Supplemental Table 3, http://links.lww.com/MENO/A682).

Sensitivity analyses based on propensity matching (participants' demographic and health characteristics are presented in Table 3), revealed a significant effect of menopausal status indicating that postmenopausal women had 0.82% (95% CI, 0.25-1.38) larger total brain volumes and 1.33% (95% CI, 0.01-2.63) larger hippocampal volumes than premenopausal women (Supplemental Table 4, http://links.lww.com/MENO/A683).

Age of menopause and brain volume

For postmenopausal women, after adjusting for all covariates, age of menopause was significantly associated with total brain volume and hippocampal volume, indicating that every 1 year delay in menopause after 45 was associated with 0.32% (95% CI, −0.35 to −0.28) smaller total brain volume and 0.31% (95%

TABLE 1. *Demographic and health characteristics for premenopausal and postmenopausal women*

Characteristics/Measures	Overall ($N = 5,072$)	PreM ($N = 735$)	PostM ($N = 4,337$)	t/χ
Age, years; mean, (SD)	60.32 (7.11)	50.44 (2.33)	61.99 (6.23)	<0.001
Age at menopause; mean, (SD)	51.14 (3.49)	-	51.14 (3.49)	-
Years since menopause; mean, (SD)	10.86 (6.63)	-	10.86 (6.63)	-
Duration of reproductive stage; mean, (SD)	38.14 (3.86)	-	38.14 (3.86)	-
Age at menarche; mean, (SD)	13.01 (1.55)	13.13 (1.49)	12.99 (1.56)	0.0239
Number of children; mean, (SD)	1.69 (1.19)	1.47 (1.16)	1.73 (1.19)	<0.001
Education college/degree; N (%)	2,497 (49.23)	409 (55.65)	2,088 (48.14)	<0.001
Hypertension; N(%)	672 (13.25)	56 (7.62)	616 (14.20)	<0.001
Diabetes; N (%)	87 (1.72)	10 (1.36)	77 (1.78)	0.518
Ever smoker; N (%)	2,383 (46.98)	338 (45.99)	2,045 (47.15)	0.523
Waist Circumference, cm; mean (SD)	81.30 (11.19)	80.64 (11.21)	81.42 (11.18)	0.0829
Adjusted total hippocampal volume, mm^3; mean (SD)	10,322 (997)	10,478 (946)	10,295 (1003)	<0.001
Adjusted total brain volume, mm^3; mean (SD)	1,522,864 (71,618)	1,567,572 (60,209)	1,515,287 (70,631)	<0.001
Unadjusted total brain volume and cerebrospinal fluid, mm^3; mean (SD)	1,146,636 (90,478)	1,176,811 (88,738)	1,141,522 (89780)	<0.001

Of the overall sample, there were 13 (0.26%) missing for hypertension, 5 (0.10%) missing for diabetes, 17 (0.34%) missing for smoking status, 4 (0.08%) missing for waist circumference, and 3 (0.06%) missing for hippocampal volume. Of postmenopausal women, there were 47 (1.08%) missing for duration of reproductive stage. Total brain volume and hippocampal volume were normalised by head size. Total hippocampal volume refers to left and right hippocampi combined

N, number; PostM, postmenopausal women; PreM, premenopausal women; SD, standard deviation.

$P < 0.05$ considered significant.

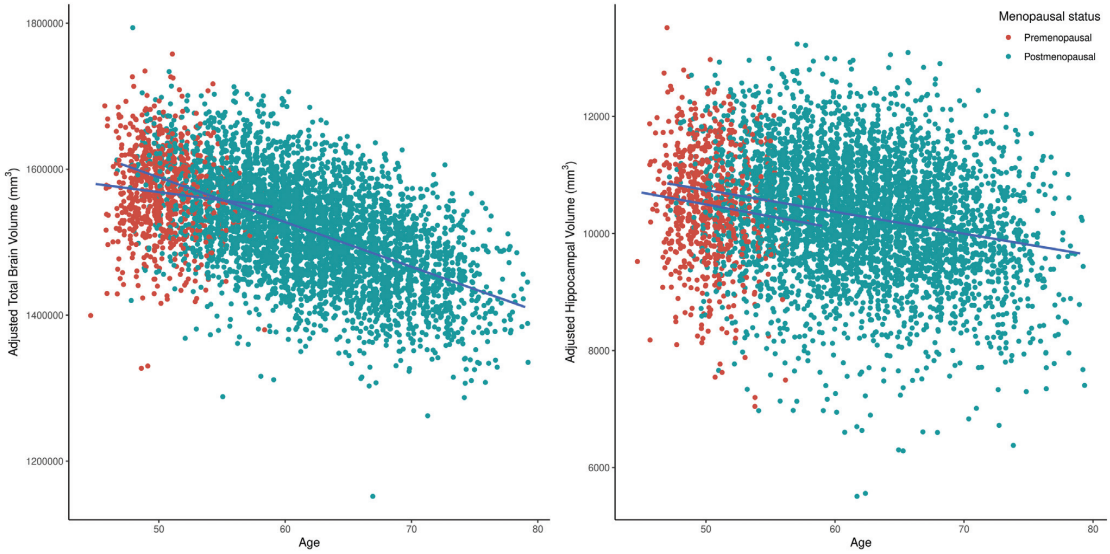

FIG. 2. Scatterplot showing the distribution of total brain volume and hippocampal volume (adjusted for head size) across time for premenopausal and postmenopausal women.

CI, −0.40 to −0.22) smaller hippocampal volume (Supplemental Table 5, http://links.lww.com/MENO/A684).

Age of menarche and brain volume

Age of menarche was significantly associated with total brain volume, indicating that every 1 year increase in age of menarche was associated with 0.10% larger total brain volume (95% CI, 0.04-0.16). This association was not observed for the hippocampus (Supplemental Table 6, http://links.lww.com/MENO/A685).

Duration of reproductive stage and brain volume

In postmenopausal women, duration of reproductive stage was significantly associated with total brain volume, indicating that every 1 year increase in duration of reproductive stage was associated with 0.09% smaller total brain volume (95% CI, −0.15 to −0.03). This association was not observed for the hippocampus (Supplemental Table 7, http://links.lww.com/MENO/A686).

DISCUSSION

This study produced two main findings. Postmenopausal women were found to have larger brain volumes than premenopausal women but also experience greater decreases in total brain volume, but not hippocampal volume, over time. In addition, early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume.

TABLE 2. *Multiple linear hierarchical regression models were computed to generate estimates for the association between menopausal status and brain volume*

Brain Volume	Predictors	Estimate	95% CI	% Diff	95% CI	*P* value	ΔR^2
Total brain volume (Model 1)	Yes - had menopause	16,980	11,308 to 22,652	1.04	1.03 to 1.04	**<0.001**	0.312
	Age	−5,970	−6,253 to −5,688	-	-	**<0.001**	
Total brain volume (Model 2)	Yes - had menopause	17,309	11,630 to 22,987	1.06	1.05 to 1.07	**<0.001**	0.009
	Age	−5,967	−6,261 to −5,673	-	-	**<0.001**	
Total brain volume (Model 3)	Menopause∗age	−3,880	−5,738 to −2,021	−0.23	−0.60 to −0.14	**<0.001**	0.002
Hippocampal volume (Model 1)	Yes - had menopause	243	151 to 336	2.15	2.12 to 2.19	**<0.001**	0.056
	Age	−36	−41 to −32	-	-	**<0.001**	
Hippocampal volume (Model 2)	Yes - had menopause	244	151 to 337	2.17	2.12 to 2.22	**<0.001**	0.005
	Age	−36	−41 to −31	-	-	**<0.001**	
Hippocampal volume (Model 3)	Menopause∗age	2	−28 to 33	0.03	0.88 to 0.21	0.886	0.000

Model 1 is adjusted for age (centered on 45), smoking history, waist circumference, and diabetes history. Model 2 is additionally adjusted for vascular/heart problems, education, physical activity, alcohol use, and number of children. Model 3 includes an interaction term for menopausal status and age. All estimates are unstandardized, ie, mm^3. Total brain volume and hippocampal volume were normalized by head size. Hippocampal volume refers to left and right hippocampi combined.
CI, confidence interval; ΔR^2, change in R^2 (the coefficient of determination); % Diff, proportional difference in brain volume between premenopausal and postmenopausal women, expressed as a percentage.
$P < 0.05$ considered significant at bold values.

TABLE 3. *Demographic and health characteristics for the propensity matched sample of premenopausal and postmenopausal women*

Characteristics/measures	Overall ($N = 734$)	PreM ($N = 367$)	PostM ($N = 367$)	t/χ
Age, years; mean, (SD)	52.01 (2.01)	52.01 (2.01)	52.01 (2.01)	1
Age at menopause; mean, (SD)	48.61 (3.03)	-	48.61 (3.03)	-
Years since menopause; mean, (SD)	3.40 (2.85)	-	3.40 (2.85)	-
Duration of reproductive stage; mean, (SD)	35.40 (3.45)	-	35.40 (3.45)	-
Age at menarche; mean, (SD)	13.21 (1.53)	13.23 (1.53)	13.18 (1.53)	0.687
Number of children; mean, (SD)	1.32 (1.14)	1.46 (1.14)	1.19 (1.12)	0.0014
Education college/degree; N (%)	371 (50.54)	205 (55.86)	166 (45.23)	<0.001
Hypertension; N (%)	54 (7.36)	28 (7.63)	26 (7.08)	0.08
Diabetes; N (%)	10 (1.36)	6 (1.63)	4 (1.09)	0.75
Ever smoker; N (%)	360 (49.05)	168 (45.78)	192 (52.32)	0.0895
Waist circumference, cm; mean (SD)	78.99 (10.31)	80.00 (10.63)	77.97 (9.88)	0.0075
Adjusted total hippocampal volume, mm^3; mean (SD)	10,502 (951)	10,432 (903)	10,571 (993)	0.0478
Adjusted total brain volume, mm^3; mean (SD)	1,569,485 (61,219)	1,563,107 (59,596)	1,575,862 (62,229)	0.0046
Unadjusted total brain volume and cerebrospinal fluid, mm^3; mean (SD)	1,175,093 (88,370)	1,177,097 (87,296)	1,173,089 (89,506)	0.539

Total brain volume and hippocampal volume were normalized by head size. Total hippocampal volume refers to left and right hippocampi combined.
Exact matching was conducted for age and nearest neighbor matching for smoking history, waist circumference, educational attainment, physical activity, alcohol intake, number of children, vascular/heart problems, and diabetes.
N, number; PostM, postmenopausal women; PreM, premenopausal women; SD, standard deviation.
$P < 0.05$ considered significant.

Previous studies have found that postmenopausal women have smaller hippocampal volumes than premenopausal women,[13,14] whereas others report no significant differences.[15,16] Notably, these studies did not precisely match premenopausal and postmenopausal women for age, possibly due to their limited sample size. This is of particular importance, given that aging and menopause both progress concurrently, which can make it difficult to determine the individual contribution of each for measures of brain health. This study is unique, due to its sample size, in its capacity to conduct propensity matching for age (and other relevant covariates) and demonstrate that postmenopausal women had 0.82% and 1.33% larger total brain and hippocampal volumes than premenopausal women, respectively, which was not previously detected.[13-16] Furthermore, postmenopausal women experienced a greater reduction in total brain volume over time than premenopausal women (−0.23%/y), but not for hippocampal volume. A possible explanation for these findings is that early age of natural menopause may be detrimental for total brain volume, but not hippocampal volume given that, as age increased the differences in hippocampal volume reduction did not significantly differ between premenopausal and postmenopausal women. Another possible explanation is that increased systemic inflammation associated with menopause might explain the current results. Indeed, higher pro-inflammatory cytokine levels have been linked with the decline in estrogen with menopause.[22,23] For example, previous research has demonstrated that postmenopausal women had higher levels of tumor necrosis factor-α (a proinflammatory cytokine) than premenopausal women, which persisted after adjustments for age and measures of fat mass.[24] Larger brain volumes are typically interpreted as reflecting better cerebral health. However, it is possible that in the initial transition period to menopause, elevated systemic inflammation might lead to an increase in brain volume. Such effects have been previously demonstrated in multiple sclerosis[25] and could explain the larger brain volumes detected in the present study in postmenopausal women. Furthermore, chronic inflammation has been associated with brain shrinkage which is consistent with the pattern of results observed in the present study.[26] Future longitudinal neuroimaging/biomarker studies are required to investigate this question further. However, one alternative interpretation for the brain volume differences is that, for unknown reasons, those with larger brain volumes were more likely to have menopause earlier. Although possible, this explanation is less likely given that we were careful to control for relevant covariates in our analyses, including age, smoking history, waist circumference, diabetes, vascular/heart problems, education, physical activity, alcohol use and number of children. Furthermore, brain volumes that were unadjusted for age (and other relevant covariates), were larger in premenopausal women than postmenopausal women (Table 1). However, after considering the effect of age, regression analyses, age-restricted analyses and age-matched analyses all consistently demonstrated that postmenopausal women had larger total brain and hippocampal volumes than premenopausal women. Matched analysis also revealed no significant differences in unadjusted headsize between premenopausal and postmenopausal women (Table 3), indicating that observed results were not attributable to headsize differences between groups. Nevertheless, it cannot be completely discounted that factors, such as sampling bias, may be present.

The underlying biological mechanism between menstruation history and measures of brain health, such as brain volume, remains unclear. Previous meta-analyses have demonstrated that postmenopausal women have an unfavorable lipid profile compared to premenopausal women and also tend to accumulate adipose tissue after menopause, which has been associated with smaller hippocampal volume.[27-29] However, these effects were predominantly attributable to aging.[27,28] Moreover, previous studies have used measures of menstruation history as a proxy for estimating estrogen exposure.[30-32]

This may be because animal studies have found that estrogen potentially exerts neuroprotective effects on the brain, particularly for the hippocampus.[33] Furthermore, estrogen receptors can be found throughout the brain, including the hippocampus,[34,35] a brain region that is sensitive to changes, particularly in the early stages of AD.[6,7] However, exogenous estrogen use has had both positive and negative associations with the brain, depending on the time of initiation, duration and type of treatment.[36-40] These results are part of the rationale for excluding women who self-reported menopausal hormone therapy use in the current study. Notably, within the context of the estrogen hypothesis, our findings are not consistent with a neuroprotective role of endogenous estrogen exposure on brain volume, given that delayed age of menopause, early age of menarche, and increasing duration of reproductive stage were negatively associated with brain volume. Although, it is important to note that women with similar menstruation duration may not necessarily have similar amounts of endogenous estrogen exposure. Furthermore, in addition to decreased endogenous production of estrogen, menopause is associated with changes in other hormones including progesterone, follicle-stimulating hormone, luteinizing hormone, and testosterone.[19,41] Therefore, these results should be carefully interpreted, given that it is possible that observed associations between menstruation history and the brain may have been moderated by any combination of these hormones. Moreover, further research is required to determine whether the negative association between age of menopause and hippocampal volume is potentially an indicator of future vulnerability for dementia.

Strengths and limitations

Key strengths of the present study include the large neuroimaging cohort ($n = 5,072$) and the use of sensitivity analyses, using propensity matching, to confirm that observed associations were not driven by confounding factors often associated with age of menopause or aging. Furthermore, women who were classified as perimenopausal were not included in the present study. This was done to ensure that a clear comparison could be made between groups, with premenopausal women acting as control participants for any effect that was observed after menopause. However, this study had a number of limitations. Menopausal status, age of menopause and age of menarche were obtained by self-report and therefore may not be accurate. In addition, imaging data was only available at one timepoint, which limited our ability to precisely determine how brain volume changed within participants over time as they progressed from premenopause to postmenopause. Moreover, the healthy participant bias for the UK Biobank cohort[42] may have somewhat contributed to the observed results. Notably, participants included in the present study were also less likely to smoke, have diabetes or hypertension and were more likely to be younger, have a college degree and have larger hippocampal and total brain volumes compared to excluded participants (Supplemental Table 1, http://links.lww.com/MENO/A680). Furthermore, the UK Biobank cohort included women who were 45 years of age and older, which may impact the generalizability of these findings, particularly to those who experienced early or premature menopause. Therefore further replication is required in other cohorts.

CONCLUSIONS

These findings indicate that menopause may contribute to brain volume beyond typical aging effects. Furthermore, critical female reproductive events including early age of menarche, delayed age of menopause and increasing duration of reproductive stage were negatively associated with brain volume. Further research is required to determine whether the negative association between age of menopause and HV is potentially an indicator of future vulnerability for dementia.

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REFERENCES

1. Nichols E, Szoeke CEI, Vollset SE, et al. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2019;18:88-106.
2. Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease: The impact of mortality on risk estimates in the Framingham Study. *Neurology* 1997;49:1498-1504.
3. Podcasy JL, Epperson CN. Considering sex and gender in Alzheimer disease and other dementias. *Dialogues Clin Neurosci* 2016;18:437-446.
4. Gilsanz P, Lee C, Corrada MM, Kawas CH, Quesenberry CP, Whitmer RA. Reproductive period and risk of dementia in a diverse cohort of health care members. *Neurology* 2019;92:e2005-e2014.
5. Georgakis MK, Kalogirou EI, Diamantaras A-A, et al. Age at menopause and duration of reproductive period in association with dementia and cognitive function: a systematic review and meta-analysis. *Psychoneuroendocrinology* 2016;73:224-243.
6. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991;82:239-259.
7. Zakzanis KK, Graham SJ, Campbell Z. A meta-analysis of structural and functional brain imaging in dementia of the Alzheimer's type: a neuroimaging profile. *Neuropsychol Rev* 2003;13:1-18.
8. Ohm TG, Müller H, Braak H, Bohl J. Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. *Neuroscience* 1995;64:209-217.
9. Tabatabaei-Jafari H, Shaw ME, Walsh E, Cherbuin N. Cognitive/functional measures predict Alzheimer's disease, dependent on hippocampal volume. *J Gerontol: Series B* 2020;75:1393-1402.
10. Tabatabaei-Jafari H, Walsh E, Shaw ME, Cherbuin N. A simple and clinically relevant combination of neuroimaging and functional indexes for the identification of those at highest risk of Alzheimer's disease. *Neurobiol Aging* 2018;69:102-110.
11. Tabatabaei-Jafari H, Shaw ME, Walsh E, Cherbuin N. Regional brain atrophy predicts time to conversion to Alzheimer's disease, dependent on baseline volume. *Neurobiol Aging* 2019;83:86-94.
12. Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nat Rev Neurosci* 2006;7:30-40.
13. Mosconi L, Rahman A, Diaz I, et al. Increased Alzheimer's risk during the menopause transition: a 3-year longitudinal brain imaging study. *PLoS One* 2018;13:e0207885.
14. Goto M, Abe O, Miyati T, et al. 3 Tesla MRI detects accelerated hippocampal volume reduction in postmenopausal women. *J Magnet Reson Imag* 2011;33:48-53.
15. Kim G-W, Park K, Jeong G-W. Effects of sex hormones and age on brain volume in post-menopausal women. *J Sex Med* 2018;15:662-670.

16. Sullivan EV, Marsh L, Pfefferbaum A. Preservation of hippocampal volume throughout adulthood in healthy men and women. *Neurobiol Aging* 2005;26:1093-1098.
17. Sudlow C, Gallacher J, Allen N, et al. UK Biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLOS Med* 2015;12:e1001779.
18. Soules MR, Sherman S, Parrott E, et al. Executive summary: stages of reproductive aging workshop (STRAW). *Climacteric* 2001;4:267-272.
19. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97:1159-1168.
20. Miller KL, Alfaro-Almagro F, Bangerter NK, et al. Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neurosci* 2016;19:1523-1536.
21. Alfaro-Almagro F, Jenkinson M, Bangerter NK, et al. Image processing and quality control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage* 2018;166:400-424.
22. Christensen A, Pike CJ. Menopause, obesity and inflammation: interactive risk factors for Alzheimer's disease. *Front Aging Neurosci* 2015;7:130.
23. Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. *Endocr Rev* 2002;23:90-119.
24. Sites CK, Toth MJ, Cushman M, et al. Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. *Fertil Steril* 2002;77:128-135.
25. Cheriyan J, Kim S, Wolansky LJ, Cook SD, Cadavid D. Impact of inflammation on brain volume in multiple sclerosis. *Arch Neurol* 2012;69:82-88.
26. Jefferson AL, Massaro JM, Wolf PA, et al. Inflammatory biomarkers are associated with total brain volume: the Framingham Heart Study. *Neurology* 2007;68:1032-1038.
27. Ambikairajah A, Walsh E, Tabatabaei-Jafari H, Cherbuin N. Fat mass changes during menopause: a metaanalysis. *Am J Obstet Gynecol* 2019;221:393.e50-409.e50.
28. Ambikairajah A, Walsh E, Cherbuin N. Lipid profile differences during menopause: a review with meta-analysis. *Menopause* 2019;26:1327-1333.
29. Ambikairajah A, Tabatabaei-Jafari H, Walsh E, Hornberger M, Cherbuin N. Longitudinal changes in fat mass and the hippocampus. *Obesity* 2020;28:1263-1269.
30. Prince MJ, Acosta D, Guerra M, et al. Reproductive period, endogenous estrogen exposure and dementia incidence among women in Latin America and China; A 10/66 population-based cohort study. *PLOS One* 2018;13:e0192889.
31. de Kleijn MJJ, van der Schouw YT, Verbeek ALM, Peeters PHM, Banga J-D, van der Graaf Y. Endogenous estrogen exposure and cardiovascular mortality risk in postmenopausal women. *Am J Epidemiol* 2002;155:339-345.
32. Fox M, Berzuini C, Knapp LA. Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. *Psychoneuroendocrinology* 2013;38:2973-2982.
33. Hara Y, Waters EM, McEwen BS, Morrison JH. Estrogen effects on cognitive and synaptic health over the lifecourse. *Physiol Rev* 2015;95:785-807.
34. Österlund MK, Grandien K, Keller E, Hurd YL. The human brain has distinct regional expression patterns of estrogen receptor α mRNA isoforms derived from alternative promoters. *J Neurochem* 2000;75:1390-1397.
35. Almey A, Milner TA, Brake WG. Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. *Horm Behav* 2015;74:125-138.
36. Boccardi M, Ghidoni R, Govoni S, et al. Effects of hormone therapy on brain morphology of healthy postmenopausal women: a Voxel-based morphometry study. *Menopause* 2006;13:584-591.
37. Erickson KI, Colcombe SJ, Raz N, et al. Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. *NeurobiolAging* 2005;26:1205-1213.
38. Resnick SM, Espeland MA, Jaramillo SA, et al. Postmenopausal hormone therapy and regional brain volumes: the WHIMS-MRI study. *Neurology* 2009;72:135-142.
39. Wnuk A, Korol DL, Erickson KI. Estrogens, hormone therapy, and hippocampal volume in postmenopausal women. *Maturitas* 2012;73:186-190.
40. Lord C, Buss C, Lupien SJ, Pruessner JC. Hippocampal volumes are larger in postmenopausal women using estrogen therapy compared to past users, never users and men: a possible window of opportunity effect. *Neurobiol Aging* 2008;29:95-101.
41. Al-Azzawi F, Palacios S. Hormonal changes during menopause. *Maturitas* 2009;63:135-137.
42. Fry A, Littlejohns TJ, Sudlow C, et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. *Am J Epidemiol* 2017;186:1026.

