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From FRONTIER to Frontier: Investigating Brain Health Risk Factors using Big Data Analysis

Dr Ananthan Ambikairajah

University of Canberra

FRONTIER (2012 - 2015)

UNIVERSITY OF CANBERRA

PhD (2018 - 2022)

UNIVERSITY OF CANBERRA

UC (2021 to present)

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About me

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Ananthan Ambikairajah

Lecturer

University of Canberra

Biography

Ananthan is a passionate neuroscientist, educator and science communicator. He is a Lecturer at the University of Canberra (UC) and a core member of the Centre for Ageing Research and Translation (CARAT) at UC. Ananthan completed his PhD in Neuroscience at the Australian National University in 2022. Ananthan received the Outstanding New Researcher Highly Commended Award in 2024 from the ACT Minister for Health. His research interests include genetic, environmental and lifestyle factors which influence ageing, brain health and disease, with a particular focus on sex-specific determinants and cardiometabolic factors. His recent research focuses on the potential for risk reduction in dementia. Ananthan has expertise in big data analyses, statistics, git, Linux and R. In 2023, he developed and continues to lead the Generative Artificial Intelligence (GenAI) Community of Practice for the Faculty of Health at UC, which aims to up-skill staff on their understanding, use and adoption of GenAI to enhance their learning, teaching, research and professional practice.

Ananthan is also a passionate educator and science communicator. Following his Undergraduate degree in Neuroscience at UNSW, he completed a Master's in Teaching (Secondary) and is a Higher Education Academy Fellow. In 2024, Ananthan received the Faculty of Health Student Nominated Award for Excellence in Teaching at UC. Ananthan regularly engages with media and his research has been covered by ABC News, Nine News, Sydney Morning Herald, the Australian Financial Review, The Australian and ABC Radio. He also hosts a podcast called Midnight Conversations, which aims to communicate research and the principles of scientific thinking to the public in an engaging and accessible way. His podcast is available on Apple Podcasts and Spotify.

Questions

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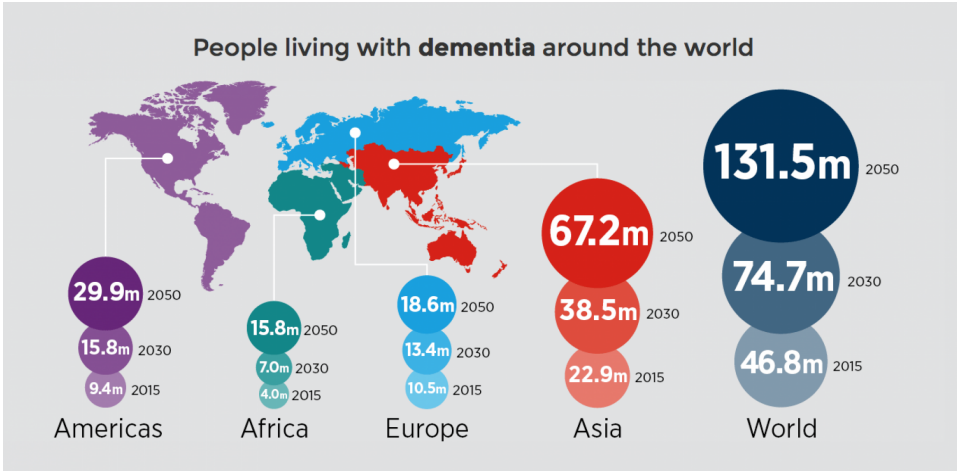
- What are the causes of dementia?
  - Mechanisms that contribute to ageing and the pathology of dementia
  - Genetics
  - Environmental and lifestyle
  - Cardiometabolic factors
  - Sex-specific factors
- How can we effectively utilise available resources to reduce dementia risk?
  - Accessible measures of brain health that accurately predict dementia risk
  - Developing prediction models across the lifecourse that quantify dementia risk which are meaningful at an individual level
  - Explore targeted interventions that improve brain health (and/or minimise rate of decline) and delay the onset/progression of dementia
- How can we effectively engage the public in scientific research, so that they can make informed decisions about their health
  - Policy makers, health professionals, the community and those with lived experience
    - Teaching
    - Science communication

Background



Prince et al. (2015)

Background

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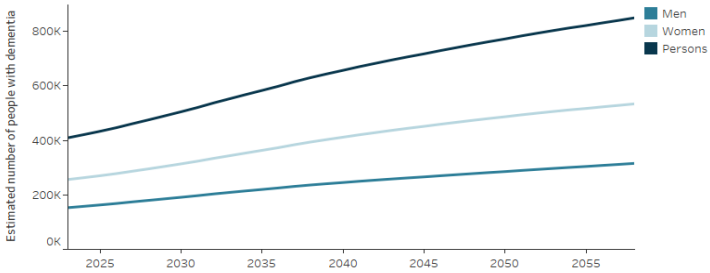
Australians living with dementia between 2023 and 2058: estimated number by sex and year



The trend of sum of Prevalence for Year. Colour shows details about Sex. The data is filtered on Year Set, which keeps 36 members.

