RESEARCH ARTICLE

Association of Reproductive History With Brain MRI Biomarkers of Dementia Risk in Midlife

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Abstract

Background and Objectives

To examine associations between indicators of estrogen exposure from women's reproductive history and brain MRI biomarkers of Alzheimer disease (AD) in midlife.

Methods

We evaluated 99 cognitively normal women 52 ± 6 years of age and 29 men 52 ± 7 years of age with reproductive history data, neuropsychological testing, and volumetric MRI scans. We used multiple regressions to examine associations among reproductive history indicators, voxel-wise gray matter volume (GMV), and memory and global cognition scores, adjusting for demographics and midlife health indicators. Exposure variables were menopause status, age at menarche, age at menopause, reproductive span, hysterectomy status, number of children and pregnancies, and use of menopause hormonal therapy (HT) and hormonal contraceptives (HC).

Results

All menopausal groups exhibited lower GMV in AD-vulnerable regions compared to men, with perimenopausal and postmenopausal groups also exhibiting lower GMV in temporal cortex compared to the premenopausal group. Reproductive span, number of children and pregnancies, and use of HT and HC were positively associated with GMV, chiefly in temporal cortex, frontal cortex, and precuneus, independent of age, *APOE* ε4 status, and midlife health indicators. Although reproductive history indicators were not directly associated with cognitive measures, GMV in temporal regions was positively associated with memory and global cognition scores.

Discussion

Reproductive history events signaling more estrogen exposure such as premenopausal status, longer reproductive span, higher number of children, and use of HT and HC were associated with larger GMV in women in midlife. Further studies are needed to elucidate sex-specific biological pathways through which reproductive history influences cognitive aging and AD risk.

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Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **CI** = confidence interval; **GM** = gray matter; **GMV** = gray matter volume; **HC** = hormonal contraceptive; **HT** = hormone therapy; **MTL** = medial temporal lobe; **TIV** = total intracranial volume; **TT** = testosterone therapy; **VOI** = volume of interest; **WCM** = Weill Cornell Medicine.

Recent studies identify female-specific reproductive history events as possible biological underpinnings of the higher prevalence of Alzheimer disease (AD) in women.[1,2] AD pathology begins in the 10- to 20-year presymptomatic phase,[3] proximate with the midlife menopause transition in women.[4-7] Preclinical evidence for neuroprotective effects of estrogens[8,9] also suggests a link between female fertility and AD.

However, the effects of estrogen exposure on AD risk remain unclear. In some studies, a longer reproductive span was associated with lower risk of dementia or cognitive decline in older postmenopausal women.[10-13] An earlier age at menarche[10] or a later age at menopause[10,12-14] was also associated with reduced risk of dementia or cognitive decline. The opposite effect has also been noted, with a longer reproductive span and an earlier age at menopause being associated with a higher dementia risk.[15] In another study, these negative associations were significant only among women carrying the *APOE* ε4 genotype,[16] the major genetic risk factor for late-onset AD.[17] In addition, other studies reported no associations between reproductive span,[12,18,19] age at menopause,[11,18,19] or age at menarche[11,15,16,18,19] and dementia risk. Number of children and number of pregnancies were also associated with a higher[14,18-20] or lower risk of dementia.[11] Furthermore, while observational studies generally indicate decreased dementia incidence with menopause hormone therapy (HT) use, clinical trials show increased dementia risk among older postmenopausal women or no effects.[21,22]

No brain imaging studies have evaluated the impact of reproductive health indicators on AD risk in midlife, when potential for preservation of cognitive function is greatest.

Herein we evaluate associations between reproductive history indicators and MRI-based gray matter (GM) volume (GMV), a well-established biomarker of neuronal aging and AD-related neurodegeneration,[23] in women in midlife at risk for AD and compared to age-controlled men.

Methods

Study Population

This observational cohort study focuses on cognitively normal women and men 40 to 65 years of age with risk factors for late-onset AD such as a family history and/or *APOE* ε4 genotype. Participants were recruited at Weill Cornell Medicine (WCM) between 2018 and 2021 by self-referral, flyers, and word of mouth, as described previously.[4-7] All participants received clinical, cognitive, laboratory, and brain MRI examinations within ≈3 months.

Exclusion criteria included medical conditions that may affect brain structure or function (e.g., stroke, head trauma, any neurodegenerative diseases, major psychiatric disorders, hydrocephalus, intracranial mass, and infarcts on MRI), use of psychoactive medications, and contraindications to MRI. Participants had Mini-Mental State Examination score of ≥26 and normal cognitive test performance by age and education.[4-7]

APOE genotype was determined with standard quantitative PCR procedures.[4-7] Participants carrying 1 or 2 copies of the *APOE* ε4 allele were grouped together as *APOE* ε4 carriers and compared to noncarriers.

Standard Protocol Approvals, Registrations, and Patient Consents

All participants provided written consent to participate in this WCM Institutional Review Board–approved study.

Data Availability

Deidentified data may be made available to qualified investigators from the WCM Institutional Review Board/Institutional Data Access on reasonable request.

Reproductive History Measures

We used questionnaires and semistructured interviews to collect information related to reproductive history from all participants, as detailed in eTable 1, links.lww.com/WNL/B612.

The following exposures were examined for all female participants:

- Menopausal status was examined as a categorical variable comparing premenopausal, perimenopausal, and postmenopausal groups, defined on the basis of the Stages of Reproductive Aging Workshop criteria[24] and laboratory hormone assessments.
- Menopause type was examined as a categorical variable comparing spontaneous and induced menopause groups (hysterectomy and/or oophorectomy before menopause).
- Age at menarche was examined as a continuous measure and after grouping responses into 2 categories: <13 and ≥13 years.[10]
- Number of children and number of pregnancies were examined as continuous measures and after grouping responses into 3 categories: 0 children, 1 child, and ≥2 children. We also collected information on age at firstborn (years).
- HT use was examined as a categorical variable comparing HT never users to past and current users. We also collected information on duration of use (years).