References

Abate, M., Schiavone, C., Di Carlo, L., & Salini, V. (2014). Prevalence of and risk factors for asymptomatic rotator cuff tears in postmenopausal women. *Menopause*, *21*(3), 275–280. https://doi.org/f5vhfz

Abdulnour, J., Doucet, E., & Brochu, M. (2012). The effect of the menopausal transition on body composition and cardiometabolic risk factors: A Montreal-Ottawa New Emerging Team group study. *Menopause*. https://doi.org/f34kt4

Abildgaard, J., Pedersen, A. T., & Green, C. J. (2013). Menopause is associated with decreased whole body fat oxidation during exercise. *American Journal of Physiology Endocrinology and Metabolism*, *304:E1227-36*.

Abu-Taha, M., Rius, C., Hermenegildo, C., Noguera, I., Cerda-Nicolas, J.-M., Issekutz, A. C., Jose, P. J., Cortijo, J., Morcillo, E. J., & Sanz, M.-J. (2009). Menopause and Ovariectomy Cause a Low Grade of Systemic Inflammation that May Be Prevented by Chronic Treatment with Low Doses of Estrogen or Losartan. *The Journal of Immunology*, *183*(2), 1393–1402. https://doi.org/b6x4bn

Adams-Campbell, L. L., Kim, K. S., Dunston, G., Laing, A. E., Bonney, G., & Demenais, F. (1996). The relationship of body mass index to reproductive factors in pre- and postmenopausal African-American women with and without breast cancer. *Obesity Research*, *4*, 451–456. https://doi.org/gg5427

Agrinier, N., Cournot, M., & Dallongeville, J. (2010). Menopause and modifiable coronary heart disease risk factors: A population based study. *Maturitas*, *65*, 237–243. https://doi.org/b5gszw

Aguado, F., Revilla, M., Hernandez, E. R., Villa, L. F., & Rico, H. (1996). Behavior of bone mass measurements. Dual energy x-ray absorptiometry total body bone mineral content, ultrasound bone velocity, and computed metacarpal radiogrammetry, with age, gonadal status, and weight in healthy women. *Investigative Radiology*, *31*, 218–222. https://doi.org/cs22bv

Aitken, R. J., Iuliis, G. N. D., & McLachlan, R. I. (2009). Biological and clinical significance of DNA damage in the male germ line. *International Journal of Andrology*, *32*(1), 46–56. https://doi.org/cs4p5w

Akahoshi, M., Soda, M., & Nakashima, E. (2001). Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. *Atherosclerosis*, *156*, 157–163. https://doi.org/dx4m84

Akioyamen, L. E., Genest, J., Chu, A., Inibhunu, H., Ko, D. T., & Tu, J. V. (2019). Risk factors for cardiovascular disease in heterozygous familial hypercholesterolemia: A systematic review and meta-analysis. *Journal of Clinical Lipidology*, *13*(1), 15–30.

https://doi.org/gjdv4g

Al-Azzawi, F., & Palacios, S. (2009). Hormonal changes during menopause. *Maturitas*, *63*(2), 135–137. https://doi.org/bhpwqw

Albanese, C. V., Cepollaro, C., Terlizzi, F., Brandi, M. L., & Passariello, R. (2009). Performance of five phalangeal QUS parameters in the evaluation of gonadal-status, age and vertebral fracture risk compared with DXA. *Ultrasound in Medicine & Biology*, *35*, 537–544. https://doi.org/c3b5tf

Albanese, E., Launer, L. J., Egger, M., Prince, M. J., Giannakopoulos, P., Wolters, F. J., & Egan, K. (2017). Body mass index in midlife and dementia: Systematic review and meta-regression analysis of 589,649 men and women followed in longitudinal studies. *Alzheimer's & Dementia : Diagnosis, Assessment & Disease Monitoring*, *8*, 165–178. https://doi.org/ggfvq8

Alberti, K. G. M. M., Zimmet, P., & Shaw, J. (2006). Metabolic syndrome—a new world-wide definition. A Consensus Statement from the International Diabetes Federation. *Diabetic Medicine*, *23*(5), 469–480. https://doi.org/ckn4w9

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N. K., Andersson, J. L. R., Griffanti, L., Douaud, G., Sotiropoulos, S. N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D. C., Zhang, H., Dragonu, I., Matthews, P. M., … Smith, S. M. (2018). Image processing and Quality Control for the first 10,000 brain imaging datasets from UK Biobank. *NeuroImage*, *166*, 400–424. https://doi.org/gcsbhf

Allali, F., El Mansouri, L., & Abourazzak, F. (2009). The effect of past use of oral contraceptive on bone mineral density, bone biochemical markers and muscle strength in healthy pre and post menopausal women. *BMC Women's Health*, *9*(31).

Almey, A., Milner, T. A., & Brake, W. G. (2015). Estrogen receptors in the central nervous system and their implication for dopamine-dependent cognition in females. *Hormones and Behavior*, *74*, 125–138. https://doi.org/f7r7n4

Aloia, J. F., Vaswani, A., Ma, R., & Flaster, E. (1995). To what extent is bone mass determined by fat-free or fat mass? *American Journal of Clinical Nutrition*, *61*, 1110–1114. https://doi.org/gg5423

Altmann, A., Tian, L., Henderson, V. W., Greicius, M. D., & Alzheimer's Disease Neuroimaging Initiative Investigators. (2014). Sex modifies the APOE-related risk of developing Alzheimer disease. *Annals of Neurology*, *75*(4), 563–573. https://doi.org/ggprjz

Amankwah, E. K., Friedenreich, C. M., & Magliocco, A. M. (2013). Anthropometric measures and the risk of endometrial cancer, overall and by tumor microsatellite status and histological subtype. *American Journal of Epidemiology*, *177*, 1378–1387. https://doi.org/f4z28b

Amarante, F., Vilodre, L. C., Maturana, M. A., & Spritzer, P. M. (2011). Women with primary ovarian insufficiency have lower bone mineral density. *Brazilian Journal of Medical and Biological Research = Revista Brasileira de Pesquisas Medicas e Biologicas*, *44*, 78–83. https://doi.org/cr6fdx

Amaro-Gahete, F. J., De-la-O, A., Jurado-Fasoli, L., Ruiz, J. R., Castillo, M. J., & Gutiérrez, Á. (2019). Effects of different exercise training programs on body composition: A randomized control trial. *Scandinavian Journal of Medicine & Science in Sports*, *29*(7), 968–979. https://doi.org/ghns66

Ambikairajah, A., Tabatabaei-Jafari, H., Hornberger, M., & Cherbuin, N. (2021). Age, menstruation history, and the brain. *Menopause*, *28*(2), 167–174. https://doi.org/ghtfz7

Ambikairajah, A., Tabatabaei-Jafari, H., Walsh, E., Hornberger, M., & Cherbuin, N. (2020). Longitudinal Changes in Fat Mass and the Hippocampus. *Obesity*, *28*(7), 1263–1269. https://doi.org/ggwqg5

Ambikairajah, A., Walsh, E., & Cherbuin, N. (2019). Lipid profile differences during menopause: A review with meta-analysis. *Menopause*, 1. https://doi.org/gf8kmj

Ambikairajah, A., Walsh, E., Tabatabaei-Jafari, H., & Cherbuin, N. (2019). Fat mass changes during menopause: A metaanalysis. *American Journal of Obstetrics and Gynecology*, *221*(5), 393–409.e50. https://doi.org/gf39q6

Amiri, P., Deihim, T., Nakhoda, K., Hasheminia, M., Montazeri, A., & Azizi, F. (2014). Metabolic syndrome and health-related quality of life in reproductive age and post-menopausal women: Tehran Lipid and Glucose Study. *Archives of Iranian Medicine*, *17*, 423–428.

Amundsen, D. W., & Diers, C. J. (1970). The age of menopause in classical greece and rome. *Human Biology*, *42*(1), 79–86.

Anagnostis, P., Christou, K., Artzouchaltzi, A.-M., Gkekas, N. K., Kosmidou, N., Siolos, P., Paschou, S. A., Potoupnis, M., Kenanidis, E., Tsiridis, E., Lambrinoudaki, I., Stevenson, J. C., & Goulis, D. G. (2019). Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: A systematic review and meta-analysis. *European Journal of Endocrinology*, *180*(1), 41–50. https://doi.org/ghjd7m

Angsuwathana, S., Leerasiri, P., & Rattanachaiyanont, M. (2007). Health check-up program for pre/postmenopausal women at Siriraj Menopause Clinic. *Journal of the Medical Association of Thailand = Chotmaihet Thangphaet*, *90*, 1–8.

Anstey, K. J., Ashby-Mitchell, K., & Peters, R. (2017). Updating the evidence on the association between serum cholesterol and risk of late-life dementia: Review and meta-analysis. *Journal of Alzheimer's Disease*, *56*(1), 215–228. https://doi.org/10.3233/jad-160826

Anstey, K. J., Cherbuin, N., Budge, M., & Young, J. (2011). Body mass index in midlife and late-life as a risk factor for dementia: A meta-analysis of prospective studies: BMI and risk of dementia. *Obesity Reviews*, *12*(5), e426–e437. https://doi.org/10.1111/j.1467-789x.2010.00825.x

Anstey, K. J., Lipnicki, D. M., & Low, L.-F. (2008). Cholesterol as a Risk Factor for Dementia and Cognitive Decline: A Systematic Review of Prospective Studies With Meta-Analysis. *The American Journal of Geriatric Psychiatry*, *16*(5), 343–354. https://doi.org/10.1097/01.jgp.0000310778.20870.ae

Ardekani, B. A., Convit, A., & Bachman, A. H. (2016). Analysis of the MIRIAD Data Shows Sex Differences in Hippocampal Atrophy Progression. *Journal of Alzheimer's Disease*, *50*(3), 847–857. https://doi.org/f79w5w

Armellini, F., Zamboni, M., & Perdichizzi, G. (1996). Computed tomography visceral adipose tissue volume measurements of Italians. Predictive equations. *European Journal of Clinical Nutrition*, *50*, 290–294.

Arthur, F. K., Adu-Frimpong, M., Osei-Yeboah, J., Mensah, F. O., & Owusu, L. (2013). The prevalence of metabolic syndrome and its predominant components among pre-and postmenopausal Ghanaian women. *BMC Research Notes*, *6*(446).

Atsma, F., Bartelink, M.-L. E. L., Grobbee, D. E., & van der Schouw, Y. T. (2006). Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: A meta-analysis. *Menopause*, *13*(2), 265. https://doi.org/bnwzg5

Aydin, Z. D. (2010). Determinants of age at natural menopause in the Isparta Menopause and Health Study: Premenopausal body mass index gain rate and episodic weight loss. *Menopause*. https://doi.org/fkwt8q

Ayub, N., Khan, S., SR, & F. (2006). Leptin levels in pre and post menopausal Pakistani women. *JPMA The Journal of the Pakistan Medical Association*, *56*, 3–5.

Bancroft, J., & Cawood, E. H. (1996). Androgens and the menopause; a study of 40-60-year-old women. *Clinical Endocrinology*, *45*, 577–587. https://doi.org/dk6456

Banno, M., Harada, Y., Taniguchi, M., Tobita, R., Tsujimoto, H., Tsujimoto, Y., Kataoka, Y., & Noda, A. (2018). Exercise can improve sleep quality: A systematic review and meta-analysis. *PeerJ*, *6*, e5172. https://doi.org/ghns9g

Barnes, J., Bartlett, J. W., van de Pol, L. A., Loy, C. T., Scahill, R. I., Frost, C., Thompson, P., & Fox, N. C. (2009). A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. *Neurobiology of Aging*, *30*(11), 1711–1723. https://doi.org/d27psh

Barnes, L. L., Wilson, R. S., Bienias, J. L., Schneider, J. A., Evans, D. A., & Bennett, D. A. (2005). Sex Differences in the Clinical Manifestations of Alzheimer Disease Pathology. *Archives of General Psychiatry*, *62*(6), 685–691. https://doi.org/cxpbgv

Bearak, J., Popinchalk, A., Alkema, L., & Sedgh, G. (2018). Global, regional, and subregional trends in unintended pregnancy and its outcomes from 1990 to 2014: Estimates from a Bayesian hierarchical model. *The Lancet Global Health*, *6*(4), e380–e389. https://doi.org/gc5qb5

Bednarek-Tupikowska, G., Filus, A., Kuliczkowska-Plaksej, J., Tupikowski, K., Bohdanowicz-Pawlak, A., & Milewicz, A. (2006). Serum leptin concentrations in pre- and postmenopausal women on sex hormone therapy. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *22*, 207–212. https://doi.org/bnwfm4

Beery, A. K., & Zucker, I. (2011). Sex bias in neuroscience and biomedical research. *Neuroscience & Biobehavioral Reviews*, *35*(3), 565–572. https://doi.org/ff34pz

Bell, R. J., Davison, S. L., Papalia, M.-A., McKenzie, D. P., & Davis, S. R. (2007). Endogenous androgen levels and cardiovascular risk profile in women across the adult life span. *Menopause*, *14*(4), 630–638. https://doi.org/dg6g6c

Ben Ali, S., Belfki-Benali, H., Ahmed, D. B., Haddad, N., Jmal, A., Abdennebi, M., & Romdhane, H. B. (2016). Postmenopausal hypertension, abdominal obesity, apolipoprotein and insulin resistance. *Clinical and Experimental Hypertension*, *38*(4), 370–374. https://doi.org/gg6p5h

Ben Ali, S., Belfki-Benali, H., Aounallah-Skhiri, H., Traissac, P., Maire, B., Delpeuch, F., Achour, N., & Ben Romdhane, H. (2014). Menopause and Metabolic Syndrome in Tunisian Women. *BioMed Research International*, *2014*, e457131. https://doi.org/gb84sb

Ben Ali, S., Jemaa, R., Ftouhi, B., Kallel, A., Feki, M., Slimene, H., & Kaabachi, N. (2011). Relationship of plasma leptin and adiponectin concentrations with menopausal status in Tunisian women. *Cytokine*, *56*(2), 338–342. https://doi.org/bfvqnn

Berg, G., Mesch, V., & Boero, L. (2004). Lipid and lipoprotein profile in menopausal transition. Effects of hormones, age and fat distribution. *Hormone and Metabolic Research = Hormon- Und Stoffwechselforschung = Hormones Et Metabolisme*, *36*, 215–220. https://doi.org/b568gt

Berge, L. N., Bonaa, K. H., & Nordoy, A. (1994). Serum ferritin, sex hormones, and cardiovascular risk factors in healthy women. *Arteriosclerosis and Thrombosis : A Journal of Vascular Biology*, *14*, 857–861. https://doi.org/d9pzdd

Berger, G. M., Naidoo, J., Gounden, N., & Gouws, E. (1995). Marked hyperinsulinaemia in postmenopausal, healthy Indian (Asian) women. *Diabetic Medicine : A Journal of the British Diabetic Association*, *12*, 788–795. https://doi.org/c4nvjd

Berstad, P., Coates, R. J., & Bernstein, L. (2010). A case-control study of body mass index and breast cancer risk in white and African-American women. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research,*

Cosponsored by the American Society of Preventive Oncology, *19*, 1532–1544. https://doi.org/cnctng

Beydoun, M. A., Beydoun, H. A., & Wang, Y. (2008). Obesity and central obesity as risk factors for incident dementia and its subtypes: A systematic review and meta-analysis. *Obesity Reviews*, *9*(3), 204–218. https://doi.org/10.1111/j.1467-789x.2008.00473.x

Bhagat, M., Mukherjee, S., & De, P. (2010). Clustering of cardiometabolic risk factors in Asian Indian women: Santiniketan women study. *Menopause*. https://doi.org/ftmktk

Bhurosy, T., & Jeewon, R. (2013). Food habits, socioeconomic status and body mass index among premenopausal and post-menopausal women in Mauritius. *Journal of Human Nutrition and Dietetics : The Official Journal of the British Dietetic Association*, *1*, 114–122. https://doi.org/f44zz4

Binder, E. F., Williams, D. B., Schechtman, K. B., Jeffe, D. B., & Kohrt, W. M. (2001). Effects of Hormone Replacement Therapy on Serum Lipids in Elderly Women. *Annals of Internal Medicine*, *134*(9_Part_1), 754–760. https://doi.org/ghnxz2

Bjelland, E. K., Hofvind, S., Byberg, L., & Eskild, A. (2018). The relation of age at menarche with age at natural menopause: A population study of 336 788 women in Norway. *Human Reproduction*, *33*(6), 1149–1157. https://doi.org/gd8pcg

Blackburn, E. H., Epel, E. S., & Lin, J. (2015). Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. *Science*, *350*(6265), 1193–1198. https://doi.org/f72kkt

Blasco, M. A. (2007). Telomere length, stem cells and aging. *Nature Chemical Biology*, *3*(10), 640–649. https://doi.org/dm7qw3

Bloom, G. S. (2014). Amyloid-β and Tau: The Trigger and Bullet in Alzheimer Disease Pathogenesis. *JAMA Neurology*, *71*(4), 505. https://doi.org/f53fj2

Blumenthal, J. A., Fredrikson, M., & Matthews, K. A. (1991). Stress reactivity and exercise training in premenopausal and postmenopausal women. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association*, *10*, 384–391. https://doi.org/c2b5hs

Bobb, J. F., Schwartz, B. S., Davatzikos, C., & Caffo, B. (2014). Cross-sectional and longitudinal association of body mass index and brain volume. *Human Brain Mapping*, *35*(1). https://doi.org/10.1002/hbm.22159

Boccardi, M., Ghidoni, R., Govoni, S., Testa, C., Benussi, L., Bonetti, M., Binetti, G., & Frisoni, G. B. (2006). Effects of hormone therapy on brain morphology of healthy postmenopausal women: A Voxel-based morphometry study. *Menopause*, *13*(4), 584–591. https://doi.org/ccjt7f

Bolanowski, M., & Nilsson, B. E. (2001). Assessment of human body composition using

dual-energy x-ray absorptiometry and bioelectrical impedance analysis. *Medical Science Monitor*, *7*, 1029–1033.

Bonithon-Kopp, C., Scarabin, P. Y., Darne, B., Malmejac, A., & Guize, L. (1990). Menopause-related changes in lipoproteins and some other cardiovascular risk factors. *International Journal of Epidemiology*, *19*, 42–48. https://doi.org/dq2fzf

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97–111. https://doi.org/10.1002/jrsm.12

Borenstein, M., Hedges, L. V., Higgins, J. P., & Rothstein, H. R. (2009). *Introduction to Meta-Analysis*. John Wiley & Sons, Ltd.

Borga, M., West, J., Bell, J. D., Harvey, N. C., Romu, T., Heymsfield, S. B., & Leinhard, O. D. (2018). Advanced body composition assessment: From body mass index to body composition profiling. *Journal of Investigative Medicine*, *66*(5), 1–9. https://doi.org/gd8vkt

Bowen, R. L., & Atwood, C. S. (2004). Living and Dying for Sex. *Gerontology*, *50*(5), 265–290. https://doi.org/d6q3b4

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica*, *82*(4), 239–259. https://doi.org/chmfx2

Brand, J. S., Onland-Moret, N. C., Eijkemans, M. J. C., Tjønneland, A., Roswall, N., Overvad, K., Fagherazzi, G., Clavel-Chapelon, F., Dossus, L., Lukanova, A., Grote, V., Bergmann, M. M., Boeing, H., Trichopoulou, A., Tzivoglou, M., Trichopoulos, D., Grioni, S., Mattiello, A., Masala, G., … van der Schouw, Y. T. (2015). Diabetes and onset of natural menopause: Results from the European Prospective Investigation into Cancer and Nutrition. *Human Reproduction*, *30*(6), 1491–1498. https://doi.org/f3nmbx

Broekmans, F. J., Soules, M. R., & Fauser, B. C. (2009). Ovarian Aging: Mechanisms and Clinical Consequences. *Endocrine Reviews*, *30*(5), 465–493. https://doi.org/10.1210/er.2009-0006

Brown, S. (2012). Shock, terror and controversy: How the media reacted to the Women's Health Initiative. *Climacteric*, *15*(3), 275–280. https://doi.org/10.3109/13697137.2012.660048

Bruehl, H., Wolf, O. T., Sweat, V., Tirsi, A., Richardson, S., & Convit, A. (2009). Modifiers of Cognitive Function and Brain Structure in Middle-Aged and Elderly Individuals with Type 2 Diabetes Mellitus. *Brain Research*, *1280*, 186–194. https://doi.org/10.1016/j.brainres.2009.05.032

Burger, H. G. (2002). Hormonal Changes in the Menopause Transition. *Recent Progress in Hormone Research*, *57*(1), 257–275. https://doi.org/10.1210/rp.57.1.257

Burger, H. G. (2006). *Physiology and endocrinology of the menopause*. 4. https://doi.org/bcxqgn

Burke, S. N., & Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, *7*(1), 30–40. https://doi.org/bnf76q

Cai, D. (2013). Neuroinflammation and neurodegeneration in overnutrition-induced diseases. *Trends in Endocrinology & Metabolism*, *24*(1), 40–47. https://doi.org/f4kkmq

Caire-Juvera, G., Arendell, L. A., Maskarinec, G., Thomson, C. A., & Chen, Z. (2008). Associations between mammographic density and body composition in Hispanic and non-Hispanic white women by menopause status. *Menopause*. https://doi.org/fhcf2z

Campesi, I., Occhioni, S., & Tonolo, G. (2016). Ageing/Menopausal status in healthy women and ageing in healthy men differently affect cardiometabolic parameters. *International Journal of Medical Sciences*, *13*, 124–132. https://doi.org/f8cszq

Canavez, F. S., Werneck, G. L., Parente, R. C. M., Celeste, R. K., & Faerstein, E. (2011). The association between educational level and age at the menopause: A systematic review. *Archives of Gynecology and Obstetrics*, *283*(1), 83–90. https://doi.org/cfw775

Cancer, C. G. on H. F. in B. (1997). Breast cancer and hormone replacement therapy: Collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. *The Lancet*, *350*(9084), 1047–1059. https://doi.org/ffhk4h

Cant, M. A., & Johnstone, R. A. (2008). Reproductive conflict and the separation of reproductive generations in humans. *Proceedings of the National Academy of Sciences*, *105*(14), 5332–5336. https://doi.org/fs8ghm

Carr, M. C. (2003). The Emergence of the Metabolic Syndrome with Menopause. *The Journal of Clinical Endocrinology & Metabolism*, *88*(6), 2404–2411. https://doi.org/2016092613291600352

Carr, M. C., Kim, K. H., & Zambon, A. (2000). Changes in LDL density across the menopausal transition. *Journal of Investigative Medicine : The Official Publication of the American Federation for Clinical Research*, *48*, 245–250.

