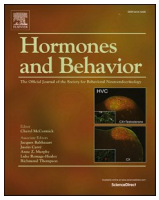
Hormones and Behavior 164 (2024) 105596

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh



Linking menopause-related factors, history of depression, *APOE ε4*, and proxies of biological aging in the UK biobank cohort

Arielle Crestol [a,b,*], Ann-Marie G. de Lange [c,d,e], Louise Schindler [c,d,e], Sivaniya Subramaniapillai [c,d], Stener Nerland [a,h], Hannah Oppenheimer [a,d], Lars T. Westlye [b,d,f], Ole A. Andreassen [b,f], Ingrid Agartz [a,f,g,h], Christian K. Tamnes [a,i], Claudia Barth [a,*]

[a] Division of Mental Health and Substance Abuse, Diakonhjemmet Hospital, Oslo, Norway
[b] Center for Precision Psychiatry, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[c] Centre for Research in Neurosciences, Department of Clinical Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne, Lausanne, Switzerland
[d] Department of Psychology, University of Oslo, Oslo, Norway
[e] Department of Psychiatry, University of Oxford, Oxford, UK
[f] KG Jebsen Centre for Neurodevelopmental Disorders, University of Oslo & Oslo University Hospital, Oslo, Norway
[g] Department of Clinical Neuroscience, Centre for Psychiatry Research, Stockholm Health Care Services, Karolinska Institute, Stockholm County Council, Stockholm, Sweden
[h] Division of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[i] PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway

ARTICLE INFO

Keywords:
Menopause
Depression
APOE ε4
Cellular aging
Magnetic resonance imaging
Brain age gap
Telomere length

ABSTRACT

In a subset of females, postmenopausal status has been linked to accelerated aging and neurological decline. A complex interplay between reproductive-related factors, mental disorders, and genetics may influence brain function and accelerate the rate of aging in the postmenopausal phase. Using multiple regressions corrected for age, in this preregistered study we investigated the associations between menopause-related factors (i.e., menopausal status, menopause type, age at menopause, and reproductive span) and proxies of cellular aging (leukocyte telomere length, LTL) and brain aging (white and gray matter brain age gap, BAG) in 13,780 females from the UK Biobank (age range 39–82). We then determined how these proxies of aging were associated with each other, and evaluated the effects of menopause-related factors, history of depression (= lifetime broad depression), and *APOE ε4* genotype on BAG and LTL, examining both additive and interactive relationships. We found that postmenopausal status and older age at natural menopause were linked to longer LTL and lower BAG. Surgical menopause and longer natural reproductive span were also associated with longer LTL. BAG and LTL were not significantly associated with each other. The greatest variance in each proxy of biological aging was most consistently explained by models with the addition of both lifetime broad depression and *APOE ε4* genotype. Overall, this study demonstrates a complex interplay between menopause-related factors, lifetime broad depression, *APOE ε4* genotype, and proxies of biological aging. However, results are potentially influenced by a disproportionate number of healthier participants among postmenopausal females. Future longitudinal studies incorporating heterogeneous samples are an essential step towards advancing female health.

1. Introduction

Characterized by the final menstrual period, menopause marks the end of females' reproductive years (Ambikairajah et al., 2022). Menopause typically occurs naturally between the ages of 45 and 55 and can only be determined with certainty retrospectively after a female has gone without a period for at least 12 consecutive months (Ambikairajah et al., 2022). Alternatively, menopause can be triggered by medical interventions such as bilateral oophorectomy (i.e., the removal of both ovaries; surgical menopause, C-Pillay and Manyonda (2022)). Preceding natural menopause, females undergo perimenopause, which lasts over several years and is associated with variability in menstrual cycle length and in circulating hormone levels (e.g., 17β-estradiol), ultimately resulting in reproductive senescence and the final menstrual period

* Corresponding authors.
E-mail addresses: arielle.crestol@studmed.uio.no (A. Crestol), claudia.barth@medisin.uio.no (C. Barth).

https://doi.org/10.1016/j.yhbeh.2024.105596
Received 13 February 2024; Received in revised form 14 June 2024; Accepted 18 June 2024
Available online 29 June 2024

(Hall, 2015; Harlow et al., 2012). After the final menstrual period, females are considered postmenopausal (Ambikairajah et al., 2022).

The transition to menopause has been linked to broad-system level changes in the female body (Barth et al., 2023; Barth and de Lange, 2020) and is often described as an inflection point in the female aging process (Brinton et al., 2015). For instance, females reportedly have longer telomeres – a marker of cellular aging – than males, but this sex difference seems to emerge after the age of 50, coinciding with menopause (Lapham et al., 2015). Telomeres are the repetitive structures at the ends of eukaryotic chromosomes that protect the chromosome from degradation and fusion. Telomere attrition naturally occurs with each cell division and is thought to drive cellular senescence (Lapham et al., 2015). A Mendelian randomization study found a causal relationship between genetically predicted leukocyte telomere length (LTL) and age at natural menopause, suggesting that an earlier age at natural menopause is linked to shorter telomeres (Schuermans et al., 2023). For instance, excessive telomere attrition has been linked to an increased risk for Alzheimer's disease (Fani et al., 2020); an age-related neurodegenerative disease most prevalent in postmenopausal females (Mauvais-Jarvis et al., 2020).

On a macroscopic level, menopause has also been linked to a substantial remodeling of the brain, with relevance to the female brain aging process. Studies in animals and humans have found decreases in gray matter (GM) and white matter (WM) volume, changes in brain functional connectivity, and increases in amyloid-beta deposition – a hallmark feature of Alzheimer's disease – during the transition to menopause (Ding et al., 2013; Lu et al., 2023; Mosconi et al., 2021; Mosconi et al., 2017). Some of these brain changes might stabilize or revert once females are postmenopausal (Mosconi et al., 2021). Although many females remain in relatively good health during and after the transition to menopause, in some females, menopause might invoke accelerated brain aging (Brinton et al., 2015). The extent to which the female brain is protected during and after the transition to menopause might depend on factors related to females' reproductive years, mental health, and genetics (Barth et al., 2023). For example, earlier age at menopause – occurring spontaneously or due to bilateral oophorectomy – has been associated with cognitive decline (Georgakis et al., 2019; Sochocka et al., 2023), increased risk of dementia and depression (Georgakis et al., 2019; Phung et al., 2010; Rocca et al., 2008), and morphological brain changes in Alzheimer's disease-sensitive brain regions such as the medial temporal lobe (Gervais et al., 2022; Steventon et al., 2023). Conversely, older age at menopause, indicative of a longer reproductive span, has been linked to lower GM and WM brain age based on brain age prediction (Schindler et al., 2022; Subramaniapillai et al., 2022). Whereas brain age is the estimated age of an individual's brain based on neuroimaging data, the brain age gap (BAG) represents the difference between brain age and chronological age. A positive BAG indicates a higher predicted brain age relative to chronological age, possibly suggesting that the brain has aged more relative to the average age-matched population data. Higher BAG has also been linked to disorders which might emerge or are exacerbated with the transition to menopause such as depression (Freeman et al., 2014; Han et al., 2020; Han et al., 2022). Whether the increased vulnerability for depression during the transition to menopause is concomitant to accelerated brain aging is debated. However, depression is a known risk factor for Alzheimer's disease later in life (Green et al., 2003) and has not only been linked to higher BAG, but also to shorter LTL, highlighting its influence on the aging process (Caraci et al., 2010; Ridout, 2016). Another risk factor for Alzheimer's disease is the apolipoprotein ε4 (*APOE ε4*) genotype. Carrying the *APOE ε4* allele has been associated with an increased risk of depression as well as shorter LTL, but results are inconclusive (Dhillon et al., 2020; Wang et al., 2019; Wikgren et al., 2012). Furthermore, in a previous study we showed that higher estradiol levels during postmenopause were associated with higher BAG, but only in females with the *APOE ε4* allele (de Lange et al., 2020). The association was reversed in females without the risk alleles.

In summary, these findings suggest that age at menopause, a history of depression, and *APOE ε4* genotype can impact the rate of aging and risk for age-related cognitive and neurodegenerative disease in females. However, these factors have often been studied in isolation and a comprehensive study investigating all these factors and their contribution to both cellular and brain aging is currently missing. Understanding how risk and resilience factors together impact cellular and brain aging may help differentiate females who undergo typical aging from those at risk of accelerated neurological decline. This knowledge is crucial for developing early interventions for high-risk individuals and is of societal importance, given that females typically spend one-third of their lives postmenopausal (Taylor et al., 2019).

In this preregistered study, we use data from the UK Biobank to investigate whether menopause-related factors, such as menopausal status, menopause type (natural vs. surgical), reproductive span (age at natural/surgical menopause – age at menarche), and age at menopause (natural and surgical) are associated with proxies of cellular aging (i.e., shorter LTL) and brain aging (i.e., higher WM BAG and GM BAG), and how these proxies of biological aging are associated with each other. We then evaluate the effects of menopause-related factors, history of depression (= lifetime broad depression; Howard et al., 2018), and *APOE ε4* genotype on BAG and LTL, examining both additive and interactive relationships.

2. Methods

2.1. Sample characteristics

The sample was drawn from the UK Biobank cohort (UKB www.ukbiobank.ac.uk). Biological females (identified by genetic sex; XX) with diffusion and T1-weighted magnetic resonance imaging (MRI) data and/or LTL data were included. LTL measures were collected at baseline (T0, $n = 203{,}627$, mean age = 56.02 ± 7.96 standard deviation (SD), range 39–70 years), and MRI data was collected at the imaging assessment point (T2, $n = 17{,}222$; mean age = 63.00 ± 7.35 SD, range 45–82 years). In line with previous work, females with disorders known to invoke brain changes were excluded based on the following ICD10 diagnoses: stroke (ICD field code I64), mental and behavioral disorders (ICD field F, including F00–F03 for AD and dementia, and F06.7 'Mild cognitive disorder', excluding all codes listed in section 2.7. 'Lifetime broad depression'), diseases of the nervous system (ICD field G, diseases of the nervous system, including inflammatory and neurodegenerative diseases, excluding G55–59) (de Lange et al., 2020; Schindler et al., 2022; Voldsbekk et al., 2021).

