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FEATURED ARTICLE

Carotid intima media thickness and white matter hyperintensity volume among midlife women

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Abstract

Introduction: Carotid atherosclerosis may be associated with brain white matter hyperintensities (WMH). Few studies consider women at midlife, a critical time for women's cardiovascular and brain health. We tested the hypothesis that higher carotid intima media thickness (IMT) would be associated with greater WMH volume (WMHV) among midlife women. We explored interactions by apolipoprotein E (*APOE*) ε4 status.

Methods: Two hundred thirty-nine women aged 45 to 67 underwent carotid artery ultrasound, phlebotomy, and magnetic resonance imaging (MRI). One hundred seventy participants had undergone an ultrasound 5 years earlier.

Results: Higher IMT was associated with greater whole brain (B[standard error (SE)] = 0.77 [.31], $P = 0.01$; multivariable) and periventricular (B[SE] = 0.80 [.30], $P = 0.008$; multivariable) WMHV. Associations were observed for IMT assessed contemporaneously with the MRI and 5 years prior to the MRI. Associations were strongest for *APOE* ε4–positive women.

Discussion: Among midlife women, higher IMT was associated with greater WMHV. Vascular risk is critical to midlife brain health, particularly for *APOE* ε4–positive women.

KEYWORDS
Alzheimer's disease, apolipoprotein E, carotid atherosclerosis, carotid intima media thickness, dementia, menopause, white matter hyperintensities, women

1 | INTRODUCTION

Alzheimer's disease and related dementias (ADRD) and cardiovascular disease (CVD) are major women's health issues. ADRD is over-represented among women and is the fourth leading cause of death in women.[1] CVD is a major health issue for women, is the leading cause of death in women, and accounts for one in every three female deaths in the United States.[2]

Midlife is of particular importance for women's brain and cardiovascular health. The neuropathological hallmarks of dementia due to ADRD, including amyloid beta and hyperphosphorylated tau, accumulate at midlife.[3,4] White matter hyperintensities (WMHs),

indicators of cerebral small vessel damage,[5] are common even in the fifth decade of life.[6–8] Definitions of midlife vary, but typically span the ages of 40 to up to 65 years.[9,10] For women, midlife includes the menopause transition, a reproductive transition accompanied by adverse changes in cognitive performance[11–13] and accelerated accumulation of atherosclerosis[14] and possibly cerebrovascular risk[15,16] beyond aging alone. Thus, midlife and the menopause transition are critical times to identify modifiable risk factors that may accelerate the neuropathology of ADRD.

Because midlife women rarely present with clinical CVD or ADRD, subclinical indicators that leverage imaging of the vasculature and brain are useful in assessing risk at midlife. Carotid intima media thickness (IMT), which indexes the thickness of the intimal and medial layers of the carotid artery, is a well-validated subclinical CVD indicator linked to future CVD.[17] The carotid artery is of particular relevance as a major supplier of blood to the brain.[18] WMHs, lesions in the white matter that are apparent on T2-weighted magnetic resonance imaging (MRI), develop in part due to small vessel disease and are linked to later dementia, cognitive decline, and mortality.[5]

Higher carotid IMT has been linked to poorer cognition and dementia later in life.[19–21] However, research examining IMT and WMHs at midlife is limited, does not assess IMT and WMHs at the same time point, and has produced mixed or null findings.[22,23] Further, a dearth of research on midlife individuals has considered carotid IMT in relation to the spatial distribution of WMHs, critical to their etiology and clinical implications.[6] Even fewer midlife studies have considered the role of apolipoprotein E (*APOE*) ε4, a major determinant of brain health.[24] Finally, no studies of IMT–WMH relationships have considered menopause, a major midlife transition with implications for women's cardiovascular[25] and brain[15,16] health.

Among a well-characterized sample of midlife women, we examine relationships between carotid IMT and WMHs, hypothesizing that greater carotid IMT will be associated with increased WMH volume (WMHV). IMT was assessed twice over time in this cohort, once at the time of the WMHV assessment and in a subset of women, 5 years prior to the WMHV assessment. Thus, we leverage the longitudinal nature of IMT assessments to test not only the cross-sectional relationships between IMT and WMHV, but also IMT assessed earlier in midlife in relation to later WMHV. We explore IMT in relation to the spatial distribution of WMHV and whether IMT–WMHV relationships vary by *APOE* ε4 status. We test these associations controlling for a range of potential confounding or explanatory factors.