- Hormonal contraceptive (HC) use was examined as a categorical variable comparing never users to past and current users. We also collected information on duration of use (years).

The following exposures were examined for postmenopausal women only:

- Age at menopause was examined as a continuous measure and after grouping responses into 2 categories: <51 and ≥51 years.[10]
- Reproductive span, the difference between age at menopause and age at menarche, was examined as a continuous measure and after grouping responses into 2 categories: <39 and ≥39 years.[10]

The following exposures were examined for male participants:

- Andropause status was examined as a categorical variable comparing preandropause vs postandropause according to the Aging Males' Symptoms scale[25] and laboratory hormone assessments.
- Testosterone therapy (TT) use was examined as a categorical variable comparing TT never users to past and current users. We also collected information on duration of use (years).
- Number of children and age at firstborn were assessed with the same procedures as above.

Cognitive Scores

We focused on tests with known sensitivity to estrogen levels,[7,26] including verbal memory (Rey Auditory Verbal Learning Test and Wechsler Memory Scale logical memory delayed recall tests), executive function (Trail Making Test B and F-A-S), and language (object naming) tests. Our main outcome was a composite memory score obtained by first *z* scoring each memory measure and then averaging the 2 measures. We also obtained a global cognition score by first computing an executive function score (average of *z*-scored executive function tests) and a language score (*z*-scored language test) and then averaging across these domains and the memory domain.

Brain Imaging Acquisition and Analysis

All participants received 3-dimensional T1-weighted MRI scans (brain volume imaging; 1.0 × 1.0 × 1.0–mm resolution, 8.2-millisecond repetition time, 3.2-millisecond echo time, 25.6-cm field of view, 256 × 256 matrix) on a 3.0T GE Discovery MR750 scanner (GE Healthcare, Chicago, IL). Image analysis was performed with a fully automated image processing pipeline.[4-6] Briefly, for each participant, MRI scans were coregistered to each other using the normalized mutual information routine of Statistical Parametric Mapping (SPM12)[27] implemented in MatLab 7.8 and processed with voxel-based morphometry, including segmentation into GM, white matter, and CSF segments, Jacobian modulation to restore GMV using the unified segmentation algorithm, high-dimensional warping (DARTEL) of the segments, and application of an 8-mm full width at half-maximum smoothing kernel.[27] We also obtained total intracranial volume (TIV) as the sum of GM, white matter, and CSF partitions.

Covariates

GMV analyses were adjusted by age and TIV, and cognitive analyses were adjusted by age. For exposures showing significant associations with outcome measures, we examined additional confounders, including *APOE* ε4 status (carrier vs noncarrier) and midlife health indicators: self-reported smoking status (current, past, or never smoker), waist-to-hip ratios, and hypertension diagnosis (as determined by our physicians using systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medications). Last, we examined exposure-specific confounders, including (1) hysterectomy status and HT use in analysis of menopausal status and reproductive span; (2) age at firstborn in analysis of number of children; (3) hysterectomy status and duration of use in analysis of HT effects; and (4) duration of use in analysis of HC effects. Analyses of menopausal status, age at menopause, and duration of reproductive span were repeated after the exclusion of participants with hysterectomy.

Statistical Analysis

Analyses were performed in Stata/MP version 15.1 (StataCorp, College Station, TX), SPSS version 25 (SPSS Inc, Chicago, IL), and SPM12. We used multiple linear regressions to examine associations between exposures (menopausal status, age at menarche, age at menopause, reproductive span, hysterectomy status, number of children, HT and HC use) and outcomes (GMV, memory and global cognition scores), including the covariates listed above. For the male cohort, analysis focused on associations between number of children and outcomes. We also tested for differences between each menopausal group and the male group.

For cognitive scores, results were examined using general linear models at $p < 0.05$, corrected for multiple comparisons. For SPM12 analysis, we used a series of voxel-based general linear models with post hoc *t* contrasts to test for associations between each exposure variable and GMV and to compare each menopause group to the male group. Statistical maps of main effects and post hoc comparisons were conservatively obtained by first applying an a priori masking image including a set of AD-vulnerable regions and then a cluster-level small-volume correction for multiple comparisons at $p < 0.05$. The masking image was generated with the Automated Anatomical Labeling atlas and comprised inferior, middle, and superior temporal gyrus; medial temporal lobe (MTL; including hippocampus, amygdala, entorhinal cortex, and parahippocampal gyrus); posterior cingulate cortex; precuneus; fusiform gyrus; inferior, middle, and superior frontal cortex; inferior and superior parietal lobule; and basal ganglia.[4,7,23] In addition, results were examined after application of an a priori GM mask to restrict analysis to GM-only voxels. Anatomic location of

significant clusters was described with Montreal Neurological Institute coordinates. GMV expressed in units of GM density was extracted using volumes of interest (VOIs) at the peak of cluster significance for further analysis using Marsbar 0.44.

Sensitivity Analysis

There is evidence that voxel-based analysis is effective for larger cortical regions but may underestimate effects in MTL,[28] a region with higher anatomical specificity for cognitive aging and AD.[23] Therefore, we performed a sensitivity analysis to test for associations between reproductive history exposures and MTL GMV as an a priori selected region using the VOI approach. We extracted and averaged GMV from MTL clusters identified in analysis of menopause status vs men, and we examined this measure as an additional MRI outcome using multiple regressions, adjusting by the same covariates as above.

We also examined associations between regional GMV extracted from the peak association clusters for each exposure, as well as from MTL, and cognitive measures. All results were considered significant at $p < 0.05$.

Results

Participants

A total of 137 participants, including 106 women and 31 men, were enrolled. Of these, 9 were excluded because of incidental findings on MRI (n = 5), artifacts on MRI (n = 1), or missing reproductive history reports (n = 3). The remaining 128 participants, including 99 women and 29 men, were examined in this study. As shown in Table 1, there were no differences between men and women in clinical or cognitive data (memory $p = 0.456$, global cognition $p = 0.764$).