2.2. MRI data acquisition and processing

See Alfaro-Almagro et al. (2018) and Miller et al. (2016) for a detailed overview of MRI data acquisition and protocols from the UKB. Processing of the T1-weighted images was conducted using a harmonized analysis pipeline, including the FreeSurfer (version 5.3) automated surface-based morphometry and subcortical segmentation (Fischl et al., 2002). We then extracted cortical thickness, area, and volume for 180 regions of interest per hemisphere using a standard set of subcortical and cortical summary statistics from FreeSurfer (Fischl et al., 2002), as well as a fine-grained cortical parcellation scheme (Glasser et al., 2016), as done in previously published brain age studies from our group (de Lange et al., 2019; Kaufmann et al., 2019; Schindler et al., 2022; Voldsbekk et al., 2021). The data from Freesurfer was residualized with respect to scanning site and intracranial volume, and quality control was conducted by removing 150 individuals with Euler numbers of SD ± 4 (Rosen et al., 2018). These features were used as inputs in the GM-specific age prediction model.

Diffusion MRI data was processed using an optimized diffusion pipeline (Maximov et al., 2021). For the WM-specific brain age prediction model, diffusion tensor imaging (DTI, Basser et al. (1994)) and

diffusion kurtosis imaging (DKI, Jensen et al. (2005)) derived metrics were estimated, as well as WM tract integrity (WMTI, Fieremans et al. (2011)) and spherical mean technique (SMT, (Kaden et al., 2016a; Kaden et al., 2016b)) metrics. WM features were extracted based on John Hopkins University (JHU) atlases for WM tracts and labels (with 0 thresholding, Mori et al. (2005)) for global mean values and regional measures of 12 tracts of interest (Beck et al., 2021; Voldsbekk et al., 2021). The diffusion-weighted data was residualized with respect to the scanning site. Passed tract-based spatial statistics (TBSS) quality control was conducted using the YTTRIUM algorithm (Maximov et al., 2021).

2.3. Brain-age prediction

BAG was used as a proxy measure of brain aging. GM and WM features derived from T1-weighted and diffusion-weighted brain scans, respectively, were used to predict age with XGBoost regressor models (eXtreme Gradient Boosting). XGBoost is a powerful and efficient algorithm that implements gradient-boosted decision trees. Parameters were tuned in a nested cross-validation using 5 inner folds for randomized search, and 10 outer folds for model validation (see here for general model setup). BAG was then calculated as the difference between predicted and chronological age, highlighting any divergence from normative aging trajectories.

2.4. Leukocyte telomere length (LTL)

LTL was used as a proxy measure of cellular aging. During the UKB baseline assessment, blood samples were collected from participants and DNA was extracted from peripheral blood leukocytes. LTL was measured using a quantitative PCR method. The ratio of telomere repeat copy number (T) related to that of a single copy gene (S; T/S ratio) was calculated. The relative LTL, adjusted for the influence of technical parameters, was log-transformed to better fit the normal distribution of the data, and standardized as *z*-scores in line with UKB recommendations for LTL. More details on measurement and validity can be found in Codd et al. (2022).

2.5. Apolipoprotein ε4 (APOE ε4) genotype

To assess the *APOE ε4* genotype, we used the extensively quality controlled UKB version 3 imputed data (Bycroft et al., 2018). The *APOE ε* genotype was approximated based on two *APOE ε* single-nucleotide polymorphisms—rs7412 and rs429358 (Lyall et al., 2016). +*APOE ε4* carrier was based on *ε3/ε4* and *ε4/ε4* combinations, and -*APOE ε4* non-carrier for *ε2/ε2*, *ε2/ ε3*, and *ε3/ ε3* combinations. Due to its ambiguity with *ε1/ε3*, the homozygous *ε2/ε4* allele combination was removed (https://www.snpedia.com/index.php/APOE).

2.6. Menopause-related factors

To assess associations between biological proxies of aging and menopausal status, females were split into three groups: premenopause, natural menopause, and surgical menopause. General menopausal status was based on the self-reported question 'Have you had your menopause (periods stopped)?' (i.e., yes = postmenopausal; no = premenopausal). All females who were ≥ 70 years old were categorized as postmenopausal irrespective of self-reported menopausal status (Ambikairajah et al., 2020). Postmenopausal females were further stratified into natural and surgical menopause (i.e., bilateral oophorectomy prior to menopause). Females were included in the surgical menopause group if they were postmenopausal and their age at bilateral oophorectomy was reported as equal to or prior to their reported age at menopause. All females with a history of bilateral oophorectomy were considered postmenopausal regardless of self-reported menopausal status. Females with a history of hysterectomy (partial or total surgical removal of the uterus) and/or bilateral oophorectomy were excluded from the natural menopause group. Given that "No" to the self-reported "had menopause" question does not differentiate between pre- and perimenopausal females, we additionally used a more sensitive approach to analyze natural menopausal status by dividing females into a premenopausal, perimenopausal, early postmenopausal, and late postmenopausal group. Criteria for fine-grained natural menopausal grouping were based on self-reported variables including time since last menstrual period, length of menstrual cycle, hormonal contraceptive (HC) use, menopausal hormone therapy (MHT) use, and age at menopause. See Table S1, supplementary materials, for details on the applied stratification criteria, which were loosely based on the Stages of Reproductive Aging Workshop (STRAW) criteria (Harlow et al., 2012). Both approaches to categorizing menopausal status were used, as only a small sub-sample of females have enough data from the UKB to match the criteria for more fine-grained natural menopausal grouping.

To study the association between reproductive span and proxies of biological aging, duration of reproductive span was calculated and analyzed separately for females who underwent natural menopause and surgical menopause. For natural menopause, reproductive span was calculated as self-reported age at menopause minus age at menarche. For the surgical menopause group, reproductive span was calculated as self-reported age at bilateral oophorectomy minus age at menarche.

Participants who had responded 'prefer not to answer', 'do not know', or a similar response were excluded when the relevant variable was included in a particular analysis. An overview of all UKB variables used in the current study can be found in Table S2, supplementary materials. For LTL and BAG, menopause-related variables collected at T0 and T2 were used respectively, where appropriate.

2.7. Lifetime broad depression

Participants were divided into two groups (case and control) based on a *lifetime broad depression phenotype* established by Howard et al. (2018). Individuals were included in the case group if they self-reported 'yes' to either of the following questions: 'Seen a general practitioner (GP) for nerves, anxiety, tension or depression' and 'Seen a psychiatrist for nerves, anxiety, tension or depression'. Individuals were also included in the case group if they received a primary or secondary diagnosis of the following depressive mood disorders from hospital inpatient records: 'Single episode depression' (ICD field code F32), 'Recurrent depression' (ICD field code F33), 'Persistent mood disorders' (ICD field code F34), 'Other mood disorders' (ICD field code F38), and 'Unspecified mood disorders' (ICD field code F39). All other individuals were included in the control group. Additionally, the following exclusions were carried out from both the case and control groups: individuals who self-reported and/or were diagnosed according to hospital records with bipolar disorder (ICD field code F30, F31, or non-cancer illness code 1291), schizophrenia (ICD field code F2*, or non-cancer illness code 1289), or a personality disorder (ICD field code F44.8), as well as individuals who were prescribed antipsychotic medications. From the control group, individuals were additionally excluded if they had a prescription for antidepressants, or if they were diagnosed with a mood disorder.

2.8. Statistical analyses

All statistical tests were conducted in R 4.2.2 and Python 3.8.0. We first created a correlation matrix (Pearson's r) to assess correlations between the dependent variables, independent variables, and age (see Fig. 1). Continuous variables were z-score standardized by subtracting the mean and dividing by the standard deviation prior to analysis. The categorical variables of menopausal status (premenopause = 0), fine-grained natural menopausal status (premenopause = 0), menopause type (natural menopause = 0), lifetime broad depression (control = 0), and *APOE ε4* status (non-carrier = 0) were dummy coded. Outliers were visually inspected with diagnostic plots. To account for multiple