RESEARCH IN CONTEXT

1. **Systematic Review**: Greater carotid intima media thickness (IMT) is associated with greater brain white matter hyperintensities (WMH) among older individuals, yet few studies consider these associations at midlife. Even fewer studies focus on women. The neuropathological hallmarks of Alzheimer's disease and related dementias accumulate at midlife. For women, midlife includes the menopause transition.
2. **Interpretation**: Greater carotid IMT was associated with greater whole brain and periventricular WMH volume (WMHV) among midlife women. Associations are most pronounced among apolipoprotein E (*APOE*) ε4 carriers.
3. **Future Directions**: Vascular health is important to women's brain health at midlife. Carotid IMT can identify midlife women at risk of poor brain health and serve as a target of intervention. Reducing midlife cardiovascular risk, particularly for *APOE* ε4 carriers, may have the potential to help preserve brain health as women age.

2 | METHODS

2.1 | Sample

MsHeart/MsBrain participants comprised the study sample. The MsHeart and MsBrain studies were single-center studies conducted among community participants. MsHeart recruited 304 women ages 40 to 60 between 2012 and 2015 for a study of menopause and cardiovascular health.[26] MsHeart participants were non-smoking, late perimenopausal or postmenopausal, free of CVD, and by design had either daily menopausal vasomotor symptoms (i.e., hot flashes, night sweats) or no menopausal vasomotor symptoms in the past 3 months. Between 2017 and 2020, 274 participants were recruited from MsHeart (N = 170) and the surrounding Pittsburgh, Pennsylvania, community (N = 104) for MsBrain, a study of brain health. MsHeart/MsBrain exclusion criteria included pregnancy; hysterectomy and/or bilateral oophorectomy; history of stroke/cerebrovascular accident; Parkinson's disease; chemotherapy; and current use of systemic estrogen or progesterone, selective estrogen receptor modulators, aromatase inhibitors, gabapentin, selective serotonin reuptake inhibitors, or serotonin norepinephrine reuptake inhibitors. MsHeart exclusion criteria also included being pre- or early perimenopausal or using insulin, calcium channel blockers, or beta blockers. MsBrain exclusion criteria also included a history of dementia, seizure disorder, and brain tumor; active substance abuse (established via urine toxicology screen and interview); history of head trauma with loss of consciousness > 60 minutes; and contraindication to MRI.

Of the 274 women enrolled in MsBrain, 239 underwent neuroimaging. Of these women, one woman was excluded due to missing IMT data; nine due to detection of brain tumor or stroke on neuroradiological review of the brain MRI, or to reported seizure disorder; and five due to a reported history of chemotherapy. The primary sample for cross-sectional models was N = 224, and due to missing phlebotomy data, N = 222 for models with blood biomarkers. For additional models, sample size for models incorporating *APOE* data was N = 214 (due to refusal of genetic testing) and incorporating time since the final menstrual period (FMP) was N = 220 (due to unobserved FMP). Finally, as not all MsBrain participants participated in MsHeart, the sample size

for MsHeart models was $N = 124$ for primary models and $N = 123$ in models with blood-based biomarkers (see Figure S1 in supporting information).

3 | DESIGN AND PROCEDURES

At the MsHeart visit, participants underwent screening, physical measurements, a medical history interview, questionnaires, fasting phlebotomy, and a carotid artery ultrasound. Approximately 5 years after the MsHeart visit (median [interquartile range (IQR)] = 4.70 [4.42, 5.00]), both MsHeart participants and community participants were recruited to undergo screening, physical measurements, a medical history interview, questionnaires, fasting phlebotomy, a carotid artery ultrasound, and brain MRI. Study procedures were reviewed and approved by the University of Pittsburgh Human Research Protection Office. All participants provided written, informed consent.

4 | MEASURES

4.1 | Carotid ultrasound

Participants underwent carotid ultrasound imaging at both MsHeart and MsBrain visits. Certified sonographers at the University of Pittsburgh's Ultrasound Research Laboratory obtained bilateral carotid images via B-mode ultrasound using a Sonoline Antares (Siemens) high-resolution duplex scanner equipped with a VF10-5 transducer according to a standardized protocol.[27] Digitized images were obtained at end-diastole from eight locations (four locations each from the left and right carotid arteries): near and far walls of the distal common carotid artery, far walls of the carotid bulb, and the internal carotid artery. Images were read using semi-automated reading software.[28] Values were obtained by electronically tracing the lumen–intima interface and the media–adventitia interface across a 1-cm segment for each of the segments. Average and maximal values were recorded for each location. Mean IMT was the mean of the mean readings across the eight locations. Reproducibility was excellent (intraclass correlation coefficient between sonographers ≥0.87, between readers = 0.92).