All women provided information about menopausal status, hysterectomy status, and HT use. The cohort included 15 premenopausal, 35 perimenopausal, and 49 postmenopausal women. Thirteen participants reported having had a hysterectomy/oophorectomy. Participants were 27% current HT users, 4% past users, and 69% never users. All HT users except 7 provided information on duration of use, which averaged 5 ± 4 years.

One participant did not provide information on HC use. The remaining 98 participants included 9% current HC users, 53% past users, and 38% never users. All HC users except 8 provided information on duration of use, which averaged 13 ± 8 years.

Eleven participants did not provide information on age at menarche. The remaining 88 participants were included in analyses of age at menarche. Of the 49 postmenopausal participants, 1 did not provide information on age at menarche, and 1 did not provide information about age at menopause. The remaining 47 postmenopausal participants with complete information were included in analyses of reproductive span.

Three participants did not provide information on number of children. Of the remaining 96 participants, 21% had no children, 17% had 1 child, and 62% had ≥2 children.

As shown in Table 1, among men, 1 participant had laboratory findings consistent with andropause and reported taking TT, and another who was not in andropause reported taking TT in the past. Thus, we were unable to test for effects of andropause or TT on outcomes. Among men, 21% had no children, 7% had 1 child, and 72% had ≥2 children, comparable to the female group.

Reproductive History Indicators and Brain Biomarkers

Menopause Status

Negative associations between menopause status and GMV were observed in inferior temporal gyrus ($p = 0.049$) and borderline negative associations were seen in inferior frontal gyrus ($p = 0.059$) in the right hemisphere (Figure 1A and eTable 2, links.lww.com/WNL/B612). On post hoc analysis, the perimenopausal and postmenopausal groups had smaller GMV in these regions compared to the premenopausal group ($p \leq 0.033$; Table 2 and Figure 1B). Results remained significant after controlling for hysterectomy status and HT use and after excluding hysterectomized participants ($p < 0.05$; Figure 1C).

As shown in Figure 1D, the postmenopausal and perimenopausal groups, and to a lesser extent the premenopausal group, exhibited lower GMV in MTL (including amygdala, hippocampus, parahippocampal gyrus, and entorhinal cortex), fusiform gyrus, and basal ganglia compared to men ($p < 0.05$; eTable 2, links.lww.com/WNL/B612). In addition, the perimenopausal and postmenopausal groups exhibited lower GMV than men in precuneus, frontal, and temporal regions ($p < 0.05$; Figure 1D and eTable 2).

Hysterectomy Status

There were no significant associations between hysterectomy status and GMV in any region.

Age at Menarche

There were no significant associations between age at menarche and GMV in any region.

Age at Menopause

There were no significant associations between age at menopause and GMV in any region.

Reproductive Lifespan

Positive associations between reproductive span and GMV were observed in a cluster encompassing superior parietal lobule and precuneus of the left hemisphere (cluster extent 129 voxels, x = −12, y = −61, z = 71, $z = 2.92$, corrected $p = 0.025$; Figure 2, A and B). Results remained significant after controlling for hysterectomy status and HT use and after excluding hysterectomized participants (Figure 2C).

Table 1 Participants' Characteristics

	Women	Men
No.	99	29
Age (SD), range, y	52 (6), 40–65	52 (7), 40–65
***APOE* ε4 status, % positive**	47	47
Ethnicity, %		
White	80	76
Asian	6	10
Black/African American	6	3
Hispanic	4	7
Mixed	6	4
Education, y	17 (2)	18 (2)
Smoking status, %		
Never smoker	80	72
Past smoker	18	8
Current smoker	2	0
Hypertension, %	7	20
Waist to hip ratio	0.85 (0.12)	0.95 (0.05)
Menopause status, % postmenopausal	50	NA
Hysterectomy status, % positive		NA
Full hysterectomy	6	
Partial hysterectomy	6	
Oophorectomy only	1	
Age at menarche (SD), range (n = 88), y	13 (1), 10–16	NA
Age at menopause (SD), range, y		NA
Entire cohort (n = 48)	51 (3), 40–58	
Nonhysterectomized participants (n = 38)	52 (3), 47–58	
Reproductive span (SD), range, y		NA
Entire cohort (n = 47)	39 (4), 28–47	
Nonhysterectomized participants (n = 37)	39 (3), 33–47	
No. of children, % (n = 96)		
0	21	21
1	17	7
2	35	45
≥3	27	27
HT status, %[a]		
Never user	69	94
Past user	4	3
Current user	27	3
HC status (n = 98), %		NA
Never user	38	
Past user	53	
Current user	9	
Cognitive measures, mean (SEM)		
Memory scores	0.03 (0.08)	−0.10 (0.15)
Global cognition scores	−0.01 (0.06)	−0.06 (0.12)

Abbreviations: HC = hormonal contraceptive; HT = hormonal therapy; NA = not applicable.
Values are means (SD) unless otherwise specified. In presence of missing data, the sample size is indicated in parentheses.
[a] Menopause HT for women and testosterone therapy for men.

For every 1-year increase in reproductive span, GMV increased by 0.01 units (95% confidence interval [CI], 0.00–0.01, p = 0.006; Table 2). Using dichotomized values and adjusting by age and TIV showed that a reproductive span ≥39 years was associated with 0.05-unit-larger GMV (95% CI 0.01–0.09) relative to a reproductive span <39 years (p = 0.013; Table 2).

We descriptively examined age at menarche and age at menopause for associations with GMV extracted from the superior parietal and precuneus cluster. Only age at menopause showed significant effects on GMV in the entire postmenopausal sample (p = 0.009) and among nonhysterectomized participants (p = 0.013; eFigure 1).