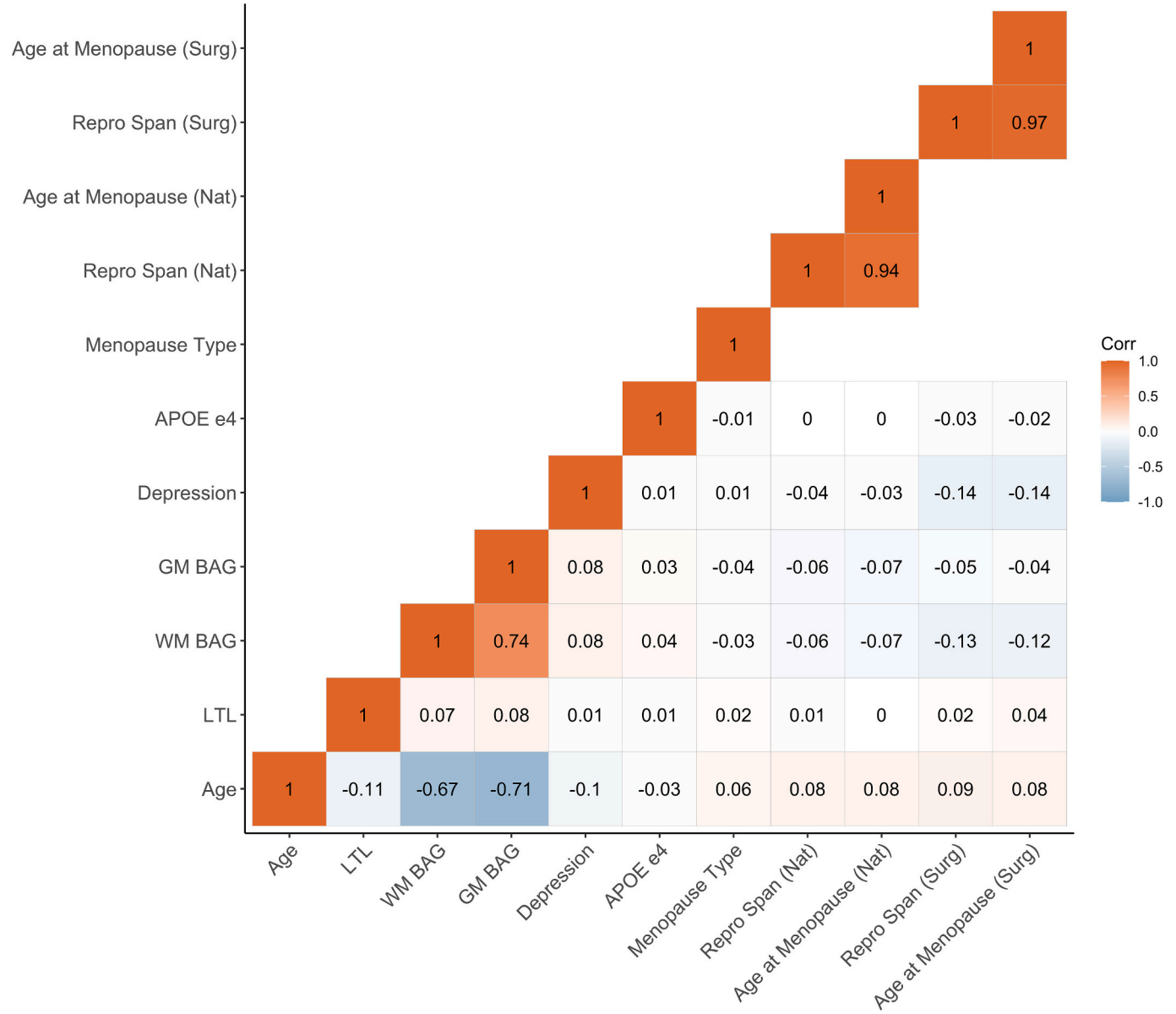


Fig. 1. Pearson correlation between primary dependent variables, independent variables, and age. Correlations between each pair of variables were computed using all complete pairs of observations on those variables. Empty fields indicate no complete pairs for that pair of variables. All measures were taken from the UKB imaging timepoint aside from leukocyte telomere length and *APOE ε4* genotype, which was collected at the baseline assessment. Abbreviations: LTL = leukocyte telomere length; WM BAG = white matter brain age gap; GM BAG = gray matter brain age gap; Menopause type = Natural vs Surgical Menopause; Repro years (nat) = reproductive span in females who underwent natural menopause; Repro years (surg) = reproductive span in females who underwent surgical menopause.

comparisons, false discovery rate (FDR) correction was applied across all dependent variables (DV, i.e., LTL, WM BAG, GM BAG) for all sets of analyses per model (1–3), separately. The sets of FDR corrections are reflected in the corresponding results tables. Chronological age was included as a covariate in all regression analyses to account for age-dependence of predictions (de Lange and Cole, 2020). The study was pre-registered on OSF; for deviations from the preregistration (see Note S1, supplementary materials).

To test for associations between proxies of biological aging and menopause-related factors, we fit separate regression models for each DV and each menopause-related factor as independent variables. Menopause-related factors include menopausal status (basic: pre- vs. natural and surgical menopause & fine-grained natural: pre- vs. peri-, early natural post- and late natural postmenopause), menopause type (natural vs. surgical), reproductive span (natural/surgical), and age at menopause (natural/surgical). The following linear model setup was used:

DV ~ Menopause-related factor + age (1)

For the next set of analyses, we assessed whether the addition of lifetime broad depression and/or *APOE ε4* genotype as main effects as well as interaction terms with menopause-related factors better describe the variation in the DV than model 1. To this end, the following linear regression models were fitted:

DV ~ Menopause-related factor + age + lifetime broad depression (2a)

DV ~ Menopause-related factor + age + *APOE ε4* (2b)

DV ~ Menopause-related factor + age + lifetime broad depression + *APOE ε4* (2c).

DV ~ Menopause-related factor*lifetime broad depression + age (2d)

DV ~ Menopause-related factor**APOE ε4* + age (2e)

DV ~ Menopause-related factor*lifetime broad depression**APOE ε4*

+ age (2f).

To compare these models for each DV and menopause-related factor, separately, and to establish which model is the best fit, we used the *aictab()* command from the AICcmodav R package. The *aictab()* command constructs model selection tables with number of parameters, Akaike Information Criterion (AIC), delta AIC, Akaike weights (model probabilities) based on AICc, QAIC, and QAICc for a set of candidate models. AIC considers simplicity of the model in addition to goodness of fit to improve predictions in new data. A lower AIC score suggests a better fit of the model. After establishing the best fitting model across all DVs and menopause-related factors (i.e., 2c), we also tested which menopause-related factor explained the most variance in the DV measures.

Lastly, we were interested in assessing the relation between cellular and brain aging alone and in the context of menopause-related factors. This was achieved by fitting an additional regression model with WM BAG or GM BAG as DV and LTL as an independent variable (either as main effect or interaction term together with menopause-related factors at the imaging timepoint) while covarying for years between the baseline timepoint (LTL) and the imaging timepoint (BAG). As model 2c was most consistently the best fit across each DV and menopause-related factor, lifetime broad depression and *APOE ε4* genotype were added as covariates.

DV ~ LTL + age + lifetime broad depression + *APOE ε4* + years between timepoints (3a).

DV ~ LTL*menopause-related factor + age + lifetime broad depression + *APOE ε4* + years between timepoints (3b).

2.9. Sensitivity analyses

First, to test whether known confounders affected our results (Beck et al., 2022; de Lange et al., 2020; Schindler et al., 2022; Voldsbekk et al., 2021), we reran model 1 adjusting for education, the Townsend deprivation index, a lifestyle score, body mass index (BMI), HC use, MHT use, and number of childbirths (sensitivity analysis 1). See supplementary Note S2 and Table S2 for details on the Townsend deprivation index and lifestyle score. For LTL and BAG, variables collected at T0 and T2 were used, respectively, where appropriate.

Second, to adjust for the potential influence of extreme values on our results, we assessed each continuous menopause-related variable (i.e., age at menarche, age at menopause, age at bilateral oophorectomy) for extreme values using a data-driven approach and excluded the corresponding participants before re-running model 1 (sensitivity analysis 2). Extreme values were identified by applying the mean absolute deviation (MAD) method from the Routliers R package using default settings (i.e., a MAD threshold of ±3).

Next, we re-ran model 1 without the inclusion of age as a covariate to ascertain whether results remained consistent, given the difficulty in disentangling chronological and endocrine aging. Models with BAG as a DV were run with age-adjusted BAG values to account for age-dependence of predictions.

Finally, earlier age at menopause has been associated with unfavorable health outcomes. Given the wide range of ages at menopause in this sample, we reran model 1, splitting postmenopausal females into three groups according to age at menopause: premature (up to 40), early (40–45), and normal (45+).

3. Results

3.1. Sample characteristics

Demographic and menopause-related characteristics for the MRI

Table 1
Sample demographics for premenopause, natural menopause, and surgical menopause groups (MRI sample).

	Menopausal Status			*p*-values		
	Pre	Post, nat	Post, surg	Pre vs Post, nat	Pre vs Post, surg	Post, nat vs Post, surg
N	920	12,554	306			
Age (years)*	51.3 ± 2.8	63.6 ± 6.7	66.3 ± 6.6	<0.001	<0.001	<0.001
Education, N (%)				<0.001	<0.001	<0.001
College/University degree	525 (57.1)	6,278 (50.0)	114 (37.3)			
O levels/GCSEs or equivalent	149 (16.2)	2,346 (18.7)	79 (25.8)			
A levels/AS levels or equivalent	148 (16.1)	1,593 (12.7)	39 (12.7)			
CSEs or equivalent	42 (4.6)	464 (3.7)	11 (3.6)			
NVQ/HND/HNC or equivalent	20 (2.2)	439 (3.5)	7 (2.3)			
Other professional qualifications	27 (2.9)	733 (5.8)	26 (8.5)			
None of the above	5 (0.5)	665 (5.3)	26 (8.5)			
Prefer not to answer	4 (0.4)	36 (0.3)	4 (1.3)			
Ethnic Background, N (%)				<0.001	0.449	0.658
White	860 (93.5)	12,212 (97.3)	294 (96.1)			
Asian	16 (1.7)	85 (0.7)	3 (1.0)			
Black	10 (1.1)	64 (0.5)	2 (0.7)			
Chinese	10 (1.1)	45 (0.4)	3 (1.0)			
Other ethnic group	6 (0.7)	66 (0.5)	2 (0.7)			
Mixed	17 (1.8)	57 (0.5)	1 (0.3)			
Prefer not to answer	1 (0.1)	15 (0.1)	1 (0.3)			
Do not know	0 (0.0)	5 (0.0)	0 (0.0)			
Townsend Deprivation Index*	−1.5 ± 2.9	−1.9 ± 2.7	−2.2 ± 2.6	<0.001	<0.001	0.070
Lifestyle Score*	1.7 ± 1.3	1.6 ± 1.2	1.7 ± 1.1	0.006	0.787	0.193
BMI (m^2/kg)*	25.9 ± 4.8	25.7 ± 4.5	26.9 ± 4.8	0.098	0.003	<0.001
Number of Live Births*	1.5 ± 1.2	1.7 ± 1.2	1.7 ± 1.2	<0.001	0.013	0.482
Lifetime broad depression, yes, N (%)	361 (40.0)	4183 (34.4)	105 (35.6)	0.001	0.203	0.716
APOE ε4, carrier, N (%)	229 (25.5)	3260 (26.6)	74 (24.7)	0.489	0.848	0.504
LTL (z-standardized)*	0.2 ± 1.0	−0.02 ± 1.0	0.08 ± 0.9	<0.001	0.033	0.102
Age at menopause*°		50.8 ± 4.3	46.9 ± 6.6			<0.001
Reproductive Span*°		37.8 ± 4.5	34.2 ± 6.8			<0.001
Menopause hormone therapy, N (%)	71 (7.7)	4016 (32.1)	230 (75.4)	<0.001	<0.001	<0.001

* Continuous data in mean ± standard deviation and categorical data as number %; ° based on age at bilateral oophorectomy for postmenopause, surgical. Abbreviations: N = sample size; nat = natural, surg = surgical, GCSE = general certificate of secondary education; NVQ = national vocational qualification; BMI = body mass index, *APOE* = apolipoprotein, LTL = leukocyte telomere length. Significant results are highlighted in bold. The results are based on Chi2 test for categorical data and *t*-test for continuous data.

sample, stratified by menopausal status, are summarized in Table 1. Sample characteristics for the LTL dataset, also stratified by menopausal status, can be found in the supplementary materials, Table S3. Density plots of age distribution by menopause group are highlighted in Fig. S1, density plots of age at menopause distribution by menopause type are shown in Fig. S2, and a detailed description of demographic differences between menopause groups is noted in Note S3. The sample sizes for the fine-grained natural menopause grouping for the LTL and MRI sample were, respectively, 33,346 and 440 premenopausal females, 8,012 and 259 perimenopausal females, 37,219 and 2,757 early postmenopausal females, and 60,222 and 8,050 late postmenopausal females (see section 2.6 for details on fine-grained natural menopausal grouping).