4.2 | WMHs

Participants underwent brain MRI at the MsBrain visit. MRI scanning was performed at the MR Research Center of the University of Pittsburgh with a 3T Siemens Tim Trio MR scanner and a Siemens 64-channel head coil. Two series of MR images were analyzed for the current study: magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequence and T2-weighted (T_2w) fluid-attenuated inversion recovery (FLAIR) sequence. MPRAGE images were acquired in the axial plane using the parameters: repetition time (TR) = 2400 ms; echo time (TE) = 2.22 ms; inversion time (TI) = 1000 ms; flip angle = 8°; field of view (FOV) = 256*240 mm; slice thickness = 0.8 mm; voxel size = 0.8 mm*0.8 mm; matrix size = 320*300; and number of slices = 208. FLAIR images were acquired in the axial plane using the parameters: TR = 9690 or 10000 ms; TE = 91 ms; TI = 2500 ms; flip angle = 135°; FOV = 256 × 256 mm; matrix = 320 × 320; slice thickness = 1.6 mm; voxel size = 0.8 mm*0.8 mm; and number of slices = 104. The small change in TR from 9690 to 10000 was performed 1 year into the study to meet specific absorption rate human safety guidelines for participants with a higher body mass index (BMI). This change slightly increased the time of acquisition but had minimal effect on image contrast.

An automated pipeline was used to segment WMHs on the T_2w FLAIR images using previously validated methods.[29,30] For each participant, cerebral and cerebellar white matter were segmented on the T_1w image and mapped into the T_2w FLAIR image space using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/) and FreeSurfer (version 7.1.1, https://surfer.nmr.mgh.harvard.edu/). As there were very few lesions in the cerebellum, cerebellar white matter represented normal appearing white matter, and its intensity mean and standard deviation were used for Z-transformation of the T_2w FLAIR image. Manual inspection of each image was performed to rule out cerebellar WMHs. A threshold of two was then applied on Z-transformed FLAIR images. This method uses individual mean and standard deviation from normal cerebellar white matter to standardize individual FLAIR images, avoiding systematic bias in seed selection between participants with significant cerebral WMHs versus those with few WMHs. Z-transformation also reduces intensity variations across individual FLAIR images.

In FreeSurfer, white matter was also parcellated according to its nearest cortex with the Desikan–Killiany atlas, which was used to generate the cortical white matter masks for frontal, temporal, parietal, and occipital lobes for the localization of WMHs. White matter parcellations corresponding to frontal cortex regions in the Desikan–Killiany atlas were combined to create a frontal cortical white matter mask to localize frontal WMHs. Cortical white matter masks were generated for temporal, parietal, and occipital lobes. These lobular cortical white matter masks did not overlap and were combined to create an overall cortical/deep white matter mask. White matter surrounding the ventricles that is not part of the cortical/deep white matter mask comprised the periventricular white matter mask. These lobular cortical masks and periventricular white matters allow us to investigate additional models of regional WMHs. The total and regional WMHV (in cubic centimeters) were normalized by intracranial volumes (ICV; nWMHs = WMHs/ICV) and log transformed for analysis.

4.3 | Additional measures

Participants underwent physical measurements, interviews, questionnaires, and phlebotomy at both MsHeart and MsBrain visits. Height was measured via a fixed stadiometer and weight via a balance beam scale. BMI was calculated (weight[kg]/height[m^2]). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were the average of three seated measurements (Dinamap v100). Demographics; medical, reproductive, and psychiatric history; medication use; and health behaviors were assessed by questionnaires/interview. Race/ethnicity

was self-reported. The time since the FMP (onset of postmenopause)[31] was calculated as the time difference between the woman's reported FMP date and the MsBrain visit date. To reduce memory effects, for women who had reached their FMP at the MsHeart visit, their FMP was the FMP date reported at MsHeart; for women who had not reached their FMP at MsHeart or who did not participate in MsHeart, the FMP date was the date that was reported at MsBrain. Education was reported as years of completed education. Women also underwent the Montreal Cognitive Assessment (MoCA), a validated measure of global cognitive performance.[32]