Source: The AIHW estimates were derived using prevalence rates from the 2015 World Alzheimer report and Withall et al. 2014, and the ABS Series B population projections.
http://aihw.gov.au

Australian Institute of Health and Welfare,
https://www.aihw.gov.au/reports/dementia/dementia-in-aus/contents/population-health-impacts-of-dementia/prevalence-of-dementia

Background

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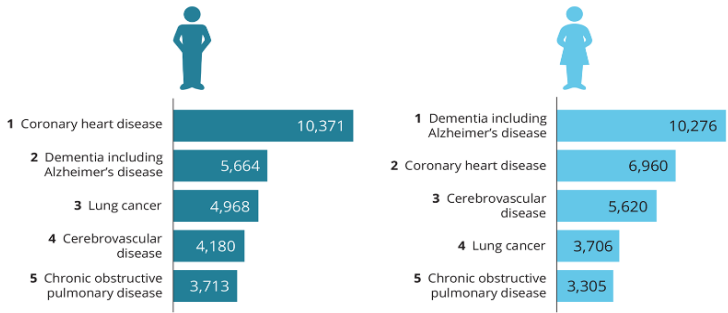
Leading underlying causes of death in Australia, by sex, 2021



Australian Institute of Health and Welfare, https://www.aihw.gov.au/reports/life-expectancy-deaths/deaths-in-australia/contents/summary

Background

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- Life expectancy for Australian Women = 85.3 years, Men = 81.2 years (born in 2020 - 2022; Australian Bureau of Statistics)
  - Consistent with global trends demonstrating women, on average, living longer (Global Women = 75.9 years, Global Men = 70.8 years, born in 2019; World Health Organization)
- Age-standardised global prevalence in females was 1.17 times (1.17–1.18) the age-standardised prevalence in males in 2016 (Nichols et al., 2019)

Background

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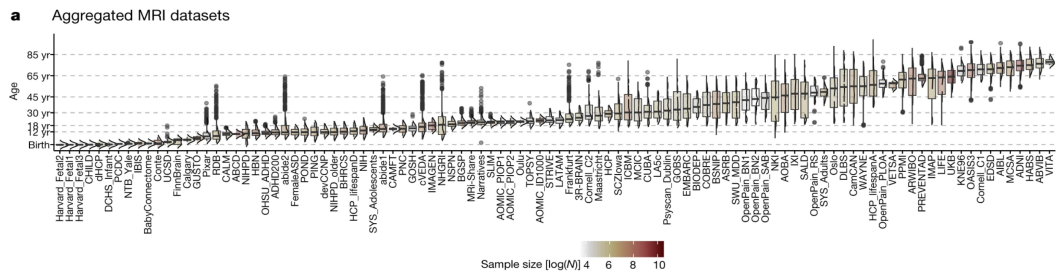
- Whilst the frequency of APOE-$\varepsilon 3/\varepsilon 4$ genotype does not differ by sex, a meta-analysis indicated that women with the APOE $\varepsilon 3/\varepsilon 4$ genotype had an increased risk for Alzheimer's disease compared with men between the ages of 65 and 75 years (Neu et al., 2017)
- Longitudinal study (mean follow up $= 4$ years) using Alzheimer's Disease Neuroimaging Initiative (ADNI) found that for those with mild cognitive impairment (MCI), cognitive decline was faster in women than men (models adjusted for age, APOE status, education, baseline MMSE) (Lin et al., 2015)

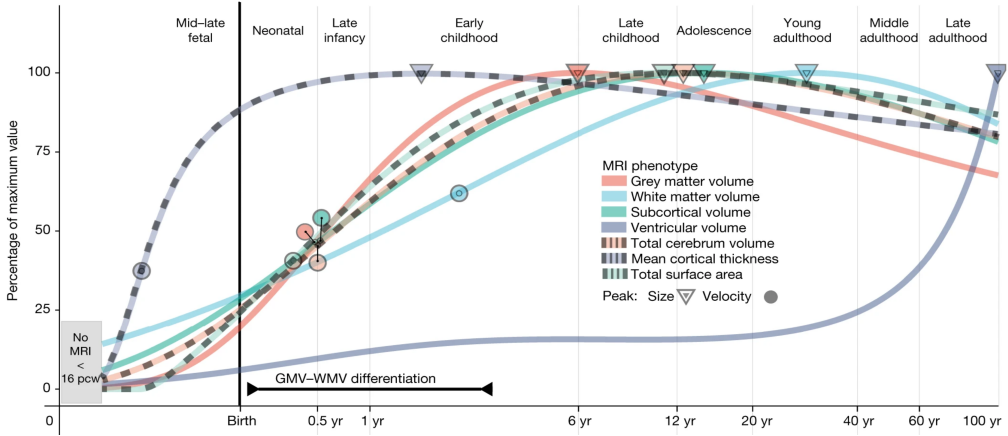
Background

- Brain charts for human lifespan
  - Aggregated 123,984 MRI scans, across more than 100 primary studies, from 101,457 human participants between 115 days post-conception to 100 years of age (Bethlehem et al., 2022)



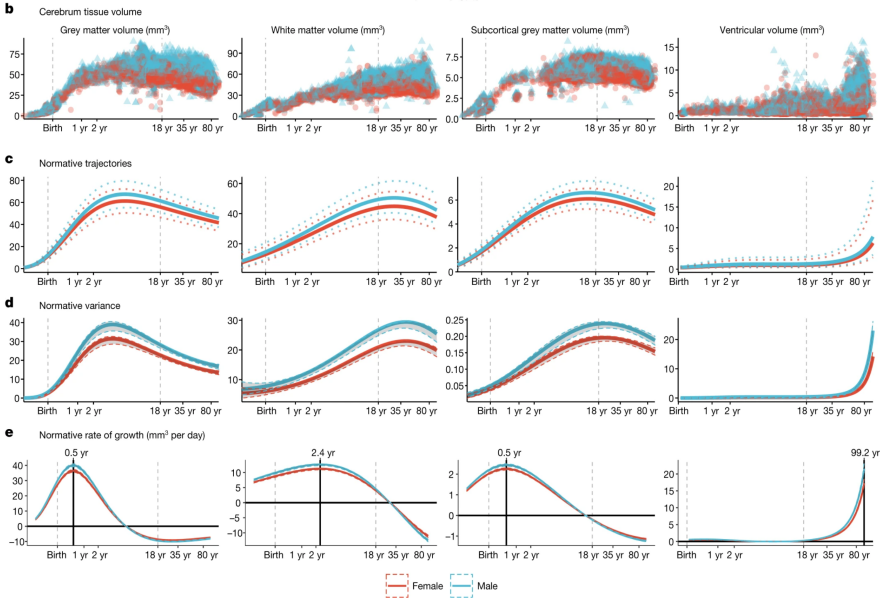
Bethlehem et al. (2022)