3.2. Brain age prediction

The age prediction accuracy for each brain age prediction model is detailed in Table 2.

The first model is based on white matter (WM) features, and the second model is based on gray matter (GM) features. Model accuracy is evaluated according to the values for R^2, RMSE, MAE, and r between predicted and chronological age. Abbreviations: RMSE = root mean square error, MAE = mean absolute error, r = Pearson's correlation, CI = confidence interval.

3.3. Menopause-related factors and proxies of biological aging (model 1)

Contrary to our hypotheses, although LTL was negatively associated with age, we found longer LTL in the natural and surgical menopausal groups compared to the premenopausal group (natural: $\beta = 0.034$, $p_{FDR} = 1.34e\text{-}04$; surgical: $\beta = 0.110$, $p_{FDR} = 1.59e\text{-}08$). Similarly, both WM BAG and GM BAG were lower in the natural and surgical menopausal groups compared to the premenopausal group (WM BAG, natural: $\beta = -1.175$, $p_{FDR} = 4.40e\text{-}18$; surgical: $\beta = -1.152$, $p_{FDR} = 4.81e\text{-}06$; GM BAG, natural: $\beta = -1.564$, $p_{FDR} = 1.87e\text{-}30$; surgical: $\beta = -1.665$, $p_{FDR} = 2.12e\text{-}11$).

When stratifying the females into four menopausal groups, we saw that the LTL results for menopausal status were driven by differences between premenopausal and early postmenopausal females ($\beta = 0.028$, $p_{FDR} = 0.01$). For the brain age measures, the menopausal status results were driven by the differences between premenopausal and early postmenopausal females as well as between premenopausal and late postmenopausal females. Specifically, BAG was significantly lower in both postmenopausal groups compared to the premenopausal females (WM BAG, early post: $\beta = -1.211$, $p_{FDR} = 1.31e\text{-}10$; late post: $\beta = -1.403$, $p_{FDR} = 5.39e\text{-}12$; GM BAG, early post: $\beta = -1.660$, $p_{FDR} = 1.04e\text{-}18$; late post: $\beta = -1.891$, $p_{FDR} = 1.50e\text{-}20$).

LTL was significantly longer in the surgical menopause group compared to the natural menopause group ($\beta = 0.076$, $p_{FDR} = 2.47e\text{-}05$). There were no statistically significant differences between these groups for WM BAG or GM BAG.

With natural and surgical menopause, a longer reproductive span was associated with longer LTL (natural: $\beta = 0.024$, $p_{FDR} = 4.00e\text{-}13$; surgical: $\beta = 0.045$, $p_{FDR} = 0.032$). However, natural and surgical reproductive span were not associated with WM BAG or GM BAG. Older age at natural menopause, but not age at surgical menopause, was associated with longer LTL ($\beta = 0.030$, $p_{FDR} = 1.50e\text{-}20$), and lower WM BAG ($\beta = -0.097$, $p_{FDR} = 0.007$) and GM BAG ($\beta = -0.085$, $p_{FDR} = 0.017$).

Associations between menopause-related factors and proxies of aging are summarized in Fig. 2 and Table S4, supplementary materials.

3.4. Menopause-related factors and proxies of biological aging - model selection (model 2a-f)

Model 2c, which included lifetime broad depression and *APOE ε4* genotype as covariates, was most consistently the best fit across all DV and menopause-related factors (see Table S5, supplementary materials). The addition of both covariates did not change the main results, but we did find shorter LTL and higher WM BAG with lifetime broad depression in the models with the following menopause-related factors: menopause group (basic/fine-grained), menopause type (natural/surgical), reproductive span (natural), and age at natural menopause (see Table S6). We found no significant main effect of lifetime broad depression on GM BAG in any model. Furthermore, *APOE ε4* genotype was associated with higher WM BAG in the models including menopause group (basic/fine-grained), reproductive span (natural), and age at menopause (natural). *APOE ε4* genotype showed no significant main effect on GM BAG and LTL in any model (see Table S6).

After establishing the best fitting model across all DV and menopause-related factors (i.e., 2c), we further tested which menopause-related factor explained the most variance in the DV measures, when accounting for lifetime broad depression, *APOE ε4* genotype, and age. Reproductive span (surgical) explained the most variances in WM BAG and GM BAG, and age at surgical menopause explained most variances for LTL (see Table S7).

3.5. Associations between proxies of cellular and brain aging (model 3a-b)

We found no statistically significant association between LTL as main effect or as interaction-term together with menopause-related factors and WM or GM BAG (see Table S8, supplementary materials).

3.6. Sensitivity analyses

Most results of model 1 were robust after either (1) adjusting for additional covariates (Table S9, supplementary materials), (2) removing extreme values (Table S10, supplementary materials), (3) not adjusting for age (Table S11, supplementary materials), or (4) splitting postmenopausal females into groups according to age at menopause (Table S13, supplementary materials). Detected extreme values are highlighted in Supplementary Table S12. Differences between model 1 and the sensitivity models are summarized in Note S4.

4. Discussion

This study explored the association between menopause-related factors, *APOE ε4* genotype, and lifetime broad depression with BAG and LTL, proxies of brain aging and cellular aging respectively. In summary, our findings showed that postmenopausal status and older age at natural menopause were linked to longer LTL and lower BAG. Surgical menopause and longer natural reproductive span were associated with longer LTL. When comparing models, the greatest variance was most consistently explained by models with the addition of both lifetime broad depression and *APOE ε4* genotype. BAG and LTL were not significantly associated with each other. Results were largely robust after covarying for potential confounders such as MHT, as well as when adding lifetime broad depression and the *APOEε4* genotype. Taken

Table 2
Age prediction accuracy for XGBoost regression models.

Model	R^2	RMSE	MAE	*r* [95 % CI]	*p*
WM	0.53 ± 0.015	5.01 ± 0.110	4.00 ± 0.075	0.74 [0.73, 0.74]	<0.0001
GM	0.60 ± 0.014	4.70 ± 0.083	3.70 ± 0.078	0.77 [0.77, 0.78]	<0.0001

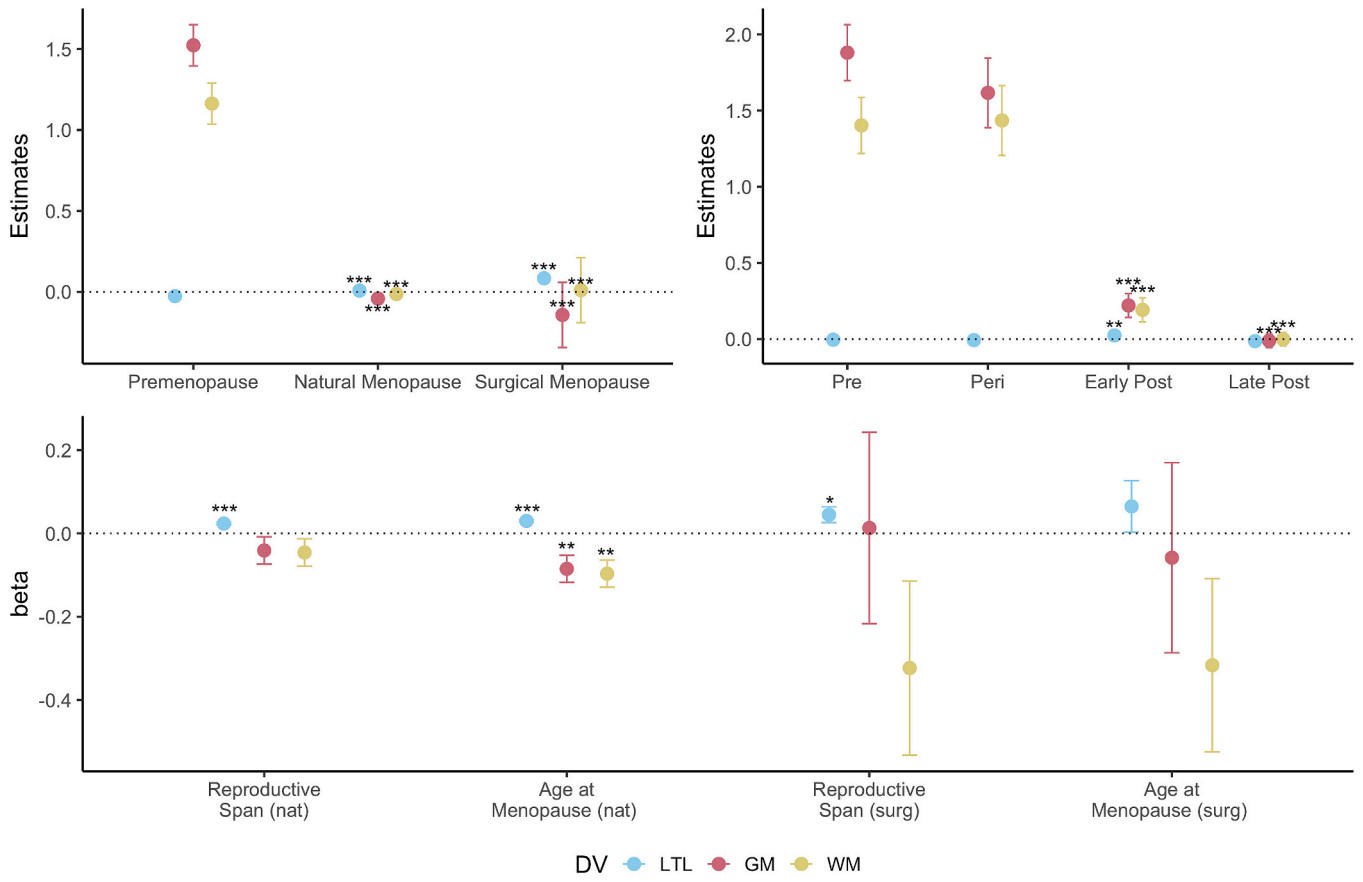


Fig. 2|. Associations between proxies of biological aging and menopause-related factors. Point plot of estimated marginal means for models with categorical independent variables (top row) and beta-values with standard error for models with continuous variables (bottom row). Estimates or beta values were derived from separate multiple regression analysis with LTL, WM, or GM as dependent variables (DV) and menopause-related variables as independent variables. All models are adjusted for age (model 1). All continuous variables were standardized prior to performing the multiple linear regression analysis (subtracting the mean and dividing by the standard deviation).

together, these results suggest that cellular and brain aging in females are influenced by an interplay of protective and risk factors.