Women underwent phlebotomy after overnight fast. Glucose, total cholesterol, high density lipoprotein cholesterol (HDL), and triglycerides were determined using enzymatic assays and insulin via immunoturbidimetric assay (Alfa Wasserman). Low-density lipoprotein (LDL) was calculated using the Friedewald equation.[33] Homeostatic model assessment (HOMA) for insulin resistance was calculated ([insulin*glucose]/22.5).[34] At the MsBrain visit, women also underwent genotyping. Genotypes for two *APOE* polymorphisms, rs429358 (*APOE* ε4) and rs7412 (*APOE* ε2), were determined using TaqMan genotyping assays.[35] Because of the strong linkage disequilibrium between the two sites, this is also treated as a three-allele *APOE* polymorphism: *APOE* ε2, *APOE* ε3, and *APOE* ε4, yielding six genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4). Participants were classified as *APOE* ε4 positive (ε2/ε4, ε3/ε4, ε4/ε4) or negative (ε2/ε2, ε2/ε3, ε3/ε3); we also considered models excluding *APOE* ε2–positive women. As findings were comparable, findings with the full sample are reported here.

4.4 | Statistical analysis

IMT, BMI, HOMA, triglycerides, and WMHV variables were log transformed for analysis. IMT assessed at MsBrain or IMT assessed at MsHeart were each tested in relation to MsBrain whole brain WMHV in linear regression models. Covariates for analyses of MsBrain IMT were from the MsBrain visit and for MsHeart IMT were from the MsHeart visit. Covariates included demographics (age, race, education) and BMI; blood pressure (DBP, anti-hypertensive medication); and other CVD risk factors (lipids, insulin resistance, associated medications). One blood pressure variable and lipid variable (selected based upon its association with WMHV) were included in models given the collinearity among blood pressure and lipid variables, respectively. Time between visits was included in models using MsHeart data. Exploratory models considered IMT in relation to regional WMHV (periventricular, deep, and frontal; temporal, parietal, occipital lobes) as well as effect modification of IMT–WMHV relationships by *APOE* ε4, covarying for demographics and CVD risk factors. *APOE* ε4–stratified models were presented. Additional exploratory models considered the average IMT and the change in IMT across MsHeart and MsBrain visits in relation to WMHV, IMT in relation to global cognitive performance, and interactions between MsBrain IMT and WMHV by age and time since the FMP. Tests were two tailed with $\alpha = 0.05$. Analyses were conducted in SAS v9.4.

5 | RESULTS

At the MsBrain visit, participants were on average 59 years old (range 45 to 67), overweight, and with a favorable CVD risk factor profile (Table 1). Most participants identified as non-Hispanic White (82%) or Black (13%).

Higher IMT was associated with greater whole brain WMHV (Table 2, Figure 1). Results were consistent for IMT assessed at the MsHeart visit and the MsBrain visit. When exploring the relationship between IMT and the spatial distribution of WMHV, higher IMT was associated with greater periventricular WMHV, and for IMT assessed at the MsHeart visit, frontal WMHV (Table 3).

We also explored interactions between *APOE* ε4 and IMT in relation to WMHV. We observed significant interactions between *APOE* ε4 and MsBrain IMT in relation to whole brain WMHV ($P = 0.047$) and occipital WMHV ($P = 0.03$). We also found interactions between *APOE* ε4 and MsHeart IMT in relation to WMHV ($P = 0.03$). Stratified models indicated that among *APOE* ε4–positive women, higher IMT was associated with greater whole brain, deep, periventricular, and occipital WMHV (Table 4). Notably, *APOE* ε4 carriers and non-carriers did not differ on demographics, CVD risk factors, IMT, or WMHV (data not shown).

