RESEARCH ARTICLE

Associations Between Age at Menopause, Vascular Risk, and 3-Year Cognitive Change in the Canadian Longitudinal Study on Aging

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Abstract

Background and Objectives

Mounting evidence supports sex differences in Alzheimer disease (AD) risk. Vascular and hormonal factors may together contribute to AD risk in female adults. We investigated whether age at menopause, vascular risk, and history of hormone therapy (HT) containing estrogens together influence cognition over a 3-year follow-up period. We hypothesized that earlier menopause and elevated vascular risk would have a synergistic association with lower cognitive scores at follow-up and that HT containing estrogens would attenuate this synergistic association to preserve cognition.

Methods

We used data from postmenopausal female participants and age-matched male participants in the Canadian Longitudinal Study on Aging. Vascular risk was calculated using a summary score of elevated blood pressure, antihypertensive medications, elevated low-density lipoprotein cholesterol, diabetes, smoking, and obesity. Cognition was measured with a global cognitive composite at baseline and 3-year follow-up. Linear models tested independent and interactive associations of age at menopause, vascular risk, and HT history with cognition at 3-year follow-up, adjusting for baseline cognition, baseline age, years of education, and test language (English/French).

Results

We included 8,360 postmenopausal female participants (mean age at baseline = 65.0 ± 8.53 years, mean age at menopause = 50.1 ± 4.62 years) and 8,360 age-matched male participants for comparison. There was an interaction between age at menopause and vascular risk, such that earlier menopause and higher vascular risk were synergistically associated with lower cognitive scores at follow-up (β = 0.013, 95% CI 0.001–0.025, $p = 0.03$). In stratified analyses, vascular risk was associated with lower cognitive scores in female participants with earlier menopause (menopausal ages 35–48 years; β = −0.044, 95% CI −0.066 to −0.022, $p < 0.001$), but not average (ages 49–52 years; β = −0.007, 95% CI −0.027 to 0.012, $p = 0.46$) or later menopause (ages 53–65 years; β = 0.003, 95% CI −0.020 to 0.025, $p = 0.82$). The negative association of vascular risk with cognition in female participants with earlier menopause was stronger than the equivalent association in age-matched male participants. HT history did not further modify the synergistic association of age at menopause and vascular risk with follow-up cognition (β = −0.005, 95% CI −0.032 to 0.021, $p = 0.69$).

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Glossary

Aβ = β-amyloid; **AD** = Alzheimer disease; **CLSA** = Canadian Longitudinal Study on Aging; **HT** = hormone therapy; **LDL** = low-density lipoprotein.

Discussion

Endocrine and vascular processes may synergistically contribute to increased risk of cognitive decline in female adults. These findings have implications for the development of sex-specific dementia prevention strategies.

Introduction

The lifetime risk of developing Alzheimer disease (AD) dementia is nearly twice as high in women when compared with that in men.[1] The underlying causes of this disparity remain largely unclear, but accumulating data point toward sex differences in AD risk factors.[2,3] In mixed-sex studies, vascular risk factors (e.g., hypertension, diabetes) are associated with cognitive decline, dementia, and AD pathology after adjusting for sex.[4-6] However, studies that analyze data separately by sex suggest that associations between vascular risk factors and cognitive decline may be stronger in female individuals compared with male individuals.[7-9] Furthermore, postmortem neuropathologic research shows that a higher proportion of female than male decedents have mixed AD and cerebrovascular pathology.[10] These sex-specific vascular contributions may partially explain the higher risk of AD observed in women.

In addition to vascular risk factors, menopausal hormonal changes have been implicated in female risk of AD. PET studies show that postmenopausal female individuals exhibit greater β-amyloid (Aβ) and tau burden compared with age-matched premenopausal female individuals and age-matched male individuals.[2,11] In addition, female individuals who experience menopause at younger (vs older) ages exhibit greater AD pathology and worse cognitive outcomes in later life.[3,12-14] Furthermore, relative to age-matched controls, female individuals with bilateral ovary removal before the average age of spontaneous menopause (i.e., oophorectomy between ages 35 and 50 years) experience greater declines in cognition[15] and hippocampal volume.[16]

Earlier menopause is also associated with worse cardiovascular outcomes.[17] Biological interactions between hormonal and vascular processes might contribute to sex differences in AD risk, but there is limited research on this topic. One cross-sectional study observed an interaction between hypertension and menopausal status on cognition, such that cognitive scores were lowest in hypertensive postmenopausal female participants.[18] These findings suggest that menopause may confer increased susceptibility to vascular-related cognitive decline.