Background



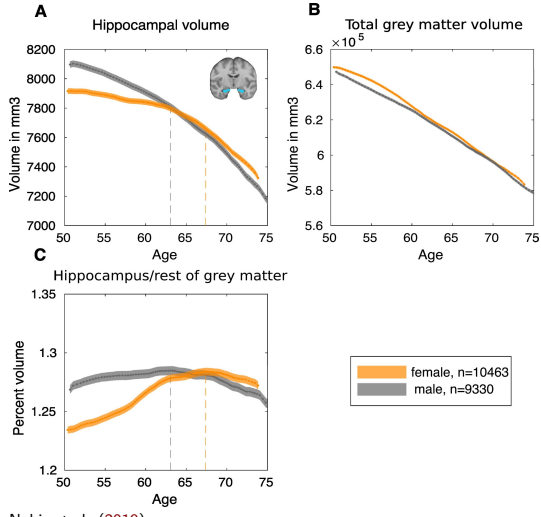
Bethlehem et al. (2022)

Background


b
Cerebrum tissue volume
Grey matter volume (mm³)
White matter volume (mm³)
Subcortical grey matter volume (mm³)
Ventricular volume (mm³)
c
Normative trajectories
d
Normative variance
e
Normative rate of growth (mm³ per day)
0.5 yr
2.4 yr
0.5 yr
99.2 yr
Birth 1 yr 2 yr 18 yr 35 yr 80 yr
Female
Male

Background

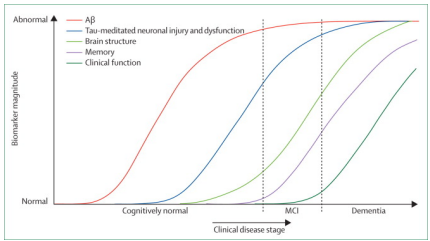
- UK Biobank (N = 19,793)
- A slight acceleration of hippocampal volume loss around age 60–65 years for females
- For both women and men, there was an increase in rate of hippocampal volume loss relative to the rest of the grey matter from around ages 67 (for women) and 63 (for men)
- Hippocampus may have particular vulnerabilities to ageing, as effects not detected in neighbouring brain areas, including parahippocampal gyrus and temporal gyrus



Nobis et al. (2019)

Background

- Evidence regarding sex differences for amyloid-β and tau burden is limited and requires further replication (Ferretti et al., 2018)
- Often statistical models adjust for sex and do not conduct sensitivity analyses that stratifies analyses by sex or investigate potential sex interactions (Beery & Zucker, 2011; McCarthy et al., 2012)
  - Example: Meta-analysis of sex differences in contribution to brain reserve (consisting of IQ, education, occupation, cognitive activity, multilingualism, socioeconomic status, physical activity, social support or marital status) identified 16 studies that included an analysis of sex (Subramaniapillai et al., 2021)



Jack et al. (2010)

Possible reasons for sex differences

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- Historical inequities, resulting in disproportionate access to education and occupational opportunities contributing to brain reserve
- Potential selective survival bias of men >65 years with a healthier cardiovascular profile and therefore, less likely to develop AD
- Interactive effects between sex/sex-specific factors and genes
- Unique neuroendocrine processes in women, including menarche, menstruation, pregnancy and menopause

Menopause

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- *Menopause* comes from the Greek words *meno*, which means month and *pause* which means stop, thus indicating the end of monthly cycles or menstruation.
- Historically understudied in the context of ageing. Over a period of 23 years (1995 to 2017), peer reviewed neuroimaging articles which focused on menopause accounted for approximately 2% of ageing literature (Taylor et al., 2019)
- The average age of menopause lies between 46 and 52 years of age (mean = 48.78, standard deviation = 1.45)(Schoenaker et al., 2014).
  - Given that 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.

Menopause

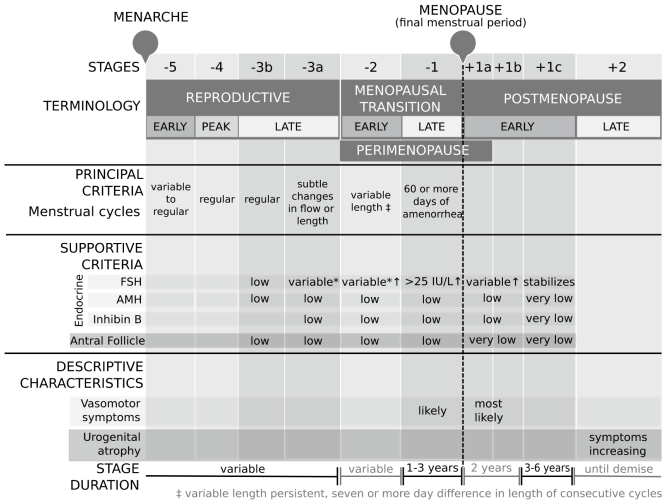

Fig. 4 STRAW + 10 staging system. *, blood drawn on cycle days 2–5; FSH, follicle stimulating hormone; AMH, anti-mullerian hormone; ↑, elevated. Figure is a modification of work found in Harlow et al. [11]

Ambikairajah et al. (2022); Harlow et al. (2012)

Menopause and brain

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- Biological/physiological changes around menopause
  - Cardiometabolic factors
- Menopause vs ageing

