Title: Age, menstruation history and the brain.

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Funding statement: No funding were sought to conduct this meta-analyses. A Ambikairajah was supported by an Australian Government Research Training Program (AGRTP) Domestic and Fee-Offset Scholarships.

Conflict of Interest: None declared.

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Words in manuscript: 3323 **Tables:** 3

Words in abstract: 335 **Figures:** 2

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 = 5072) 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.

Key words: menopause; neuroimaging; UK Biobank; premenopausal; postmenopausal

1. 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.[1] 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%).[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, 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 21-34 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 prior to 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.

2. METHODS

2.1 Participants

The UK Biobank study is a large population based cohort which consists of 502506 participants aged 37-73 years at baseline who were recruited from the National Health Service central registers.[17] Of those participants, 11243 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.[18,19] 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 = 1045), (2) ever used menopausal hormone therapy (MHT; n = 3441) or (3) ever had a stroke (n = 76), 5072 women with meeting inclusion criteria were available for analysis (premenopausal = 735 and postmenopausal = 4337). Differences between those who were included and excluded have been reported in Supplementary Table 1. A flowchart describing sample selection is presented in Figure 1.

2.2 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.

2.3 Measures

2.3.1 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 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.

2.3.2 Neuroimaging

2.3.2.1 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.[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 x 1 x 1 mm; field of view = 208 x 256 x 256 matrix.[20]

2.3.2.2 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.[20,21] 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.

2.3.3 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.

2.4 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 1431 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.

3. 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 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 (Supplementary Table 2). A scatterplot showing the distribution of total brain volume and hippocampal volume across time for premenopausal and postmenopausal women is presented in Figure 2.

3.1 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 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 2). These findings were consistent in an age restricted sample of 1431 women (premenopausal = 720; postmenopausal = 711), aged 45 to 55 (Supplementary Table 3). 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 (Supplementary Table 3). 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 (Supplementary Table 3).

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 (Supplementary Table 4).

3.2 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 (Supplementary Table 5).

3.3 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 (Supplementary Table 6).

3.4 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 (Supplementary Table 7).

4. 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,[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%/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.[22,23] 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.[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 Alzheimer's disease.[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 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.[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 HV is potentially an indicator of future vulnerability for dementia.

4.1 Strengths and Limitations

Key strengths of the current study include the large neuroimaging cohort (n = 5072) 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[42] 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 (Supplementary Table 1). 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.

5. 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.

Acknowledgements

We would like to acknowledge and thank all UK Biobank participants and the UK Biobank team for their work.

Data sharing

This research has been conducted using the UK Biobank resource under application number 47813. Researchers can apply to use the UK Biobank resource and access the data used. No additional data are available.

Contributors

AA contributed to the design of the study, conducted all statistical analyses and managed all aspects of manuscript writing, preparation and submission. HT-J contributed to the design of the study, provided methodological input, theoretical expertise and contributed to the editing of the manuscript. MH contributed to the design of the study, provided methodological input, theoretical expertise and contributed to the editing of the manuscript. NC contributed to the design of the study, 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.

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In Text Figure Legends:

Figure 1 Flowchart describing sample selection.

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

Supplemental Digital Content

- Supplemental Digital Content 1. Table, which describes demographic and health characteristics of included and excluded participants.
- Supplemental Digital Content 2. Table, which describes the age and brain volume analysis.
- Supplemental Digital Content 3. Table, which describes the menopausal status and brain volume analysis in the age-restricted sample.
- Supplemental Digital Content 4. Table, which describes the menopausal status and brain volume analysis in the propensity matched sample.
- Supplemental Digital Content 5. Table, which describes the age of menopause and brain volume analysis.
- Supplemental Digital Content 6. Table, which describes the age of menarche and brain volume analysis.
- Supplemental Digital Content 7. Table, which describes the duration of reproductive stage and brain volume analysis.