If younger age at menopause exacerbates the risk of cognitive decline, hormone therapy (HT)—which partially replenishes estrogens—might further influence cognitive outcomes. However, findings on the benefits and risks of HT for cognitive and brain health are conflicting. Data from observational studies and small clinical trials suggest that HT is associated with reduced risk of cognitive decline and AD dementia.[19,20] However, the seminal Women's Health Initiative Memory Study reported a significantly higher incidence of dementia among conjugated equine estrogen-plus-progestin HT users vs placebo.[21] The conflicting HT findings may relate to heterogeneity in factors such as reproductive health history, age at HT initiation, health status, and HT formulations.[21-24]

The aim of this study was to investigate associations between age at menopause, vascular risk, and prospective cognition in the Canadian Longitudinal Study on Aging (CLSA). We first examined independent and interactive associations of age at menopause and vascular risk on cognition at 3-year follow-up in postmenopausal female participants. To contextualize effects observed in female participants, we compared associations of vascular risk with prospective cognition in female participants with earlier, average, or later menopause to the equivalent associations in groups of age-matched male participants. We hypothesized that earlier menopause and elevated vascular risk would synergistically drive lower cognitive scores at follow-up. We further hypothesized that the negative associations of vascular risk with prospective cognition would be stronger in female participants with earlier menopause than in age-matched male participants. Finally, we investigated whether history of HT containing estrogens modified the synergistic association of age at menopause and vascular risk with cognition. We hypothesized that HT would attenuate the interactive association of earlier menopause and elevated vascular risk with lower cognitive scores at follow-up.

Methods

Participants

We included data from participants in the CLSA Comprehensive Cohort. CLSA study design and procedures have been previously described.[25] In brief, the CLSA is a population-based observational study that started in 2011. Participants were randomly recruited from a ≤50 km radius at 11 data collection sites across Canada. Of prospective participants contacted, 10% responded, and approximately 45% of those individuals

participated in the study. Participants are adults aged 45–85 years without significant cognitive impairment at baseline, as determined by trained interviewers. Participants are deemed free from significant cognitive impairment if they can understand the purpose of the study and provide informed consent. The CLSA does not classify cognitive status beyond this criterion. Participants completed questionnaires, cognitive testing, and in-depth physical assessments at baseline (2011–2015) and 3-year follow-up (2015–2018). During manuscript preparation, cognitive test data were available for the baseline and first follow-up visit.

Participants were asked to self-report their sex at birth as "female," "male," or "do not know." Participants were also asked to self-report their current gender identity as "female," "male," "transgender woman/transwoman," "transgender man/transman," "genderqueer," or "other specified." We included participants who self-reported both their sex at birth and current gender identity as "female" and who also self-reported being postmenopausal at baseline. Participants who reported hysterectomy were excluded because they were not asked at what age hysterectomy occurred (n = 2,212, 15.9% of cisgender female participants). No data were available for history of oophorectomy. We included an equivalent number of age-matched participants who identified both their sex at birth and current gender identity as "male" using nearest-neighbour matching. Participants who did not complete cognitive testing at both baseline and follow-up or who had missing data for main exposures (i.e., age at menopause, vascular risk) or covariates were excluded. The participant selection process is described in eFigure 1.

Standard Protocol Approvals, Registrations and Patient Consents

The CLSA received research ethics approval in all provinces where data collection took place. All participants provided written informed consent. We followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for cohort studies.

Baseline Vascular Risk

To quantify vascular risk, we used a score that considered the presence/absence of 6 factors, modified from a previously used method.[6] The score included the following: (1) current smoking, (2) elevated blood pressure, defined as systolic blood pressure >120 mm Hg or diastolic blood pressure >80 mm Hg, (3) treatment for hypertension, defined as the use of blood pressure–lowering medications based on participants' medication records, (4) obesity, defined as body mass index ≥30 kg/m^2 (calculated using height and weight), (5) diabetes, defined as self-reported or physician-diagnosed diabetes, and (6) elevated low-density lipoprotein (LDL) cholesterol, defined as ≥3.5 mmol/L in serum, measured in nonfasting venipuncture blood samples taken at baseline. Lipid profiles were measured by clinical analyzer (Roche Diagnostics Cobas 800 series) at Calgary Laboratory Services, and LDL cholesterol was estimated using the Friedewald formula. For each participant, the number of factors present was summed to provide a total score ranging 0–6. If participants were missing data on >2 factors, the score was set to missing (n = 8, 0.03%). If participants were missing data on ≤2 factors, the score was computed using available data and scaled to the full 6-point range. Of included participants, n = 110 (0.7%) were missing data on 2 factors, and n = 1,937 (11.6%) were missing data on 1 factor.