Fat mass changes around menopause

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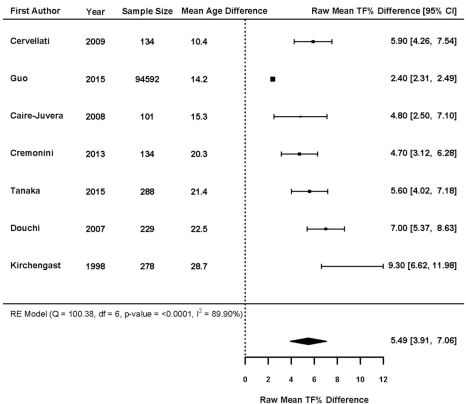

Systematic Reviews ajog.org

Fat mass changes during menopause: a metaanalysis

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

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

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

Ambikairajah, Walsh, Tabatabaei-Jafari, et al. (2019)

Fat mass changes around menopause

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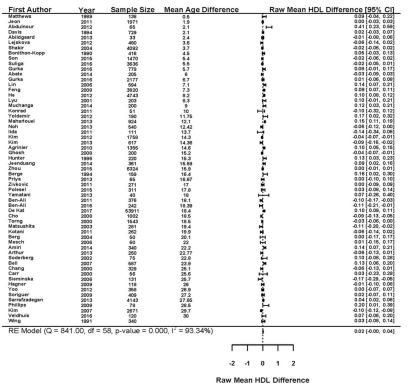
- Fat mass significantly increased between premenopause and postmenopause women
  - Ageing significantly accounted for unexplained variance in fat mass
  - Longitudinal trajectories for changes in women in SR matched typical trends for fat mass increases in women aged 18-45 i.e. no detectable effect of menopause on rate of change
  - No interaction (fat mass ~ age * menopausal status)
- Change in fat mass distribution, with increasing central fat and decreases in leg fat
  - Hormonal shifts around menopause (i.e. higher testosterone to estrogen ratio) may have contributed to enhanced central fat deposition
  - Subgroup analyses based on hormone replacement therapy (HRT) use
    - When we included women using HRT there was a significant increase in body fat percentage and a significant decrease in trunk fat percentage, which suggested a possible protective role of HRT in preventing/reducing trunk fat deposition, although, not in preventing overall fat mass gain. Consistent with a previous meta-analysis of 8 randomised control trials, which found that postmenopausal women using HRT had less WC and TF% compared to placebo (Salpeter et al., 2006).

Lipid changes around menopause



Menopause: The Journal of The North American Menopause Society
Vol. 26, No. 11, pp. 1327-1333
DOI: 10.1097/GME.0000000000001403
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REVIEW ARTICLE

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

Ananthan Ambikairajah, BSc, MTeach, PhDc, Erin Walsh, PhD, and Nicolas Cherbuin, PhD

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 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

Ambikairajah, Walsh, & Cherbuin (2019)

Lipid changes around menopause

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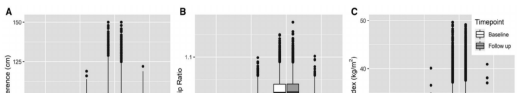
- Age explained some, but not all of the differences in lipid levels between premenopausal and postmenopausal women ($R^2 = 9.71\%$ to 40.08%)
- Sensitivity analyses of studies with a mean age difference of 5 years or less between premenopausal and postmenopausal women revealed no significant difference in the magnitude, direction or significance of effects compared to initial estimates for HDL, LDL, and total cholesterol.
  - May suggest an effect of menopause, but could also be other factors including group differences given insufficient longitudinal studies were available for meta-analysis.

Cardiometabolic factors and brain health



Original Article
OBESITY BIOLOGY AND INTEGRATED PHYSIOLOGY

Obesity

Longitudinal Changes in Fat Mass and the Hippocampus

Anantha 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.

Obesity (2020) **28**, 1263–1269.

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

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

Ambikairajah et al. (2020)

Cardiometabolic factors and brain health

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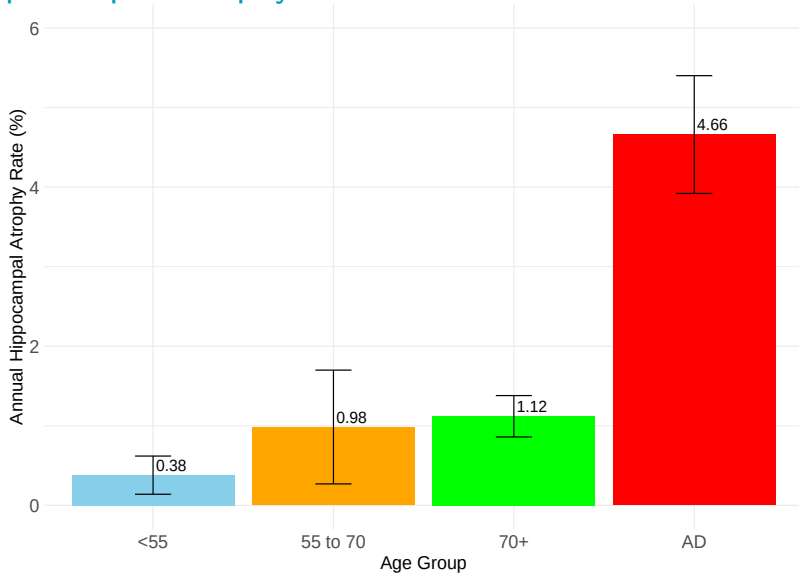
- Individuals with chronic overweight/obesity had significantly lower hippocampal volumes (WC: 1.13%; WTHR: 0.79% and BMI: 0.49%) when compared with those who maintained a normal level of fat mass (i.e. WC: $<$ 80 cm in women and $<$ 94 cm in men; WTHR: $<$ 0.85 in women and $<$ 0.90 in men and BMI: $<$ 25 kg/m^2 in women and men) at baseline and follow up (average follow up = 7.66 years)
- 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 maintained fat mass within the normal range across assessments (WC: 0.73%; WTHR: 0.55% and BMI: 0.48%)
- 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.