We conducted several secondary analyses. We considered the average IMT across visits in relation to WMHV. The average IMT across visits was associated with higher whole brain WMHV (B[standard error (SE)] = 1.08 [.43], $P = 0.01$) and periventricular WMHV (B[SE] = 1.20 [.43], $P = 0.006$); associations were most pronounced among *APOE* ε4 carriers (whole brain WMHV: B[SE] = 2.58 [.97], $P = 0.02$ and periventricular WMHV: B[SE] = 2.35 [.98], $P = 0.02$) in multivariable models. Change in IMT was not significantly associated with WMHV (data not shown). We considered relationships between IMT and global cognitive performance; higher IMT was not significantly associated with MoCA scores (B[SE] = −1.76 [1.06], $P = 0.096$; adjusted for age, race/ethnicity, education), and there were not significant interactions by *APOE ε4* status. We explored whether reproductive age (the time since the FMP) modified relationships between MsBrain IMT and WMHV. Interactions were observed between time since the FMP and IMT in relation to whole brain WMHV ($P = 0.04$) and periventricular WMHV ($P = 0.047$) such that associations between IMT and WMHV were primarily observed for women of older reproductive age (further from their FMP), controlling for chronologic age and covariates Table (S1 in supporting information). Interactions between IMT and age in relation to WMHV were not significant (P's = 0.40 to 0.97). Thus, associations between IMT and WMHV were most pronounced among women who were of older reproductive age, irrespective of their chronologic age.

6 | DISCUSSION

In this study of midlife women, higher IMT was associated with greater WMHV, and specifically whole brain and periventricular WMHV. Associations were particularly apparent for *APOE* ε4 carriers, among whom

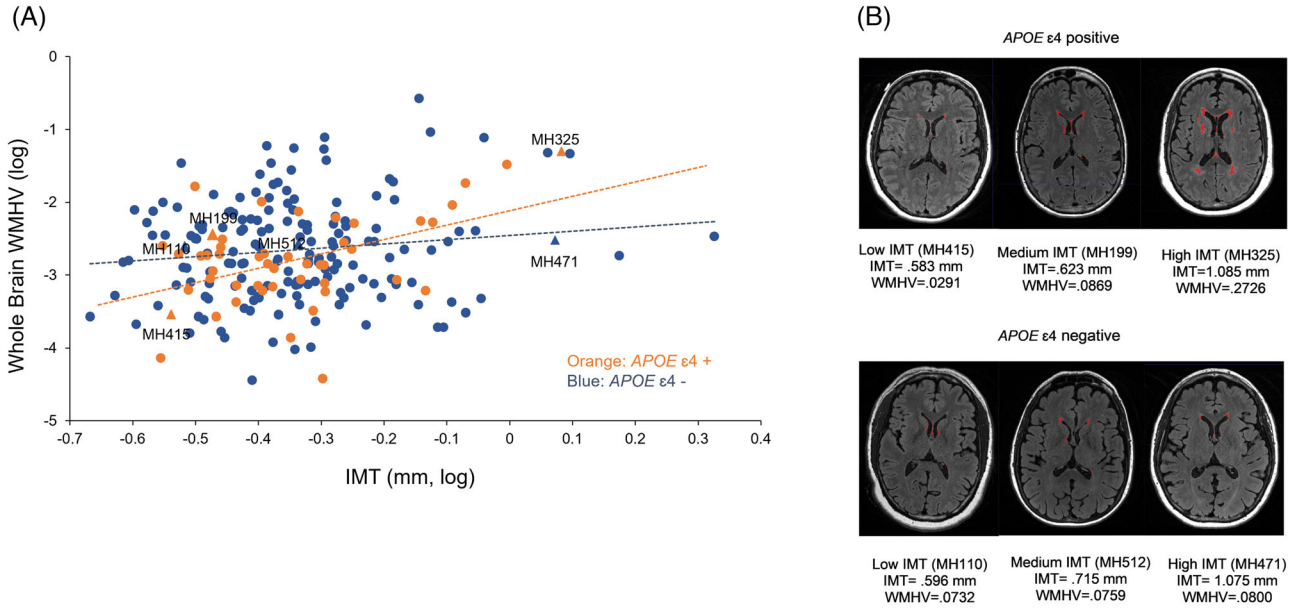

FIGURE 1 (A) Scatterplot of raw relationship between IMT (log) and WMHV (log) at the MsBrain visit by *APOE* ε4 status (orange = *APOE* ε4 positive, blue = *APOE* ε4 negative); (B) MRI scans of white matter hyperintensity volumes in representative women with low, medium, and high IMT by *APOE* ε4 status. Notes: WMHV values normalized by ICV; IMT represents mean IMT over eight locations of carotid artery; WMHV expressed as mm^3/Intracranial volume (in mm^3). *APOE*, apolipoprotein E; ICV, intracranial volume; IMT, intima media thickness; WMHV, white matter hyperintensity volume

higher IMT was associated with greater total, deep, periventricular, and occipital WMHV.