Menopause History and HT History

At baseline, female participants were asked to report whether they had experienced menopause, defined as "menstrual periods stopped for at least 1 year and did not restart." If participants responded affirmatively, they were asked to self-report the age at which menopause occurred. Participants who reported improbable ages of spontaneous menopause (i.e., <35 or >65 years; n = 120, 1.3%) were excluded. To minimize the potential influence of menopause symptoms on cognitive test performance—which can persist for several years after the final menstrual period[26]—we included only participants who were at least 2 years post menopause at baseline (n = 447 excluded, 5.1%).

Female participants were asked to report their lifetime history of HT, including type, age at initiation, and duration of therapy. For type, participants were asked to indicate whether they took "both estrogen and progesterone," "estrogen (e.g., premarin and estrace)," "progesterone (e.g., prometrium and provera)," "estrogen gel or cream applied to the skin (e.g., estraderm and estrogel)," or "intrauterine device with progesterone." Because most forms of HT are hypothesized to influence dementia risk through estrogen-related neuroprotection,[27] we excluded participants who reported progesterone-only therapies (n = 221, 2.6%) from the HT analyses. We also excluded participants with unknown HT type (n = 445, 5.3%) and topical estrogens (n = 228, 2.7%). Consistent with previous methodology in the CLSA,[28] we excluded participants who reported starting HT more than 10 years before menopause or at an age younger than 30 years because these participants might have confused HT with hormonal contraceptives (n = 89, 1.06%). We additionally excluded participants with unknown HT duration (n = 16, 0.19%). Finally, because time of HT initiation relative to menopause may affect dementia risk,[3,22,23] we categorized participants based on whether HT was initiated within the clinically recommended time frame (i.e., younger than 60 years of age or less than 10 years after menopause) or outside of it.[29] Due to the limited number of participants who initiated HT outside of this time frame (n = 47; 1.97% of users of systemic HT containing estrogens), we did not conduct a separate analysis for this subgroup, and these participants were excluded from HT analyses.

Assessment of Cognition

Cognition was assessed with a neuropsychological battery completed at baseline and follow-up. Tests were administered in either English or French.[30] To capture early changes

associated with AD, we created a composite score of tests of episodic memory, language, and executive function. The tests included a modified version of the Rey Auditory Verbal Learning Test (average of Trial 1 immediate recall and 5-minute delayed recall scores),[31] Animal Fluency,[32] Controlled Oral Word Association Test,[33] the Stroop Test (interference condition),[34] and the Mental Alteration Test.[35] We standardized cognitive test scores using the baseline data of the analytic sample (i.e., all postmenopausal female and age-matched male participants) and averaged the standardized scores for each test to compute the composite. We took several steps to ensure the accuracy and reliability of the cognitive composite. First, we excluded highly improbable test scores (i.e., scores more than 10 SDs above or below the cohort mean). This resulted in the exclusion of the Stroop Test for 2 participants. In addition, to ensure comparability of the composite between baseline and follow-up, we included only cognitive tests that were available at both baseline and follow-up for each participant.

Statistical Analyses

Analyses were performed in R (version 4.1.2). We used *t* tests and χ^2 tests to compare demographic characteristics between female and male participants and between female participants with and without history of HT containing estrogens. Analysis of variance and χ^2 tests were used to compare demographic characteristics among female participants with earlier, average, or later menopause, defined by tertiles. Linear regression models tested the independent and interactive associations of age at menopause (in years) and baseline vascular risk score on cognitive composite scores at 3-year follow-up, adjusting for baseline cognitive composite scores. All models additionally adjusted for baseline age, years of education, and test language (English/French). Models that included only female participants included a covariate for history of HT containing estrogens (yes/no). *APOE* genotype data were missing for a sizeable proportion of participants in the main analytic sample (n = 1,081 of 8,360), so we did not adjust for *APOE* ε4 carriage in the main models. *APOE* ε4 carriage was considered as a covariate in sensitivity analyses.[36] All *p* values were 2-sided with a significance threshold set at $p < 0.05$. We did not correct for multiple comparisons because all models tested a priori hypotheses and used a cognitive composite score as the outcome.