Number of Children and Pregnancies

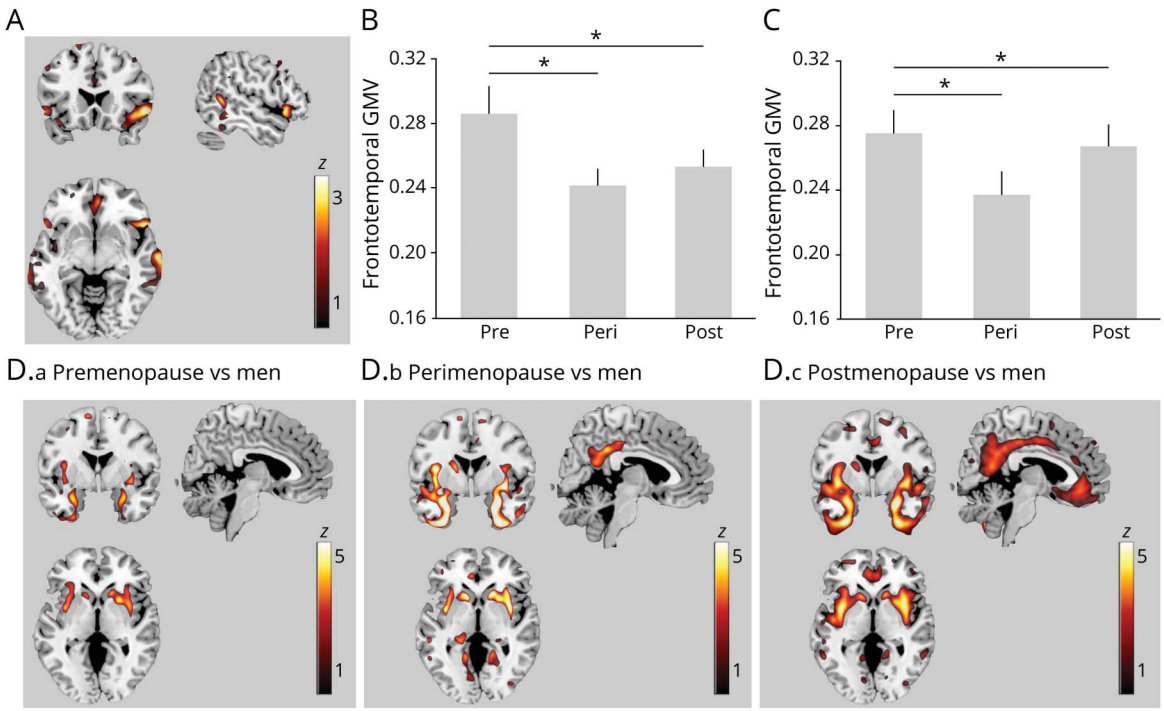
In women, number of children was positively associated with GMV in inferior and middle frontal gyri and middle and inferior temporal gyri ($p \leq 0.021$; Figure 3A and eTable 3, links.lww.com/WNL/B612). In these regions, for every 1-unit increase in number of children, GMV increased by 0.02 units (95% CI 0.01–0.03, $p \leq 0.001$; Table 2 and Figure 3B). Number of pregnancies was also positively associated with GMV in middle temporal gyri ($p < 0.05$; Table 2). Results remained significant after controlling for age at firstborn. On post hoc analysis, having ≥2 children was associated with larger GMV in the above frontal and temporal regions compared to having no children ($p \leq 0.012$), whereas no differences were found between the uniparous and nulliparous groups (Table 2).

Among men, there were no significant associations between number of children and GMV. Assessing results at a more liberal $p < 0.001$, uncorrected, did not yield significant results.

HT

Positive associations between HT use and GMV were observed in superior frontal gyrus and supramarginal gyrus bilaterally; middle temporal gyrus and frontal pole of the right

Figure 1 Associations Between Menopause Status and GMV



(A) Statistical parametric maps (SPMs) showing negative associations between menopause status and regional gray matter (GM) volume (GMV), adjusted for age and total intracranial volume (TIV). Anatomic location and statistics are reported in eTable 2, links.lww.com/WNL/B612. (B) Plots representing age- and TIV-adjusted mean (±SEM) GMV extracted at the peak of statistical significance, expressed in units of GM density, comparing premenopausal (PRE), perimenopausal (PERI), and postmenopausal (POST) groups in the entire cohort. (C) Plots representing GMV by menopause status among nonhysterectomized participants. (D.a-D.c) SPMs showing GMV differences between each menopausal group and men, adjusted by age and TIV. Anatomic location and statistics are reported in eTable 2. SPMs are superimposed on a standardized MRI and represented on a color-coded scale with corresponding *z* score values. *Significant at $p < 0.05$.

hemisphere; and inferior temporal gyrus, fusiform gyrus, and medial frontal gyrus of the left hemisphere ($p \leq 0.015$; Figure 4A and eTable 4, links.lww.com/WNL/B612). In these regions, HT users had larger GMV compared to never users ($p = 0.001$; Table 2 and Figure 4B). Results remained significant after adjusting by duration of HT use and after excluding hysterectomized participants (Figure 4B).

Hormonal Contraceptives

Positive associations between HC use and GMV were observed in precuneus, fusiform gyrus, superior parietal lobule, angular gyrus, and inferior frontal gyrus of the left hemisphere and in fusiform gyrus of the right hemisphere ($p \leq 0.005$; Figure 4C and eTable 4, links.lww.com/WNL/B612). Results remained significant after adjusting by duration of HC use as a covariate. In these regions, past and present users had larger GMV than never users ($p < 0.001$; Table 2 and Figure 4D).

Because both HT and HC were positively associated with GMV, we tested for interaction effects of these exposures on GMV at the peak of significance for each contrast: precuneus for HC and superior frontal gyrus for HT. Although the interaction term did not reach significance, participants reporting use of both HC and HT (n = 19) showed larger GMV than HC and HT never users (n = 26) in both regions (12% and 22%, respectively, $p \leq 0.027$; eFigure 2, links.lww.com/WNL/B612).