These findings underscore the importance of cardiovascular health to women's brain health at midlife. While prior work has investigated IMT in relation to WMHV, it has focused on later life individuals. The few studies in which both IMT and WMHV were assessed at midlife (yet typically 4 to 5 years apart) show conflicting results. For example, among Framingham Study participants who underwent carotid ultrasound at an average age of 58 and brain MRI 4 years later, higher IMT of the internal carotid artery was associated with greater large WMHV.[22] Conversely, among CARDIA participants who underwent carotid ultrasound at an average age of 46 and MRI 5 years later, IMT was not associated with WMHV.[23] We found robust associations between IMT and WMHV. Our study is notable. First, we assessed IMT both 5 years prior to our WMHV assessment as well as at the same time point as WMHV. Prior midlife studies typically assess WMHV years after the carotid assessment, which is a limitation as IMT changes over time. We were able to assess IMT at both time points in relation to WMHV. We found that IMT assessed at both time points, as well as the average IMT across the visits, was associated with greater whole brain WMHV at the second visit. However, only concurrent measurements revealed associations between IMT and WMHV in the deep white matter and in the occipital lobe in *APOE* ε4 carriers, indicating that these associations emerged over time. Our participants were assessed late in midlife (average age 59), similar to Framingham participants, whereas CARDIA participants were younger; thus, associations between IMT and WMHV likely emerge later in midlife. We further explored a modifying role of *APOE* ε4 status, which was a key effect modifier. Our findings suggest that CVD risk reduction in late midlife may be critical to preventing degradations in brain health as women age.

We also examined IMT in relation to the spatial distribution of WMHV. IMT was related to whole brain WMHV as well as periventricular WMHV. Similarly, the Rotterdam Study of elderly adults found higher carotid atherosclerosis associated with periventricular white matter lesions,[36] which in turn were associated with more rapid cognitive decline.[37] Other work has indicated adverse CVD risk factors such as blood pressure[38] as particularly related to frontal WMHs. Notably, associations between IMT and WMHV here persisted controlling for CVD risk factors. Further, work has shown that frontal WMHs might be those that emerge earlier in midlife.[6] Interestingly, we found that higher IMT earlier in midlife (assessed 5 years prior to the WMHV assessment) was particularly associated with greater frontal WMHV.

IMT was associated with particularly widespread WMHV among *APOE* ε4 carriers. Among *APOE* ε4 carriers, higher IMT was associated with greater whole brain, periventricular, deep, and occipital WMHV. Importantly, the *APOE* ε4 genotype confers particular risk for dementia in women.[24] Prior work indicates increased accumulation of WMHV among *APOE* ε4 carriers and suggests that *APOE* ε4 may exacerbate the effects of vascular[39] or cardiometabolic[40] risk factors on white matter. Our findings demonstrate the particularly deleterious impact of vascular risk among *APOE* ε4 carriers.

Menopause is a critical reproductive transition during which women show increased vascular remodeling, stiffening, and accumulation of IMT with advancing menopause stage beyond aging alone.[14,41] Other work suggests increases in WMHV with menopause beyond age.[15,16] Secondary models suggested reproductive age as an effect modifier,

TABLE 1 Participant characteristics

N	224
Age, M (SD)	59.19 (4.27)
Race/ethnicity, N (%)	
White	184 (82.14)
Black	29 (12.95)
Asian or mixed race/ethnicity	11 (4.91)
Years of education, M (SD)	15.75 (2.37)
BMI, median (IQR)	26.71 (23.79, 31.83)
SBP, mmHg, M (SD)	118.37 (14.14)
DBP, mmHg, M (SD)	68.26 (8.84)
LDL-C, mg/dL, M (SD)	119.75 (35.76)
HDL-C, mg/dL, M (SD)	70.66 (20.85)
Triglycerides, mg/dL, median (IQR)	91.00 (69.00, 122.00)
HOMA, median (IQR)	2.75 (1.21, 4.01)
Menopause stage (postmenopausal), N (%)	222 (99.11)
Years since the final menstrual period, median (IQR)	7.79 (5.71, 12.16)
Anti-hypertensive medication use, N (%)	40 (17.86)
Lipid-lowering medication use, N (%)	35 (15.63)
Diabetes medication use, N (%)	8 (3.57)
APOE ε4 positive, N (%)b	48 (22.43)
IMT (MsBrain), mm, Median (IQR)	0.70 (0.62, 0.76)
IMT (MsHeart), mm, median (IQR)	0.66 (0.61, 0.75)
IMT, change, mm, M (SD)	0.04 (0.06)
WMHV, Median (IQR)[a]	
Whole brain	0.065 (0.043, 0.102)
Deep	0.013 (0.007, 0.027)
Periventricular	0.050 (0.033, 0.078)
Frontal	0.003 (0.002, 0.006)
Parietal	0.001 (0.0001, 0.003)
Temporal	0.003 (0.001, 0.006)
Occipital	0.003 (0.001, 0.009)