In the present study, postmenopausal females showed longer LTL and lower WM and GM BAG across both basic and fine-grained models of menopausal status (model 1). Early postmenopausal females were driving the significant association for LTL between the premenopausal and natural postmenopausal females, and both early and late postmenopausal females were driving the association for WM and GM BAG. There were no significant differences between the premenopausal and perimenopausal groups (model 1). Lapham et al. (2015) showed an overall negative association between age and LTL similar to the current study, but only up to 75 years, after which age and LTL were positively associated, indicative of a survival bias. A similar bias could be at play in the current study, with postmenopausal females showing an association of longer LTL with more years of survival.

The effects of menopausal status on brain health are debated. Menopause has been associated with decreases in GM and WM brain structures as well as changes in brain connectivity, metabolic function, and amyloid beta deposition (Mosconi et al., 2021; Mosconi et al., 2017). However, three separate papers studying the impact of menopausal status on total brain volume have reported contradictory results, despite all three analyzing data from the UKB. One study reported larger total brain volume in postmenopausal compared to premenopausal females (Ambikairajah et al., 2020), another reported smaller total brain volume (Than et al., 2021), and one reported no significant impact of menopausal status on total brain volume (Costantino et al., 2023). These apparently opposing results highlight the influence of methodological considerations when studying menopausal status. For example, in these studies, the authors either chose to match for age, covary for age, and/or assess the interaction between menopause and age. In the current study, we opted to co-vary for age in all primary models, then ran supplementary analyses without covarying for age. We did not age-match, given that there was little overlap in age between the premenopausal and postmenopausal groups, as seen in Fig. S1. Disentangling the influence of endocrine and chronological aging in females is a major challenge in menopause research.

Using variables accessible from the UKB, females were stratified into more fine-grained natural menopause groups. However, given the limited data available for these groupings, it is possible that there remained an overlap between the pre- and perimenopausal groups, as females may have been misclassified. This may explain why no differences were seen between the pre- and perimenopausal groups. Further, the significant results comparing premenopausal and postmenopausal females may have been capturing the difference between *perimenopausal* and postmenopausal females. Perimenopause has been described as a neuroendocrine transition state (Brinton et al., 2015). Estradiol acts as a master regulator of the metabolic system in the female brain via its network of estrogen receptors. The decline in estradiol during perimenopause disrupts the bioenergetic system of the brain, which can lead to menopausal symptoms such as neurocognitive disturbances. After the transition to menopause, most females revert to their baseline health, while in a subset of females this uncoupling is thought to increase the risk of accelerated aging and neurodegenerative diseases (Brinton et al., 2015). Our results may be capturing the disturbance during perimenopause that later stabilizes in most postmenopausal females, which could explain why the postmenopausal groups are presenting with less

apparent aging than the premenopausal group. This can be observed in Fig. 2, where a steady decline in estimated marginal means for BAG values is seen across all 4 fine-grained natural menopause groups.

The current results may also be partly explained by a *healthy volunteer bias* in the UKB sample (Fry et al., 2017). We accounted for biases to the best of our ability with inclusion/exclusion criteria (e.g., ICD10 diagnoses), running analyses both with and without adjusting for age, running sensitivity analyses excluding extreme values and adjusting for known confounders, and further running subgroup analyses (e.g., fine-grained menopause grouping and age at menopause grouping). However, UKB participants are considered healthier than the general population based on several lifestyle and health-related factors (Fry et al., 2017). Individuals who participate in research studies tend to increasingly diverge from the general population with increased age, with older adults proving to be much healthier than their counterparts from the population at large (Golomb et al., 2012). This selection bias is unfortunately a common problem in geriatric research, with issues typically stemming from survivor bias and bias due to loss at follow-up (Banack et al., 2019). In the current study, the postmenopausal groups are significantly older than the premenopausal group and the natural postmenopausal group appears to be healthier based on lifestyle scores and lifetime broad depression levels. Overall, the disproportionate number of healthier older adults in this cross-sectional sample is likely distorting results between menopausal groups. Moving forward, research utilizing longitudinal designs and more inclusive samples is needed to eliminate some of these biases. Furthermore, future studies should integrate strategies to avoid healthy volunteer biases as early as during study design, particularly when including older individuals. For example, minimizing barriers to participation by providing alternatives such as home visits whenever possible could help reduce some of these biases (Banack et al., 2019).

LTL was significantly longer in the surgical menopause group compared to natural menopause, although no effect of menopause type was observed for WM or GM BAG (model 1). These results are not in line with previous research, which indicates that while shorter LTL is associated with premature menopause, the relationship is attenuated in females with surgical menopause (Schuermans et al., 2023). It is again possible that a *healthy volunteer bias* is seen here, given that surgical menopause is often associated with unfavorable health outcomes (Parker et al., 2009), yet there are no apparent differences between surgical and natural menopause groups based on lifestyle scores. The surgical menopause group was also significantly older than the natural menopause group, which again might be yielding an amplified divergence between the females who underwent surgical menopause in this cohort and those who transitioned naturally. Further, we do not have data on reasoning for undergoing a bilateral oophorectomy in this study.

Both reproductive span and age at menopause are considered proxies of lifetime endogenous estrogen exposure. Thus, we expected to see similar results between age at menopause and reproductive span. Longer reproductive span was associated with longer LTL, but not WM or GM BAG, regardless of menopause type (model 1). However, the association between LTL and surgical reproductive span lost significance in the sensitivity analyses after adding covariates and removing extreme values. Older age at natural menopause was linked to longer LTL as well as lower WM and GM BAG, but no associations were found with age at surgical menopause. After accounting for known confounds, age at natural menopause was also no longer significantly linked to GM BAG. Overall, natural reproductive span was positively associated with LTL, and higher natural age at menopause was linked to longer LTL and lower WM BAG. Neither age at surgical menopause nor surgical reproductive span were associated with LTL or BAG after sensitivity analyses. These findings are consistent with research which describes a positive association between LTL and age at natural menopause, but not surgical menopause (Gray et al., 2014; Schuermans et al., 2023). The discrepancy in results between age at menopause and reproductive span for BAG might be the result of inaccurate recollection of age at menarche. Alternatively, reproductive span may be a more precise representation of estradiol accumulation than age at menopause, given that age at menarche is also considered. Our results align with prior studies which have shown an association between older age at natural menopause, longer reproductive span, and lower WM BAG (Schindler et al., 2022; Subramaniapillai et al., 2022). However, Schindler et al. (2022) also saw a significant relation between reproductive span and GM BAG. Both sensitivity analysis methods and sample inclusion differed in the current study from the study by Schindler and colleagues, which might account for this difference in results.

It has been debated whether cumulative estradiol exposure plays a protective role in accelerated aging and neurodegeneration (Suzuki et al., 2006; Wise et al., 2009). Inconsistencies in the literature might have arisen given that estradiol does not function in isolation. When comparing the fit of models with the addition/interaction of lifetime broad depression and *APOE ε4* genotype, adding both variables was the best fit across all DVs and menopause-related factors (model 2). Our results are aligned with our previous work showing *APOE ε4* genotype as a potential modulator for estradiol's impact on brain aging, wherein higher estradiol levels among postmenopausal females were associated with higher BAG in *APOE ε4* carriers, while the reverse was true for non-carriers (de Lange et al., 2020). Inconsistent results have been reported on the link between *APOE ε4* genotype and LTL in nondemented individuals, with one study reporting longer LTL in *APOE ε4* carriers (Wikgren et al., 2012), and another reporting shorter LTL in *APOE* ε4 carriers (Dhillon et al., 2020). The inconsistencies in these cross-sectional studies might be explained by additional factors. For example, Jacobs et al. (2013) conducted a longitudinal study to assess the link between *APOE* ε4 genotype, LTL, and MHT in postmenopausal females. They found that the *APOE* ε4 genotype was linked to accelerated LTL shortening. However, an interaction with MHT was reported such that *APOE* ε4 carriers who remained on MHT did not exhibit this accelerated LTL shortening. In contrast, the group of non-*APOE* ε4 carriers showed LTL lengthening when they went off MHT, demonstrating the dynamic interplay of female-specific factors and genetic risk for AD in females. The *APOE* ε4 genotype is associated with sex differences in AD, as female *APOE* ε4 carriers have an increased risk of developing AD compared to their male counterparts (Holland et al., 2013; Ungar et al., 2014). It is therefore likely that additional factors such as menopausal status in females were influencing the contradictory results between studies on LTL and *APOE* ε4 genotype.

The *APOE* ε4 genotype has also been associated with increased risk of depression, as well as increased severity of depressive symptoms (Wang et al., 2019). While depression in isolation has also been associated with higher BAG (Han et al., 2020; Han et al., 2022) and LTL (Ridout, 2016), to our knowledge this is the first study to consider lifetime broad depression and BAG in the context of female-specific factors. Future studies are warranted to incorporate female-specific experiences of depression such as premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression. Overall, our results suggest that various factors might function in tandem to impact the rate of cellular and brain aging in middle-aged to older females.

When analyzing the link between cellular and brain aging alone and in the context of menopause-related factors, LTL was not significantly associated with either WM or GM BAG (model 3). However, baseline and follow-up assessments were approximately 8 years apart, which could be confounding these results. Two studies linking LTL and brain structures in the UKB and the Dallas Heart Study found significant associations between LTL with total and regional brain volumes (King et al., 2014; Topiwala et al., 2023). Another study reported a significant link between LTL and BAG in individuals with mild cognitive impairment (MCI), although these results cannot be generalized to healthy aging (Yu et al., 2022). From all three studies, only one included sex as a variable of interest (King et al., 2014), while the others included sex as a covariate, omitting to state whether sex differences were apparent. Notably, King et al. (2014) found that when accounting for sex, the significant

associations observed between LTL and several brain regions were not significant in females. These results highlight the necessity to include sex and sex-specific variables in aging research.