Reproductive History Indicators and Cognition

There were no significant associations between reproductive history indicators and memory or global cognition scores in women or men (Table 3).

Sensitivity Analysis

Associations Between Reproductive History Indicators and MTL GMV

With the VOI approach, in women, MTL GMV was negatively associated with menopause status ($p \leq 0.041$) and positively associated with HC use ($p = 0.017$) and number of children ($p = 0.026$; eTable 5, links.lww.com/WNL/B612). For every 1-unit increase in number of children, MTL GMV increased by 0.01 unit (95% CI 0.00–0.01), which was driven by having ≥2 children compared to having no children ($p = 0.028$; eTable 5). In men, there were no significant associations between number of children and MTL GMV ($p = 0.875$).

Associations Between Regional GMV and Cognition

As shown in eTable 6, links.lww.com/WNL/B612, inferior temporal and MTL GMVs were positively associated with

Table 2 Associations Between Female Reproductive History Indicators and GMV

	Model 1				Model 2			
	Coefficient	95% CI	*p* Value	R^2 value	Coefficient	95% CI	*p* Value	R^2 value
Menopause status								
Premenopause	Ref			0.315	Ref			0.339
Perimenopause	−0.04	−0.07, 0.02	0.033		−0.06	−0.09, −0.02	0.006	
Postmenopause	−0.06	−0.11, −0.01	0.014		−0.08	−0.13, −0.03	0.003	
Reproductive span								
Numeric	0.01	0.00, 0.01	0.006	0.174	0.01	0.00, 0.01	0.041	0.304
<39 y	Ref			0.146	Ref			0.296
≥39 y	0.05	0.01, 0.09	0.013		0.04	0.00, 0.08	0.051	
No. of children								
Numeric	0.02	0.01, 0.03	<0.001	0.358	0.03	0.01, 0.04	<0.001	0.413
0	Ref			0.342	Ref			0.380
1	0.00	−0.04, 0.04	0.873		0.00	−0.04, 0.05	0.940	
≥2	0.04	0.01, 0.07	0.012		0.05	0.02, 0.09	0.003	
No. of pregnancies	0.01	0.00, 0.02	0.028	0.298	0.01	0.00, 0.02	0.018	0.323
HT use	0.05	0.02, 0.08	0.001	0.200	0.05	0.02, 0.08	0.003	0.214
HC use	0.06	0.03, 0.09	<0.001	0.317	0.06	0.03, 0.09	<0.001	0.278

Abbreviations: CI = confidence interval; GMV = gray matter volume; HC = hormonal contraceptives; HT = menopause hormone therapy; Ref = referent. Model 1: adjusted for age and intracranial volume; model 2: adjusted for age, intracranial volume, *APOE* ε4 status, and midlife health variables. GMV measures are extracted from the peak association cluster for each exposure, e.g., inferior temporal gyrus for menopause status, precuneus for reproductive span and HC use, inferior frontal gyrus for number of children, and superior frontal gyrus for HT use (eTables 2–4, links.lww.com/WNL/B612).

memory scores ($p \leq 0.034$). MTL GMV was also positively associated with global cognition scores ($p = 0.018$).

Discussion

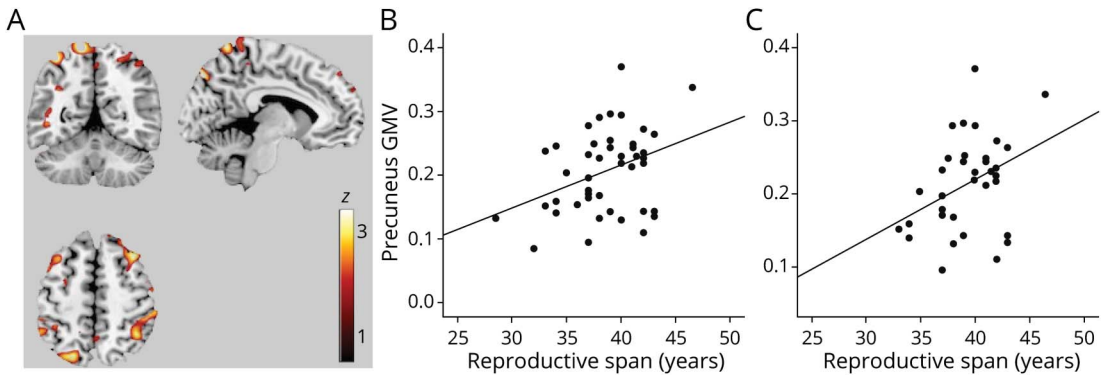
In a cohort of well-characterized midlife women at risk for AD, with the use of voxel-based morphometry and VOI analysis, some reproductive history indicators signaling longer estrogen exposure were associated with larger MRI-derived GMV in brain regions vulnerable to cognitive aging and AD. These indicators included premenopausal status, a longer reproductive span, higher number of children and pregnancies, and use of HT and HC. Results were independent of age, *APOE* ε4 status, midlife health indicators, and exposure-specific confounders.

These results are in line with preclinical work indicating neuroprotective effects of estrogen in women[8,9] and provide neurophysiologic correlates to epidemiologic evidence of associations between indices of prolonged estrogen exposure and lower risk of dementia or cognitive decline.[10-13]

Multiple lines of work identify endocrine aging as a driver of brain aging and AD risk in women,[2,8,9] with menopause marking a dramatic decline in estrogen production along with onset of multiple physical and cognitive symptoms quite distinct from the gradual tapering of testosterone in male andropause.[8,9] Estrogen, especially 17β-estradiol, has been shown to promote neuronal resilience by reducing inflammation, tau hyperphosphorylation, and β-amyloid (Aβ)–induced neurotoxicity, whereas estrogen deprivation after menopause has been linked to increased neuronal aging and AD risk.[8,9] We previously reported that women undergoing the menopause transition exhibit reduced GMV, as well as brain hypometabolism and higher Aβ burden, compared to premenopausal women and to age-controlled men.[4-7] Present findings confirm associations between the menopause transition and presence of lower GMV in cortical and subcortical regions vulnerable to aging and AD, and expand on prior work by identifying reproductive history factors that are positively associated with GMV, and may thus offset the impact of menopause on brain aging.