Castracane, V. D., Kraemer, R. R., Franken, M. A., Kraemer, G. R., & Gimpel, T. (1998). Serum leptin concentration in women: Effect of age, obesity, and estrogen administration. *Fertility and Sterility*, *70*, 472–477. https://doi.org/bw7f53

Catsburg, C., Kirsh, V. A., & Soskolne, C. L. (2014). Associations between anthropometric characteristics, physical activity, and breast cancer risk in a Canadian cohort. *Breast Cancer Research and Treatment*, *145*, 545–552. https://doi.org/gg5429

Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or

older. *The Lancet*, *361*(9355), 393–395. https://doi.org/cv2m77

Cecchini, R. S., Costantino, J. P., & Cauley, J. A. (2012). Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. *Cancer Prevention Research (Philadelphia, Pa*, *5*, 583–592. https://doi.org/gg5428

Cervellati, C., Pansini, F. S., & Bonaccorsi, G. (2009). Body mass index is a major determinant of abdominal fat accumulation in pre-, peri- and post-menopausal women. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *25*, 413–417. https://doi.org/csjtvr

Chain, A., Crivelli, M., Faerstein, E., & Bezerra, F. F. (2017). Association between fat mass and bone mineral density among Brazilian women differs by menopausal status: The Pro-Saude Study. *Nutrition*, *33*, 14–19. https://doi.org/f9jjrc

Chang, C. J., Wu, C. H., Yao, W. J., Yang, Y. C., Wu, J. S., & Lu, F. H. (2000). Relationships of age, menopause and central obesity on cardiovascular disease risk factors in Chinese women. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*, *24*, 1699–1704. https://doi.org/fxbtsr

Chaput, J.-P., & Tremblay, A. (2012). Sleeping Habits Predict the Magnitude of Fat Loss in Adults Exposed to Moderate Caloric Restriction. *Obesity Facts*, *5*(4), 561–566. https://doi.org/f373vh

Chen, C., Ye, Y., Zhang, Y., Pan, X.-F., & Pan, A. (2019). Weight change across adulthood in relation to all cause and cause specific mortality: Prospective cohort study. *BMJ*, *367*, l5584. https://doi.org/ggcc93

Chen, J.-H., Hales, C. N., & Ozanne, S. E. (2007). DNA damage, cellular senescence and organismal ageing: Causal or correlative? *Nucleic Acids Research*, *35*(22), 7417–7428. https://doi.org/c3qjsf

Chêne, G., Beiser, A., Au, R., Preis, S. R., Wolf, P. A., Dufouil, C., & Seshadri, S. (2015). Gender and incidence of dementia in the Framingham Heart Study from mid-adult life. *Alzheimer's & Dementia*, *11*(3), 310–320. https://doi.org/f26tc7

Cherbuin, N., Sargent-Cox, K., Fraser, M., Sachdev, P., & Anstey, K. J. (2015). Being overweight is associated with hippocampal atrophy: The PATH Through Life Study. *International Journal of Obesity*, *39*(10), 1509–1514. https://doi.org/10.1038/ijo.2015.106

Cheriyan, J., Kim, S., Wolansky, L. J., Cook, S. D., & Cadavid, D. (2012). Impact of Inflammation on Brain Volume in Multiple Sclerosis. *Archives of Neurology*, *69*(1), 82–88. https://doi.org/fzj374

Chlebowski, R. T., Rohan, T. E., Manson, J. E., Aragaki, A. K., Kaunitz, A., Stefanick, M. L., Simon, M. S., Johnson, K. C., Wactawski-Wende, J., O'Sullivan, M. J., Adams-

Campbell, L. L., Nassir, R., Lessin, L. S., & Prentice, R. L. (2015). Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone: Analyses of Data From 2 Women's Health Initiative Randomized Clinical Trials. *JAMA Oncology*, *1*(3), 296–305. https://doi.org/10.1001/jamaoncol.2015.0494

Cho, G. J., Lee, J. H., & Park, H. T. (2008). Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome. *Menopause*.

Christensen, A., & Pike, C. J. (2015). Menopause, obesity and inflammation: Interactive risk factors for Alzheimer's disease. *Frontiers in Aging Neuroscience*, *7*. https://doi.org/10.3389/fnagi.2015.00130

Christin-Maitre, S. (2013). History of oral contraceptive drugs and their use worldwide. *Best Practice & Research Clinical Endocrinology & Metabolism*, *27*(1), 3–12. https://doi.org/f4pvv7

Cifkova, R., Pitha, J., Lejskova, M., Lanska, V., & Zecova, S. (2008). Blood pressure around the menopause: A population study. *Journal of Hypertension*, *26*, 1976–1982. https://doi.org/bnv7vr

Cole, J. H. (2020). Multimodality neuroimaging brain-age in UK biobank: Relationship to biomedical, lifestyle, and cognitive factors. *Neurobiology of Aging*, *92*, 34–42. https://doi.org/ggt557

Collaboration, O. S. (2015). Estimating the reproducibility of psychological science. *Science*, *349*(6251). https://doi.org/68c

Collaborative Group on Epidemiological Studies of Ovarian Cancer. (2015). Menopausal hormone use and ovarian cancer risk: Individual participant meta-analysis of 52 epidemiological studies. *The Lancet*, *385*(9980), 1835–1842. https://doi.org/f3hdc7

Cooper, R., Blell, M., Hardy, R., Black, S., Pollard, T. M., Wadsworth, M. E. J., Pearce, M. S., & Kuh, D. (2006). Validity of age at menarche self-reported in adulthood. *Journal of Epidemiology & Community Health*, *60*(11), 993–997. https://doi.org/dzfdbw

Copeland, A. L., Martin, P. D., Geiselman, P. J., Rash, C. J., & Kendzor, D. E. (2006). Predictors of pretreatment attrition from smoking cessation among pre- and postmenopausal, weight-concerned women. *Eating Behaviors*, *7*, 243–251. https://doi.org/cfr7hb

Cortés, M. E., Carrera, B., Rioseco, H., Pablo del Río, J., & Vigil, P. (2015). The Role of Kisspeptin in the Onset of Puberty and in the Ovulatory Mechanism: A Mini-review. *Journal of Pediatric and Adolescent Gynecology*, *28*(5), 286–291. https://doi.org/10.1016/j.jpag.2014.09.017

Cramer, D. W., & Xu, H. (1996). Predicting age at menopause. *Maturitas*, *23*(3), 319–326. https://doi.org/c6kdmh

Cramer, D. W., Xu, H., & Harlow, B. L. (1995). Family history as a predictor of early

menopause*. *Fertility and Sterility*, *64*(4), 740–745. https://doi.org/ghhrbz

Cremonini, E., Bonaccorsi, G., & Bergamini, C. M. (2013). Metabolic transitions at menopause: In post-menopausal women the increase in serum uric acid correlates with abdominal adiposity as assessed by DXA. *Maturitas*, *75*, 62–66. https://doi.org/f2j3jm

Croft, D. P., Brent, L. J. N., Franks, D. W., & Cant, M. A. (2015). The evolution of prolonged life after reproduction. *Trends in Ecology & Evolution*, *30*(7), 407–416. https://doi.org/f7j64z

Croll, P. H., Bos, D., Ikram, M. A., Rivadeneira, F., Voortman, T., & Vernooij, M. W. (2019). Body Composition Is Not Related to Structural or Vascular Brain Changes. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00559

Cui, L. H., Shin, M. H., & Kweon, S. S. (2007). Relative contribution of body composition to bone mineral density at different sites in men and women of South Korea. *Journal of Bone and Mineral Metabolism*, *25*, 165–171. https://doi.org/dzkxhd

Currais, A. (2015). Ageing and inflammation – A central role for mitochondria in brain health and disease. *Ageing Research Reviews*, *21*, 30–42. https://doi.org/ghjngm

Cutler, R. G., Kelly, J., Storie, K., Pedersen, W. A., Tammara, A., Hatanpaa, K., Troncoso, J. C., & Mattson, M. P. (2004). Involvement of oxidative stress-induced abnormalities in ceramide and cholesterol metabolism in brain aging and Alzheimer's disease. *Proceedings of the National Academy of Sciences*, *101*(7), 2070–2075. https://doi.org/bndq93

D'Haeseleer, E., Depypere, H., Claeys, S., & Van Lierde, K. M. (2011). The relation between body mass index and speaking fundamental frequency in premenopausal and postmenopausal women. *Menopause*. https://doi.org/bdvhjb

da Câmara, S. M., Zunzunegui, M. V., Pirkle, C., Moreira, M. A., & Maciel, Á. C. (2015). Menopausal status and physical performance in middle aged women: A cross-sectional community-based study in Northeast Brazil. *PLoS One*, *10*(3), e0119480. https://doi.org/f7ddzm

Dallongeville, J., Marecaux, N., Isorez, D., Zylbergberg, G., Fruchart, J. C., & Amouyel, P. (1995). Multiple coronary heart disease risk factors are associated with menopause and influenced by substitutive hormonal therapy in a cohort of French women. *Atherosclerosis*, *118*, 123–133. https://doi.org/dthkqx

Dancey, D. R., Hanly, P. J., Soong, C., Lee, B., & Hoffstein, V. (2001). Impact of menopause on the prevalence and severity of sleep apnea. *Chest*, *120*, 151–155. https://doi.org/ctcp9h

Darwin, C., & Bynum, W. F. (2009). *The origin of species by means of natural selection: Or, the preservation of favored races in the struggle for life*. AL Burt New York.

Davis, C. E., Pajak, A., & Rywik, S. (1994). Natural menopause and cardiovascular disease risk factors. *The Poland and US Collaborative Study on Cardiovascular Disease Epidemiology.*

Annals of Epidemiology, *4*, 445–448.

Davis, S. R., Castelo-Branco, C., Chedraui, P., Lumsden, M. A., Nappi, R. E., Shah, D., Villaseca, P., & Day 2012, W. G. of the I. M. S. for W. M. (2012). Understanding weight gain at menopause. *Climacteric*, *15*(5), 419–429. https://doi.org/gg5g49

Davis, S. R., Dinatale, I., Rivera-Woll, L., & Davison, S. (2005). Postmenopausal hormone therapy: From monkey glands to transdermal patches. *Journal of Endocrinology*, *185*(2), 207–222. https://doi.org/dqphc4

Davison, S. L., Bell, R., Donath, S., Montalto, J. G., & Davis, S. R. (2005). Androgen Levels in Adult Females: Changes with Age, Menopause, and Oophorectomy. *The Journal of Clinical Endocrinology & Metabolism*, *90*(7), 3847–3853. https://doi.org/10.1210/jc.2005-0212

de Bruijn, R. F., & Ikram, M. A. (2014). Cardiovascular risk factors and future risk of Alzheimer's disease. *BMC Medicine*, *12*(1), 130. https://doi.org/f6pw7s

de Kleijn, M. J. J., van der Schouw, Y. T., Verbeek, A. L. M., Peeters, P. H. M., Banga, J.-D., & van der Graaf, Y. (2002). Endogenous Estrogen Exposure and Cardiovascular Mortality Risk in Postmenopausal Women. *American Journal of Epidemiology*, *155*(4), 339–345. https://doi.org/c46tcs

de Vet, A., Laven, J. S. E., de Jong, F. H., Themmen, A. P. N., & Fauser, B. C. J. M. (2002). Antimüllerian hormone serum levels: A putative marker for ovarian aging. *Fertility and Sterility*, *77*(2), 357–362. https://doi.org/cz4579

de Villiers, T. J., Hall, J. E., Pinkerton, J. V., Pérez, S. C., Rees, M., Yang, C., & Pierroz, D. D. (2016). Revised global consensus statement on menopausal hormone therapy. *Maturitas*, *91*, 153–155. https://doi.org/gg7vnw

De Bont, R., & van Larebeke, N. (2004). Endogenous DNA damage in humans: A review of quantitative data. *Mutagenesis*, *19*(3), 169–185. https://doi.org/dzvj6t

De Kat, A. C., Dam, V., Onland-Moret, N. C., Eijkemans, M. J. C., Broekmans, F. J. M., & Van Der Schouw, Y. T. (2017). Unraveling the associations of age and menopause with cardiovascular risk factors in a large population-based study. *BMC Medicine*, *15*(1), 2.

De Koning, L., Merchant, A. T., Pogue, J., & Anand, S. S. (2007). Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: Meta-regression analysis of prospective studies. *European Heart Journal*, *28*(7), 850–856. https://doi.org/cbffbc

Demerath, E. W., Rogers, N. L., & Reed, D. (2011). Significant associations of age, menopausal status and lifestyle factors with visceral adiposity in African-American and European-American women. *Annals of Human Biology*, *38*, 247–256. https://doi.org/d4zc63

den Tonkelaar, I., Seidell, J. C., van Noord, P. A., Baanders-van Halewijn, E. A., & Ouwehand, I. J. (1990). Fat distribution in relation to age, degree of obesity, smoking habits, parity and estrogen use: A cross-sectional study in 11,825 Dutch women participating in the

DOM-project. *International Journal of Obesity*, *14*(9), 753–761.

Deng, W., Aimone, J. B., & Gage, F. H. (2010). New neurons and new memories: How does adult hippocampal neurogenesis affect learning and memory? *Nature Reviews Neuroscience*, *11*(5), 339–350. https://doi.org/fswhpz

Depmann, M., Eijkemans, M. J. C., Broer, S. L., Tehrani, F. R., Solaymani-Dodaran, M., Azizi, F., Lambalk, C. B., Randolph, J. F., Jr., Harlow, S. D., Freeman, E. W., Sammel, M. D., Verschuren, W. M. M., van der Schouw, Y. T., Mol, B. W., & Broekmans, F. J. M. (2018). Does AMH Relate to Timing of Menopause? Results of an Individual Patient Data Meta-Analysis. *The Journal of Clinical Endocrinology & Metabolism*, *103*(10), 3593–3600. https://doi.org/10.1210/jc.2018-00724

Derby, C. A., Crawford, S. L., Pasternak, R. C., Sowers, M., Sternfeld, B., & Matthews, K. A. (2009). Lipid changes during the menopause transition in relation to age and Weight: The study of women's health across the nation. *American Journal of Epidemiology*, *169*(11). https://doi.org/b2978j

Dmitruk, A., Czeczelewski, J., Czeczelewska, E., Golach, J., & Parnicka, U. (2018). Body composition and fatty tissue distribution in women with various menstrual status. *Roczniki Panstwowego Zakladu Higieny*, *69*, 95–101.

Donato, G. B., Fuchs, S. C., Oppermann, K., Bastos, C., & Spritzer, P. M. (2006). Association between menopause status and central adiposity measured at different cutoffs of waist circumference and waist-to-hip ratio. Menopause. *Menopause*. https://doi.org/dbbq74

Douchi, T., Kosha, S., & Uto, H. (2003). Precedence of bone loss over changes in body composition and body fat distribution within a few years after menopause. *Maturitas*, *46*, 133–138. https://doi.org/crds33

Douchi, T., Oki, T., Nakamura, S., Ijuin, H., Yamamoto, S., & Nagata, Y. (1997). The effect of body composition on bone density in pre- and postmenopausal women. *Maturitas*, *27*, 55–60. https://doi.org/crzpg4

Douchi, T., Yamamoto, S., Yoshimitsu, N., Andoh, T., Matsuo, T., & Nagata, Y. (2002). Relative contribution of aging and menopause to changes in lean and fat mass in segmental regions. *Maturitas*, *42*, 301–306. https://doi.org/fnw479

Douchi, T., Yonehara, Y., Kawamura, Y., Kuwahata, A., Kuwahata, T., & Iwamoto, I. (2007). Difference in segmental lean and fat mass components between pre-and postmenopausal women. *Menopause*, *14*(5), 875–878. https://doi.org/btt6j7

Driscoll, I., Beydoun, M. A., An, Y., Davatzikos, C., Ferrucci, L., Zonderman, A. B., & Resnick, S. M. (2012). Midlife obesity and trajectories of brain volume changes in older adults. *Human Brain Mapping*, *33*(9), 2204–2210. https://doi.org/10.1002/hbm.21353

Dubois, E. F., Bergh, J. P., Smals, A. G., Meerendonk, C. W., Zwinderman, A. H., &

Schweitzer, D. H. (2001). Comparison of quantitative ultrasound parameters with dual energy X-ray absorptiometry in pre- and postmenopausal women. *The Netherlands Journal of Medicine*, *58*, 62–70. https://doi.org/c8j9fg

Dudek, M., Ziarniak, K., & Sliwowska, J. H. (2018). Kisspeptin and Metabolism: The Brain and Beyond. *Frontiers in Endocrinology*, *9*. https://doi.org/10.3389/fendo.2018.00145

Duval, S., & Tweedie, R. (2000a). A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *Journal of the American Statistical Association*, *95*, 89–98.

Duval, S., & Tweedie, R. (2000b). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*, *56*(2). https://doi.org/cz42tj

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ*, *315*(7109), 629–634. https://doi.org/d36qsq

Ekdahl, C. T., Claasen, J.-H., Bonde, S., Kokaia, Z., & Lindvall, O. (2003). Inflammation is detrimental for neurogenesis in adult brain. *Proceedings of the National Academy of Sciences*, *100*(23), 13632–13637. https://doi.org/dgcff3

Elia, M., Ritz, P., & Stubbs, R. J. (2000). Total energy expenditure in the elderly. *European Journal of Clinical Nutrition*, *54*(3), S92–S103. https://doi.org/bsq2jv

Ellis, S., Franks, D. W., Nattrass, S., Currie, T. E., Cant, M. A., Giles, D., Balcomb, K. C., & Croft, D. P. (2018). Analyses of ovarian activity reveal repeated evolution of post-reproductive lifespans in toothed whales. *Scientific Reports*, *8*(1), 12833. https://doi.org/gd7b7b

Engmann, N. J., Golmakani, M. K., Miglioretti, D. L., Sprague, B. L., & Kerlikowske, K. (2017). Population-attributable risk proportion of clinical risk factors for breast cancer. *JAMA Oncology*, *3*, 1228–1236. https://doi.org/gg543b

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences*, *101*(49), 17312–17315. https://doi.org/b2nwws

Erickson, K. I., Colcombe, S. J., Elavsky, S., McAuley, E., Korol, D. L., Scalf, P. E., & Kramer, A. F. (2007). Interactive effects of fitness and hormone treatment on brain health in postmenopausal women. *Neurobiology of Aging*, *28*(2), 179–185. https://doi.org/ct5pxw

Erickson, K. I., Colcombe, S. J., Raz, N., Korol, D. L., Scalf, P., Webb, A., Cohen, N. J., McAuley, E., & Kramer, A. F. (2005). Selective sparing of brain tissue in postmenopausal women receiving hormone replacement therapy. *Neurobiology of Aging*, *26*(8), 1205–1213. https://doi.org/b4ddnt

Erickson, K. I., Voss, M. W., Prakash, R. S., Chaddock, L., & Kramer, A. F. (2010). A

cross-sectional study of hormone treatment and hippocampal volume in postmenopausal women: Evidence for a limited window of opportunity. *Neuropsychology*, *24*(1), 68–76. https://doi.org/10.1037/a0017292

Ertungealp, E., Seyisoglu, H., Erel, C. T., Senturk, L. M., & Gezer, A. (1999). Changes in bone mineral density with age, menopausal status and body mass index in Turkish women. *Climacteric : The Journal of the International Menopause Society*, *2*, 45–51. https://doi.org/c5bf5q

Essenberg, J. M., Fagan, L., & Malerstein, A. J. (1951). Chronic poisoning of the ovaries and testes of albino rats and mice by nicotine and cigarette smoke. *Obstetrical & Gynecological Survey*, *6*(3), 426–427. https://doi.org/bh7mcm

Ettinger, B., Pressman, A., & Silver, P. (1999). Effect of Age on Reasons for Initiation and Discontinuation of Hormone Replacement Therapy. *Menopause*, *6*(4), 282–289. https://doi.org/10.1097/00042192-199906040-00003

Ettinger, B., Wang, S. M., Leslie, R. S., Patel, B. V., Boulware, M. J., Mann, M. E., & McBride, M. (2012). Evolution of postmenopausal hormone therapy between 2002 and 2009. *Menopause (New York, N.Y.)*, *19*(6), 610–615. https://doi.org/fzf29m

Exalto, L. G., Whitmer, R. A., Kappele, L. J., & Biessels, G. J. (2012). An update on type 2 diabetes, vascular dementia and Alzheimer's disease. *Experimental Gerontology*, *47*(11), 858–864. https://doi.org/f4dk64

Feng, Y., Hong, X., & Wilker, E. (2008). Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases. *Atherosclerosis*, *196*, 590–597. https://doi.org/bhb8q3

Feyereisen, E., Lozano, D. H. M., Taieb, J., Hesters, L., Frydman, R., & Fanchin, R. (2006). Anti-Müllerian hormone: Clinical insights into a promising biomarker of ovarian follicular status. *Reproductive BioMedicine Online*, *12*(6), 695–703. https://doi.org/bfgt4n

Field, A. P., Miles, J., & Field, Z. (2012). *Discovering statistics using R*. Sage.

Finkel, T., & Holbrook, N. J. (2000). Oxidants, oxidative stress and the biology of ageing. *Nature*, *408*(6809), 239–247. https://doi.org/d3fcz4

Finkelstein, E. A., Fiebelkorn, I. C., & Wang, G. (2003). National Medical Spending Attributable To Overweight And Obesity: How Much, And Who's Paying? Further evidence that overweight and obesity are contributing to the nation's health care bill at a growing rate. *Health Affairs*, *22*(Suppl1), W3–219. https://doi.org/bhfw9s

Floud, S., Simpson, R. F., Balkwill, A., Brown, A., Goodill, A., Gallacher, J., Sudlow, C., Harris, P., Hofman, A., Parish, S., Reeves, G. K., Green, J., Peto, R., & Beral, V. (2020). Body mass index, diet, physical inactivity, and the incidence of dementia in 1 million UK women. *Neurology*, *94*(2), e123–e132. https://doi.org/ggfvfq

Fontana, L., Eagon, J. C., Trujillo, M. E., Scherer, P. E., & Klein, S. (2007). Visceral Fat Adipokine Secretion Is Associated With Systemic Inflammation in Obese Humans. *Diabetes*, *56*(4), 1010–1013. https://doi.org/10.2337/db06-1656

Ford, K., Sowers, M., Crutchfield, M., Wilson, A., & Jannausch, M. (2005). A longitudinal study of the predictors of prevalence and severity of symptoms commonly associated with menopause. *Menopause*, *12*(3), 308–317. https://doi.org/cp5nq9

Formica, C., Loro, M. L., Gilsanz, V., & Seeman, E. (1995). Inhomogeneity in body fat distribution may result in inaccuracy in the measurement of vertebral bone mass. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, *10*, 1504–1511. https://doi.org/dhqv4m

Fox, M., Berzuini, C., & Knapp, L. A. (2013). Cumulative estrogen exposure, number of menstrual cycles, and Alzheimer's risk in a cohort of British women. *Psychoneuroendocrinology*, *38*(12), 2973–2982. https://doi.org/f5rpwt

Franke, K., Ziegler, G., Klöppel, S., & Gaser, C. (2010). Estimating the age of healthy subjects from T1-weighted MRI scans using kernel methods: Exploring the influence of various parameters. *NeuroImage*, *50*(3), 883–892. https://doi.org/bp7m63

Franklin, R. M., Ploutz-Snyder, L., & Kanaley, J. A. (2009). Longitudinal changes in abdominal fat distribution with menopause. *Metabolism: clinical and experimental*, *58*, 311–315. https://doi.org/fjjq3d

Fraser, M. A., Shaw, M. E., & Cherbuin, N. (2015). A systematic review and meta-analysis of longitudinal hippocampal atrophy in healthy human ageing. *NeuroImage*, *112*, 364–374. https://doi.org/10.1016/j.neuroimage.2015.03.035

Freeman, E. W., Sammel, M. D., Lin, H., & Gracia, C. R. (2012). Anti-Mullerian Hormone as a Predictor of Time to Menopause in Late Reproductive Age Women. *The Journal of Clinical Endocrinology & Metabolism*, *97*(5), 1673–1680. https://doi.org/10.1210/jc.2011-3032

Freitas, A. A., & de Magalhães, J. P. (2011). A review and appraisal of the DNA damage theory of ageing. *Mutation Research/Reviews in Mutation Research*, *728*(1), 12–22. https://doi.org/cdfknm

Friedenreich, C. M., Courneya, K. S., & Bryant, H. E. (2002). Case-control study of anthropometric measures and breast cancer risk. *International Journal of Cancer*, *99*, 445–452. https://doi.org/dvt4pm

Friedenreich, C., Cust, A., & Lahmann, P. H. (2007). Anthropometric factors and risk of endometrial cancer: The European prospective investigation into cancer and nutrition. *Cancer Causes & Control : CCC*, *18*, 399–413. https://doi.org/d8kct9

Fry, A., Littlejohns, T. J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., & Allen, N. E. (2017). Comparison of Sociodemographic and Health-Related Characteristics

of UK Biobank Participants With Those of the General Population. *American Journal of Epidemiology*, *186*(9), 1026. https://doi.org/gcj6pm

Fu, X., Ma, X., Lu, H., He, W., Wang, Z., & Zhu, S. (2011). Associations of fat mass and fat distribution with bone mineral density in pre- and postmenopausal Chinese women. Osteoporosis international : A journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. *Osteoporosis International*, *22*(1), 113–119. https://doi.org/dfzbhf

Fuh, J.-L., Wang, S.-J., Lee, S.-J., Lu, S.-R., & Juang, K.-D. (2003). Quality of life and menopausal transition for middle-aged women on Kinmen island. *Quality of Life Research*, *12*(1), 53–61. https://doi.org/fwj438

Fukami, K., Koike, K., Hirota, K., Yoshikawa, H., & Miyake, A. (1995). Perimenopausal changes in serum lipids and lipoproteins: a 7-year longitudinal study. *Maturitas*, *22*(3). https://doi.org/cn5tfn

Gackowski, D., Rozalski, R., Siomek, A., Dziaman, T., Nicpon, K., Klimarczyk, M., Araszkiewicz, A., & Olinski, R. (2008). Oxidative stress and oxidative DNA damage is characteristic for mixed Alzheimer disease/vascular dementia. *Journal of the Neurological Sciences*, *266*(1), 57–62. https://doi.org/dm9g7w

Gage, F. H. (2002). Neurogenesis in the Adult Brain. *Journal of Neuroscience*, *22*(3), 612–613. https://doi.org/gkmsxj

Gambacciani, M., Ciaponi, M., Cappagli, B., Benussi, C., De Simone, L., & Genazzani, A. R. (1999). Climacteric modifications in body weight and fat tissue distribution. *Climacteric*, *2*, 37–44. https://doi.org/d299wv

Gaskins, A. J., Zhang, C., & Perkins, N. J. (2010). A longitudinal study of serum lipoproteins in relation to endogenous reproductive hormones during the menstrual cycle: Findings from the BioCycle study. *The Journal of Clinical Endocrinology & Metabolism*, *95*(9).