The UKB is an excellent large-scale and publicly available dataset. However, several limitations apply. The ethnic background of the sample is homogeneous, and as highlighted above, a *healthy volunteer bias* might influence the results of this study. Further, while the UKB provides access to several female-specific variables, the way these variables are recorded might not be reliable or adhere to best practices. For example, menopause is recorded based on whether menstrual periods have stopped (yes/no). However, menopause is characterized by the absence of a menstrual period for 12 consecutive months, and perimenopause is not considered in this self-report questionnaire. The STRAW criteria, which is regarded as the gold standard for menopausal staging, recommends the usage of a full battery questionnaire in addition to hormonal assessments (Harlow et al., 2012). The UKB also lacks detailed information on menopausal symptoms, which can further modulate the risk for accelerated aging at menopause (Brinton et al., 2015). Initiatives are now being established to address limitations in research on female-specific factors by pooling existing datasets (such as the Enhancing Neuroimaging Genetics through Meta-Analyses (ENIGMA)-Neuroendocrinology Working Group; Heller et al., 2024) and harmonizing new data collection (such as the Ann S. Bowers Women's Brain Health Initiative). These initiatives can help increase power, reproducibility, and generalizability of female brain health studies.

In conclusion, this cross-sectional study demonstrates the complex interplay between menopause-related factors, lifetime broad depression, *APOE ε4* genotype, and proxies of cellular aging and brain aging, with results potentially being influenced by a disproportionate number of healthier participants among postmenopausal females. In the future, longitudinal studies incorporating heterogeneous samples are warranted. Further, standardized practices for the collection of female-specific variables in large-scale datasets are an essential step towards advancing female health.

CRediT authorship contribution statement

Arielle Crestol: Visualization, Methodology, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **Ann-Marie G. de Lange:** Methodology, Funding acquisition, Conceptualization, Writing – review & editing. **Louise Schindler:** Conceptualization, Writing – review & editing. **Sivaniya Subramaniapillai:** Funding acquisition, Conceptualization, Writing – review & editing. **Stener Nerland:** Conceptualization, Writing – review & editing. **Lars T. Westlye:** Funding acquisition, Conceptualization, Writing – review & editing. **Ole A. Andreassen:** Supervision, Conceptualization, Writing – review & editing. **Ingrid Agartz:** Supervision, Conceptualization, Writing – review & editing. **Christian K. Tamnes:** Supervision, Funding acquisition, Conceptualization, Writing – review & editing. **Claudia Barth:** Visualization, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization, Writing – review & editing, Writing – original draft. **Hannah Oppenheimer:** Writing – review & editing, Writing – original draft.

Data availability statement

The data that support the findings of this study are available through the UK Biobank application procedure (https://www.ukbiobank.ac.uk/enable-your-research/register); scripts are available from the authors upon request.

Acknowledgements

This research has been conducted using the UKB under Application 27412. UKB has received ethics approval from the National Health Service National Research Ethics Service (ref 11/NW/0382). The work was performed on the Service for Sensitive Data (TSD) platform, owned by the University of Oslo, operated, and developed by the TSD service group at the University of Oslo IT-Department (USIT).

Funding

While working on this study, the authors received funding from the Research Council of Norway [CKT: 223273, 288083, 323951; LTW: 223273, 249795, 273345, 298646, 300768; IA: 213700, 223273, 250358; OAA: 324499], the South-Eastern Norway Regional Health Authority [CB: 2023037, 2022103, CKT: 2021070, 2023012, 500189; LTW: 2018076, 2019101, IA: 2017097, 2019104, 2020020], the European Research Council under the European Union's Horizon 2020 research and innovation programme [LTW: 802998; OAA: 847776], the Swiss National Science Foundation [AMGdL: PZ00P3_193658; SS: TMPFP3_217174], and the Natural Sciences and Engineering Research Council of Canada [SS].

Conflict of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2024.105596.

References

Alfaro-Almagro, F., Jenkinson, M., Bangerter, N.K., Andersson, J.L.R., Griffanti, L., Douaud, G., Sotiropoulos, S.N., Jbabdi, S., Hernandez-Fernandez, M., Vallee, E., Vidaurre, D., Webster, M., McCarthy, P., Rorden, C., Daducci, A., Alexander, D.C., Zhang, H., Dragonu, I., Matthews, P.M., Miller, K.L., Smith, S.M., 2018. Image processing and quality control for the first 10,000 brain imaging datasets from UK biobank. Neuroimage 166, 400–424.

Ambikairajah, A., Tabatabaei-Jafari, H., Hornberger, M., Cherbuin, N., 2020. Age, menstruation history, and the brain. Menopause 28, 167–174.

Ambikairajah, A., Walsh, E., Cherbuin, N., 2022. A review of menopause nomenclature. Reprod. Health 19 (1), 29. https://doi.org/10.1186/s12978-022-01336-7.

Banack, H.R., Kaufman, J.S., Wactawski-Wende, J., Troen, B.R., Stovitz, S.D., 2019. Investigating and remediating selection Bias in geriatrics research: the selection Bias toolkit. J. Am. Geriatr. Soc. 67 (9), 1970–1976. https://doi.org/10.1111/jgs.16022.

Barth, C., Crestol, A., de Lange, A.-M.G., Galea, L.A.M., 2023. Sex steroids and the female brain across the lifespan: insights into risk of depression and Alzheimer's disease. The Lancet Diabetes & Endocrinology 11 (12), 926–941.

Barth, C., de Lange, A.G., 2020. Towards an understanding of women's brain aging: the immunology of pregnancy and menopause. Front. Neuroendocrinol. 58, 100850.

Basser, P.J., Mattiello, J., LeBihan, D., 1994. MR diffusion tensor spectroscopy and imaging. Biophys. J. 66, 259–267.

Beck, D., de Lange, A.G., Maximov, I.I., Richard, G., Andreassen, O.A., Nordvik, J.E., Westlye, L.T., 2021. White matter microstructure across the adult lifespan: a mixed longitudinal and cross-sectional study using advanced diffusion models and brain-age prediction. Neuroimage 224, 117441.

Beck, D., de Lange, A.G., Pedersen, M.L., Alnaes, D., Maximov, I.I., Voldsbekk, I., Richard, G., Sanders, A.M., Ulrichsen, K.M., Dorum, E.S., Kolskar, K.K., Hogestol, E. A., Steen, N.E., Djurovic, S., Andreassen, O.A., Nordvik, J.E., Kaufmann, T., Westlye, L.T., 2022. Cardiometabolic risk factors associated with brain age and accelerate brain ageing. Hum. Brain Mapp. 43, 700–720.

Brinton, R.D., Yao, J., Yin, F., Mack, W.J., Cadenas, E., 2015. Perimenopause as a neurological transition state. Nat. Rev. Endocrinol. 11, 393–405.

Bycroft, C., Freeman, C., Petkova, D., Band, G., Elliott, L.T., Sharp, K., Motyer, A., Vukcevic, D., Delaneau, O., O'Connell, J., Cortes, A., Welsh, S., Young, A., Effingham, M., McVean, G., Leslie, S., Allen, N., Donnelly, P., Marchini, J., 2018. The UK biobank resource with deep phenotyping and genomic data. Nature 562, 203–209.

C-Pillay, O., Manyonda, I., 2022. The surgical menopause. Best Pract. Res. Clin. Obstet. Gynaecol. 81, 111–118.

Caraci, F., Copani, A., Nicoletti, F., Drago, F., 2010. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. Eur. J. Pharmacol. 626, 64–71.

Codd, V., Denniff, M., Swinfield, C., Warner, S.C., Papakonstantinou, M., Sheth, S., Nanus, D.E., Budgeon, C.A., Musicha, C., Bountziouka, V., Wang, Q., Bramley, R., Allara, E., Kaptoge, S., Stoma, S., Jiang, T., Butterworth, A.S., Wood, A.M., Di Angelantonio, E., Thompson, J.R., Danesh, J.N., Nelson, C.P., Samani, N.J., 2022. Measurement and initial characterization of leukocyte telomere length in 474,074 participants in UK biobank. Nat Aging 2, 170–179.

Costantino, M., Pigeau, G., Parent, O., Ziolkowski, J., Devenyi, G.A., Gervais, N.J., Chakravarty, M.M., 2023. Menopause, brain anatomy. Cognition and Alzheimer's Disease. eLife 12. https://doi.org/10.7554/eLife.91038.1.

de Lange, A.G., Barth, C., Kaufmann, T., Maximov, I.I., van der Meer, D., Agartz, I., Westlye, L.T., 2020. Women's brain aging: effects of sex-hormone exposure, pregnancies, and genetic risk for Alzheimer's disease. Hum. Brain Mapp. 41, 5141–5150.

de Lange, A.G., Cole, J.H., 2020. Commentary: correction procedures in brain-age prediction. Neuroimage Clin 26, 102229.

de Lange, A.G., Kaufmann, T., van der Meer, D., Maglanoc, L.A., Alnaes, D., Moberget, T., Douaud, G., Andreassen, O.A., Westlye, L.T., 2019. Population-based neuroimaging reveals traces of childbirth in the maternal brain. Proc. Natl. Acad. Sci. USA 116, 22341–22346.

Dhillon, V.S., Deo, P., Chua, A., Thomas, P., Fenech, M., 2020. Shorter telomere length in carriers of APOE-epsilon4 and high plasma concentration of glucose, Glyoxal and other advanced glycation end products (AGEs). J. Gerontol. A Biol. Sci. Med. Sci. 75, 1894–1898.

Ding, F., Yao, J., Rettberg, J.R., Chen, S., Brinton, R.D., 2013. Early decline in glucose transport and metabolism precedes shift to ketogenic system in female aging and Alzheimer's mouse brain: implication for bioenergetic intervention. PLoS One 8, e79977.

Fani, L., Hilal, S., Sedaghat, S., Broer, L., Licher, S., Arp, P.P., van Meurs, J.B.J., Ikram, M.K., Ikram, M.A., 2020. Telomere length and the risk of Alzheimer's disease: the Rotterdam study. J. Alzheimers Dis. 73, 707–714.

Fieremans, E., Jensen, J.H., Helpern, J.A., 2011. White matter characterization with diffusional kurtosis imaging. Neuroimage 58, 177–188.

Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., van der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., Montillo, A., Makris, N., Rosen, B., Dale, A.M., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33, 341–355.

Freeman, E.W., Sammel, M.D., Boorman, D.W., Zhang, R., 2014. Longitudinal pattern of depressive symptoms around natural menopause. JAMA Psychiatry 71, 36–43.

Fry, A., Littlejohns, T.J., Sudlow, C., Doherty, N., Adamska, L., Sprosen, T., Collins, R., Allen, N.E., 2017. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am. J. Epidemiol. 186, 1026–1034.

Georgakis, M.K., Beskou-Kontou, T., Theodoridis, I., Skalkidou, A., Petridou, E.Th., 2019. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. Psychoneuroendocrinology 106, 9–19. https://doi.org/10.1016/j.psyneuen.2019.03.013.