Among endogenous exposures, a longer reproductive span was associated with larger superior parietal and precuneus GMV independent of age, hysterectomy status, and HT use. A later age at menopause also correlated with GMV in these regions, whereas age at menarche did not. These data are

Figure 2 Associations Between Reproductive Span and GMV

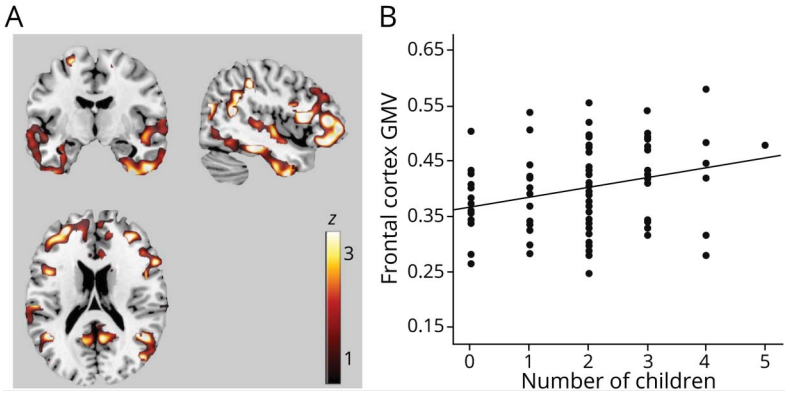


(A) Statistical parametric maps (SPMs) showing positive associations between reproductive span years and regional gray matter volume (GMV) at $p < 0.05$, cluster level corrected, adjusted for age and total intracranial volume. SPMs are superimposed on a standardized MRI and represented on a color-coded scale with corresponding *z* score values. (B) Plots depicting correlations between reproductive years and GMV extracted at the peak of statistical significance in the entire cohort and (C) among nonhysterectomized participants.

consistent with prior work demonstrating positive associations between reproductive span, especially in the presence of older age at menopause, and risk of dementia or cognitive decline.[10-13] However, other studies reported increased dementia risk with longer reproductive spans and older age at menopause[15,16] or no associations.[12,18] Negative studies generally focused on older postmenopausal women,[15,16] excluded those with hysterectomy/oophorectomy,[15,16] and in some cases did not assess HT or HC exposure[16] or reported effects only in *APOE* ε4 carriers,[16] which could account for the mixed findings. Our study differs from these reports in 3 main respects: it focuses on midlife women, includes information on all relevant variables, and uses neuroimaging measures instead of dementia incidence as the primary endpoint. The presymptomatic phase of AD corresponds with midlife years,[3] during which estrogen levels in women begin to decline. Because estrogen exposures occur before or concomitant with menopause, our approach enables closer examination of the impact of reproductive factors on the brain while avoiding possible effects of attrition, recall, and survival bias. In fact, our results are consistent with epidemiologic studies examining younger women with a narrower window of age at menopause.[10,11]

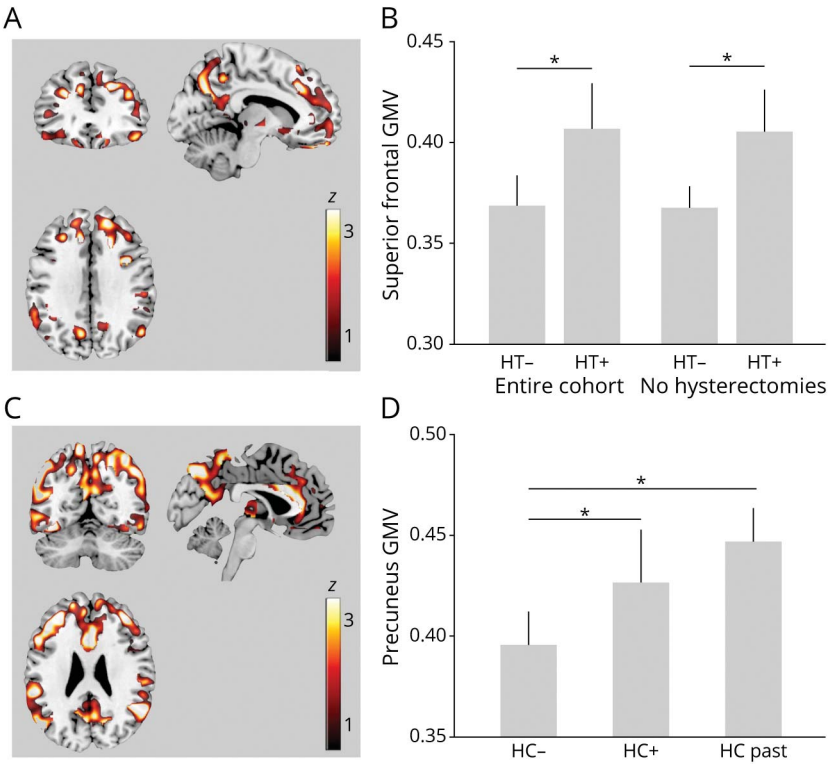
Number of children and number of pregnancies were also associated with larger GMV in frontal and temporal regions of midlife women, whereas no associations were observed among men. This is consistent with epidemiologic reports indicating a lower risk of cognitive decline or AD for older parous compared to nulliparous women,[11,29] although results are mixed.[14,19,20] The largest epidemiologic study to date showed no long-term influence of pregnancy history on age-related cognitive function.[30] Contrasting results between imaging and clinical studies might be in part due to the timing of the observations; the effects of motherhood on the brain are likely more discernible in midlife, thus closer in time to childbirth, than in older age or at postmortem. Imaging studies of new mothers have consistently reported beneficial effects of pregnancy and childbirth on brain structure and function.[31] Pregnancy entails higher levels of estrogens, which may have beneficial effects in terms of cumulative estrogen