Gaspard, U. J., Gottal, J.-M., & van den Brûle, F. A. (1995). Postmenopausal changes of lipid and glucose metabolism: A review of their main aspects. *Maturitas*, *21*(3), 171–178. https://doi.org/10.1016/0378-5122(95)00901-v

GBD 2019 Collaborators. (2021). Global mortality from dementia: Application of a new method and results from the Global Burden of Disease Study 2019. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *7*(1), e12200.

Genazzani, A. R., & Gambacciani, M. (2006). Effect of climacteric transition and hormone replacement therapy on body weight and body fat distribution. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *22*, 145–150. https://doi.org/bgbjrp

Georgakis, M. K., Kalogirou, E. I., Diamantaras, A.-A., Daskalopoulou, S. S., Munro, C. A.,

Lyketsos, C. G., Skalkidou, A., & Petridou, E. Th. (2016). Age at menopause and duration of reproductive period in association with dementia and cognitive function: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *73*, 224–243. https://doi.org/f3trwz

Ghosh, A. (2008). Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women. *Cardiovascular Journal of Africa*, *19*, 183–187.

Ghosh, A., & Bhagat, M. (2010). Anthropometric and body composition characteristics in pre- and postmenopausal Asian Indian women: Santiniketan women study. *Anthropologischer Anzeiger; Bericht uber die biologisch-anthropologische Literatur*, *68*, 1–10. https://doi.org/10.1127/0003-5548/2010/0005

Gilsanz, P., Lee, C., Corrada, M. M., Kawas, C. H., Quesenberry, C. P., & Whitmer, R. A. (2019). Reproductive period and risk of dementia in a diverse cohort of health care members. *Neurology*, *92*(17), e2005–e2014. https://doi.org/gf9gm5

Glass, C. K., Saijo, K., Winner, B., Marchetto, M. C., & Gage, F. H. (2010). Mechanisms Underlying Inflammation in Neurodegeneration. *Cell*, *140*(6), 918–934. https://doi.org/d6s8cc

Godsland, I. F. (2001). Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: Analysis of studies published from 1974–2000. *Fertility and Sterility*, *75*(5). https://doi.org/ckcqft

Goto, M., Abe, O., Miyati, T., Inano, S., Hayashi, N., Aoki, S., Mori, H., Kunimatsu, A., Ino, K., Iida, K., Yano, K., & Ohtomo, K. (2011). Accelerated hippocampal volume reduction in post-menopausal women: An additional study with Atlas-based method. *Radiological Physics and Technology*, *4*(2), 185–188. https://doi.org/fp52wv

Gould, E., Woolley, C., Frankfurt, M., & McEwen, B. (1990). Gonadal steroids regulate dendritic spine density in hippocampal pyramidal cells in adulthood. *The Journal of Neuroscience*, *10*(4), 1286–1291. https://doi.org/gg5rtp

Grady, D., Gebretsadik, T., Kerlikowske, K., Ernster, V., & Petitti, D. (1995). Hormone replacement therapy and endometrial cancer risk: A meta-analysis. *Obstetrics & Gynecology*, *85*(2), 304–313. https://doi.org/df5xxw

Gram, I. T., Funkhouser, E., & Tabar, L. (1997). Anthropometric indices in relation to mammographic patterns among peri-menopausal women. *International Journal of Cancer*, *73*, 323–326. https://doi.org/b28587

Gregor, M. F., & Hotamisligil, G. S. (2011). Inflammatory Mechanisms in Obesity. *Annual Review of Immunology*, *29*(1), 415–445. https://doi.org/c3bq8v

Grodstein, F., Stampfer, M. J., Colditz, G. A., Willett, W. C., Manson, J. E., Joffe, M., Rosner, B., Fuchs, C., Hankinson, S. E., Hunter, D. J., Hennekens, C. H., & Speizer, F. E. (1997). Postmenopausal Hormone Therapy and Mortality. *New England Journal of*

Medicine, *336*(25), 1769–1776. https://doi.org/dcm7hn

Grundy, S. M., Cleeman, J. I., & Bairey Merz, C. N. (2004). Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Journal of the American College of Cardiology*, *44*(3). https://doi.org/fgqqtx

Guerrero, R. T. L., Novotny, R., Wilkens, L. R., Chong, M., White, K. K., Shvetsov, Y. B., Buyum, A., Badowski, G., & Blas-Laguaña, M. (2017). Risk factors for breast cancer in the breast cancer risk model study of Guam and Saipan. *Cancer Epidemiology*, *50*, 221–233. https://doi.org/gcm67j

Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C. L., & Anis, A. H. (2009). The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*, *9*(1), 88. https://doi.org/dh3czz

Guo, W., Bradbury, K. E., Reeves, G. K., & Key, T. J. (2015). Physical activity in relation to body size and composition in women in UK Biobank. *Annals of Epidemiology*, *25*(6), 406–413.e6. https://doi.org/f7dmkm

Gurka, M. J., Vishnu, A., Santen, R. J., & DeBoer, M. D. (2016). Progression of metabolic syndrome severity during the menopausal transition. *Journal of the American Heart Association*, *5*. https://doi.org/gg5425

Hadji, P., Hars, O., & Bock, K. (2000). The influence of menopause and body mass index on serum leptin concentrations. *European Journal of Endocrinology*, *143*, 55–60. https://doi.org/fcxk58

Hagner, W., Hagner-Derengowska, M., Wiacek, M., & Zubrzycki, I. Z. (2009). Changes in level of V · O2max, blood lipids, and waist circumference in the response to moderate endurance training as a function of ovarian aging. *Menopause*, *16*(5), 1009–1013. https://doi.org/fwvgg6

Hamer, M., & Batty, G. D. (2019). Association of body mass index and waist-to-hip ratio with brain structure: UK Biobank study. *Neurology*, *92*(6), e594–e600. https://doi.org/10.1212/wnl.0000000000006879

Han, D., Nie, J., & Bonner, M. R. (2006). Lifetime adult weight gain, central adiposity, and the risk of pre- and postmenopausal breast cancer in the Western New York exposures and breast cancer study. *International Journal of Cancer*, *119*, 2931–2937. https://doi.org/fvgdq2

Hara, Y., Waters, E. M., McEwen, B. S., & Morrison, J. H. (2015). Estrogen Effects on Cognitive and Synaptic Health Over the Lifecourse. *Physiological Reviews*, *95*(3), 785–807. https://doi.org/f7qvqk

Harlow, B. L., & Signorello, L. B. (2000). Factors associated with early menopause. *Maturitas*, *35*(1), 3–9. https://doi.org/d3mk66

Harlow, S. D., Cain, K., Crawford, S., Dennerstein, L., Little, R., Mitchell, E. S., Nan, B., Randolph, J. F., Taffe, J., & Yosef, M. (2006). Evaluation of Four Proposed Bleeding Criteria for the Onset of Late Menopausal Transition. *The Journal of Clinical Endocrinology & Metabolism*, *91*(9), 3432–3438. https://doi.org/10.1210/jc.2005-2810

Harlow, S. D., Crawford, S., Dennerstein, L., Burger, H. G., Mitchell, E. S., Sowers, M.-F., & for the ReSTAGE Collaboration. (2007). Recommendations from a multi-study evaluation of proposed criteria for Staging Reproductive Aging. *Climacteric*, *10*(2), 112–119. https://doi.org/10.1080/13697130701258838

Harlow, S. D., Gass, M., Hall, J. E., Lobo, R., Maki, P., Rebar, R. W., Sherman, S., Sluss, P. M., de Villiers, T. J., & for the STRAW + 10 Collaborative Group. (2012). Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. *The Journal of Clinical Endocrinology & Metabolism*, *97*(4), 1159–1168. https://doi.org/2016092613074600892

Harlow, S. D., Mitchell, E. S., Crawford, S., Nan, B., Little, R., & Taffe, J. (2008). The ReSTAGE Collaboration: Defining optimal bleeding criteria for onset of early menopausal transition. *Fertility and Sterility*, *89*(1), 129–140. https://doi.org/bswzhp

Harman, D. (1972). The Biologic Clock: The Mitochondria? *Journal of the American Geriatrics Society*, *20*(4), 145–147. https://doi.org/ggmjw7

Harting, G. H., Moore, C. E., Mitchell, R., & Kappus, C. M. (1984). Relationship of menopausal status and exercise level to HDL-cholesterol in women. *Experimental Aging Research*, *10*, 13–18. https://doi.org/c8czgg

Hawkes, K., O'Connell, J. F., & Blurton Jones, N. G. (1997). Hadza Women's Time Allocation, Offspring Provisioning, and the Evolution of Long Postmenopausal Life Spans. *Current Anthropology*, *38*(4), 551–577. https://doi.org/b7xssg

Hawkes, K., O'Connell, J. F., Jones, N. G. B., Alvarez, H., & Charnov, E. L. (1998). Grandmothering, menopause, and the evolution of human life histories. *Proceedings of the National Academy of Sciences*, *95*(3), 1336–1339. https://doi.org/dz6pxz

Hayflick, L., & Moorhead, P. S. (1961). The serial cultivation of human diploid cell strains. *Experimental Cell Research*, *25*(3), 585–621. https://doi.org/bc9ck9

He, L., Tang, X., & Li, N. (2012). Menopause with cardiovascular disease and its risk factors among rural Chinese women in Beijing: a population-based study. *Maturitas*, *72*, 132–138. https://doi.org/f2jxr9

Heijer, T. den, Hofman, A., Koudstaal, P. J., & Breteler, M. M. B. (2005). Serum lipids and hippocampal volume: The link to Alzheimer's disease? *Annals of Neurology*, *57*(5), 779–780. https://doi.org/dwp3w3

Hemsell, D. L., Grodin, J. M., Brenner, P. F., Siiteri, P. K., & Macdonald, P. C. (1974).

Plasma Precursors of Estrogen. II. Correlation of the Extent of Conversion of Plasma Androstenedione to Estrone with Age. *The Journal of Clinical Endocrinology & Metabolism*, *38*(3), 476–479. https://doi.org/10.1210/jcem-38-3-476

Henderson, K. D., Bernstein, L., Henderson, B., Kolonel, L., & Pike, M. C. (2008). Predictors of the Timing of Natural Menopause in the Multiethnic Cohort Study. *American Journal of Epidemiology*, *167*(11), 1287–1294. https://doi.org/d256bf

Herbig, U., Ferreira, M., Condel, L., Carey, D., & Sedivy, J. M. (2006). Cellular Senescence in Aging Primates. *Science*, *311*(5765), 1257–1257. https://doi.org/cx4zcj

Hickey, M., Davis, S. R., & Sturdee, D. W. (2005). Treatment of menopausal symptoms: What shall we do now? *The Lancet*, *366*(9483), 409–421. https://doi.org/cp3ts3

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal*, *327*(557).

Higgins, J., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions Version 5.1. 0. The Cochrane Collaboration*.

Hipkiss, A. R. (2006). Accumulation of altered proteins and ageing: Causes and effects. *Experimental Gerontology*, *41*(5), 464–473. https://doi.org/bzwmx5

Hipp, M. S., Kasturi, P., & Hartl, F. U. (2019). The proteostasis network and its decline in ageing. *Nature Reviews Molecular Cell Biology*, *20*(7), 421–435. https://doi.org/ggx6v5

Hirose, K., Tajima, K., Hamajima, N., Takezaki, T., Inoue, M., Kuroishi, T., & Miura, S. (2003). Impact of established risk factors for breast cancer in nulligravid Japanese women. *Breast Cancer*, *10*(1), 45. https://doi.org/bbrx3h

Hjartaker, A., Adami, H. O., Lund, E., & Weiderpass, E. (2005). Body mass index and mortality in a prospectively studied cohort of Scandinavian women: The women's lifestyle and health cohort study. *European Journal of Epidemiology*, *20*, 747–754. https://doi.org/fh3wvb

Ho, S., Wu, S., Chan, S., & Sham, A. (2010). Menopausal transition and changes of body composition: A prospective study in Chinese perimenopausal women. *International Journal of Obesity*, *34*(1265).

Hodis, H. N., Mack, W. J., Henderson, V. W., Shoupe, D., Budoff, M. J., Hwang-Levine, J., Li, Y., Feng, M., Dustin, L., Kono, N., Stanczyk, F. Z., Selzer, R. H., & Azen, S. P. (2016). Vascular Effects of Early versus Late Postmenopausal Treatment with Estradiol. *New England Journal of Medicine*, *374*(13), 1221–1231. https://doi.org/f8gdtj

Hodson, L., Banerjee, R., Rial, B., Arlt, W., Adiels, M., Boren, J., Marinou, K., Fisher, C., Mostad, I. L., Stratton, I. M., Barrett, P. H. R., Chan, D. C., Watts, G. F., Harnden, K., Karpe, F., & Fielding, B. A. (2015). Menopausal Status and Abdominal Obesity Are Significant Determinants of Hepatic Lipid Metabolism in Women. *Journal of the*

American Heart Association, *4*(10), e002258. https://doi.org/10.1161/jaha.115.002258

Hsia, J., Langer, R. D., Manson, J. E., Kuller, L., Johnson, K. C., Hendrix, S. L., Pettinger, M., Heckbert, S. R., Greep, N., Crawford, S., Eaton, C. B., Kostis, J. B., Caralis, P., Prentice, R., & Women's Health Initiative Investigators. (2006). Conjugated Equine Estrogens and Coronary Heart Disease: The Women's Health Initiative. *Archives of Internal Medicine*, *166*(3), 357–365. https://doi.org/10.1001/archinte.166.3.357

Hsu, Y.-H., Venners, S. A., Terwedow, H. A., Feng, Y., Niu, T., Li, Z., Laird, N., Brain, J. D., Cummings, S. R., Bouxsein, M. L., Rosen, C. J., & Xu, X. (2006). Relation of body composition, fat mass, and serum lipids to osteoporotic fractures and bone mineral density in Chinese men and women. *The American Journal of Clinical Nutrition*, *83*(1), 146–154. https://doi.org/gf7d58

Hu, X., Pan, X., & Ma, X. (2005). Contribution of a first-degree family history of diabetes to increased serum adipocyte fatty acid binding protein levels independent of body fat content and distribution. *International Journal of Obesity*, *40*, 1649–1654. https://doi.org/f9crcz

Hua, X., Hibar, D. P., Lee, S., Toga, A. W., Jack, C. R., Weiner, M. W., & Thompson, P. M. (2010). Sex and age differences in atrophic rates: An ADNI study with n=1368 MRI scans. *Neurobiology of Aging*, *31*(8), 1463–1480. https://doi.org/fmszwt

Hudson, A. D., & Kauffman, A. S. (2022). Metabolic actions of kisspeptin signaling: Effects on body weight, energy expenditure, and feeding. *Pharmacology & Therapeutics*, *231*, 107974. https://doi.org/10.1016/j.pharmthera.2021.107974

Hunter, G., Kekes-Szabo, T., Treuth, M., Williams, M., Goran, M., & Pichon, C. (1996). Intra-abdominal adipose tissue, physical activity and cardiovascular risk in pre-and post-menopausal women. *International Journal of Obesity and Related Metabolic Disorders: Journal of the International Association for the Study of Obesity*, *20*, 860–865.

Hussain, M. A., Song, W.-J., & Wolfe, A. (2015). There is Kisspeptin – And Then There is Kisspeptin. *Trends in Endocrinology & Metabolism*, *26*(10), 564–572. https://doi.org/10.1016/j.tem.2015.07.008

Iida, T., Domoto, T., & Takigawa, A. (2011). Relationships among blood leptin and adiponectin levels, fat mass, and bone mineral density in Japanese pre-and postmenopausal women. *Hiroshima Journal of Medical Sciences*, *60*, 71–78.

Ilich-Ernst, J., Brownbill, R. A., Ludemann, M. A., & Fu, R. (2002). Critical factors for bone health in women across the age span: How important is muscle mass? *Medscape Women's Health*, *7*(2).

Ioannidis, J. P. A. (2005). Why Most Published Research Findings Are False. *PLOS Medicine*, *2*(8), e124. https://doi.org/chhf6b

Ioannidis, J. P. A., Munafò, M. R., Fusar-Poli, P., Nosek, B. A., & David, S. P. (2014).

Publication and other reporting biases in cognitive sciences: Detection, prevalence, and prevention. *Trends in Cognitive Sciences*, *18*(5), 235–241. https://doi.org/f5345b

Ito, M., Hayashi, K., Uetani, M., Yamada, M., Ohki, M., & Nakamura, T. (1994). Association between anthropometric measures and spinal bone mineral density. *Investigative Radiology*, *29*, 812–816. https://doi.org/drqm5j

Jack Jr., C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E., Snyder, H. M., ... Silverberg, N. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia*, *14*(4), 535–562. https://doi.org/gdhffb

Jacobs, B., Driscoll, L., & Schall, M. (1997). Life-span dendritic and spine changes in areas 10 and 18 of human cortex: A quantitative golgi study. *Journal of Comparative Neurology*, *386*(4), 661–680. https://doi.org/dxs6zp

Jacobs, E. G., Kroenke, C., Lin, J., Epel, E. S., Kenna, H. A., Blackburn, E. H., & Rasgon, N. L. (2013). Accelerated Cell Aging in Female APOE-ϵ4 Carriers: Implications for Hormone Therapy Use. *PLoS ONE*, *8*(2), e54713. https://doi.org/ghcnnv

Jaff, N. G., Norris, S. A., Snyman, T., Toman, M., & Crowther, N. J. (2015). Body composition in the Study of Women Entering and in Endocrine Transition (SWEET): A perspective of African women who have a high prevalence of obesity and HIV infection. *Metabolism: Clinical and Experimental*, *64*, 1031–1041. https://doi.org/gg543c

Jagust, W., Harvey, D., Mungas, D., & Haan, M. (2005). Central Obesity and the Aging Brain. *Archives of Neurology*, *62*(10), 1545–1548. https://doi.org/10.1001/archneur.62.10.1545

Janssen, I., Powell, L. H., Crawford, S., Lasley, B., & Sutton-Tyrrell, K. (2008). Menopause and the metabolic syndrome: The study of women's health across the nation. *Archives of Internal Medicine*, *168*, 1568–1575. https://doi.org/brdf7g

Janssen, I., Powell, L. H., Jasielec, M. S., & Kazlauskaite, R. (2015). Covariation of change in bioavailable testosterone and adiposity in midlife women. *Obesity*, *23*, 488–494. https://doi.org/f79wpn

Jarrard, L. E. (1993). On the role of the hippocampus in learning and memory in the rat. *Behavioral and Neural Biology*, *60*(1), 9–26. https://doi.org/dp2djx

Jasienska, G., Ziomkiewicz, A., Gorkiewicz, M., & Pajak, A. (2005). Body mass, depressive symptoms and menopausal status: An examination of the "Jolly Fat" hypothesis. *Women's Health Issues : Official Publication of the Jacobs Institute of Women's Health*, *15*, 145–151. https://doi.org/frnxmq

Jeenduang, N., Trongsakul, R., Inhongsa, P., & Chaidach, P. (2014). The prevalence of metabolic syndrome in premenopausal and postmenopausal women in Southern Thai-

land. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *30*, 573–576. https://doi.org/gg543d

Jefferson, A. L., Massaro, J. M., Wolf, P. A., Seshadri, S., Au, R., Vasan, R. S., Larson, M. G., Meigs, J. B., Keaney, J. F., Lipinska, I., Kathiresan, S., Benjamin, E. J., & DeCarli, C. (2007). Inflammatory biomarkers are associated with total brain volume. *Neurology*, *68*(13), 1032–1038. https://doi.org/c6ctwj

Jensen, J., Nilas, L., & Christiansen, C. (1990). Influence of menopause on serum lipids and lipoproteins. *Maturitas*, *12*(4). https://doi.org/cfgcmb

Jeon, Y. K., Lee, J. G., & Kim, S. S. (2011). Association between bone mineral density and metabolic syndrome in pre- and postmenopausal women. *Endocrine Journal*, *58*, 87–93. https://doi.org/d4csq9

Julien, C., Tremblay, C., Phivilay, A., Berthiaume, L., Émond, V., Julien, P., & Calon, F. (2010). High-fat diet aggravates amyloid-beta and tau pathologies in the 3xTg-AD mouse model. *Neurobiology of Aging*, *31*(9), 1516–1531. https://doi.org/d7r3q7

Jurimae, J., & Jurimae, T. (2007). Plasma adiponectin concentration in healthy pre- and postmenopausal women: Relationship with body composition, bone mineral, and metabolic variables. *American Journal of Physiology Endocrinology and Metabolism*, *293:E42-7*.