Gervais, N.J., Gravelsins, L., Brown, A., Reuben, R., Karkaby, L., Baker-Sullivan, E., Mendoza, L., Lauzon, C., Almey, A., Foulkes, W.D., Bernardini, M.Q., Jacobson, M., Velsher, L., Rajah, M.N., Olsen, R.K., Grady, C., Einstein, G., 2022. Scene memory and hippocampal volume in middle-aged women with early hormone loss. Neurobiol. Aging 117, 97–106. https://doi.org/10.1016/j.neurobiolaging.2022.05.003.

Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., Smith, S.M., Van Essen, D. C., 2016. A multi-modal parcellation of human cerebral cortex. Nature 536, 171–178.

Golomb, B.A., Chan, V.T., Evans, M.A., Koperski, S., White, H.L., Criqui, M.H., 2012. The Older the Better: Are Elderly Study Participants More Non-representative? A cross-sectional analysis of clinical trial and observational study samples, BMJ Open, p. 2.

Gray, K.E., Schiff, M.A., Fitzpatrick, A.L., Kimura, M., Aviv, A., Starr, J.R., 2014. Leukocyte telomere length and age at menopause. Epidemiology 25, 139–146.

Green, R.C., Cupples, L.A., Kurz, A., Auerbach, S., Go, R., Sadovnick, D., Duara, R., Kukull, W.A., Chui, H., Edeki, T., Griffith, P.A., Friedland, R.P., Bachman, D., Farrer, L., 2003. Depression as a risk factor for Alzheimer disease: the MIRAGE study. Arch. Neurol. 60, 753–759.

Hall, J.E., 2015. Endocrinology of the menopause. Endocrinol. Metab. Clin. N. Am. 44, 485–496.

Han, L.K.M., Dinga, R., Hahn, T., Ching, C.R.K., Eyler, L.T., Aftanas, L., Aghajani, M., Aleman, A., Baune, B.T., Berger, K., Brak, I., Filho, G.B., Carballedo, A., Connolly, C. G., Couvy-Duchesne, B., Cullen, K.R., Dannlowski, U., Davey, C.G., Dima, D., Duran, F.L.S., Enneking, V., Filimonova, E., Frenzel, S., Frodl, T., Fu, C.H.Y., Godlewska, B.R., Gotlib, I.H., Grabe, H.J., Groenewold, N.A., Grotegerd, D., Gruber, O., Hall, G.B., Harrison, B.J., Hatton, S.N., Hermesdorf, M., Hickie, I.B., Ho, T.C., Hosten, N., Jansen, A., Kahler, C., Kircher, T., Klimes-Dougan, B., Kramer, B., Krug, A., Lagopoulos, J., Leenings, R., MacMaster, F.P., MacQueen, G., McIntosh, A., McLellan, Q., McMahon, K.L., Medland, S.E., Mueller, B.A., Mwangi, B., Osipov, E., Portella, M.J., Pozzi, E., Reneman, L., Repple, J., Rosa, P.G. P., Sacchet, M.D., Samann, P.G., Schnell, K., Schrantee, A., Simulionyte, E., Soares, J. C., Sommer, J., Stein, D.J., Steinstrater, O., Strike, L.T., Thomopoulos, S.I., van Tol, M.J., Veer, I.M., Vermeiren, R., Walter, H., van der Wee, N.J.A., van der Werff, S.J.A., Whalley, H., Winter, N.R., Wittfeld, K., Wright, M.J., Wu, M.J., Volzke, H., Yang, T.T., Zannias, V., de Zubicaray, G.I., Zunta-Soares, G.B., Abe, C., Alda, M., Andreassen, O.A., Boen, E., Bonnin, C.M., Canales-Rodriguez, E.J., Cannon, D., Caseras, X., Chaim-Avancini, T.M., Elvsashagen, T., Favre, P., Foley, S. F., Fullerton, J.M., Goikolea, J.M., Haarman, B.C.M., Hajek, T., Henry, C., Houenou, J., Howells, F.M., Ingvar, M., Kuplicki, R., Lafer, B., Landen, M., Machado-Vieira, R., Malt, U.F., McDonald, C., Mitchell, P.B., Nabulsi, L., Otaduy, M.C.G., Overs, B.J., Polosan, M., Pomarol-Clotet, E., Radua, J., Rive, M.M., Roberts, G., Ruhe, H.G., Salvador, Sarro, S., Satterthwaite, T.D., Savitz, J., Schene, A.H., Schofield, P.R., Serpa, M.H., Sim, K., Soeiro-de-Souza, M.G., Sutherland, A.N., Temmingh, H.S., Timmons, G.M., Uhlmann, A., Vieta, E., Wolf, D.H., Zanetti, M.V., Jahanshad, N., Thompson, P.M., Veltman, D.J., Penninx, B., Marquand, A.F., Cole, J. H., Schmaal, L., 2020. Brain aging in major depressive disorder: results from the ENIGMA major depressive disorder working group. Mol. Psychiatry. 26, 5124–5139.

Han, L.K.M., Dinga, R., Leenings, R., Hahn, T., Cole, J.H., Aftanas, L.I., Amod, A.R., Besteher, B., Colle, R., Corruble, E., Couvy-Duchesne, B., Danilenko, K.V., Fuentes-Claramonte, P., Gonul, A.S., Gotlib, I.H., Goya-Maldonado, R., Groenewold, N.A., Hamilton, P., Ichikawa, N., Ipser, J.C., Itai, E., Koopowitz, S.-M., Li, M., Okada, G., Okamoto, Y., Churikova, O.S., Osipov, E.A., Penninx, B.W.J.H., Pomarol-Clotet, E., Rodríguez-Cano, E., Sacchet, M.D., Shinzato, H., Sim, K., Stein, D.J., Uyar-Demir, A., Veltman, D.J., Schmaal, L., 2022. A large-scale ENIGMA multisite replication study of brain age in depression. Neuroimage: Reports 2, 100149.

Harlow, S.D., Gass, M., Hall, J.E., Lobo, R., Maki, P., Rebar, R.W., Sherman, S., Sluss, P. M., de Villiers, T.J., Group, S.C, 2012. Executive summary of the stages of reproductive aging workshop + 10: addressing the unfinished agenda of staging reproductive aging. J. Clin. Endocrinol. Metab. 97, 1159–1168.

Heller, C., Barth, C., Silk, T.J., Vijayakumar, N., Carmona, S., Martínez-García, M., Kikinis, Z., Thomopoulos, S.I., Jahanshad, N., Salminen, L., Lawrence, K., Thompson, P.M., Petersen, N., 2024. The Enigma-Neuroendocrinology Working Group to bridge gaps in female mental health research. Nat. Mental Health 2 (4), 348–350. https://doi.org/10.1038/s44220-024-00224-2.

Holland, D., Desikan, R.S., Dale, A.M., McEvoy, L.K., Alzheimer's Disease Neuroimaging, I., 2013. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. AJNR Am. J. Neuroradiol. 34, 2287–2293.

Howard, D.M., Adams, M.J., Shirali, M., Clarke, T.K., Marioni, R.E., Davies, G., Coleman, J.R.I., Alloza, C., Shen, X., Barbu, M.C., Wigmore, E.M., Gibson, J., andMe Research, T., Hagenaars, S.P., Lewis, C.M., Ward, J., Smith, D.J., Sullivan, P.F., Haley, C.S., Breen, G., Deary, I.J., McIntosh, A.M., 2018. Genome-wide association study of depression phenotypes in UK biobank identifies variants in excitatory synaptic pathways. Nat. Commun. 9, 1470.

Jacobs, E.G., Kroenke, C., Lin, J., Epel, E.S., Kenna, H.A., Blackburn, E.H., Rasgon, N.L., 2013. Accelerated cell aging in female APOE-epsilon4 carriers: implications for hormone therapy use. PLoS One 8, e54713.

Jensen, J.H., Helpern, J.A., Ramani, A., Lu, H., Kaczynski, K., 2005. Diffusional kurtosis imaging: the quantification of non-gaussian water diffusion by means of magnetic resonance imaging. Magn. Reson. Med. 53, 1432–1440.

Kaden, E., Kelm, N.D., Carson, R.P., Does, M.D., Alexander, D.C., 2016a. Multi-compartment microscopic diffusion imaging. Neuroimage 139, 346–359.

Kaden, E., Kruggel, F., Alexander, D.C., 2016b. Quantitative mapping of the per-axon diffusion coefficients in brain white matter. Magn. Reson. Med. 75, 1752–1763.

Kaufmann, T., van der Meer, D., Doan, N.T., Schwarz, E., Lund, M.J., Agartz, I., Alnaes, D., Barch, D.M., Baur-Streubel, R., Bertolino, A., Bettella, F., Beyer, M.K., Boen, E., Borgwardt, S., Brandt, C.L., Buitelaar, J., Celius, E.G., Cervenka, S., Conzelmann, A., Cordova-Palomera, A., Dale, A.M., de Quervain, D.J.F., Di Carlo, P., Djurovic, S., Dorum, E.S., Eisenacher, S., Elvsashagen, T., Espeseth, T., Fatouros-Bergman, H., Flyckt, L., Franke, B., Frei, O., Haatveit, B., Haberg, A.K., Harbo, H.F., Hartman, C.A., Heslenfeld, D., Hoekstra, P.J., Hogestol, E.A., Jernigan, T.L., Jonassen, R., Jonsson, E.G., Karolinska Schizophrenia, P., Kirsch, P., Kloszewska, I., Kolskar, K.K., Landro, N.I., Le Hellard, S., Lesch, K.P., Lovestone, S., Lundervold, A., Lundervold, A.J., Maglanoc, L.A., Malt, U.F., Mecocci, P., Melle, I., Meyer-Lindenberg, A., Moberget, T., Norbom, L.B., Nordvik, J.E., Nyberg, L., Oosterlaan, J., Papalino, M., Papassotiropoulos, A., Pauli, P., Pergola, G., Persson, K., Richard, G., Rokicki, J., Sanders, A.M., Selbaek, G., Shadrin, A.A., Smeland, O.B., Soininen, H., Sowa, P., Steen, V.M., Tsolaki, M., Ulrichsen, K.M., Vellas, B., Wang, L., Westman, E., Ziegler, G.C., Zink, M., Andreassen, O.A., Westlye, L.T., 2019. Common brain disorders are associated with heritable patterns of apparent aging of the brain. Nat. Neurosci. 22, 1617–1623.