Figure 3 Associations Between Number of Children and GMV



(A) Statistical parametric maps (SPMs) showing positive associations between number of children and regional gray matter volume (GMV) at $p < 0.05$, cluster level corrected, adjusted for age and total intracranial volume. SPMs are superimposed on a standardized MRI and represented on a color-coded scale with corresponding *z* score values. Anatomic location and statistics are reported in eTable 3, links.lww.com/WNL/B612. See legend for Figure 1B for plots depicting associations between number of children and GMV.

Figure 4 Associations Between Exogenous Estrogen Exposures and GMV



Statistical parametric maps (SPMs) showing positive associations between (A) menopause hormonal therapy (HT) and gray matter volume (GMV) and (C) hormonal contraceptive (HC) use and GMV, at $p < 0.05$, cluster level corrected, adjusted for age and total intracranial volume (TIV). SPMs are superimposed on a standardized MRI and represented on a color-coded scale with corresponding z score values. Anatomic location and statistics are reported in eTable 4, links.lww.com/WNL/B612. Plots representing age- and TIV-adjusted mean (+SEM) GMV extracted at the peak of statistical significance, comparing (B) HT users (HT+) and never users (HT−) in the entire cohort and among nonhysterectomized participants and (D) HC current users (HC+), past users (HC-past), and never users (HC−). *$p < 0.05$.

exposure throughout a woman's life. While circulating estrogen concentrations tend to be lower in parous compared to nulliparous women,[20] parity seems to render the brain more responsive to estrogen later in life,[32] which might contribute to favorable brain aging trajectories.

For exogeneous estrogen exposures, we observed positive effects of both HT and HC on GMV in several regions. This finding is consistent with observational studies reporting a protective effect of HT on cognitive aging and AD risk,[33-35] especially among younger (50-59 years) women,[36] and with neuroimaging studies indicating enhancing effects of HT on brain structure and function.[37] On the other hand, clinical trials reported increased dementia risk among postmenopausal women ≥65 years of age treated with estrogen-plus-progestin HT[38] and no effects with estrogen-alone HT,[39] while recent studies of early postmenopausal women showed no effects of HT on cognition.[40,41] Currently, the efficacy of HT is thought to depend on timing of treatment with respect to age at menopause, with benefits pertaining to early initiation.[21,22] Our findings that HT use in midlife is associated with larger GMV support evidence that HT near the time of menopause, as opposed to later in life, may support brain aging.

Positive effects of HC use on GMV are consistent with imaging observations that HC users in their 20s exhibited larger regional GMV compared to nonusers in some of the same cortical regions identified in the present study.[42-44] However, the long-term effects of HC on brain and cognition have seldom been investigated. To the best of our knowledge, the only study that looked at HC in relation to AD risk reported no associations between HC use and incidence of dementia.[15] Because HC use typically ends with menopause, it is possible that its effects wane after the end of exposure. Nonetheless, in our cohort, middle-aged women who took HC during their reproductive years and later took HT for menopause had larger regional GMV compared to never users of both, which warrants further investigation.

While reproductive history indicators were not directly associated with cognitive performance, GMV in temporal clusters positively correlated with memory and global cognition, suggesting possible mediation effects. In fact, while self-reports of poor memory and concentration are common in women undergoing the menopause transition,[45] menopause itself has not been associated with functional impairment or deficits on cognitive testing.[21,22,26] It is possible that the protective reproductive history factors identified here may offset the neurologic effects of the menopause transition and help explain the lack of cognitive impairment after menopause.[26] Nonetheless, while we focused on cognitive tests known to be sensitive to estrogen changes, it is possible that different tests might yield different results. Because our sample was highly educated, results may not apply to women of diverse educational status. Longitudinal studies are warranted

Table 3 Associations Between Reproductive History Indicators and Cognition

	Memory				Global cognition			
	Coefficient	95% CI	*p* Value	R^2 value	Coefficient	95% CI	*p* Value	R^2 value
Menopause status								
Premenopause	Ref			0.042	Ref			0.031
Perimenopause	−0.12	−0.67, 0.42	0.815		−0.15	− 0.49, 0.19	0.697	
Postmenopause	0.13	−0.60, 0.86	0.820		−0.23	− 0.71, 0.25	0.697	
Age at menarche								
Numeric	0.01	−0.12, 0.14	0.918	0.022	0.02	− 0.07, 0.10	0.803	0.032
<13 y	Ref			0.022	Ref			0.032
≥13 y	−0.02	− 0.38, 0.34	0.918		0.04	− 0.18, 0.26	0.803	
Age at menopause								
Numeric	−0.06	−0.13, 0.02	0.264	0.101	−0.05	− 0.10, 0.02	0.275	0.088
<51 y	Ref			0.082	Ref			0.117
≥51 y	−0.39	−0.90, 0.12	0.264		−0.38	−0.72, 0.04	0.261	
Reproductive span								
Numeric	−0.07	−0.14, 0.01	0.261	0.101	−0.06	−0.11, −0.02	0.198	0.158
<39 y	Ref			0.098	Ref			0.091
≥39 y	−0.42	−0.91, 0.06	0.261		−0.32	−0.65, 0.01	0.275	
Hysterectomy status	−0.12	−0.63, 0.40	0.815	0.033	−0.08	−0.42, 0.26	0.803	0.025
HT use	−0.22	−0.60, 0.16	0.452	0.044	−0.12	−0.36, 0.12	0.697	0.031
HC use	0.31	−0.04, 0.66	0.261	0.064	0.09	−0.13, 0.3	0.697	0.027
No. of pregnancies	0.09	0.01, 0.18	0.210	0.072	0.04	−0.02, 0.09	0.580	0.025
No. of children (women)								
Numeric	0.11	−0.03, 0.25	0.338	0.050	0.02	−0.07, 0.11	0.803	0.003
0	Ref			0.095				0.009
1	0.585	0.04, 1.13	0.210		0.098	−0.25, 0.45	0.803	
≥2	0.540	0.12, 0.96	0.210		0.127	−0.15, 0.41	0.697	
No. of children (men)								
Numeric	−0.06	−0.34, 0.22	0.815	0.012	0.00	−0.19, 0.19	0.976	0.012
0	Ref			0.044	Ref			0.057
1	−0.687	−2.08, 0.71	0.524		−0.48	−1.41, 0.47	0.697	
≥2	−0.162	−0.96, 0.64	0.815		−0.07	−0.61, 0.48	0.845	