Rate of Hippocampal Atrophy



Fraser et al. (2015); Barnes et al. (2009)

Cardiometabolic factors and brain health

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- Largest magnitude of effect was consistently observed for WC, likely because of its correlation with visceral fat
- Subgroup analysis in women consistently revealed lower hippocampal volumes for OS, ON, and NO compared to NS group for WC. However, results were not consistent across WTHR and BMI.
  - Possibly demonstrates the utility of WC to measure visceral fat
  - May reflect changes after menopause (Ambikairajah, Walsh, Tabatabaei-Jafari, et al., 2019)

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.

Cardiometabolic factors and brain health

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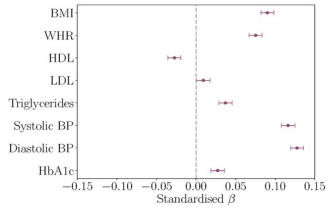

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Cardiometabolic health across menopausal years is linked to white matter hyperintensities up to a decade later

Louise S. Schindler[1,2,3]*, Sivaniya Subramaniapillai[1,2], Ananthan Ambikairajah[4,5], Claudia Barth[6,7], Arielle Crestol[6,7], Irene Voldsbekk[2,7], Dani Beck[2,8,7], Tiril P. Gurholt[7], Anya Topiwala[9], Sana Suri[3,9], Klaus P. Ebmeier[3], Ole A. Andreassen[7,10], Bogdan Draganski[1,11], Lars T. Westlye[7,10] and Ann-Marie G. de Lange[1,2,3]*

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Introduction: The menopause transition is associated with several cardiometabolic risk factors. Poor cardiometabolic health is further linked to microvascular brain lesions, which can be detected as white matter hyperintensities (WMHs) using T2-FLAIR magnetic resonance imaging (MRI) scans. Females show higher risk for WMHs post-menopause, but it remains unclear whether changes

Schindler et al. (2023)

Cardiometabolic factors and brain health

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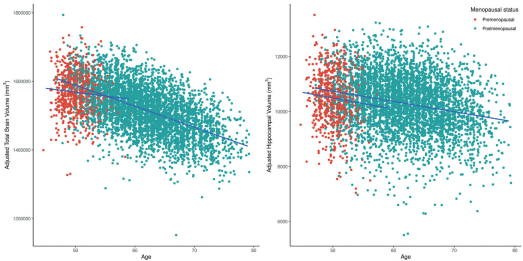
- Postmenopausal women had a poorer cardiometabolic profile compared with premenopausal women, beyond the effects of age
- Poorer cardiometabolic health, as indicated by higher baseline levels of blood lipids, blood pressure, long term blood glucose, as well as longitudinal changes in BMI and WHR, were associated with larger white matter hyperintensities

Menopause and brain health



Ambikairajah et al. (2021)

Menopause: The Journal of The North American Menopause Society
Vol. 28, No. 2, pp. 000–000
DOI: 10.1097/GME.0000000000001658

ORIGINAL STUDY

Age, menstruation history, and the brain

Ananthan Ambikairajah, BSc, MTeach, PhDc,[1] Hossein Tabatabaei-Jafari, MD,[1] Michael Hornberger, PhD,[2] and Nicolas Cherbuin, PhD[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 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 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

Menopause and brain health

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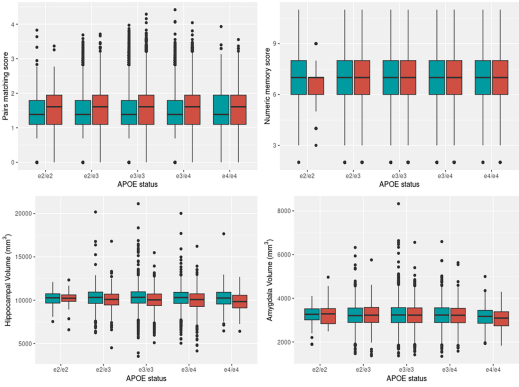
- Postmenopausal women experienced 0.23% greater reduction in total brain volume than premenopausal women for every 1 year increase in age. This interactive effect was not detected for the hippocampus.
- For postmenopausal women, every 1 year delay in age of menopause after 45 was associated with 0.32% smaller total brain volume and 0.31% smaller hippocampal brain volume.
- In the UK Biobank sample, postmenopausal women had 1.06% larger total brain volume and 2.17% larger hippocampal volume than premenopausal women. This effect was consistent across all analyses (multiple regression models, which controlled for age; propensity matching analysis which exact matched for age; age-restricted analyses between 45-55 years)
  - Between and within group variability

HRT, APOE, Age and Brain



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RESEARCH ARTICLE

WILEY

Investigating the synergistic effects of hormone replacement therapy, apolipoprotein E and age on brain health in the UK Biobank

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Abstract

Global prevalence of Alzheimer's Disease has a strong sex bias, with women representing approximately two-thirds of the patients. Yet, the role of sex-specific risk factors during midlife reduction hormone replacement therapy (HRT) and their

