

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 of 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 AD⁷ 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 ($n = 1,045$), (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.

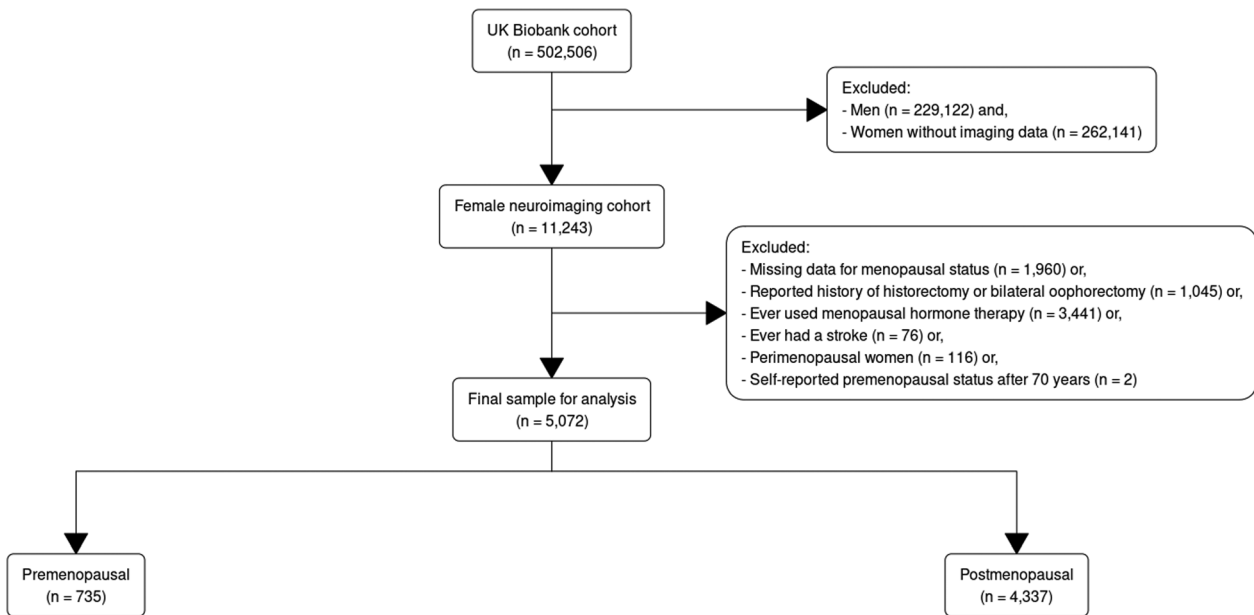


FIG. 1. Flowchart describing sample selection.

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 = $1 \times 1 \times 1$ mm; field of view = $208 \times 256 \times 256$ 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 anti-diabetic 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 (89,780)	<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.

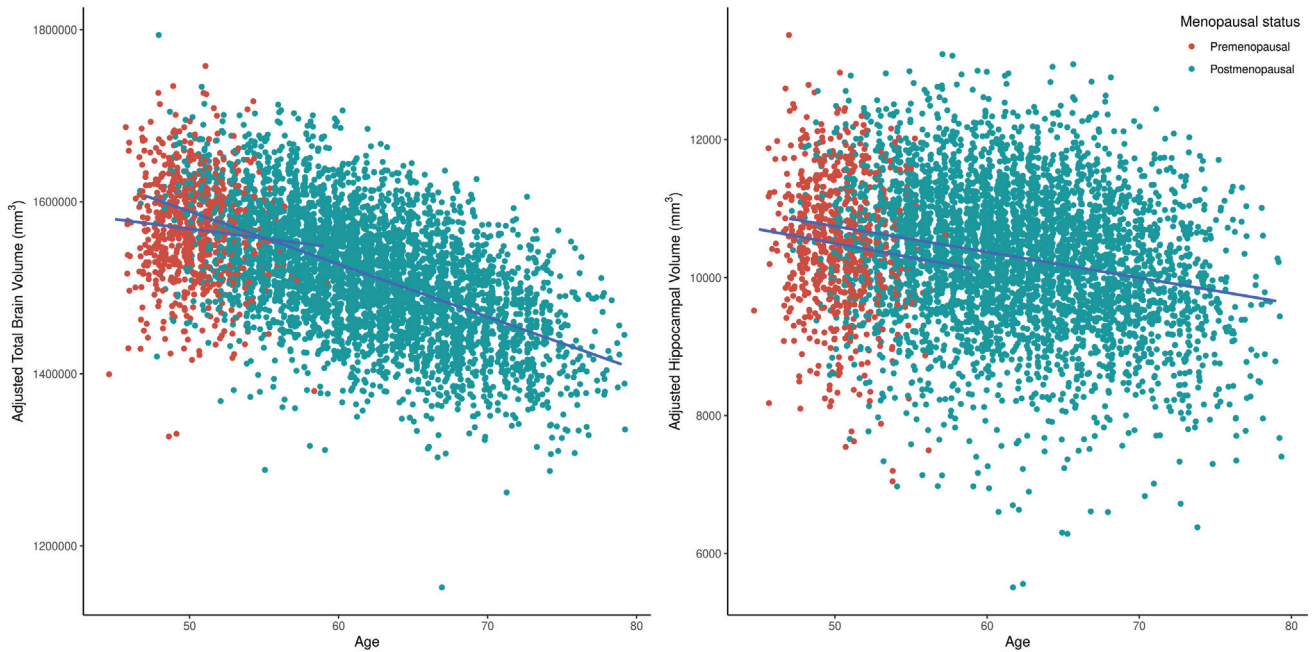


FIG. 2. Scatterplot showing the distribution of total brain volume and hippocampal volume (adjusted for head size) across time for premenopausal and postmenopausal women.

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 sclerosis²⁵ 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 cohort⁴² 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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