Jurk, D., Wilson, C., Passos, J. F., Oakley, F., Correia-Melo, C., Greaves, L., Saretzki, G., Fox, C., Lawless, C., Anderson, R., Hewitt, G., Pender, S. L., Fullard, N., Nelson, G., Mann, J., van de Sluis, B., Mann, D. A., & von Zglinicki, T. (2014). Chronic inflammation induces telomere dysfunction and accelerates ageing in mice. *Nature Communications*, *5*(1), 4172. https://doi.org/f589fc

Kadam, N., Chiplonkar, S., Khadilkar, A., Divate, U., & Khadilkar, V. (2010). Low bone mass in urban Indian women above 40 years of age: Prevalence and risk factors. *Gynecological Endocrinology : The Official Journal of the International Society of Gynecological Endocrinology*, *26*, 909–917. https://doi.org/d85wzz

Kang, E. K., Park, H. W., Baek, S., & Lim, J. Y. (2016). The association between trunk body composition and spinal bone mineral density in korean males versus females: A farmers' cohort for agricultural work-related musculoskeletal disorders (FARM) study. *Journal of Korean Medical Science*, *31*, 1595–1603. https://doi.org/f8zmnb

Karageorgi, S., Hankinson, S. E., & Kraft, P. (2010). Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976–2004. *Int. J. Cancer*, 9. https://doi.org/cx98h7

Karakelides, H., & Nair, K. S. (2005). Sarcopenia of Aging and Its Metabolic Impact. *Current Topics in Developmental*. https://doi.org/fpd8r5

Karas, G. B., Scheltens, P., Rombouts, S. A. R. B., Visser, P. J., van Schijndel, R. A.,

Fox, N. C., & Barkhof, F. (2004). Global and local gray matter loss in mild cognitive impairment and Alzheimer's disease. *NeuroImage*, *23*(2), 708–716. https://doi.org/10.1016/j.neuroimage.2004.07.006

Karasek, M., & Reiter, R. J. (2002). Melatonin and aging. *Neuro Endocrinology Letters*, *23 Suppl 1*, 14–16.

Karvonen-Gutierrez, C., & Kim, C. (2016). Association of Mid-Life Changes in Body Size, Body Composition and Obesity Status with the Menopausal Transition. *Healthcare*, *4*(3), 42. https://doi.org/10.3390/healthcare4030042

Kaufer-Horwitz, M., Pelaez-Robles, K., Lazzeri-Arteaga, P., Goti-Rodriguez, L. M., & Avila-Rosas, H. (2005). Hypertension, overweight and abdominal adiposity in women. An analytical perspective. *Archives of Medical Research*, *36*, 404–411. https://doi.org/bs4tbd

Kelley, G. A., & Kelley, K. S. (2009). Impact of progressive resistance training on lipids and lipoproteins in adults: A meta-analysis of randomized controlled trials. *Preventive Medicine*, *48*(1), 9–19. https://doi.org/cbbqw6

Kelley, G. A., & Kelley, K. S. (2005). Aerobic exercise and lipids and lipoproteins in men: A meta-analysis of randomized controlled trials. *The Journal of Men's Health and Gender*, *3*(1), 61–70. https://doi.org/bv5qrw

Kelley, G. A., Kelley, K. S., & Tran, Z. V. (2004). Aerobic Exercise and Lipids and Lipoproteins in Women: A Meta-Analysis of Randomized Controlled Trials. *Journal of Women's Health*, *13*(10), 1148–1164. https://doi.org/brtwcx

Kelly, T., Yang, W., Chen, C.-S., Reynolds, K., & He, J. (2008). Global burden of obesity in 2005 and projections to 2030. *International Journal of Obesity*, *32*(9), 1431–1437. https://doi.org/b2pqh9

Kevenaar, M. E., Meerasahib, M. F., Kramer, P., van de Lang-Born, B. M. N., de Jong, F. H., Groome, N. P., Themmen, A. P. N., & Visser, J. A. (2006). Serum Anti-Müllerian Hormone Levels Reflect the Size of the Primordial Follicle Pool in Mice. *Endocrinology*, *147*(7), 3228–3234. https://doi.org/10.1210/en.2005-1588

Kim, G.-W., Park, K., & Jeong, G.-W. (2018). Effects of Sex Hormones and Age on Brain Volume in Post-Menopausal Women. *The Journal of Sexual Medicine*, *15*(5), 662–670. https://doi.org/gdqg8q

Kim, H. M., Park, J., Ryu, S. Y., & Kim, J. (2007). The effect of menopause on the metabolic syndrome among Korean women: The Korean National Health and Nutrition Examination Survey, 2001. *Diabetes Care*, *30*, 701–706.

Kim, J. H., Choi, H. J., Kim, M. J., Shin, C. S., & Cho, N. H. (2012). Fat mass is negatively associated with bone mineral content in Koreans. *Osteoporosis International*, *23*(7), 2009–2016. https://doi.org/bh4848

Kim, S., Lee, J. Y., & Im, J. A. (2013). Association between serum osteocalcin and insulin resistance in postmenopausal, but not premenopausal, women in Korea. *Menopause*, *20*, 1061–1066. https://doi.org/f5qthq

Kim, Y. M., Kim, S. H., Kim, S., Yoo, J. S., Choe, E. Y., & Won, Y. J. (2016). Variations in fat mass contribution to bone mineral density by gender, age, and body mass index: The Korea National Health and Nutrition Examination Survey (KNHANES) 2008–2011. *Osteoporosis International*, *27*(8), 2543–2554. https://doi.org/f8wztv

Kirchengast, S., Gruber, D., Sator, M., & Huber, J. (1998). Impact of the age at menarche on adult body composition in healthy pre- and postmenopausal women. *American Journal of Physical Anthropology*, *105*, 9–20. https://doi.org/bmscwh

Kirchengast, S., Hartmann, B., & Huber, J. (1996). Serum levels of sex hormones, thyroid hormones, growth hormone, IGF I, and cortisol and their relations to body fat distribution in healthy women dependent on their menopausal status. *Zeitschrift Fur Morphologie Und Anthropologie*, *81*, 223–234.

Kirkwood, T. B. L., & Shanley, D. P. (2010). The connections between general and reproductive senescence and the evolutionary basis of menopause. *Annals of the New York Academy of Sciences*, *1204*(1), 21–29. https://doi.org/dsf9vg

Knapp, K. M., Blake, G. M., Spector, T. D., & Fogelman, I. (2001). Multisite quantitative ultrasound: Precision, age-and menopause-related changes, fracture discrimination, and T-score equivalence with dual-energy X-ray absorptiometry. *Osteoporosis International*, *12*(6), 456–464. https://doi.org/cxzzhv

Knutson, K. L. (2012). Does inadequate sleep play a role in vulnerability to obesity? *American Journal of Human Biology*, *24*(3), 361–371. https://doi.org/fz3xmx

Koh, S. J., Hyun, Y. J., & Choi, S. Y. (2008). Influence of age and visceral fat area on plasma adiponectin concentrations in women with normal glucose tolerance. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *389*, 45–50. https://doi.org/fwxdxc

Kohn, G. E., Rodriguez, K. M., Hotaling, J., & Pastuszak, A. W. (2019). The History of Estrogen Therapy. *Sexual Medicine Reviews*, *7*(3), 416–421. https://doi.org/gjpst4

Kolovou, G. D., & Bilianou, H. G. (2008). Influence of Aging and Menopause on Lipids and Lipoproteins in Women. *Angiology*, *59*(2_suppl), 54S–57S. https://doi.org/10.1177/0003319708319645

Kongnyuy, E. J., Norman, R. J., Flight, I. H., & Rees, M. C. (1999). Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: Weight and body fat distribution. *The Cochrane Library*.

Konrad, T., Bär, F., & Schneider, F. (2011). Factors influencing endothelial function in healthy pre-and post-menopausal women of the EU-RISC study. *Diabetes and Vascular*

Disease Research, *8*, 229–236. https://doi.org/b9bv88

Kontogianni, M. D., Dafni, U. G., Routsias, J. G., & Skopouli, F. N. (2004). Blood leptin and adiponectin as possible mediators of the relation between fat mass and BMD in perimenopausal women. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, *19*, 546–551. https://doi.org/bmz2vk

Konukoglu, D., Serin, O., & Ercan, M. (2000). Plasma leptin levels in obese and non-obese postmenopausal women before and after hormone replacement therapy. *Maturitas*, *36*, 203–207. https://doi.org/bh66mg

Koran, M. E. I., Wagener, M., & Hohman, T. J. (2017). Sex differences in the association between AD biomarkers and cognitive decline. *Brain Imaging and Behavior*, *11*(1), 205–213. https://doi.org/gg6w36

Koskova, I., Petrasek, R., & Vondra, K. (2007). Weight, body composition and fat distribution of Czech women in relation with reproductive phase: A cross-sectional study. *Prague Medical Report*, *108*, 13–26.

Kotani, K., Chen, J. T., & Taniguchi, N. (2011). The relationship between adiponectin and blood pressure in premenopausal and postmenopausal women. *Clinical and Investigative Medicine Medecine Clinique Et Experimentale*, *34:E125-30*.

Kraemer, R. R., Synovitz, L. B., Gimpel, T., Kraemer, G. R., Johnson, L. G., & Castracane, V. D. (2001). Effect of estrogen on serum DHEA in younger and older women and the relationship of DHEA to adiposity and gender. *Metabolism: Clinical and Experimental*, *50*, 488–493. https://doi.org/dn75hv

Kreisberg, R. A., & Kasim, S. (1987). Cholesterol metabolism and aging. *The American Journal of Medicine*, *82*(1), 54–60. https://doi.org/drr94d

Kryston, T. B., Georgiev, A. B., Pissis, P., & Georgakilas, A. G. (2011). Role of oxidative stress and DNA damage in human carcinogenesis. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *711*(1), 193–201. https://doi.org/bgbvxh

Kuk, J. L., Lee, S., Heymsfield, S. B., & Ross, R. (2005). Waist circumference and abdominal adipose tissue distribution: Influence of age and sex. *American Journal of Clinical Nutrition*, *81*, 1330–1334. https://doi.org/c5m7

Kuk, J. L., Saunders, T. J., Davidson, L. E., & Ross, R. (2009). Age-related changes in total and regional fat distribution. *Ageing Research Reviews*, *8*(4), 339–348. https://doi.org/10.1016/j.arr.2009.06.001

Kurth, F., Levitt, J. G., Phillips, O. R., Luders, E., Woods, R. P., Mazziotta, J. C., Toga, A. W., & Narr, K. L. (2013). Relationships between gray matter, body mass index, and waist circumference in healthy adults. *Human Brain Mapping*, *34*(7), 1737–1746. https://doi.org/10.1002/hbm.22021

Lahdenperä, M., Lummaa, V., Helle, S., Tremblay, M., & Russell, A. F. (2004). Fitness benefits of prolonged post-reproductive lifespan in women. *Nature*, *428*(6979), 178–181. https://doi.org/ds43zr

Laitinen, K., Valimaki, M., & Keto, P. (1991). Bone mineral density measured by dual-energy X-ray absorptiometry in healthy Finnish women. *Calcified Tissue International*, *48*(4), 224–231. https://doi.org/fpgjjf

Lane, M., Robker, R. L., & Robertson, S. A. (2014). Parenting from before conception. *Science*, *345*(6198), 756–760. https://doi.org/ghjqjc

Larsson, U., Karlsson, J., & Sullivan, M. (2002). Impact of overweight and obesity on health-related quality of life—a Swedish population study. *International Journal Of Obesity*, *26*(417).

Lee, C. G., Carr, M. C., & Murdoch, S. J. (2009). Adipokines, inflammation, and visceral adiposity across the menopausal transition: A prospective study. *The Journal of Clinical Endocrinology and Metabolism*, *94*, 1104–1110. https://doi.org/10.1210/jc.2008-0701

Leidy, L. E. (1996). Timing of Menopause in Relation to Body Size and Weight Change. *Human Biology*, *68*(6), 967–982.

Lejskova, M., Alusik, S., Valenta, Z., Adamkova, S., & Pitha, J. (2012). Natural postmenopause is associated with an increase in combined cardiovascular risk factors. *Physiological Research*, *61*, 587–596. https://doi.org/gg543g

Lemaitre, J.-F., & Gaillard, J.-M. (2017). Reproductive senescence: New perspectives in the wild. *Biological Reviews*, *92*(4), 2182–2199. https://doi.org/ggkjxx

Letenneur, L., Gilleron, V., Commenges, D., Helmer, C., Orgogozo, J. M., & Dartigues, J. F. (1999). Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *Journal of Neurology, Neurosurgery & Psychiatry*, *66*(2), 177–183. https://doi.org/d4zqwr

Ley, C. J., Lees, B., & Stevenson, J. C. (1992). Sex- and menopause-associated changes in body-fat distribution. *The American Journal of Clinical Nutrition*, *55*, 950–954. https://doi.org/gg543f

Lin, K. A., Choudhury, K. R., Rathakrishnan, B. G., Marks, D. M., Petrella, J. R., & Doraiswamy, P. M. (2015). Marked gender differences in progression of mild cognitive impairment over 8 years. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *1*(2), 103–110. https://doi.org/gg6c6g

Lin, M. T., & Beal, M. F. (2006). Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature*, *443*(7113), 787–795. https://doi.org/fp5x5s

Lin, W. Y., Yang, W. S., & Lee, L. T. (2005). Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan. *Inter-*

national Journal of Obesity, *30*, 912–917. https://doi.org/b7cgbv

Lindquist, O., & Bengtsson, C. (1980). Serum lipids, arterial blood pressure and body weight in relation to the menopause: Results from a population study of women in Goteborg, Sweden. *Scandinavian Journal of Clinical and Laboratory Investigation*, *40*, 629–636. https://doi.org/cz5v57

Lindsay, R., Cosman, F., Herrington, B. S., & Himmelstein, S. (1992). Bone mass and body composition in normal women. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, *7*, 55–63. https://doi.org/c3q82t

Liu, H.-H., & Li, J.-J. (2015). Aging and dyslipidemia: A review of potential mechanisms. *Ageing Research Reviews*, *19*, 43–52. https://doi.org/ghk7z5

Liu-Ambrose, T., Kravetsky, L., Bailey, D., Sherar, L., Mundt, C., Baxter-Jones, A., Khan, K. M., & McKay, H. A. (2006). Change in lean body mass is a major determinant of change in areal bone mineral density of the proximal femur: A 12-year observational study. *Calcified Tissue International*, *79*(3), 145–151. https://doi.org/b6fkk6

Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S. G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, *396*(10248), 413–446. https://doi.org/d5g5

Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S. G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., Cooper, C., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Larson, E. B., Ritchie, K., Rockwood, K., Sampson, E. L., … Mukadam, N. (2017). Dementia prevention, intervention, and care. *The Lancet*, *390*(10113), 2673–2734. https://doi.org/gcpbzc

López-Armada, M. J., Riveiro-Naveira, R. R., Vaamonde-García, C., & Valcárcel-Ares, M. N. (2013). Mitochondrial dysfunction and the inflammatory response. *Mitochondrion*, *13*(2), 106–118. https://doi.org/f4thfg

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2013). The Hallmarks of Aging. *Cell*, *153*(6), 1194–1217. https://doi.org/f42f5g

Lord, C. J., & Ashworth, A. (2012). The DNA damage response and cancer therapy. *Nature*, *481*(7381), 287–294. https://doi.org/fzfs5f

Lord, C., Buss, C., Lupien, S. J., & Pruessner, J. C. (2008). Hippocampal volumes are larger in postmenopausal women using estrogen therapy compared to past users, never users and men: A possible window of opportunity effect. *Neurobiology of Aging*, *29*(1), 95–101. https://doi.org/10.1016/j.neurobiolaging.2006.09.001

Lord, C., Engert, V., Lupien, S. J., & Pruessner, J. C. (2010). Effect of sex and estrogen therapy on the aging brain: A voxel-based morphometry study. *Menopause (New York, N.Y.)*, *17*(4), 846–851. https://doi.org/bmd6m8

Lovejoy, J. C., Champagne, C. M., Jonge, L., Xie, H., & Smith, S. (2005). Increased visceral fat and decreased energy expenditure during the menopausal transition. *International Journal of Obesity*, *32*, 949–958. https://doi.org/bmvtv2

Low, L.-F., Anstey, K. J., Maller, J., Kumar, R., Wen, W., Lux, O., Salonikas, C., Naidoo, D., & Sachdev, P. (2006). Hormone replacement therapy, brain volumes and white matter in postmenopausal women aged 60–64 years. *NeuroReport*, *17*(1), 101–104. https://doi.org/bpc9mm

Lu, A. T., Quach, A., Wilson, J. G., Reiner, A. P., Aviv, A., Raj, K., Hou, L., Baccarelli, A. A., Li, Y., Stewart, J. D., Whitsel, E. A., Assimes, T. L., Ferrucci, L., & Horvath, S. (2019). DNA methylation GrimAge strongly predicts lifespan and healthspan. *Aging*, *11*(2), 303–327. https://doi.org/gftvdf

Lu, T., Pan, Y., Kao, S.-Y., Li, C., Kohane, I., Chan, J., & Yankner, B. A. (2004). Gene regulation and DNA damage in the ageing human brain. *Nature*, *429*(6994), 883–891. https://doi.org/bcz8zz

Lyu, L. C., Yeh, C. Y., Lichtenstein, A. H., Li, Z., Ordovas, J. M., & Schaefer, E. J. (2001). Association of sex, adiposity, and diet with HDL subclasses in middle-aged Chinese. *American Journal of Clinical Nutrition*, *74*, 64–71. https://doi.org/gg543j

Macdonald, H. M., New, S. A., Campbell, M. K., & Reid, D. M. (2005). Influence of weight and weight change on bone loss in perimenopausal and early postmenopausal Scottish women. *Osteoporosis International*, *16*(2), 163–171. https://doi.org/fgcrfc

Maharlouei, N., Bellissimo, N., Ahmadi, S. M., & Lankarani, K. B. (2013). Prevalence of metabolic syndrome in pre- and postmenopausal Iranian women. *Climacteric*, *16*, 561–567. https://doi.org/gg543h

Malacara, J. M., Cetina, T., & Bassol, S. (2002). Symptoms at pre- and postmenopause in rural and urban women from three States of Mexico. *Maturitas*, *43*, 11–19. https://doi.org/btzt76

Manabe, E., Aoyagi, K., Tachibana, H., & Takemoto, T. (1999). Relationship of intra-abdominal adiposity and peripheral fat distribution to lipid metabolism in an island population in western Japan: Gender differences and effect of menopause. *The Tohoku Journal of Experimental Medicine*, *188*, 189–202. https://doi.org/crnh74

Manczak, M., Anekonda, T. S., Henson, E., Park, B. S., Quinn, J., & Reddy, P. H. (2006). Mitochondria are a direct site of Aβ accumulation in Alzheimer's disease neurons: Implications for free radical generation and oxidative damage in disease progression. *Human*

Molecular Genetics, *15*(9), 1437–1449. https://doi.org/b3gxrt

Manini, T. M. (2010). Energy expenditure and aging. *Ageing Research Reviews*, *9*(1), 1–11. https://doi.org/dhmndb

Manjer, J., Kaaks, R., Riboli, E., & Berglund, G. (2001). Risk of breast cancer in relation to anthropometry, blood pressure, blood lipids and glucose metabolism: A prospective study within the Malmo Preventive Project. *European Journal of Cancer Prevention : The Official Journal of the European Cancer Prevention Organisation (ECP*, *10*, 33–42. https://doi.org/bvg5rf

Manly, J. J., Merchant, C. A., Jacobs, D. M., Small, S. A., Bell, K., Ferin, M., & Mayeux, R. (2000). Endogenous estrogen levels and Alzheimer's disease among postmenopausal women. *Neurology*, *54*(4), 833–837. https://doi.org/gcpbbc

Mannisto, S., Pietinen, P., Pyy, M., Palmgren, J., Eskelinen, M., & Uusitupa, M. (1996). Body-size indicators and risk of breast cancer according to menopause and estrogen-receptor status. *International Journal of Cancer*, *68*, 8–13. https://doi.org/cnps2c

Manson, J. E., Aragaki, A. K., Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Chlebowski, R. T., Howard, B. V., Thomson, C. A., Margolis, K. L., Lewis, C. E., Stefanick, M. L., Jackson, R. D., Johnson, K. C., Martin, L. W., Shumaker, S. A., Espeland, M. A., & Wactawski-Wende, J. (2017). Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. *JAMA*, *318*(10), 927–938. https://doi.org/gf9hrh

Markstrom, E., Svensson, Ec., Shao, R., Svanberg, B., & Billig, H. (2002). Survival factors regulating ovarian apoptosis – dependence on follicle differentiation. *Reproduction*, *123*(1), 23–30. https://doi.org/cmcc3z

Marquer, C., Devauges, V., Cossec, J.-C., Liot, G., Lécart, S., Saudou, F., Duyckaerts, C., Léveque-Fort, S., & Potier, M.-C. (2011). Local cholesterol increase triggers amyloid precursor protein-Bacel clustering in lipid rafts and rapid endocytosis. *The FASEB Journal*, *25*(4), 1295–1305. https://doi.org/c9gx2w

Martini, G., Valenti, R., Giovani, S., & Nuti, R. (1997). Age-related changes in body composition of healthy and osteoporotic women. *Maturitas*, *27*, 25–33. https://doi.org/fvmb46

Marwaha, R. K., Garg, M. K., Tandon, N., Mehan, N., Sastry, A., & Bhadra, K. (2013). Relationship of body fat and its distribution with bone mineral density in Indian population. *Journal of Clinical Densitometry : The Official Journal of the International Society for Clinical Densitometry*, *16*, 353–359. https://doi.org/f466vf

Matsushita, H., Kurabayashi, T., Tomita, M., Kato, N., & Tanaka, K. (2003). Effects of uncoupling protein 1 and Beta3-adrenergic receptor gene polymorphisms on body

size and serum lipid concentrations in Japanese women. *Maturitas*, *45*, 39–45. https://doi.org/cnp9wr

Matsuzaki, M., Kulkarni, B., & Kuper, H. (2017). Association of hip bone mineral density and body composition in a rural indian population: The andhra pradesh children and parents study (APCAPS. *PLoS One*, *12:e0167114*.

Matthews, K. A., Kuller, L. H., Wing, R. R., Meilahn, E. N., & Plantinga, P. (1996). Prior to Use of Estrogen Replacement Therapy, Are Users Healthier than Nonusers? *American Journal of Epidemiology*, *143*(10), 971–978. https://doi.org/gg7vrx

Matthews, K. A., Meilahn, E., Kuller, L. H., Kelsey, S. F., Caggiula, A. W., & Wing, R. R. (1989). Menopause and risk factors for coronary heart disease. *The New England Journal of Medicine*, *321*, 641–646. https://doi.org/b7zrsn

Mattison, DonaldR., & Thorgeirsson, SnorriS. (1978). Smoking and industrial pollution, and their effects on menopause and ovarian cancer. *The Lancet*, *311*(8057), 187–188. https://doi.org/fsqnmt

McAloon, C. J., Boylan, L. M., & Hamborg, T. (2016). The changing face of cardiovascular disease 2000–2012: An analysis of the world health organisation global health estimates data. *International Journal of Cardiology*, *224*, 256–264. https://doi.org/gg5426

McCarthy, M. M., Arnold, A. P., Ball, G. F., Blaustein, J. D., & Vries, G. J. D. (2012). Sex Differences in the Brain: The Not So Inconvenient Truth. *Journal of Neuroscience*, *32*(7), 2241–2247. https://doi.org/gg2hds

Medawar, P. B. (1952). *An unsolved problem of biology*.