Estrogen use, *APOE*, and cognitive decline

Evidence of gene–environment interaction

K. Yaffe, MD; M. Haan, DrPH; A. Byers, MPH; C. Tangen, DrPH; and L. Kuller, MD, DrPH

Article abstract—*Objective:* *APOE*-ε4 increases the risk of cognitive decline, while elderly women who take estrogen may have less risk of cognitive decline. The authors sought to determine whether estrogen use modifies the association between *APOE*-ε4 and cognitive decline. *Method:* As part of the Cardiovascular Health Study, 3,393 Medicare-eligible women (≥65 years) were randomly selected and recruited from Sacramento County, CA; Washington County, MD; Forsyth County, NC; and Pittsburgh, PA. Cognitive testing was administered annually; the authors studied the 2,716 women with cognitive testing on ≥2 visits. They analyzed change in score on the Modified Mini-Mental State Examination (3MS) as a function of estrogen use, *APOE* genotype, and baseline common and internal carotid artery wall thickening. *Results:* A total of 297 (11%) women were current estrogen users and 336 (12%) were past estrogen users. Over the 6-year average follow-up, baseline current users declined 1.5 points on the 3MS whereas never users declined 2.7 points ($p = 0.023$). Compared with ε4-negative women, ε4-positive women had a greater adjusted hazard ratio of cognitive impairment (3MS < 80), hazard risk [HR] = 1.47; 95% CI, 1.13 to 1.90. There was an interaction between estrogen use and ε4 presence ($p = 0.037$). Among ε4-negative women, current estrogen use reduced the risk of adjusted cognitive impairment compared with never users by almost half (HR = 0.59; 95% CI, 0.36 to 0.99), whereas, it did not reduce the risk among ε4-positive women (current use, HR = 1.33; 95% CI, 0.74 to 2.42). Compared with never use, current estrogen use was associated with less internal and common carotid wall thickening in ε4-negative women but not in ε4-positive women (p for interaction < 0.05 for both). Differences remained after adjusting for age, education, race, and stroke. *Conclusions:* Estrogen use was associated with less cognitive decline among ε4-negative women but not ε4-positive women. Potential mechanisms, including carotid atherosclerosis, by which ε4 may interact with estrogen and cognition warrant further investigation. **Key words:** Estrogen—*APOE*—Cognitive decline—Elderly women.

NEUROLOGY 2000;54:1949–1953

Yaffe et al. (2000)

HRT, APOE, Age and Brain

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Saleh et al. Alzheimer's Research & Therapy (2023) 15:10
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Alzheimer's Research & Therapy

RESEARCH Open Access

Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk *APOE4* women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort

Rasha N. M. Saleh[1*], Michael Hornberger[1], Craig W. Ritchie[2] and Anne Marie Minihane[1]

Abstract

Background The risk of dementia is higher in women than men. The metabolic consequences of estrogen decline during menopause accelerate neuropathology in women. The use of hormone replacement therapy (HRT) in the prevention of cognitive decline has shown conflicting results. Here we investigate the modulating role of *APOE* genotype and age at HRT initiation on the heterogeneity in cognitive response to HRT.

Methods The analysis used baseline data from participants in the European Prevention of Alzheimer's Dementia (EPAD) cohort (total *n*= 1906, women= 1178, 61.8%). Analysis of covariate (ANCOVA) models were employed to test the independent and interactive impact of *APOE* genotype and HRT on select cognitive tests, such as MMSE, RBANS, dot counting, Four Mountain Test (FMT), and the supermarket trolley test (SMT), together with volumes of the medial temporal lobe (MTL) regions by MRI. Multiple linear regression models were used to examine the impact of age of HRT initiation according to *APOE4* carrier status on these cognitive and MRI outcomes.

Results *APOE4* HRT users had the highest RBANS delayed memory index score (β-*APOE**HRT interaction = 0.009) compared to *APOE4* non-users and to non-*APOE4* carriers, with 6–10% larger entorhinal (left) and amygdala (right and left) volumes (β-interaction= 0.002, 0.003, and 0.005 respectively). Earlier introduction of HRT was associated with larger right (standardized β= −0.555, p=0.035) and left hippocampal volumes (standardized β= −0.577, p=0.028) only in *APOE4* carriers.

Conclusion HRT introduction is associated with improved delayed memory and larger entorhinal and amygdala volumes in *APOE4* carriers only. This may represent an effective targeted strategy to mitigate the higher life-time risk of AD in this large at-risk population subgroup. Confirmation of findings in a fit for purpose RCT with prospective recruitment based on *APOE* genotype is needed to establish causality.

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Rasha N. M. Saleh

Introduction

More than two-thirds of Alzheimer's disease (AD) patients are women [1, 2]. The recent 2022 Global Burden

Saleh et al. (2023)

HRT, APOE, Age and Brain

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Neurobiology of Aging 33 (2012) 1129–1137

NEUROBIOLOGY OF AGING

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Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline

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[b] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

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Abstract

Associations between postmenopausal hormone therapy (HT) and cognitive decline may depend on apolipoprotein E (APOE) status or timing of initiation. We included 16,514 Nurses' Health Study participants aged 70–81 years who were followed since 1976 and completed up to 3 telephone cognitive assessments (2 years apart), between 1995 and 2006. The tests assessed general cognition (Telephone Interview of Cognitive Status; TICS), verbal memory, and category fluency. We used longitudinal analyses to estimate differences in cognitive decline across hormone groups. APOE genotype was available in 3697 participants. Compared with never users, past or current HT users showed modest but statistically significant worse rates of decline in the TICS: the multivariable-adjusted difference in annual rate of decline in the TICS among current estrogen only users versus never users was −0.04 (95% confidence interval, −0.07 to −0.004); for current estrogen + progestin users, the mean difference was −0.05 (95% confidence interval, −0.10 to −0.002). These differences were equivalent to those observed in women who are 1–2 years apart in age. We observed no protective associations with early timing of hormone initiation. We found suggestive interactions with APOE e4 status (e.g., on TICS, *p* interaction, 0.10), where the fastest rate of decline was observed among APOE e4 carriers who were current HT users. Regardless of timing of initiation, HT may be associated with worse rates of decline in general cognition, especially among those with an APOE e4 allele.