Abbreviations: CI = confidence interval; HC = hormonal contraceptives; HT = menopause hormone therapy; Ref = referent.
Results are adjusted by age.

to assess whether brain and cognitive aging trajectories differ as a function of reproductive history and AD predisposition.

This study has multiple strengths. First, we examined several reproductive history indicators, which independently and in combination may serve as proxies for estrogen exposures that occur throughout the life course. Second, we examined a large sample of well-characterized middle-aged women with simultaneous brain MRI scans, cognitive assessments, and health , including medical history and *APOE* ε4 status for all participants. In addition, we collected data on HT and HC, including duration of use, and number of pregnancies and

children, with a male comparison group, and age at first birth. Another strength is the multivariable approach, which enabled examination of the confounding and interacting roles of different exposures on outcome measures.

We were unable to assess the accuracy of self-reported age at menarche. While prior work has shown moderate to high correlations between repeated measures of self-reported age at menarche,[46] more work is needed to confirm lack of associations between age at menarche and GMV. We are confident about the accuracy of self-reported age at menopause because the majority of our postmenopausal participants were within 10 years of their menopause diagnosis, which was clinician-confirmed in many cases.

Prior work indicates that induced menopause influences dementia risk, especially that due to bilateral oophorectomy, with younger age associated with greater risk of dementia and higher neuropathology burden.[47,48] Because only 7% of our participants had oophorectomies, we were likely underpowered to detect significant effects. While we included only participants who had surgery before menopause, we did not have precise information on the timing of surgery, which may also lead to underestimation of possible associations.

MRI-derived GMV measures are sensitive to neuronal aging and to early AD-related neurodegeneration.[23] However, because these measures are not specific to AD, caution is required in interpreting these results as related to AD risk. Longitudinal studies and analysis of Aβ and tau markers are needed to examine the predictive value of the observed associations. In addition, more work is needed to elucidate the biological pathways by which different estrogen-associated processes affect brain aging and AD risk and to test for anatomic interactions among exposures' effects.

Because all our participants were cognitively normal and 40 to 65 years of age, few would have had substantial neuropathologic burden,[3] making this cohort an ideal population for identification of early risk markers and testing of preventive strategies. It is important to note that some of the reproductive factors showing associations with GMV are potentially modifiable, and targeted risk factor modification has shown promise in real-world clinical settings.[49] For example, while age at menopause is in part genetically linked, lifestyle and environmental factors also play a role.[45]

We caution that the present results were found in healthy, well-educated, carefully screened research participants, including mostly White people of generally middle/high socioeconomic status, which limits the generalizability of our findings. No studies have yet been conducted to investigate reproductive history effects on AD biomarkers based on ethnicity. Clinical evidence of higher frequency and severity of menopausal symptoms in Black and Hispanic women[50] strongly argues for examination of outcomes across ethnic groups. Another limitation is our inability to generalize to gender-diverse patient populations and to those taking gender-affirming HT.

Overall, our brain imaging findings identify reproductive history events associated with GMV vulnerability (the menopause transition) and resilience (longer reproductive span, number of children, HT and HC use) in midlife women. Understanding sex-specific biological pathways through which reproductive history modulates brain aging is crucial to inform preventive efforts and therapeutic development.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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Lacey Loughlin, BA	Weill Cornell Medicine, New York, NY	Major role in data acquisition, obtained the official approvals, data management, interpreted the data, drafted the manuscript
Steven Jett, MA	Weill Cornell Medicine, New York, NY	Major role in data acquisition, obtained the official approvals, data management, reviewed the manuscript for intellectual content
Cenai Zhang, MS	Weill Cornell Medicine, New York, NY	Major role in data acquisition, obtained the official approvals, data management and statistical analysis, interpreted the data, drafted the manuscript
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Hollie Hristov, NP	Weill Cornell Medicine, New York, NY	Major role in data acquisition, reviewed the manuscript for intellectual content

Appendix *(continued)*

Name	Location	Contribution
Silky Pahlajani, MD	Weill Cornell Medicine, New York, NY	Major role in data acquisition, reviewed the manuscript for intellectual content
Richard Isaacson, MD	Weill Cornell Medicine, New York, NY	Major role in data acquisition, reviewed the manuscript for intellectual content
Jonathan P. Dyke, PhD	Weill Cornell Medicine, New York, NY	Major role in data acquisition, image data processing, reviewed the manuscript for intellectual content
Hooman Kamel, MD	Weill Cornell Medicine, New York, NY	Procured funding, reviewed the manuscript for intellectual content
Roberta Diaz Brinton, PhD	University of Arizona, Tucson	Procured funding, reviewed the manuscript for intellectual content
Lisa Mosconi, PhD	Weill Cornell Medicine, New York, NY	Designed and conceptualized study, image data processing, interpreted the data, drafted and revised the manuscript for intellectual contents, procured funding

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