Meek, M. D., & Finch, G. L. (1999). Diluted Mainstream Cigarette Smoke Condensates Activate Estrogen Receptor and Aryl Hydrocarbon Receptor-Mediated Gene Transcription. *Environmental Research*, *80*(1), 9–17. https://doi.org/ctzgf8

Menarche, menopause, and breast cancer risk: Individual participant meta-analysis, including 118 964 women with breast cancer from 117 epidemiological studies. (2012). *The Lancet Oncology*, *13*(11), 1141–1151. https://doi.org/f2f6sw

Meng, X., & D'Arcy, C. (2012). Education and Dementia in the Context of the Cognitive Reserve Hypothesis: A Systematic Review with Meta-Analyses and Qualitative Analyses. *PLoS ONE*, *7*(6). https://doi.org/f3zxpg

Mesch, V. R., Boero, L. E., & Siseles, N. O. (2006). Metabolic syndrome throughout the menopausal transition: Influence of age and menopausal status. *Climacteric*, *9*, 40–48. https://doi.org/cwftb9

Metcalfe, N. B., & Alonso-Alvarez, C. (2010). Oxidative stress as a life-history constraint: The role of reactive oxygen species in shaping phenotypes from conception to death. *Functional Ecology*, *24*(5), 984–996. https://doi.org/dh8djb

Meza-Munoz, D. E., Fajardo, M. E., Perez-Luque, E. L., & Malacara, J. M. (2006). Factors associated with estrogen receptors-alpha (ER-alpha) and -beta (ER-beta) and progesterone receptor abundance in obese and non obese pre- and post-menopausal women. *Steroids*, *71*, 498–503. https://doi.org/d2nxft

Mikkola, T. S., Gissler, M., Merikukka, M., Tuomikoski, P., & Ylikorkala, O. (2013). Sex differences in age-related cardiovascular mortality. *PloS One*, *8:e63347*.

Miller, A. A., & Spencer, S. J. (2014). Obesity and neuroinflammation: A pathway to cognitive impairment. *Brain, Behavior, and Immunity*, *42*, 10–21. https://doi.org/f6phhf

Miller, K. L., Alfaro-Almagro, F., Bangerter, N. K., Thomas, D. L., Yacoub, E., Xu, J., Bartsch, A. J., Jbabdi, S., Sotiropoulos, S. N., Andersson, J. L., Griffanti, L., Douaud, G., Okell, T. W., Weale, P., Dragonu, I., Garratt, S., Hudson, S., Collins, R., Jenkinson, M., … Smith, S. M. (2016). Multimodal population brain imaging in the UK Biobank prospective epidemiological study. *Nature Neuroscience*, *19*(11), 1523–1536. https://doi.org/f89khc

Minatoya, M., Kutomi, G., & Shima, H. (2014). Relation of serum adiponectin levels and obesity with breast cancer: A Japanese case-control study. *Asian Pacific Journal of Cancer Prevention : APJCP*, *15*, 8325–8330. https://doi.org/gg543n

Ming, G., & Song, H. (2011). Adult Neurogenesis in the Mammalian Brain: Significant Answers and Significant Questions. *Neuron*, *70*(4), 687–702. https://doi.org/b3qt48

Mishra, G. D., Pandeya, N., Dobson, A. J., Chung, H.-F., Anderson, D., Kuh, D., Sandin, S., Giles, G. G., Bruinsma, F., Hayashi, K., Lee, J. S., Mizunuma, H., Cade, J. E., Burley, V., Greenwood, D. C., Goodman, A., Simonsen, M. K., Adami, H.-O., Demakakos, P., & Weiderpass, E. (2017). Early menarche, nulliparity and the risk for premature and early natural menopause. *Human Reproduction*, *32*(3), 679–686. https://doi.org/bxrh

Mo, D., Hsieh, P., & Yu, H. (2017). The relationship between osteoporosis and body composition in pre- and postmenopausal women from different ethnic groups in China. *Ethnicity & Health*, *22*, 295–310. https://doi.org/gg5424

Molina-García, L., Hidalgo-Ruiz, M., Cocera-Ruíz, E. M., Conde-Puertas, E., Delgado-Rodríguez, M., & Martínez-Galiano, J. M. (2019). The delay of motherhood: Reasons, determinants, time used to achieve pregnancy, and maternal anxiety level. *PLOS ONE*, *14*(12), e0227063. https://doi.org/ghp2r4

Montagne, A., Barnes, S. R., Sweeney, M. D., Halliday, M. R., Sagare, A. P., Zhao, Z., Toga, A. W., Jacobs, R. E., Liu, C. Y., Amezcua, L., Harrington, M. G., Chui, H. C., Law, M., & Zlokovic, B. V. (2015). Blood-Brain Barrier Breakdown in the Aging Human Hippocampus. *Neuron*, *85*(2), 296–302. https://doi.org/f6xbwg

Monteiro, R., & Azevedo, I. (2010). Chronic Inflammation in Obesity and the Metabolic Syndrome. *Mediators of Inflammation*, *2010*, 1–10. https://doi.org/10.1155/2010/289645

Moore, A. M., Coolen, L. M., Porter, D. T., Goodman, R. L., & Lehman, M. N. (2018). KNDy Cells Revisited. *Endocrinology*, *159*(9), 3219–3234. https://doi.org/2019041122253794100

Mortensen, E. L., & Høgh, P. (2001). A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology*, *57*(1), 89–95. https://doi.org/ghch36

Mosconi, L., Rahman, A., Diaz, I., Wu, X., Scheyer, O., Hristov, H. W., Vallabhajosula, S., Isaacson, R. S., de Leon, M. J., & Brinton, R. D. (2018). Increased Alzheimer's risk during the menopause transition: A 3-year longitudinal brain imaging study. *PLoS ONE*, *13*(12). https://doi.org/gfrn99

Moslehi, N., Mirmiran, P., Tehrani, F. R., & Azizi, F. (2017). Current Evidence on Associations of Nutritional Factors with Ovarian Reserve and Timing of Menopause: A Systematic Review. *Advances in Nutrition*, *8*(4), 597–612. https://doi.org/gkfrnq

Moyer, V. A., & U.S. Preventive Services Task Force. (2013). Menopausal hormone therapy for the primary prevention of chronic conditions: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine*, *158*(1), 47–54. https://doi.org/gg78m8

Mrak, R. E. (2009). Alzheimer-type neuropathological changes in morbidly obese elderly individuals. *Clinical Neuropathology*, *28*(1), 40–45. https://doi.org/fbb6kk

Muchanga Sifa, M. J., Lepira, F. B., Longo, A. L., Sumaili, E. K., Makulo, J. R., Mbelambela, E. P., Tozin, R., Ngatu, N. R., & Suganuma, N. (2014). Prevalence and predictors of metabolic syndrome among Congolese pre- and postmenopausal women. *Climacteric: The Journal of the International Menopause Society*, *17*(4), 442–448. https://doi.org/gg543k

Muka, T., Oliver-Williams, C., Kunutsor, S., Laven, J. S. E., Fauser, B. C. J. M., Chowdhury, R., Kavousi, M., & Franco, O. H. (2016). Association of Age at Onset of Menopause and Time Since Onset of Menopause With Cardiovascular Outcomes, Intermediate Vascular Traits, and All-Cause Mortality: A Systematic Review and Meta-analysis. *JAMA Cardiology*, *1*(7), 767–776. https://doi.org/gghrkh

Murabito, J. M., Yang, Q., Fox, C., Wilson, P. W. F., & Cupples, L. A. (2005). Heritability of Age at Natural Menopause in the Framingham Heart Study. *The Journal of Clinical Endocrinology & Metabolism*, *90*(6), 3427–3430. https://doi.org/10.1210/jc.2005-0181

Murray, C. J., Barber, R. M., & Foreman, K. J. (2015). Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: Quantifying the epidemiological transition. *The Lancet*, *386*, 2145–2191. https://doi.org/f3m494

Must, A., Phillips, S. M., Naumova, E. N., Blum, M., Harris, S., Dawson-Hughes, B., & Rand, W. M. (2002). Recall of Early Menstrual History and Menarcheal Body Size: After

30 Years, How Well Do Women Remember? *American Journal of Epidemiology*, *155*(7), 672–679. https://doi.org/bbxp72

Muti, P., Stanulla, M., & Micheli, A. (2000). Markers of insulin resistance and sex steroid hormone activity in relation to breast cancer risk: A prospective analysis of abdominal adiposity, sebum production, and hirsutism (Italy. *Cancer Causes & Control : CCC*, *11*, 721–730. https://doi.org/fthbvw

Nagel, G., Altenburg, H.-P., Nieters, A., Boffetta, P., & Linseisen, J. (2005). Reproductive and dietary determinants of the age at menopause in EPIC-Heidelberg. *Maturitas*, *52*(3), 337–347. https://doi.org/czd4rs

Nelson, H. D., Humphrey, L. L., Nygren, P., Teutsch, S. M., & Allan, J. D. (2002). Postmenopausal Hormone Replacement Therapy: Scientific Review. *JAMA*, *288*(7), 872–881. https://doi.org/10.1001/jama.288.7.872

Nelson, L. R., & Bulun, S. E. (2001). Estrogen production and action. *Journal of the American Academy of Dermatology*, *45*(3), S116–S124. https://doi.org/fvg9qn

Neu, S. C., Pa, J., Kukull, W., Beekly, D., Kuzma, A., Gangadharan, P., Wang, L.-S., Romero, K., Arneric, S. P., Redolfi, A., Orlandi, D., Frisoni, G. B., Au, R., Devine, S., Auerbach, S., Espinosa, A., Boada, M., Ruiz, A., Johnson, S. C., … Toga, A. W. (2017). Apolipoprotein E Genotype and Sex Risk Factors for Alzheimer Disease: A Meta-analysis. *JAMA Neurology*, *74*(10), 1178–1189. https://doi.org/gghdws

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., Mullany, E. C., Biryukov, S., Abbafati, C., Abera, S. F., Abraham, J. P., Abu-Rmeileh, N. M. E., Achoki, T., AlBuhairan, F. S., Alemu, Z. A., Alfonso, R., Ali, M. K., Ali, R., Guzman, N. A., … Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. *The Lancet*, *384*(9945), 766–781. https://doi.org/szv

Ng, S. P., Korda, R., Clements, M., Latz, I., Bauman, A., Bambrick, H., Liu, B., Rogers, K., Herbert, N., & Banks, E. (2011). Validity of self-reported height and weight and derived body mass index in middle-aged and elderly individuals in Australia. *Australian and New Zealand Journal of Public Health*, *35*(6), 557–563. https://doi.org/dgcvr5

Nichols, E., Szoeke, C. E. I., Vollset, S. E., Abbasi, N., Abd-Allah, F., Abdela, J., Aichour, M. T. E., Akinyemi, R. O., Alahdab, F., Asgedom, S. W., Awasthi, A., Barker-Collo, S. L., Baune, B. T., Béjot, Y., Belachew, A. B., Bennett, D. A., Biadgo, B., Bijani, A., Bin Sayeed, M. S., … Murray, C. J. L. (2019). Global, regional, and national burden of Alzheimer's disease and other dementias, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(1), 88–106. https://doi.org/gf6rvx

Nitta, J., Nojima, M., & Ohnishi, H. (2016). Weight gain and alcohol drinking associations with breast cancer risk in japanese postmenopausal women - results from the japan collaborative cohort (JACC) study. *Asian Pacific Journal of Cancer Prevention : APJCP*, *17*, 1437–1443. https://doi.org/gg543p

Niu, H., Álvarez-Álvarez, I., Guillén-Grima, F., & Aguinaga-Ontoso, I. (2017). Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis. *Neurología (English Edition)*, *32*(8), 523–532. https://doi.org/10.1016/j.nrleng.2016.02.009

Noh, H. M., Song, Y. M., Park, J. H., Kim, B. K., & Choi, Y. H. (2013). Metabolic factors and breast cancer risk in Korean women. *Cancer Causes & Control : CCC*, *24*, 1061–1068. https://doi.org/gg543m

Norbury, C. J., & Zhivotovsky, B. (2004). DNA damage-induced apoptosis. *Oncogene*, *23*(16), 2797–2808. https://doi.org/b5tw26

Nordestgaard, B. G., & Varbo, A. (2014). Triglycerides and cardiovascular disease. *The Lancet*, *384*(9943), 626–635. https://doi.org/f2tkvs

Nordin, B. E., Need, A. G., Bridges, A., & Horowitz, M. (1992). Relative contributions of years since menopause, age, and weight to vertebral density in postmenopausal women. *The Journal of Clinical Endocrinology and Metabolism*, *74*, 20–23.

Ohayon, M. M., Carskadon, M. A., Guilleminault, C., & Vitiello, M. V. (2004). Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: Developing normative sleep values across the human lifespan. *Sleep*, *27*(7), 1255–1273. https://doi.org/ggqjjk

Ohm, T. G., Müller, H., Braak, H., & Bohl, J. (1995). Close-meshed prevalence rates of different stages as a tool to uncover the rate of Alzheimer's disease-related neurofibrillary changes. *Neuroscience*, *64*(1), 209–217. https://doi.org/cgvswj

Ohta, H., Kuroda, T., & Onoe, Y. (2010). Familial correlation of bone mineral density, birth data and lifestyle factors among adolescent daughters, mothers and grandmothers. *Journal of Bone and Mineral Metabolism*, *28*, 690–695. https://doi.org/b5n55g

Oktay, K., Turan, V., Titus, S., Stobezki, R., & Liu, L. (2015). BRCA Mutations, DNA Repair Deficiency, and Ovarian Aging1. *Biology of Reproduction*, *93*(3). https://doi.org/gjr9jc

Oldroyd, B., Stewart, S. P., Truscott, J. G., Westmacott, C. F., & Smith, M. A. (1998). Age related changes in body composition. *Oldroyd, B., Stewart, S. P., Truscott, J. G., Westmacott, C. F., & Smith, M. A. (1998). Age Related Changes in Body Composition. Applied Radiation and Isotopes: Including Data, Instrumentation and Methods for Use in Agriculture, Industry and Medicine*, *49*(5-6), 589.

Österlund, M. K., Grandien, K., Keller, E., & Hurd, Y. L. (2000). The Human Brain Has Distinct Regional Expression Patterns of Estrogen Receptor α mRNA Isoforms

Derived from Alternative Promoters. *Journal of Neurochemistry*, *75*(4), 1390–1397. https://doi.org/dr4kz8

Pacholczak, R., Klimek-Piotrowska, W., & Kuszmiersz, P. (2016). Associations of anthropometric measures on breast cancer risk in pre- and postmenopausal women–a case-control study. *Journal of Physiological Anthropology*, *35*(7).

Palacios, S., Henderson, V. W., Siseles, N., Tan, D., & Villaseca, P. (2010). Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric*, *13*(5), 419–428. https://doi.org/fd6h2s

Pappolla, M. A., Smith, M. A., Bryant-Thomas, T., Bazan, N., Petanceska, S., Perry, G., Thal, L. J., Sano, M., & Refolo, L. M. (2002). Cholesterol, oxidative stress, and Alzheimer's disease: Expanding the horizons of Pathogenesis1 1This article is part of a series of reviews on "Causes and Consequences of Oxidative Stress in Alzheimer's Disease." The full list of papers may be found on the homepage of the journal. *Free Radical Biology and Medicine*, *33*(2), 173–181. https://doi.org/bxbzzw

Parente, R. C., Faerstein, E., Celeste, R. K., & Werneck, G. L. (2008). The relationship between smoking and age at the menopause: A systematic review. *Maturitas*, *61*(4), 287–298. https://doi.org/cp6vx7

Park, J. K., Lim, Y.-H., Kim, K.-S., Kim, S. G., Kim, J. H., Lim, H. G., & Shin, J. (2013). Body fat distribution after menopause and cardiovascular disease risk factors: Korean National Health and Nutrition Examination Survey 2010. *Journal of Women's Health*, *22*(7), 587–594. https://doi.org/gg5422

Park, J.-H., Song, Y.-M., Sung, J., Lee, K., Kim, Y. S., Kim, T., & Cho, S.-I. (2012). The association between fat and lean mass and bone mineral density: The Healthy Twin Study. *Bone*, *50*(4), 1006–1011. https://doi.org/fzvwhf

Park, Y. M., White, A. J., Nichols, H. B., O'Brien, K. M., Weinberg, C. R., & Sandler, D. P. (2017). The association between metabolic health, obesity phenotype and the risk of breast cancer. *International Journal of Cancer*, *140*, 2657–2666. https://doi.org/gg543q

Patel, S. R., Malhotra, A., White, D. P., Gottlieb, D. J., & Hu, F. B. (2006). Association between reduced sleep and weight gain in women. *American Journal of Epidemiology*, *164*(10), 947–954. https://doi.org/b45kz4

Pavlica, T., Mikalacki, M., & Matic, R. (2013). Relationship between BMI and skinfold thicknesses to risk factors in premenopausal and postmenopausal women. *Collegium Antropologicum*, *2*, 119–124.

Penn, D. J., & Smith, K. R. (2007). Differential fitness costs of reproduction between the sexes. *Proceedings of the National Academy of Sciences*, *104*(2), 553–558. https://doi.org/fntcxd

Perissinotto, E., Pisent, C., Sergi, G., Grigoletto, F., Enzi, G., & Group, I. W. (2002).

Anthropometric measurements in the elderly: Age and gender differences. *British Journal of Nutrition*, *87*, 177–186. https://doi.org/b8wdgc

Pfeilschifter, J., Köditz, R., Pfohl, M., & Schatz, H. (2002). Changes in Proinflammatory Cytokine Activity after Menopause. *Endocrine Reviews*, *23*(1), 90–119. https://doi.org/10.1210/edrv.23.1.0456

Phillips, G. B., Jing, T., & Heymsfield, S. B. (2008). Does insulin resistance, visceral adiposity, or a sex hormone alteration underlie the metabolic syndrome? *Studies in Women. Metabolism: Clinical and Experimental*, *57*, 838–844. https://doi.org/bmr835

Piers, L. S., Soares, M. J., McCormack, L. M., & O'Dea, K. (1998). Is there evidence for an age-related reduction in metabolic rate? *Journal of Applied Physiology*, *85*(6), 2196–2204. https://doi.org/ghns6q

Pike, C. J., Carroll, J. C., Rosario, E. R., & Barron, A. M. (2009). Protective actions of sex steroid hormones in Alzheimer's disease. *Frontiers in Neuroendocrinology*, *30*(2), 239–258. https://doi.org/bw4q4x

Pike, M. C., Peters, R. K., Cozen, W., Probst-Hensch, N. M., Wan, P. C., Mack, T. M., & Felix, J. C. (1997). Estrogen-progestin replacement therapy and endometrial cancer. *Journal of the National Cancer Institute*, *89*(15), 1110–1116. https://doi.org/d3j8b8

Pinkerton, J. V. (2020). Hormone Therapy for Postmenopausal Women. *New England Journal of Medicine*, *382*(5), 446–455. https://doi.org/ggjqfp

Podcasy, J. L., & Epperson, C. N. (2016). Considering sex and gender in Alzheimer disease and other dementias. *Dialogues in Clinical Neuroscience*, *18*(4), 437–446.

Polesel, D. N., Hirotsu, C., Nozoe, K. T., Boin, A. C., Bittencourt, L., Tufik, S., Andersen, M. L., & Hachul, H. (2015). Waist circumference and postmenopause stages as the main associated factors for sleep apnea in women: A cross-sectional population-based study. *Menopause*, *22*(8), 835–844. https://doi.org/f7nxj7

Pollan, M., Lope, V., & Miranda-Garcia, J. (2012). Adult weight gain, fat distribution and mammographic density in Spanish pre- and post-menopausal women (DDM-Spain. *Breast Cancer Research and Treatment*, *134*, 823–838. https://doi.org/f36mrc

Pontzer, H., Yamada, Y., Sagayama, H., Ainslie, P. N., Andersen, L. F., Anderson, L. J., Arab, L., Baddou, I., Bedu-Addo, K., Blaak, E. E., Blanc, S., Bonomi, A. G., Bouten, C. V. C., Bovet, P., Buchowski, M. S., Butte, N. F., Camps, S. G., Close, G. L., Cooper, J. A., … Consortium, I. D. D. (2021). Daily energy expenditure through the human life course. *Science*.

Portaluppi, F., Pansini, F., Manfredini, R., & Mollica, G. (1997). Relative influence of menopausal status, age, and body mass index on blood pressure. *Hypertension*, *29*(4), 976–979. https://doi.org/gg6p5g

Powers, E. T., Morimoto, R. I., Dillin, A., Kelly, J. W., & Balch, W. E. (2009). Biological and chemical approaches to diseases of proteostasis deficiency. *Annual Review of Biochemistry*, *78*, 959–991. https://doi.org/frcfp4

Prasad, K., & Kalra, J. (1993). Oxygen free radicals and hypercholesterolemic atherosclerosis: Effect of vitamin E. *American Heart Journal*, *125*(4), 958–973. https://doi.org/dc6dfq

Prince, C., Sharp, G. C., Howe, L. D., Fraser, A., & Richmond, R. C. (2022). The relationships between women's reproductive factors: A Mendelian randomisation analysis. *BMC Medicine*, *20*(1), 103. https://doi.org/10.1186/s12916-022-02293-5

Prince, M. J., Acosta, D., Guerra, M., Huang, Y., Jimenez-Velazquez, I. Z., Rodriguez, J. J. L., Salas, A., Sosa, A. L., Chua, K.-C., Dewey, M. E., Liu, Z., Mayston, R., & Valhuerdi, A. (2018). Reproductive period, endogenous estrogen exposure and dementia incidence among women in Latin America and China; A 10/66 population-based cohort study. *PLOS ONE*, *13*(2), e0192889. https://doi.org/gc3nxg

Priya, T., Chowdhury, M. G., & Vasanth, K. (2013). Assessment of serum leptin and resistin levels in association with the metabolic risk factors of pre- and post-menopausal rural women in South India. *Diabetes & Metabolic Syndrome*, *7*, 233–237. https://doi.org/gg543r

Raha, S., & Robinson, B. H. (2000). Mitochondria, oxygen free radicals, disease and ageing. *Trends in Biochemical Sciences*, *25*(10), 502–508. https://doi.org/bp74bs

Raji, C. A., Ho, A. J., Parikshak, N., Becker, J. T., Lopez, O. L., Kuller, L. H., Hua, X., Leow, A. D., Toga, A. W., & Thompson, P. M. (2010). Brain Structure and Obesity. *Human Brain Mapping*, *31*(3), 353–364. https://doi.org/10.1002/hbm.20870

Rance, N. E. (2009). Menopause and the human hypothalamus: Evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. *Peptides*, *30*(1), 111–122. https://doi.org/10.1016/j.peptides.2008.05.016

Rance, N. E., Dacks, P. A., Mittelman-Smith, M. A., Romanovsky, A. A., & Krajewski-Hall, S. J. (2013). Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: A novel hypothesis on the mechanism of hot flushes. *Frontiers in Neuroendocrinology*, *34*(3), 211–227. https://doi.org/10.1016/j.yfrne.2013.07.003

Rantalainen, T., Nikander, R., & Heinonen, A. (2010). Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. *Bone*, *46*, 964–969. https://doi.org/ds65q5

Raz, N., Ghisletta, P., Rodrigue, K. M., Kennedy, K. M., & Lindenberger, U. (2010). Trajectories of brain aging in middle-aged and older adults: Regional and individual differences. *NeuroImage*, *51*(2), 501–511. https://doi.org/fjqh5n

Razmjou, S., Abdulnour, J., Bastard, J.-P., Fellahi, S., Doucet, É., Brochu, M., Lavoie, J.-M.,

Rabasa-Lhoret, R., & Prud'homme, D. (2018). Body composition, cardiometabolic risk factors, physical activity, and inflammatory markers in premenopausal women after a 10-year follow-up: A MONET study. *Menopause*, *25*(1), 89–97. https://doi.org/gfk2jz

Reina, P., Cointry, G. R., & Nocciolino, L. (2015). Analysis of the independent power of age-related, anthropometric and mechanical factors as determinants of the structure of radius and tibia in normal adults. A pQCT study. *Journal of Musculoskeletal & Neuronal Interactions*, *15*, 10–22.