Keywords: Cohort studies; Cognitive aging; Risk factors in epidemiology; MCI; Memory

Kang & Grodstein (2012)

HRT, APOE, Age and Brain

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Among ϵ4-negative women, those currently taking estrogen had a 1.5 ± 1.0 (95% CI) smaller 3MS point decline over 6 years compared with the never users ($p = 0.003$) (table 2). Past estrogen users' change in scores did not differ from never users ($p = 0.83$). Among ϵ4-positive women, current or past estrogen use was not associated with the amount of cognitive decline (compared with never use: $p = 0.37$ for current use; $p = 0.79$ for past use). There was an interaction between estrogen use, *APOE*-ϵ4, and cognitive decline ($p = 0.037$). After adjusting for age, education, race, and stroke history, the interaction between *APOE* and estrogen use remained but lessened somewhat in statistical significance ($p = 0.06$).

Yaffe et al. (2000)

HRT, APOE, Age and Brain

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Table 2 Cognitive outcomes scores (mean±SEM) according to HRT use and *APOE4* genotype status

	Non-E4							E4							P_{APOE}	P_{HRT}	$P_{APOE*HRT}$
	No-HRT	*n*	HRT	*n*	Total	*n*	*p*-HRT	No-HRT	*n*	HRT	*n*	Total	*n*	*p*-HRT			
MMSE total score	28.49 ±0.07	603	28.43 ±0.36	50	28.49 ±0.07	653	0.607	28.15 ±0.11	350	28.22 ±0.30	30	28.16 ±0.10	380	0.960	0.565	0.724	0.782
Dot counting score	16.60 ±0.22	389	17.05 ±1.06	32	16.62 ±0.22	421	0.726	16.24 ±0.30	235	17.44 ±0.71	21	16.32 ±0.29	256	0.848	0.953	0.942	0.710
RBANS scores																	
RBANS total scale	103.57 ±0.62	600	105.04 ±2.78	49	103.63 ±0.61	649	0.921	100.52 ±0.85	351	106.68 ±3.44	29	100.88 ±0.83	380	0.045	0.488	0.128	0.097
RBANS attention index	97.65 ±0.70	601	102.61 ±2.73	28	97.86 ±0.68	629	0.222	97.23 ±0.93	352	102.23 ±3.34	29	97.51 ±0.90	381	0.706	0.818	0.297	0.652
RBANS delayed memory index	102.09 ±0.59	602	102.07 ±2.46	28	102.09 ±0.58	630	0.757	98.29 ±0.85	352	108.37 ±2.79	29	98.85 ±0.81	381	**0.002**	0.695	0.027[a]	0.009[a]
RBANS immediate memory index	106.55 ±0.58	602	105.18 ±30	28	106.49 ±0.57	630	0.854	101.65 ±0.87	352	105.59 ±3.83	29	101.87 ±0.85	381	0.150	0.434	0.307	0.209
RBANS language index	100.10 ±0.47	602	100.79 ±2.61	28	100.13 ±0.47	630	0.752	99.30 ±0.69	353	101.50 ±2.84	29	99.42 ±0.67	382	0.303	0.399	0.536	0.311
RBANS visuo-constructional index	105.16 ±0.65	602	106.82 ±2.95	28	105.23 ±0.63	630	0.310	104.66 ±0.92	352	108.32 ±2.91	29	104.87 ±0.88	381	0.483	0.163	0.938	0.233
FMT total score	8.31 ±0.43	32	9.33 ±0.33	3	8.40 ±0.40	35	0.803	7.48 ±0.55	33	10.50 ±1.50	3	7.77 ±0.56	36	0.195	0.449	0.271	0.439
SMT total score	6.54 ±0.63	34	6.33 ±0.88	3	6.53 ±0.58	37	0.781	5.14 ±0.54	33	10.00 ±1.53	4	5.53 ±0.55	37	0.158	0.549	0.451	0.241

Mean ± SEM of cognitive test scores stratified according to *APOE* genotype and HRT use. Significant *P* values for *APOE* genotype, HRT, and *APOE**HRT are shown, using the ANCOVA model (MANCOVA for RBANS scores). *p*-HRT within each *APOE* genotype is calculated using the pairwise comparison of the estimated marginal mean with Bonferroni adjustment for multiple comparison. Age, years of education, marital status, handedness, and CDR were used as covariates. *HRT* hormone replacement therapy, *MMSE* Mini-Mental State Examination, *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status. *FMT* four mountain test, *SMT* supermarket trolley test. *P*-significant <0.05. [a] insignificant after FDR correction for multiple comparison. Bold: significant after FDR correction

Saleh et al. (2023)

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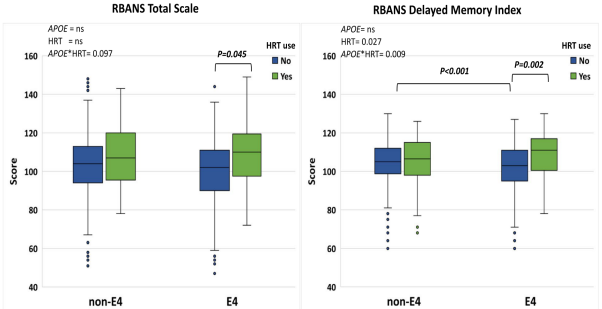

Fig. 1 Box plots showing the mean scores of RBANS total scale (left) and RBANS delayed memory index (right) in non-*APOE4* versus *APOE4* stratified according to HRT use. Pairwise comparison within each genotype group was carried out on the estimated marginal mean (within the MANCOVA model), after adjustment for age, years of education, marital status, handedness, and CDR). Statistical results in the upper left corner show *P* values of *APOE* genotype, HRT, and APOE*HRT for RBANS total scale (left) and delayed memory index (right) using the MANCOVA model. Non-*APOE4* *n*= 630 (no-HRT *n*=602, HRT *n*= 28), *APOE4* *n*= 381 (no-HRT *n*=352, HRT *n*= 29)

Saleh et al. (2023)

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Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline

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Keywords: Cohort studies; Cognitive aging; Risk factors in epidemiology; MCI; Memory

Kang & Grodstein (2012)

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HRT could cut Alzheimer's risk in some women - early study

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HRT could ward off Alzheimer's among at-risk women

Date: January 14, 2023

Source: University of East Anglia

Summary: Hormone Replacement Therapy (HRT) could help prevent Alzheimer's Dementia among women at risk of developing the disease -- according to new research.