First, we investigated whether earlier menopause and elevated vascular risk were independently associated with lower cognitive scores at 3-year follow-up among postmenopausal female participants. In a separate model, we examined whether elevated vascular risk was related to cognitive scores at follow-up in male participants. To test whether the association between vascular risk and prospective cognition differed between sexes, we modeled the interaction between sex and vascular risk on follow-up cognition.

Next, we tested whether earlier menopause and greater vascular risk were synergistically associated with prospective cognition in female participants. To do so, we examined the interaction between age at menopause and vascular risk on follow-up cognition. We also examined associations between vascular risk and follow-up cognition in participants stratified by age at menopause: earlier (35–48 years), average (49–52 years), or later (53–65 years), determined by tertile split. To contextualize the associations observed in female participants, we compared the standardized effect sizes of the associations of vascular risk with follow-up cognition in female participants with earlier, average, or later menopause to the corresponding association in male participants age-matched to each tertile.

Finally, we examined whether history of HT containing estrogens modified the cognitive outcomes associated with earlier age at menopause and/or greater vascular risk. First, we tested the 3-way interaction between age at menopause, vascular risk, and HT history on follow-up cognition. The model was adjusted for the same covariates described earlier, including baseline cognition, baseline age, years of education, and test language, along with the addition of cumulative HT exposure (i.e., length of time used in years). Next, we examined the 2-way interaction between HT history and vascular risk on follow-up cognition (adjusting for age at menopause) and the 2-way interaction between HT history and age at menopause on follow-up cognition (adjusting for vascular risk). These latter analyses allowed us to assess whether history of HT containing estrogens moderated the independent associations of earlier menopause and elevated vascular risk on prospective cognition.

To assess the robustness of our findings, in sensitivity analyses, we repeated the main models adding the following covariates: annual household income, lipid-modifying medication use, self-reported weekly physical activity, depression symptoms, alcohol (in number of drinks per week), *APOE* ε4, and history of heart disease and stroke. Because smoking is known to increase the risk of early menopause,[37] we reran main analyses using a modified vascular risk score that excluded smoking. Finally, although our focus was on an aggregate measure of vascular risk, post hoc analyses explored whether there were interactive associations of age at menopause and each individual vascular risk factor with cognition.

Data Availability

Data are available from the CLSA (clsa-elcv.ca) for researchers who meet the criteria for access to deidentified CLSA data.

Results

Participant Characteristics

Table 1 summarizes the demographic characteristics of the study participants by sex. We included 8,360 postmenopausal female participants and 8,360 age-matched male participants. eTable 1 summarizes the demographic characteristics of female participants by tertile of age at menopause.