Note: At the MsBrain visit.
[a]WMHV expressed as mm^3/intracranial volume; [b]*APOE* ε4 positive: ε2/ε4, ε3/ε4, ε4/ε4.
Abbreviations: *APOE* , apolipoprotein E; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein-cholesterol; HOMA, homeostatic model assessment; IMT, intima media thickness; IQR, interquartile range; LDL-C, low-density lipoprotein-cholesterol; SBP, systolic blood pressure; SD, standard deviation; WMHV, white matter hyperintensity volume.

TABLE 2 Association of IMT at MsBrain and MsHeart visits and WMHV

	Whole brain WMHV
	B(SE)
IMT (MsBrain)	**0.77 (.31)***
IMT (MsHeart)	**1.10 (.42)***

*$P < 0.05$; MsBrain model: $N = 222$; MsHeart model: $N = 123$.
Notes: IMT in mm; WMHV expressed as mm^3/Intracranial volume (in mm^3).
Bold indicates statistical significance.
Adjusted for age, race, education, log BMI, DBP, blood pressure lowering medication, HOMA (log), HDL-C, lipid medication, diabetes medication, and for MsHeart IMT model, time between visits.
Abbreviations: B, beta; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; IMT, intima media thickness; SE, standard error; WMHV, white matter hyperintensity volume.

with higher IMT associated with greater whole brain, periventricular, and occipital WMHV among women further from their FMP (> 7.79 years). Interactions by age were not observed, pointing to the modifying effects of reproductive aging, not chronologic aging, in IMT–WMHV relationships. These findings indicate the potential importance of considering reproductive aging in women's brain health. Women of older reproductive age, irrespective of their chronologic age, may warrant particular attention.

The mechanisms that may link carotid atherosclerosis to WMHV are multiple. While it must be acknowledged that IMT is a measure of large vessel disease and WMHV of small vessel disease, there may be important shared mechanisms. For example, standard CVD risk factors are risk factors for both greater IMT and WMHV, and particularly elevated blood pressure. However, controlling for blood pressure did not account for associations. Other CVD risk factors, such as increased adiposity, greater insulin resistance, and adverse lipid profiles may also link IMT to WMHV; notably, we controlled for these factors and associations persisted. Further, atherosclerosis of the carotid artery has been linked to hemodynamic changes including lower cerebral blood flow.[23] Thus, as the carotid artery is a major conduit of blood to the brain, carotid atherosclerosis may be related to WMHV through its supply of blood to the brain. Future work should continue to investigate underlying mechanisms.

This work had limitations. Whereas the IMT was measured twice over midlife, WMHV was assessed once, precluding analyses of change in WMHV over midlife or greater insight into the temporal pattern of relationships. We considered WMHV as our outcome; future work should also consider time of flight and susceptibility weighted imaging to allow examination of markers of cerebral small vessel disease earlier in the pathophysiologic process. Moreover, sample sizes for MsHeart analyses were more limited than that of primary analyses. The timing of the FMP was recalled, and while repeated assessments of the FMP enhanced precision, FMP reports likely incorporated error. Some of the older women in this sample might not be considered in midlife. Further, we conducted multiple secondary and

TABLE 3 Relationship of IMT at MsBrain and MsHeart visits to spatial distribution of WMHV

	WMHV					
	Deep B(SE)	Periventricular B(SE)	Frontal B(SE)	Occipital B(SE)	Parietal B(SE)	Temporal B(SE)
IMT (MsBrain)	0.51 (.49)	**0.80 (.30)****	0.83 (.55)	0.27 (.77)	0.43 (.86)	0.04 (.60)
IMT (MsHeart)	0.73 (.63)	**1.23 (.41)****	**1.53 (.74)***	0.67 (.86)	0.92 (1.11)	0.49 (.83)

$^{\dagger}P < 0.10$; $^{*}P < 0.05$; $^{**}P < 0.01$; MsBrain models $N = 222$; MsHeart models, $N = 123$.