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UC launches ageing research centre

Australian Ageing Agenda February 23, 2024

The Centre for Ageing Research and Translation's projects focus on dementia, innovative care models and workforce.

https://www.australianageingagenda.com.au/noticeboard/uc-launches-ageing-research-centre/

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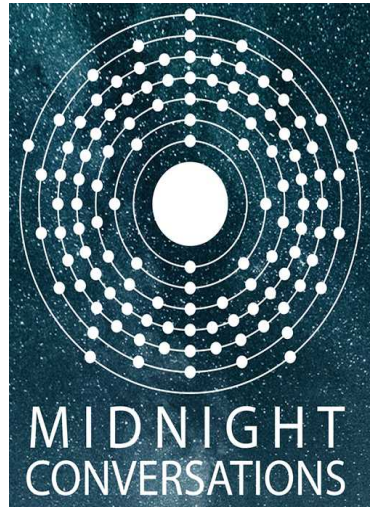

Quantifying the contributions to brain ageing

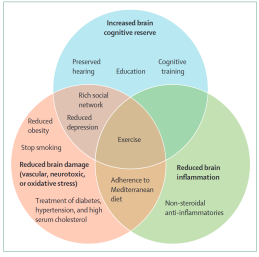

Figure 5: Potential brain mechanisms for preventive strategies in dementia

Livingston et al. (2017)

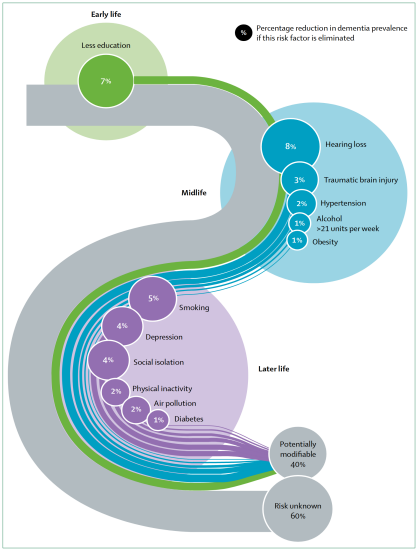

Figure 7: Population attributable fraction of potentially modifiable risk factors for dementia

Livingston et al. (2020)

Much more work to do

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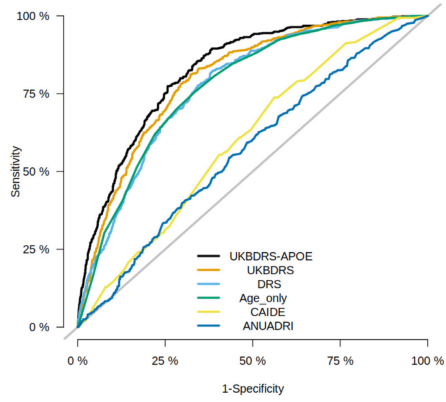
Table 2 Discrimination accuracy of models across the training and test sets

	UKB train	UKB test	WHII
N	176 611	44 151	2934
Baseline model			
Age only	0.75 (0.75 to 0.75)	0.77 (0.75 to 0.79)	0.74 (0.69 to 0.78)
UKBDRS			
UKBDRS	0.79 (0.78 to 0.79)	0.80 (0.78 to 0.82)	0.77 (0.72 to 0.81)
UKBDRS-APOE	0.81 (0.81 to 0.81)	0.83 (0.81 to 0.84)	0.80 (0.75 to 0.85)
Other risk scores			
CAIDE	0.60 (0.60 to 0.60)	0.60 (0.58 to 0.63)	0.69 (0.64 to 0.74)
DRS	0.76 (0.76 to 0.76)	0.77 (0.76 to 0.79)	0.74 (0.69 to 0.78)
ANU-ADRI	0.57 (0.57 to 0.57)	0.57 (0.54 to 0.59)	0.52 (0.45 to 0.58)

AUCs are reported with 95% confidence intervals indicated in parentheses. 0.9% of the UKB sample had missing data for one variable of the ANU-ADRI score (BMI). Therefore, all individuals with missing data on the ANU-ADRI were first excluded before evaluating the AUC for the ANU-ADRI.
ANU-ADRI, Australian National University Alzheimer's Disease Risk Index; AUC, area under the curve ; BMI, body mass index; CAIDE, Cardiovascular Risk Factors, Aging and Dementia; DRS, Dementia Risk Score; UKB, UK Biobank; UKBDRS, UK Biobank Dementia Risk Score; WHII, Whitehall II.



Anatürk et al. (2023)

Questions

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- What are the causes of dementia?
  - Mechanisms that contribute to ageing and the pathology of dementia
  - Genetics
  - Environmental and lifestyle
  - Cardiometabolic factors
  - Sex-specific factors
- How can we effectively utilise available resources to reduce dementia risk?
  - Accessible measures of brain health that accurately predict dementia risk
  - Developing prediction models across the lifecourse that quantify dementia risk which are meaningful at an individual level
  - Explore targeted interventions that improve brain health (and/or minimise rate of decline) and delay the onset/progression of dementia
- How can we effectively engage the public in scientific research, so that they can make informed decisions about their health
  - Policy makers, health professionals, the community and those with lived experience
    - Teaching
    - Science communication

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