Resnick, S. M., Espeland, M. A., Jaramillo, S. A., Hirsch, C., Stefanick, M. L., Murray, A. M., Ockene, J., Davatzikos, C., & For the Women's Health Initiative Memory Study. (2009). Postmenopausal hormone therapy and regional brain volumes: The WHIMS-MRI Study. *Neurology*, *72*(2), 135–142. https://doi.org/10.1212/01.wnl.0000339037.76336.cf

Revilla, M., Villa, L. F., Hernandez, E. R., Sanchez-Atrio, A., Cortes, J., & Rico, H. (1997). Influence of weight and gonadal status on total and regional bone mineral content and on weight-bearing and non-weight-bearing bones, measured by dual-energy X-ray absosorptiometry. *Maturitas*, *28*, 69–74. https://doi.org/bhznkw

Revilla, M., Villa, L. F., Sanchez-Atrio, A., Hernandez, E. R., & Rico, H. (1997). Influence of body mass index on the age-related slope of total and regional bone mineral content. *Calcified Tissue International*, *61*(2). https://doi.org/bqkwjz

Rhodes, D., Fairall, L., Simonsson, T., Court, R., & Chapman, L. (2002). Telomere architecture. *EMBO Reports*, *3*(12), 1139–1145. https://doi.org/d3d82h

Rice, M. S., Bertrand, K. A., & Lajous, M. (2015). Reproductive and lifestyle risk factors and mammographic density in Mexican women. *Annals of Epidemiology*, *25*, 868–873. https://doi.org/f7wps7

Rico, H., Aguado, F., Arribas, I., Hernandez, E. R., Villa, L. F., Seco, C., & Gervas, J. J. (2001). Behavior of phalangeal bone ultrasound in normal women with relation to gonadal status and body mass index. *Osteoporosis International*, *12*(6), 450–455. https://doi.org/fqswcv

Rico, H., Arribas, I., Casanova, F. J., Duce, A. M., Herna, E. R., & Cortes-Prieto, J. (2002). Bone mass, bone metabolism, gonadal status and body mass index. *Osteoporosis International*, *13*(5), 379–387. https://doi.org/cdm6mw

Riddle, W. R., DonLevy, S. C., & Lee, H. (2010). Modeling brain tissue volumes over the lifespan: Quantitative analysis of postmortem weights and in vivo MR images. *Magnetic Resonance Imaging*, *28*(5), 716–720. https://doi.org/cg73z7

Riedel, B. C., Thompson, P. M., & Brinton, R. D. (2016). Age, APOE and sex: Triad of risk of Alzheimer's disease. *The Journal of Steroid Biochemistry and Molecular Biology*, *160*, 134–147. https://doi.org/f8qn7v

Ritchie, H., & Roser, M. (2018). Causes of Death. *Our World in Data*.

Ritchie, S. J., Dickie, D. A., Cox, S. R., Hernandez, M. del C. V., Corley, J., Royle, N. A., Pattie, A., Aribisala, B. S., Redmond, P., Maniega, S. M., Taylor, A. M., Sibbett, R., Gow, A. J., Starr, J. M., Bastin, M. E., Wardlaw, J. M., & Deary, I. J. (2015). Brain volumetric changes and cognitive ageing during the eighth decade of life. *Human Brain Mapping*, *36*(12), 4910–4925. https://doi.org/f76ng3

Roberts, S. B., & Rosenberg, I. (2006). Nutrition and Aging: Changes in the Regulation of Energy Metabolism With Aging. *Physiological Reviews*, *86*(2), 651–667. https://doi.org/b778xk

Rocca, W. A., Bower, J. H., Maraganore, D. M., Ahlskog, J. E., Grossardt, B. R., De Andrade, M., & Melton, L. 3rd. (2007). Increased risk of cognitive impairment or dementia in women who underwent oophorectomy before menopause. *Neurology*, *69*(11), 1074–1083. https://doi.org/fvz2hz

Roelfsema, F., & Veldhuis, J. D. (2016). Growth Hormone Dynamics in Healthy Adults Are Related to Age and Sex and Strongly Dependent on Body Mass Index. *Neuroendocrinology*, *103*, 335–344. https://doi.org/gg543t

Rogers, N. H., Perfield, J. W., Strissel, K. J., Obin, M. S., & Greenberg, A. S. (2009). Reduced Energy Expenditure and Increased Inflammation Are Early Events in the Development of Ovariectomy-Induced Obesity. *Endocrinology*, *150*(5), 2161–2168. https://doi.org/10.1210/en.2008-1405

Rolls, B. J., Dimeo, K. A., & Shide, D. J. (1995). Age-related impairments in the regulation of food intake. *The American Journal of Clinical Nutrition*, *62*(5), 923–931. https://doi.org/ghnwjm

Roman Lay, A. A., do Nascimento, C. F., Horta, B. L., & Dias Porto Chiavegatto Filho, A. (2020). Reproductive factors and age at natural menopause: A systematic review and meta-analysis. *Maturitas*, *131*, 57–64. https://doi.org/gkfnqz

Romero-Aleshire, M. J., Diamond-Stanic, M. K., Hasty, A. H., Hoyer, P. B., & Brooks, H. L. (2009). Loss of ovarian function in the VCD mouse-model of menopause leads to insulin resistance and a rapid progression into the metabolic syndrome. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *297*(3), R587–R592. https://doi.org/dgpj7j

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., Allison, T. G., Batsis, J. A., Sert-Kuniyoshi, F. H., & Lopez-Jimenez, F. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity*, *32*(6), 959–966. https://doi.org/fdsg47

Rometo, A. M., Krajewski, S. J., Voytko, M. L., & Rance, N. E. (2007). Hypertrophy and increased kisspeptin gene expression in the hypothalamic infundibular nucleus of

postmenopausal women and ovariectomized monkeys. *Journal of Clinical Endocrinology and Metabolism*, *92*(7), 2744–2750. https://doi.org/10.1210/jc.2007-0553

Rosenbaum, M., Nicolson, M., & Hirsch, J. (1996). Effects of gender, body composition, and menopause on plasma concentrations of leptin. *The Journal of Clinical Endocrinology and Metabolism*, *81*, 3424–3427.

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological Bulletin*, *86*(3), 638–641. https://doi.org/d5sxt3

Rossouw, J. E., Anderson, G. L., Prentice, R. L., LaCroix, A. Z., Kooperberg, C., Stefanick, M. L., Jackson, R. D., Beresford, S. A., Howard, B. V., Johnson, K. C., Kotchen, J. M., Ockene, J., & Investigators, W. G. for the W. H. I. (2002). Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results From the Women's Health Initiative randomized controlled trial. *JAMA*, *288*(3), 321–333. https://doi.org/fwdr43

Ruth, K. S., Day, F. R., Hussain, J., Martínez-Marchal, A., Aiken, C. E., Azad, A., Thompson, D. J., Knoblochova, L., Abe, H., Tarry-Adkins, J. L., Gonzalez, J. M., Fontanillas, P., Claringbould, A., Bakker, O. B., Sulem, P., Walters, R. G., Terao, C., Turon, S., Horikoshi, M., ... Perry, J. R. B. (2021). Genetic insights into biological mechanisms governing human ovarian ageing. *Nature*, *596*(7872), 393–397. https://doi.org/gqs3

Ruth, K. S., Perry, J. R. B., Henley, W. E., Melzer, D., Weedon, M. N., & Murray, A. (2016). Events in Early Life are Associated with Female Reproductive Ageing: A UK Biobank Study. *Scientific Reports*, *6*(1), 1–9. https://doi.org/f8kk4g

Sallis, J. F. (2000). Age-related decline in physical activity: A synthesis of human and animal studies: *Medicine & Science in Sports & Exercise*, 1598–1600. https://doi.org/crhkrv

Salomaa, V., Rasi, V., & Pekkanen, J. (1995). Association of hormone replacement therapy with hemostatic and other cardiovascular risk factors. *The FINRISK Hemostasis Study. Arteriosclerosis, Thrombosis, and Vascular Biology*, *15*, 1549–1555. https://doi.org/ccr7t9

Salpeter, S. R., Walsh, J. M. E., Ormiston, T. M., Greyber, E., Buckley, N. S., & Salpeter, E. E. (2006). Meta-analysis: Effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes, Obesity and Metabolism*, *8*(5), 538–554. https://doi.org/cvv9nk

Sarrafzadegan, N., Khosravi-Boroujeni, H., Esmaillzadeh, A., Sadeghi, M., Rafieian-Kopaei, M., & Asgary, S. (2013). The association between hypertriglyceridemic waist phenotype, menopause, and cardiovascular risk factors. *Archives of Iranian Medicine*, *16*, 161–166.

Scahill, R. I., Frost, C., Jenkins, R., Whitwell, J. L., Rossor, M. N., & Fox, N. C. (2003). A Longitudinal Study of Brain Volume Changes in Normal Aging Using Serial Registered Magnetic Resonance Imaging. *Archives of Neurology*, *60*(7), 989–994. https://doi.org/

cv6fps

Schaberg-Lorei, G., Ballard, J. E., McKeown, B. C., & Zinkgraf, S. A. (1990). Body composition alterations consequent to an exercise program for pre and postmenopausal women. *The Journal of Sports Medicine and Physical Fitness*, *30*, 426–433.

Schoenaker, D. A., Jackson, C. A., Rowlands, J. V., & Mishra, G. D. (2014). Socioeconomic position, lifestyle factors and age at natural menopause: A systematic review and meta-analyses of studies across six continents. *International Journal of Epidemiology*, *43*(5), 1542–1562. https://doi.org/f6nw9d

Schwarz, S., Völzke, H., Alte, D., Schwahn, C., Grabe, H. J., Hoffmann, W., John, U., & Dören, M. (2007). Menopause and determinants of quality of life in women at midlife and beyond: The study of health in pomerania (SHIP). *Menopause*, *14*(1), 123–134. https://doi.org/cp2j95

Sedgh, G., Singh, S., & Hussain, R. (2014). Intended and Unintended Pregnancies Worldwide in 2012 and Recent Trends. *Studies in Family Planning*, *45*(3), 301–314. https://doi.org/f6h2nm

Seshadri, S., Wolf, P. A., Beiser, A., Au, R., McNulty, K., White, R., & D'Agostino, R. B. (1997). Lifetime risk of dementia and Alzheimer's disease: The impact of mortality on risk estimates in the Framingham Study. *Neurology*, *49*(6), 1498–1504. https://doi.org/gg9jwp

Shafiee, G., Keshtkar, A., Soltani, A., Ahadi, Z., Larijani, B., & Heshmat, R. (2017). Prevalence of sarcopenia in the world: A systematic review and meta-analysis of general population studies. *Journal of Diabetes & Metabolic Disorders*, *16*(21).

Shakir, Y. A., Samsioe, G., Nyberg, P., Lidfeldt, J., & Nerbrand, C. (2004). Cardiovascular risk factors in middle-aged women and the association with use of hormone therapy: Results from a population-based study of Swedish women. *The Women's Health in the Lund Area (WHILA) Study. Climacteric*, *7*, 274–283.

Sherk, V. D., Malone, S. P., Bemben, M. G., Knehans, A. W., Palmer, I. J., & Bemben, D. A. (2011). Leptin, fat mass, and bone mineral density in healthy pre- and postmenopausal women. *Journal of Clinical Densitometry : The Official Journal of the International Society for Clinical Densitometry*, *14*, 321–325. https://doi.org/dqsmjh

Shibata, H., Matsuzaki, T., & Hatano, S. (1979). Relationship of relevant factors of atherosclerosis to menopause in Japanese women. *American Journal of Epidemiology*, *109*, 420–424. https://doi.org/gg543s

Shumaker, S. A., Legault, C., Kuller, L., Rapp, S. R., Thal, L., Lane, D. S., Fillit, H., Stefanick, M. L., Hendrix, S. L., Lewis, C. E., Masaki, K., Coker, L. H., & for the Women's Health Initiative Memory Study. (2004). Conjugated Equine Estrogens and Incidence of Probable Dementia and Mild Cognitive Impairment in Postmenopausal

WomenWomen's Health Initiative Memory Study. *JAMA*, *291*(24), 2947–2958. https://doi.org/10.1001/jama.291.24.2947

Shumaker, S. A., Legault, C., Rapp, S. R., Thal, L., Wallace, R. B., Ockene, J. K., Hendrix, S. L., Iii, B. N. J., Assaf, A. R., Jackson, R. D., Kotchen, J. M., Wassertheil-Smoller, S., Wactawski-Wende, J., & Investigators, for the W. (2003). Estrogen Plus Progestin and the Incidence of Dementia and Mild Cognitive Impairment in Postmenopausal Women: The Women's Health Initiative Memory Study: A Randomized Controlled Trial. *JAMA*, *289*(20), 2651–2662. https://doi.org/dt2tv9

Sieminska, L., Wojciechowska, C., & Foltyn, W. (2006). The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause. *Endokrynologia Polska*, *57*, 15–22.

Siervogel, R. M., Wisemandle, W., & Maynard, L. M. (1998). Serial changes in body composition throughout adulthood and their relationships to changes in lipid and lipoprotein levels: The Fels Longitudinal Study. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *18*, 1759–1764. https://doi.org/brb49w

Silberstein, S. D., & Merriam, G. R. (2000). Physiology of the Menstrual Cycle. *Cephalalgia*, *20*(3), 148–154. https://doi.org/bcqxzs

Simpson, E. R., & Davis, S. R. (2001). Minireview: Aromatase and the Regulation of Estrogen Biosynthesis—Some New Perspectives. *Endocrinology*, *142*(11), 4589–4594. https://doi.org/10.1210/endo.142.11.8547

Sites, C. K., Toth, M. J., Cushman, M., L'Hommedieu, G. D., Tchernof, A., Tracy, R. P., & Poehlman, E. T. (2002). Menopause-related differences in inflammation markers and their relationship to body fat distribution and insulin-stimulated glucose disposal. *Fertility and Sterility*, *77*(1), 128–135. https://doi.org/bts8k8

Skorupskaite, K., George, J. T., & Anderson, R. A. (2014). The kisspeptin-GnRH pathway in human reproductive health and disease. *Human Reproduction Update*, *20*(4), 485–500. https://doi.org/10.1093/humupd/dmu009

Skrzypczak, M., & Szwed, A. (2005). Assessment of the body mass index and selected physiological parameters in pre- and post-menopausal women. *Homo : internationale Zeitschrift fur die vergleichende Forschung am Menschen*, *56*, 141–152.

Skrzypczak, M., Szwed, A., Pawlińska-Chmara, R., & Skrzypulec, V. (2007). Assessment of the BMI, WHR and W/Ht in pre-and postmenopausal women. *Anthropological Review*, *70*, 3–13. https://doi.org/d9wkwd

Smith, D. C., Prentice, R., Thompson, D. J., & Herrmann, W. L. (1975). Association of Exogenous Estrogen and Endometrial Carcinoma. *New England Journal of Medicine*, *293*(23), 1164–1167. https://doi.org/fj2xf7

Smith-DiJulio, K., Mitchell, E. S., & Woods, N. F. (2005). Concordance of retrospective and prospective reporting of menstrual irregularity by women in the menopausal transition. *Climacteric*, *8*(4), 390–397. https://doi.org/d2zdc5

Snieder, H., MacGregor, A. J., & Spector, T. D. (1998). Genes Control the Cessation of a Woman's Reproductive Life: A Twin Study of Hysterectomy and Age at Menopause1. *The Journal of Clinical Endocrinology & Metabolism*, *83*(6), 1875–1880. https://doi.org/10.1210/jcem.83.6.4890

Soderberg, S., Ahren, B., Eliasson, M., Dinesen, B., & Olsson, T. (2002). The association between leptin and proinsulin is lost with central obesity. *Journal of Internal Medicine*, *252*, 140–148. https://doi.org/b5srqb

Son, M. K., Lim, N. K., & Lim, J. Y. (2015). Difference in blood pressure between early and late menopausal transition was significant in healthy Korean women. *BMC Women's Health*, *15*(64).

Soreca, I., Rosano, C., Jennings, J. R., Sheu, L. K., Kuller, L. H., Matthews, K. A., Aizenstein, H. J., & Gianaros, P. J. (2009). Gain in Adiposity Across 15 Years is Associated With Reduced Gray Matter Volume in Healthy Women: *Psychosomatic Medicine*, *71*(5), 485–490. https://doi.org/10.1097/psy.0b013e3181a5429d

Soriguer, F., Morcillo, S., Hernando, V., Valdés, S., de Adana, M. S. R., Olveira, G., Fuentes, E. G., González, I., Tapia, M. J., & Esteva, I. (2009). Type 2 diabetes mellitus and other cardiovascular risk factors are no more common during menopause: Longitudinal study. *Menopause*, *16*(4), 817–821. https://doi.org/bt5kcc

Soules, M. R., Sherman, S., Parrott, E., Rebar, R., Santoro, N., Utian, W., & Woods, N. (2001). Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Climacteric*, *4*(4), 267–272. https://doi.org/10.1080/cmt.4.4.267.272

Sowers, M., Zheng, H., & Tomey, K. (2007). Changes in body composition in women over six years at midlife: Ovarian and chronological aging. *The Journal of Clinical Endocrinology & Metabolism*, *92*, 895–901. https://doi.org/10.1210/jc.2006-1393

Staessen, J., Bulpitt, C. J., Fagard, R., Lijnen, P., & Amery, A. (1989). The influence of menopause on blood pressure. *Journal of Human Hypertension*, *3*, 427–433.

Stampfer, M. J., & Colditz, G. A. (1991). Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Preventive Medicine*, *20*(1), 47–63. https://doi.org/cbf2xv

Stefanick, M. L., Mackey, S., Sheehan, M., Ellsworth, N., Haskell, W. L., & Wood, P. D. (1998). Effects of Diet and Exercise in Men and Postmenopausal Women with Low Levels of HDL Cholesterol and High Levels of LDL Cholesterol. *New England Journal of Medicine*, *339*(1), 12–20. https://doi.org/fdz33g

Steiger, P., Cummings, B., SR, DM, S., NE, G., & H.K. (1992). Age-related decrements in bone mineral density in women over 65. *Journal of Bone and Mineral Research*, *7*, 625–632. https://doi.org/cjcwzx

Steinkellner, A. R., Denison, S. E., Eldridge, S. L., Lenzi, L. L., Chen, W., & Bowlin, S. J. (2012). A decade of postmenopausal hormone therapy prescribing in the United States: Long-term effects of the Women's Health Initiative. *Menopause (New York, N.Y.)*, *19*(6), 616–621. https://doi.org/f32dm6

Sternfeld, B., Wang, H., Quesenberry, C. P., Abrams, B., Everson-Rose, S. A., Greendale, G. A., Matthews, K. A., Torrens, J. I., & Sowers, M. (2004). Physical Activity and Changes in Weight and Waist Circumference in Midlife Women: Findings from the Study of Women's Health Across the Nation. *American Journal of Epidemiology*, *160*(9), 912–922. https://doi.org/fvszb5

Stevens, G. A., Singh, G. M., Lu, Y., Danaei, G., Lin, J. K., Finucane, M. M., Bahalim, A. N., McIntire, R. K., Gutierrez, H. R., Cowan, M., Paciorek, C. J., Farzadfar, F., Riley, L., Ezzati, M., & the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group (Body Mass Index). (2012). National, regional, and global trends in adult overweight and obesity prevalences. *Population Health Metrics*, *10*(1), 22. https://doi.org/f9smkf

Stolk, L., Perry, J. R. B., Chasman, D. I., He, C., Mangino, M., Sulem, P., Barbalic, M., Broer, L., Byrne, E. M., Ernst, F., Esko, T., Franceschini, N., Gudbjartsson, D. F., Hottenga, J.-J., Kraft, P., McArdle, P. F., Porcu, E., Shin, S.-Y., Smith, A. V., ... Lunetta, K. L. (2012). Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nature Genetics*, *44*(3), 260–268. https://doi.org/fxm58v

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., Moher, D., Becker, B. J., Sipe, T. A., & Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: A proposal for reporting. *Jama*, *283*(15), 2008–2012. https://doi.org/ff8g6m

Stubbins, R. E., Najjar, K., Holcomb, V. B., Hong, J., & Núñez, N. P. (2012). Oestrogen alters adipocyte biology and protects female mice from adipocyte inflammation and insulin resistance. *Diabetes, Obesity and Metabolism*, *14*(1), 58–66. https://doi.org/ds2nc3

Suarez-Ortegon, M. F., Arbelaez, A., Mosquera, M., Mendez, F., & Aguilar-de Plata, C. (2012). C-reactive protein, waist circumference, and family history of heart attack are independent predictors of body iron stores in apparently healthy premenopausal women. *Biological Trace Element Research*, *148*, 135–138. https://doi.org/f3323c

Sudheimer, K. D., O'Hara, R., Spiegel, D., Powers, B., Kraemer, H. C., Neri, E., Weiner, M., Hardan, A., Hallmayer, J., & Dhabhar, F. S. (2014). Cortisol, cytokines, and hippocampal volume interactions in the elderly. *Frontiers in Aging Neuroscience*, *6*, 153.

https://doi.org/gf48jh

Sudlow, C., Gallacher, J., Allen, N., Beral, V., Burton, P., Danesh, J., Downey, P., Elliott, P., Green, J., Landray, M., Liu, B., Matthews, P., Ong, G., Pell, J., Silman, A., Young, A., Sprosen, T., Peakman, T., & Collins, R. (2015). UK Biobank: An Open Access Resource for Identifying the Causes of a Wide Range of Complex Diseases of Middle and Old Age. *PLOS Medicine*, *12*(3), e1001779. https://doi.org/bfn8

Suliga, E., Koziel, D., Ciesla, E., Rebak, D., & Gluszek, S. (2016). Factors associated with adiposity, lipid profile disorders and the metabolic syndrome occurrence in premenopausal and postmenopausal women. *PLoS One*, *11:e0154511*.

Sullivan, E. V., Marsh, L., & Pfefferbaum, A. (2005). Preservation of hippocampal volume throughout adulthood in healthy men and women. *Neurobiology of Aging*, *26*(7), 1093–1098. https://doi.org/b95k6s

Sumner, A. E., Falkner, B., Kushner, H., & Considine, R. V. (1998). Relationship of leptin concentration to gender, menopause, age, diabetes, and fat mass in African Americans. *Obesity Research*, *6*, 128–133. https://doi.org/gg543x

Sun, L., Tan, L., Yang, F., Luo, Y., Li, X., Deng, H.-W., & Dvornyk, V. (2012). Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause: *Menopause: The Journal of The North American Menopause Society*, *19*(2), 126–132. https://doi.org/frqv4t

Svejme, O., Ahlborg, H. G., Nilsson, J.-Å., & Karlsson, M. K. (2012). Early menopause and risk of osteoporosis, fracture and mortality: A 34-year prospective observational study in 390 women. *BJOG: An International Journal of Obstetrics & Gynaecology*, *119*(7), 810–816. https://doi.org/f23g3t

Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., & Gortmaker, S. L. (2011). The global obesity pandemic: Shaped by global drivers and local environments. *The Lancet*, *378*(9793), 804–814. https://doi.org/d3c8fc

Tabatabaei-Jafari, H., Initiative (ADNI), for the A. D. N., Shaw, M. E., Initiative (ADNI), for the A. D. N., Walsh, E., Initiative (ADNI), for the A. D. N., Cherbuin, N., Initiative (ADNI), for the A. D. N., & Initiative (ADNI), for the A. D. N. (2020). Cognitive/Functional Measures Predict Alzheimer's Disease, Dependent on Hippocampal Volume. *The Journals of Gerontology: Series B*, *75*(7), 1393–1402. https://doi.org/gf4f4p

Tabatabaei-Jafari, H., Shaw, M. E., & Cherbuin, N. (2015). Cerebral atrophy in mild cognitive impairment: A systematic review with meta-analysis. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring*, *1*(4), 487–504. https://doi.org/ggtc5t

Tabatabaei-Jafari, H., Shaw, M. E., Walsh, E., & Cherbuin, N. (2019). Regional brain atrophy predicts time to conversion to Alzheimer's disease, dependent on baseline volume.