Notes: IMT in mm; WMHV as mm^3/intracranial volume (in mm^3). Adjusted for age, race, education, BMI (log), DBP, HOMA (log), HDL-C, blood pressure lowering medication, lipid medication, diabetes medication, and for MsHeart IMT models, time between visits.

Abbreviations: B, beta; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; IMT, intima media thickness; SE, standard error; WMHV, white matter hyperintensity volume.

TABLE 4 IMT in relation to WMHV, stratified by *APOE* ε4 status

	WMHV						
	Whole brain B(SE)	Deep B(SE)	Peri-ventricular B(SE)	Frontal B(SE)	Occipital B(SE)	Parietal B(SE)	Temporal B(SE)
APOE ε4 negative							
IMT (MsBrain)	0.37 (.35)	−0.07 (.58)	0.48 (.34)	0.78 (.66)	−0.82 (.88)	−0.55 (1.00)	−0.41 (.70)
IMT (MsHeart)	0.31 (.46)	−0.42 (.73)	0.55 (.46)	0.83 (.88)	−0.67 (.97)	−0.92 (1.30)	−0.87 (.97)
APOE ε4 positive							
IMT (MsBrain)	**1.82 (.64)****	**2.67 (.87)****	**1.49 (.65)***	0.38 (1.19)	**5.58 (1.61)****	2.80 (1.80)	1.11 (1.45)
IMT (MsHeart)	**2.28 (.77)****	1.88 (1.41)	**2.34 (.67)***	0.86 (1.81)	1.99 (2.49)	3.26 (2.52)	3.54 (2.15)

$^{\dagger}P < 0.10$; $^{*}P < 0.05$; $^{**}P < 0.01$.

Notes: *APOE* ε4 positive: $N = 48$ (MsBrain models), $N = 28$ (MsHeart models); *APOE* ε4 negative: $N = 166$ (MsBrain models), $N = 86$ (MsHeart models). IMT in mm; WMHV as mm^3/intracranial volume (in mm^3). Adjusted for age, race, education, BMI (log), DBP, HOMA (log), HDL-C, blood pressure lowering medication, lipid medication, diabetes medication, and MsHeart IMT models, time between visits.

Abbreviations: *APOE*, apolipoprotein E; B, beta; BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high density lipoprotein cholesterol; HOMA, homeostatic model assessment; IMT, intima media thickness; SE, standard error; WMHV, white matter hyperintensity volume.

exploratory models here, which should be regarded with caution due to multiple testing and potential chance findings; further replication should be undertaken. This study included cisgender women only and included relatively few racial/ethnic minority women, limiting our understanding of associations in groups not well represented here (e.g., Latinas, Native American, and Asian women).

This study had several strengths. It used imaging of the vasculature and the brain among well-characterized midlife women. IMT and WMHV were assessed at the same visit, while also leveraging carotid assessments twice over midlife. We considered the spatial distribution of WMHV and controlled for multiple potential confounding/explanatory factors. We considered effect modification by *APOE* ε4, underscoring its critical role in IMT–WMHV relationships. Finally, we studied midlife women, a group at particular risk of adverse changes in cardiovascular and neurocognitive health among whom risk stratification and intervention at midlife is critical.

In sum, higher carotid IMT was associated with greater whole brain and periventricular WMHV among midlife women. Associations were particularly pronounced among *APOE* ε4 carriers. These findings demonstrate the importance of vascular health to women's brain health at midlife. Carotid IMT can identify midlife women at particular risk of poor brain health and serve as an important modifiable target of intervention. These findings underscore the importance of reducing midlife cardiovascular risk, particularly for *APOE* ε4 carriers, to preserve women's brain health as they age.

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CONFLICTS OF INTEREST

Dr. Thurston is a consultant for Astellas, Bayer, Happify Health, and Hello Therapeutics. Dr. Aizenstein is an advisor to Eisai. Dr. Maki is a consultant for Abbvie, Balchem, and Pfizer; advisor to Astellas, Bayer, and Johnson&Johnson. Drs Wu, Chang, Derby, and Barinas-Mitchell have no disclosures relevant to the manuscript. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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