King, K.S., Kozlitina, J., Rosenberg, R.N., Peshock, R.M., McColl, R.W., Garcia, C.K., 2014. Effect of leukocyte telomere length on total and regional brain volumes in a large population-based cohort. JAMA Neurol. 71, 1247–1254.

Lapham, K., Kvale, M.N., Lin, J., Connell, S., Croen, L.A., Dispensa, B.P., Fang, L., Hesselson, S., Hoffmann, T.J., Iribarren, C., Jorgenson, E., Kushi, L.H., Ludwig, D., Matsuguchi, T., McGuire, W.B., Miles, S., Quesenberry Jr., C.P., Rowell, S., Sadler, M., Sakoda, L.C., Smethurst, D., Somkin, C.P., Van Den Eeden, S.K., Walter, L., Whitmer, R.A., Kwok, P.Y., Risch, N., Schaefer, C., Blackburn, E.H., 2015. Automated assay of telomere length measurement and informatics for 100,000 subjects in the genetic epidemiology research on adult health and aging (GERA) cohort. Genetics 200, 1061–1072.

Lu, W., Sun, Y., Gao, H., Qiu, J., 2023. A review of multi-modal magnetic resonance imaging studies on perimenopausal brain: a hint towards neural heterogeneity. Eur. Radiol. 33, 5282–5297.

Lyall, D.M., Ward, J., Ritchie, S.J., Davies, G., Cullen, B., Celis, C., Bailey, M.E., Anderson, J., Evans, J., McKay, D.F., McIntosh, A.M., Sattar, N., Smith, D.J., Deary, I. J., Pell, J.P., 2016. Alzheimer disease genetic risk factor APOE e4 and cognitive abilities in 111,739 UK biobank participants. Age Ageing 45, 511–517.

Mauvais-Jarvis, F., Bairey Merz, N., Barnes, P.J., Brinton, R.D., Carrero, J.J., DeMeo, D. L., De Vries, G.J., Epperson, C.N., Govindan, R., Klein, S.L., Lonardo, A., Maki, P.M., McCullough, L.D., Regitz-Zagrosek, V., Regensteiner, J.G., Rubin, J.B., Sandberg, K., Suzuki, A., 2020. Sex and gender: modifiers of health, disease, and medicine. Lancet 396, 565–582.

Maximov, II, van der Meer, D., de Lange, A.G., Kaufmann, T., Shadrin, A., Frei, O., Wolfers, T., Westlye, L.T., 2021. Fast qualitY conTrol meThod foR derIved diffUsion metrics (YTTRIUM) in big data analysis: U.K. biobank 18,608 example. Hum. Brain Mapp. 42, 3141–3155.

Miller, K.L., Alfaro-Almagro, F., Bangerter, N.K., Thomas, D.L., Yacoub, E., Xu, J., Bartsch, A.J., Jbabdi, S., Sotiropoulos, S.N., Andersson, J.L., Griffanti, L., Douaud, G., Okell, T.W., Weale, P., Dragonu, I., Garratt, S., Hudson, S., Collins, R., Jenkinson, M., Matthews, P.M., Smith, S.M., 2016. Multimodal population brain

imaging in the UK biobank prospective epidemiological study. Nat. Neurosci. 19, 1523–1536.
Mori, S., Wakana, S., Van Zijl, P.C., Nagae-Poetscher, L., 2005. MRI Atlas of Human White Matter. Elsevier.
Mosconi, L., Berti, V., Dyke, J., Schelbaum, E., Jett, S., Loughlin, L., Jang, G., Rahman, A., Hristov, H., Pahlajani, S., Andrews, R., Matthews, D., Etingin, O., Ganzer, C., de Leon, M., Isaacson, R., Brinton, R.D., 2021. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. Sci. Rep. 11, 10867.
Mosconi, L., Berti, V., Quinn, C., McHugh, P., Petrongolo, G., Osorio, R.S., Connaughty, C., Pupi, A., Vallabhajosula, S., Isaacson, R.S., de Leon, M.J., Swerdlow, R.H., Brinton, R.D., 2017. Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. PLoS One 12, e0185926.
Parker, W.H., Jacoby, V., Shoupe, D., Rocca, W., 2009. Effect of bilateral oophorectomy on women's long-term health. Womens Health (Lond) 5, 565–576.
Phung, T.K., Waltoft, B.L., Laursen, T.M., Settnes, A., Kessing, L.V., Mortensen, P.B., Waldemar, G., 2010. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. Dement. Geriatr. Cogn. Disord. 30, 43–50.
Ridout, K.K., Ridout, S.J., Price, L.H., Sen, S., Tyrka, A.R., 2016. Depression and telomere length: A meta analysis. J. Affect. Disord. 191, 237–247.
Rocca, W.A., Grossardt, B.R., Geda, Y.E., Gostout, B.S., Bower, J.H., Maraganore, D.M., de Andrade, M., Melton 3rd, L.J., 2008. Long-term risk of depressive and anxiety symptoms after early bilateral oophorectomy. Menopause 15, 1050–1059.
Rosen, A.F.G., Roalf, D.R., Ruparel, K., Blake, J., Seelaus, K., Villa, L.P., Ciric, R., Cook, P. A., Davatzikos, C., Elliott, M.A., Garcia de La Garza, A., Gennatas, E.D., Quarmley, M., Schmitt, J.E., Shinohara, R.T., Tisdall, M.D., Craddock, R.C., Gur, R. E., Gur, R.C., Satterthwaite, T.D., 2018. Quantitative assessment of structural image quality. Neuroimage 169, 407–418.
Schindler, L.S., Subramaniapillai, S., Barth, C., van der Meer, D., Pedersen, M.L., Kaufmann, T., Maximov, I.I., Linge, J., Leinhard, O.D., Beck, D., Gurholt, T.P., Voldsbekk, I., Suri, S., Ebmeier, K.P., Draganski, B., Andreassen, O.A., de Lange, A.-M.G., 2022. Associations between Abdominal Adipose Tissue, Reproductive Span, and Brain Characteristics in Post-Menopausal Women. Clinical, NeuroImage, p. 103239.
Schuermans, A., Nakao, T., Uddin, M.M., Hornsby, W., Ganesh, S., Shadyab, A.H., Liu, S., Haring, B., Shufelt, C.L., Taub, M.A., Mathias, R.A., Kooperberg, C., Reiner, A.P., Bick, A.G., Manson, J.E., Natarajan, P., Honigberg, M.C., 2023. Age at menopause, leukocyte telomere length, and coronary artery disease in postmenopausal women. Circ. Res. 133, 376–386.
Sochocka, M., Karska, J., Pszczołowska, M., Ochnik, M., Fułek, M., Fułek, K., Kurpas, D., Chojdak-Łukasiewicz, J., Rosner-Tenerowicz, A., Leszek, J., 2023. Cognitive decline in early and premature menopause. Int. J. Mol. Sci. 24(7), Article 7 https://doi.org/10.3390/ijms24076566.
Steventon, J.J., Lancaster, T.M., Baker, E.S., Bracher-Smith, M., Escott-Price, V., Ruth, K. S., Davies, W., Caseras, X., Murphy, K., 2023. Menopause age, reproductive span and hormone therapy duration predict the volume of medial temporal lobe brain structures in postmenopausal women. Psychoneuroendocrinology 158, 106393. https://doi.org/10.1016/j.psyneuen.2023.106393.
Subramaniapillai, S., Suri, S., Barth, C., Maximov, I.I., Voldsbekk, I., van der Meer, D., Gurholt, T.P., Beck, D., Draganski, B., Andreassen, O.A., Ebmeier, K.P., Westlye, L.T., de Lange, A.G., 2022. Sex- and age-specific associations between cardiometabolic risk and white matter brain age in the UK biobank cohort. Hum. Brain Mapp. 43, 3759–3774.
Suzuki, S., Brown, C.M., Wise, P.M., 2006. Mechanisms of neuroprotection by estrogen. Endocrine 29, 209–215.
Taylor, C.M., Pritschet, L., Yu, S., Jacobs, E.G., 2019. Applying a Women's health Lens to the study of the aging brain. Front. Hum. Neurosci. 13, 224.
Than, S., Moran, C., Beare, R., Vincent, A.J., Collyer, T.A., Wang, W., Callisaya, M.L., Thomson, R., Phan, T.G., Fornito, A., Srikanth, V.K., 2021. Interactions between age, sex, menopause, and brain structure at midlife: a UK biobank study. J. Clin. Endocrinol. Metab. 106, 410–420.
Topiwala, A., Nichols, T.E., Williams, L.Z.J., Robinson, E.C., Alfaro-Almagro, F., Taschler, B., Wang, C., Nelson, C.P., Miller, K.L., Codd, V., Samani, N.J., Smith, S.M., 2023. Telomere length and brain imaging phenotypes in UK biobank. PLoS One 18, e0282363.
Ungar, L., Altmann, A., Greicius, M.D., 2014. Apolipoprotein E, gender, and Alzheimer's disease: an overlooked, but potent and promising interaction. Brain Imaging Behav. 8, 262–273.
Voldsbekk, I., Barth, C., Maximov, I.I., Kaufmann, T., Beck, D., Richard, G., Moberget, T., Westlye, L.T., de Lange, A.G., 2021. A history of previous childbirths is linked to women's white matter brain age in midlife and older age. Hum. Brain Mapp. 42, 4372–4386.
Wang, W.W., Liu, X.L., Ruan, Y., Wang, L., Bao, T.H., 2019. Depression was associated with apolipoprotein E ε4 allele polymorphism: a meta-analysis. Iran. J. Basic Med. Sci. 22, 112–117.
Wikgren, M., Maripuu, M., Karlsson, T., Nordfjall, K., Bergdahl, J., Hultdin, J., Del-Favero, J., Roos, G., Nilsson, L.G., Adolfsson, R., Norrback, K.F., 2012. Short telomeres in depression and the general population are associated with a hypocortisolemic state. Biol. Psychiatry 71, 294–300.
Wise, P.M., Suzuki, S., Brown, C.M., 2009. Estradiol: a hormone with diverse and contradictory neuroprotective actions. Dialogues Clin. Neurosci. 11, 297–303.
Yu, J., Mathi Kanchi, M., Rawtaer, I., Feng, L., Kumar, A.P., Kua, E.H., Mahendran, R., Alzheimer's Disease Neuroimaging, I., 2022. Differences between multimodal brain-age and chronological-age are linked to telomere shortening. Neurobiol. Aging 115, 60–69.