Neurobiology of Aging, *83*, 86–94. https://doi.org/gg4tjr

Tabatabaei-Jafari, H., Walsh, E., Shaw, M. E., & Cherbuin, N. (2018). A simple and clinically relevant combination of neuroimaging and functional indexes for the identification of those at highest risk of Alzheimer's disease. *Neurobiology of Aging*, *69*, 102–110. https://doi.org/gg4tjq

Taheri, S., Lin, L., Austin, D., Young, T., & Mignot, E. (2004). Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. *PLOS Medicine*, *1*(3), e62. https://doi.org/d86c44

Tanaka, N. I., Hanawa, S., & Murakami, H. (2015). Accuracy of segmental bioelectrical impedance analysis for predicting body composition in pre- and postmenopausal women. *Journal of Clinical Densitometry : The Official Journal of the International Society for Clinical Densitometry*, *18*, 252–259. https://doi.org/f7cbxz

Taylor, C. M., Pritschet, L., Yu, S., & Jacobs, E. G. (2019). Applying a Women's Health Lens to the Study of the Aging Brain. *Frontiers in Human Neuroscience*, *13*. https://doi.org/gk58sn

Team, R. C. (2016). *R: A language and environment for statistical computing*. R Foundation for Statistical Computing.

Team, Rs. (2012). *RStudio: Integrated development for R*. RStudio, Inc.

Terrón, M. P., Delgado-Adámez, J., Pariente, J. A., Barriga, C., Paredes, S. D., & Rodríguez, A. B. (2013). Melatonin reduces body weight gain and increases nocturnal activity in male Wistar rats. *Physiology & Behavior*, *118*, 8–13. https://doi.org/f46sxr

Thaler, J. P., Yi, C.-X., Schur, E. A., Guyenet, S. J., Hwang, B. H., Dietrich, M. O., Zhao, X., Sarruf, D. A., Izgur, V., Maravilla, K. R., Nguyen, H. T., Fischer, J. D., Matsen, M. E., Wisse, B. E., Morton, G. J., Horvath, T. L., Baskin, D. G., Tschöp, M. H., & Schwartz, M. W. (2012). Obesity is associated with hypothalamic injury in rodents and humans. *The Journal of Clinical Investigation*, *122*(1), 153–162. https://doi.org/fzswwd

Thomas, F., Renaud, F., Benefice, E., de Meeüs, T., & Guegan, J. F. (2001). International variability of ages at menarche and menopause: Patterns and main determinants. *Human Biology*, *73*(2), 271–290. https://doi.org/dp9qsv

Thomas, T., Burguera, B., Melton III, L. J., Atkinson, E. J., O'Fallon, W. M., Riggs, B. L., & Khosla, S. (2000). Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. *Metabolism*, *49*(10), 1278–1284. https://doi.org/d45wc7

Tolson, K. P., Garcia, C., Yen, S., Simonds, S., Stefanidis, A., Lawrence, A., Smith, J. T., & Kauffman, A. S. (2014). Impaired kisspeptin signaling decreases metabolism and promotes glucose intolerance and obesity. *The Journal of Clinical Investigation*, *124*(7), 3075–3079.

https://doi.org/10.1172/JCI71075

Torgerson, D. J., Thomas, R. E., & Reid, D. M. (1997). Mothers and daughters menopausal ages: Is there a link? *European Journal of Obstetrics & Gynecology and Reproductive Biology*, *74*(1), 63–66. https://doi.org/bnjnsd

Torng, P. L., Su, T. C., & Sung, F. C. (2000). Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women: The Chin-Shan Community Cardiovascular Cohort Study. *Atherosclerosis*, *153*, 413–421. https://doi.org/cvh677

Toth, M. J., Tchernof, A., Sites, C. K., & Poehlman, E. T. (2000). Effect of menopausal status on body composition and abdominal fat distribution. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity*, *24*, 226–231. https://doi.org/c27fk9

Trayhurn, P. (2005). Endocrine and signalling role of adipose tissue: New perspectives on fat. *Acta Physiologica Scandinavica*, *184*(4), 285–293. https://doi.org/dsstpr

Treloar, S. A., Kim-Anh, D., & Martin, N. G. (1998). Genetic influences on the age at menopause. *The Lancet*, *352*(9134), 1084–1085. https://doi.org/ct9mn6

Tremollieres, F. A., Pouilles, J. M., & Ribot, C. A. (1996). Relative influence of age and menopause on total and regional body composition changes in postmenopausal women. *American Journal of Obstetrics and Gynecology*, *175*, 1594–1600. https://doi.org/fdvcmx

Trifunovic, A., & Larsson, N.-G. (2008). Mitochondrial dysfunction as a cause of ageing. *Journal of Internal Medicine*, *263*(2), 167–178. https://doi.org/bs9pn8

Trikudanathan, S., Pedley, A., & Massaro, J. M. (2013). Association of female reproductive factors with body composition: The Framingham Heart Study. *The Journal of Clinical Endocrinology and Metabolism*, *98*, 236–244. https://doi.org/10.1210/jc.2012-1785

Tschanz, J. T., Corcoran, C. D., Schwartz, S., Treiber, K., Green, R. C., Norton, M. C., Mielke, M. M., Piercy, K., Steinberg, M., Rabins, P. V., Leoutsakos, J.-M., Welsh-Bohmer, K. A., Breitner, J. C. S., & Lyketsos, C. G. (2011). Progression of Cognitive, Functional, and Neuropsychiatric Symptom Domains in a Population Cohort With Alzheimer Dementia: The Cache County Dementia Progression Study. *The American Journal of Geriatric Psychiatry*, *19*(6), 532–542. https://doi.org/bwxqjj

Tsilidis, K. K., Allen, N. E., Key, T. J., Dossus, L., Lukanova, A., Bakken, K., Lund, E., Fournier, A., Overvad, K., Hansen, L., Tjønneland, A., Fedirko, V., Rinaldi, S., Romieu, I., Clavel-Chapelon, F., Engel, P., Kaaks, R., Schütze, M., Steffen, A., ... Riboli, E. (2011). Oral contraceptive use and reproductive factors and risk of ovarian cancer in the European Prospective Investigation into Cancer and Nutrition. *British Journal of Cancer*, *105*(9), 1436–1442. https://doi.org/d3bh2h

Tucsek, Z., Toth, P., Sosnowska, D., Gautam, T., Mitschelen, M., Koller, A., Szalai, G.,

Sonntag, W. E., Ungvari, Z., & Csiszar, A. (2014). Obesity in Aging Exacerbates Blood–Brain Barrier Disruption, Neuroinflammation, and Oxidative Stress in the Mouse Hippocampus: Effects on Expression of Genes Involved in Beta-Amyloid Generation and Alzheimer's Disease. *The Journals of Gerontology: Series A*, *69*(10), 1212–1226. https://doi.org/f6mtvs

Tziomalos, K., & Charsoulis, F. (2004). Endocrine effects of tobacco smoking. *Clinical Endocrinology*, *61*(6), 664–674. https://doi.org/dwcgvg

United Nations. (2019). *Contraceptive Use by Method 2019: Data Booklet*. UN. https://doi.org/10.18356/1bd58a10-en

Utian, W. H. (1999). The International Menopause menopause-related terminology definitions. *Climacteric*, *2*(4), 284–286. https://doi.org/10.3109/13697139909038088

Valdes, A., Andrew, T., Gardner, J., Kimura, M., Oelsner, E., Cherkas, L., Aviv, A., & Spector, T. (2005). Obesity, cigarette smoking, and telomere length in women. *The Lancet*, *366*(9486), 662–664. https://doi.org/fc9v94

Valenzuela, M. J., & Sachdev, P. (2006). Brain reserve and dementia: A systematic review. *Psychological Medicine*, *36*(4), 441–454. https://doi.org/cghmhw

van Asselt, K. M., Kok, H. S., Pearson, P. L., Dubas, J. S., Peeters, P. H. M., te Velde, E. R., & van Noord, P. A. H. (2004). Heritability of menopausal age in mothers and daughters. *Fertility and Sterility*, *82*(5), 1348–1351. https://doi.org/fgnfwz

van Rooij, I. A. J. (2002). Serum anti-Mullerian hormone levels: A novel measure of ovarian reserve. *Human Reproduction*, *17*(12), 3065–3071. https://doi.org/fvfdrd

Van Kempen, T. A., Milner, T. A., & Waters, E. M. (2011). Accelerated Ovarian Failure: A novel, chemically induced animal model of menopause. *Brain Research*, *1379*, 176–187. https://doi.org/bd9frz

Van Pelt, R. E., Davy, K. P., Stevenson, E. T., Wilson, T. M., Jones, P. P., Desouza, C. A., & Seals, D. R. (1998). Smaller differences in total and regional adiposity with age in women who regularly perform endurance exercise. *American Journal of Physiology-Endocrinology And Metabolism*, *275*(4), E626–E634. https://doi.org/gg6q88

Vekic, J., Zeljkovic, A., Stefanovic, A., Jelic-Ivanovic, Z., & Spasojevic-Kalimanovska, V. (2019). Obesity and dyslipidemia. *Metabolism*, *92*, 71–81. https://doi.org/gf9s37

Veldhuis, J. D., Dyer, R. B., Trushin, S. A., Bondar, O. P., Singh, R. J., & Klee, G. G. (2016). Interleukins 6 and 8 and abdominal fat depots are distinct correlates of lipid moieties in healthy pre- and postmenopausal women. *Endocrine*, *54*, 671–680. https://doi.org/gg543v

Viechtbauer, W. (2010). Conducting meta-analyses in R with the metafor. *Journal of Statistical Software*, *36*, 1–48. https://doi.org/gckfpj

Vigier, B., Picard, J.-Y., Tran, D., Legeai, L., & Josso, N. (1984). Production of Anti-Müllerian

Hormone: Another Homology between Sertoli and Granulosa Cells. *Endocrinology*, *114*(4), 1315–1320. https://doi.org/10.1210/endo-114-4-1315

Vollset, S. E., Goren, E., Yuan, C.-W., Cao, J., Smith, A. E., Hsiao, T., Bisignano, C., Azhar, G. S., Castro, E., Chalek, J., Dolgert, A. J., Frank, T., Fukutaki, K., Hay, S. I., Lozano, R., Mokdad, A. H., Nandakumar, V., Pierce, M., Pletcher, M., ... Murray, C. J. L. (2020). Fertility, mortality, migration, and population scenarios for 195 countries and territories from 2017 to 2100: A forecasting analysis for the Global Burden of Disease Study. *The Lancet*, S0140673620306772. https://doi.org/gg53xk

von Zglinicki, T. (2002). Oxidative stress shortens telomeres. *Trends in Biochemical Sciences*, *27*(7), 339–344. https://doi.org/dwjpsx

Wald, C., & Wu, C. (2010). Of Mice and Women: The Bias in Animal Models. *Science*, *327*(5973), 1571–1572. https://doi.org/cmczjz

Walker, K. A., Hoogeveen, R. C., Folsom, A. R., Ballantyne, C. M., Knopman, D. S., Windham, B. G., Jack, C. R., & Gottesman, R. F. (2017). Midlife systemic inflammatory markers are associated with late-life brain volume: The ARIC study. *Neurology*, *89*(22), 2262–2270. https://doi.org/gcnx72

Wallace, W. H. B., & Kelsey, T. W. (2010). Human Ovarian Reserve from Conception to the Menopause. *PLOS ONE*, *5*(1), e8772. https://doi.org/bj3jsv

Wang, F., Ma, X., & Hao, Y. (2012). Serum glycated albumin is inversely influenced by fat mass and visceral adipose tissue in Chinese with normal glucose tolerance. *PLoS One*, *7:e51098*.

Wang, W. S., Wahlqvist, M. L., Hsu, C. C., Chang, H. Y., Chang, W. C., & Chen, C. C. (2012). Age- and gender-specific population attributable risks of metabolic disorders on all-cause and cardiovascular mortality in Taiwan. *BMC Public Health*, *12*(111).

Wang, W., Zhao, L. J., Liu, Y. Z., Recker, R. R., & Deng, H. W. (2005). Genetic and environmental correlations between obesity phenotypes and age at menarche. *International Journal of Obesity*, *30*, 1595–1600. https://doi.org/dj4pcb

Ward, M. A., Bendlin, B. B., McLaren, D. G., Hess, T. M., Gallagher, C. L., Kastman, E. K., Rowley, H. A., Asthana, S., Carlsson, C. M., Sager, M. A., & Johnson, S. C. (2010). Low HDL Cholesterol is Associated with Lower Gray Matter Volume in Cognitively Healthy Adults. *Frontiers in Aging Neuroscience*, *2*. https://doi.org/10.3389/fnagi.2010.00029

Wee, J., Sng, B. Y., Shen, L., Lim, C. T., Singh, G., & Das De, S. (2013). The relationship between body mass index and physical activity levels in relation to bone mineral density in premenopausal and postmenopausal women. *Archives of Osteoporosis*, *8*(162).

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2014). Newcastle-Ottawa quality assessment scale cohort studies. *University of Ottawa*.

Wentzensen, N., & Trabert, B. (2015). Hormone therapy: Short-term relief, long-term consequences. *The Lancet*, *385*(9980), 1806–1808. https://doi.org/f3hdb9

Whitmer, R. A., Quesenberry, C. P., Zhou, J., & Yaffe, K. (2011). Timing of hormone therapy and dementia: The critical window theory revisited. *Annals of Neurology*, *69*(1), 163–169. https://doi.org/dbzwnf

Widya, R. L., de Roos, A., Trompet, S., de Craen, A. J., Westendorp, R. G., Smit, J. W., van Buchem, M. A., van der Grond, J., & PROSPER Study Group. (2011). Increased amygdalar and hippocampal volumes in elderly obese individuals with or at risk of cardiovascular disease. *The American Journal of Clinical Nutrition*, *93*(6), 1190–1195. https://doi.org/10.3945/ajcn.110.006304

Williams, G. C. (1957). Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution*, *11*(4), 398–411. https://doi.org/b8msb4

Williams, P. T., & Krauss, R. M. (1997). Associations of age, adiposity, menopause, and alcohol intake with low-density lipoprotein subclasses. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *17*, 1082–1090. https://doi.org/b53b7w

Wilson, P. F., D'Agostino, R. B., Sullivan, L., Parise, H., & Kannel, W. B. (2002). Overweight and obesity as determinants of cardiovascular risk: The framingham experience. *Archives of Internal Medicine*, *162*, 1867–1872. https://doi.org/bwggbf

Wing, R. R., Matthews, K. A., Kuller, L. H., Meilahn, E. N., & Plantinga, P. L. (1991). Weight gain at the time of menopause. *Archives of Internal Medicine*, *151*, 97–102.

Withrow, D., & Alter, D. (2011). The economic burden of obesity worldwide: A systematic review of the direct costs of obesity. *Obesity Reviews*, *12*, 131–141. https://doi.org/ddvfxn

Wnuk, A., Korol, D. L., & Erickson, K. I. (2012). Estrogens, hormone therapy, and hippocampal volume in postmenopausal women. *Maturitas*, *73*(3), 186–190. https://doi.org/10.1016/j.maturitas.2012.07.001

Wolf, H., Hensel, A., Arendt, T., Kivipelto, M., Winblad, B., & Gertz, H.-J. (2004). Serum lipids and hippocampal volume: The link to Alzheimer's disease? *Annals of Neurology*, *56*(5), 745–749. https://doi.org/bpzxv3

Wood, P. D., Stefanick, M. L., Dreon, D. M., Frey-Hewitt, B., Garay, S. C., Williams, P. T., Superko, H. R., Fortmann, S. P., Albers, J. J., Vranizan, K. M., Ellsworth, N. M., Terry, R. B., & Haskell, W. L. (1988). Changes in Plasma Lipids and Lipoproteins in Overweight Men during Weight Loss through Dieting as Compared with Exercise. *New England Journal of Medicine*, *319*(18), 1173–1179. https://doi.org/fc2rff

Woolley, C. S., & McEwen, B. S. (1992). Estradiol mediates fluctuation in hippocampal synapse density during the estrous cycle in the adult rat [published erratum appears in J Neurosci 1992 Oct;12(10):following table of contents]. *Journal of Neuroscience*, *12*(7),

2549–2554. https://doi.org/gg5rtx

Woolley, C., Gould, E., Frankfurt, M., & McEwen, B. (1990). Naturally occurring fluctuation in dendritic spine density on adult hippocampal pyramidal neurons. *The Journal of Neuroscience*, *10*(12), 4035–4039. https://doi.org/gg5rtn

World Health Organization. (1980). *Research on the menopause: Report of a WHO scientific group [meeting held in Geneva from 8 to 12*.

World Health Organization. (1996). *Research on the menopause in the 1990s: Report of a WHO scientific group*.

World Health Organization. (2000). *Obesity: Preventing and managing the global epidemic*.

World Health Organization. (2007). *Prevention and control of noncommunicable diseases: Implementation of the global strategy: Report by the Secretariat*.

World Health Organization. (2011). *Waist circumference and waist-hip ratio: Report of a WHO expert consultation, Geneva, 8-11 December 2008*. World Health Organization.

World Health Organization. (2013). In *Women's Health*. https://www.who.int/en/news-room/fact-sheets/detail/women-s-health.

Wu, Y., Zhai, L., & Zhang, D. (2014). Sleep duration and obesity among adults: A meta-analysis of prospective studies. *Sleep Medicine*, *15*(12), 1456–1462. https://doi.org/ghnswg

Xu, L., Nicholson, P., Wang, Q. J., Wang, Q., Alen, M., & Cheng, S. (2010). Fat mass accumulation compromises bone adaptation to load in Finnish women: A cross-sectional study spanning three generations. *Journal of Bone and Mineral Research : The Official Journal of the American Society for Bone and Mineral Research*, *25*, 2341–2349. https://doi.org/fsps7c

Yaffe, K., Sawaya, G., Lieberburg, I., & Grady, D. (1998). Estrogen Therapy in Postmenopausal Women: Effects on Cognitive Function and Dementia. *JAMA*, *279*(9), 688–695. https://doi.org/c28h6p

Yamatani, H., Takahashi, K., Yoshida, T., Takata, K., & Kurachi, H. (2013). Association of estrogen with glucocorticoid levels in visceral fat in postmenopausal women. *Menopause*.

Yannakoulia, M., Melistas, L., Solomou, E., & Yiannakouris, N. (2007). Association of eating frequency with body fatness in pre-and postmenopausal women. *Obesity*, *15*(1), 100–106. https://doi.org/bm9432

Yasui, T., Hayashi, K., Mizunuma, H., Kubota, T., Aso, T., Matsumura, Y., Lee, J.-S., & Suzuki, S. (2012). Factors associated with premature ovarian failure, early menopause and earlier onset of menopause in Japanese women. *Maturitas*, *72*(3), 249–255. https://doi.org/f2jzjk

Yoldemir, T., & Erenus, M. (2012). The prevalence of metabolic syndrome in pre- and post-menopausal women attending a tertiary clinic in Turkey. *European Journal of Obstetrics,*

Gynecology, and Reproductive Biology, *164*, 172–175. https://doi.org/f4cjvk

Yoo, H. J., Park, M. S., & Yang, S. J. (2012). The differential relationship between fat mass and bone mineral density by gender and menopausal status. *Journal of Bone and Mineral Metabolism*, *30*, 47–53. https://doi.org/b9t3pb

Yoo, K. Y., Kim, H., & Shin, H. R. (1998). Female sex hormones and body mass in adolescent and postmenopausal Korean women. *Journal of Korean medical science*, *13*, 241–246. https://doi.org/gg543w

Yoshimoto, N., Nishiyama, T., & Toyama, T. (2011). Genetic and environmental predictors, endogenous hormones and growth factors, and risk of estrogen receptor-positive breast cancer in Japanese women. *Cancer Science*, *102*, 2065–2072. https://doi.org/bh8qtg

Zakzanis, K. K., Graham, S. J., & Campbell, Z. (2003). A Meta-Analysis of Structural and Functional Brain Imaging in Dementia of the Alzheimer's Type: A Neuroimaging Profile. *Neuropsychology Review; New York*, *13*(1), 1–18. https://doi.org/10.1023/a:1022318921994

Zavos, A., & Valachis, A. (2016). Risk of chemotherapy-induced amenorrhea in patients with breast cancer: A systematic review and meta-analysis. *Acta Oncologica*, *55*(6), 664–670. https://doi.org/f3rz9z

Žeželj, S. P., Cvijanović, O., Mičović, V., Bobinac, D., Crnčević-Orlić, Ž., & Malatestinić, G. (2010). Effect of Menopause, Anthropometry, Nutriton and Lifestyle on Bone Status of Women in the Northern Mediterranean. *West Indian Medical Journal*, *59*(5), 494.

Zhao, D., Guallar, E., & Ouyang, P. (2018). Endogenous sex hormones and incident cardiovascular disease in post-menopausal women. *Journal of the American College of Cardiology*, *71*, 2555–2566. https://doi.org/gdpjj6

Zhong, N., Wu, X. P., & Xu, Z. R. (2005). Relationship of serum leptin with age, body weight, body mass index, and bone mineral density in healthy mainland Chinese women. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, *351*, 161–168. https://doi.org/d3cjmr

Zhou, J.-L., Lin, S.-Q., Shen, Y., Chen, Y., Zhang, Y., & Chen, F.-L. (2010). Serum lipid profile changes during the menopausal transition in Chinese women: A community-based cohort study. *Menopause*, *17*(5), 997–1003. https://doi.org/fxg782

Zhou, Y., Zhou, X., & Guo, X. (2015). Prevalence and risk factors of hypertension among pre- and post-menopausal women: A cross-sectional study in a rural area of northeast China. *Maturitas*, *80*, 282–287. https://doi.org/f25v8h

Ziegler, D. V., Wiley, C. D., & Velarde, M. C. (2015). Mitochondrial effectors of cellular senescence: Beyond the free radical theory of aging. *Aging Cell*, *14*(1), 1–7. https://doi.org/gcbq2s

Ziel, H. K., & Finkle, W. D. (1975). Increased Risk of Endometrial Carcinoma among

Users of Conjugated Estrogens. *New England Journal of Medicine*, *293*(23), 1167–1170. https://doi.org/crmmcv

Zivkovic, T. B., Vuksanovic, M., & Jelic, M. A. (2011). Obesity and metabolic syndrome during the menopause transition in Serbian women. *Climacteric*, *14*, 643–648. https://doi.org/cm5cdd