Table Demographics for Postmenopausal Female and Age-Matched Male Participants

Sex	Cisgender female (n = 8,360)	Cisgender male (n = 8,360)	SMD	*p* Value
Baseline age, y, mean (SD)	65.0 (8.53)	65.0 (8.53)	<0.001	>0.99
Age at menopause, y, mean (SD)	50.1 (4.62)	—	—	—
Time since menopause, y, mean (SD)	14.9 (9.39)	—	—	—
Race/ethnicity, n (%)				
Arab	17 (0.20)	28 (0.33)	0.03	0.14
Black	49 (0.59)	61 (0.73)	0.02	0.29
Chinese	60 (0.72)	62 (0.74)	0.003	0.93
Filipino	16 (0.19)	7 (0.08)	−0.03	0.10
Japanese	8 (0.10)	20 (0.24)	0.04	0.04
Korean	1 (0.01)	3 (0.04)	0.02	0.62
Latin American	25 (0.30)	26 (0.31)	0.002	>0.99
Other[a]	124 (1.48)	110 (1.32)	−0.01	0.39
South Asian	46 (0.55)	98 (1.17)	0.07	<0.001
Southeast Asian	15 (0.18)	16 (0.19)	0.003	>0.99
West Asian	9 (0.11)	14 (0.17)	0.02	0.40
White	8,090 (96.8)	8,018 (95.9)	−0.05	0.003
Years of education, mean (SD)	14.6 (2.33)	14.98 (2.43)	−0.17	<0.001
Annual household income, n (%)				
<$20,000	470 (5.62)	271 (3.24)	−0.13	<0.001
$20,000–$49,999	2,238 (29.1)	1,431 (18.0)	−0.27	<0.001
$50,000–$99,999	2,852 (37.1)	3,043 (38.2)	0.02	0.16
$100,000–$149,999	1,216 (15.8)	1,757 (22.1)	0.16	<0.001
≥$150,000	909 (11.8)	1,461 (18.3)	0.18	<0.001
Vascular risk score, 0–6, mean (SD); median (IQR)	1.63 (1.23); 1.20 (1.00–2.40)	1.80 (1.20); 2.00 (1.00–3.00)	0.14	<0.001
Elevated blood pressure, n (%)	4,007 (48.5)	4,728 (56.9)	0.17	<0.001
Blood pressure–lowering medications, n (%)	2,798 (33.5)	3,524 (42.2)	0.18	<0.001
Current smoking, n (%)	616 (7.4)	746 (8.9)	0.06	<0.001
Obesity, n (%)	2,313 (27.8)	2,471 (29.7)	0.04	0.008
Diabetes, n (%)	1,288 (15.5)	1,699 (20.4)	0.13	<0.001
Elevated LDL cholesterol, n (%)	2,300 (31.2)	1,503 (20.2)	−0.25	<0.001
History of stroke, n (%)	122 (1.46)	166 (1.99)	0.04	0.01
History of heart disease, n (%)	708 (8.47)	1,325 (15.9)	0.23	<0.001
Language, French, n (%)	1,669 (20.0)	1,514 (18.1)	0.05	0.002
History of systemic hormone therapy containing estrogens, n (%)	2,474 (29.6)	—	—	—

IQR = interquartile range; LDL = low-density lipoprotein; SMD = standardized mean difference of male participants relative to female participants.
p Values represent the results of *t* tests and χ^2 tests comparing female participants with male participants.
[a] Includes participants who self-reported their race/ethnicity as "Asian-Dutch" (n = 1), "Australian Aboriginal" (n = 1), "Canadian" (n = 12), "Caribbean" (n = 3), "Caucasian" (n = 2), "East Asian" (n = 1), "Eurasian" (n = 2), "Fiji" (n = 1), "Gypsy" (n = 1), "Italian" (n = 5), "Jamaican" (n = 2), "Jewish" (n = 14), "Jewish/White" (n = 1), "Maori" (n = 1), "Mediterranean" (n = 1), "Mi'kmaq" (n = 1), "Micmac" (n = 4), "Mikmaq" (n = 1), "Miqma" (n = 1), "Mixed" (n = 3), "Mixed race" (n = 1), "Native" (n = 2), "Northern European" (n = 1), "West Indian" (n = 4), and "West Indies" (n = 1).

Independent Associations of Age at Menopause and Vascular Risk With Prospective Cognition in Postmenopausal Female Participants and Age-Matched Male Participants

Earlier age at menopause and higher vascular risk were independently associated with lower follow-up cognitive scores in female participants (age at menopause: β = 0.029, 95% CI 0.017–0.041, $p < 0.001$; vascular risk: β = −0.016, 95% CI −0.028 to −0.004, $p = 0.009$; see eTable 2 for full model). Specifically, for every 1 SD increase in menopause age, cognitive scores at follow-up increased by 0.029 SD. For every 1 SD increase in the vascular risk score, there was a 0.016 SD decrease in cognitive scores at follow-up.

In a separate model that included only male participants, vascular risk was also associated with lower cognitive scores at follow-up (β = −0.020, 95% CI −0.032 to −0.008, $p = 0.001$; eTable 3). Next, we tested whether the association of vascular risk with prospective cognition differed by sex. The interaction between vascular risk and sex was not significant, suggesting that the association of vascular risk with cognition did not differ between entire groups of female and male participants (β = 0.001, 95% CI −0.015 to 0.018, $p = 0.90$; eTable 4).

Synergistic Associations of Age at Menopause and Vascular Risk With Prospective Cognition

There was a significant interaction between age at menopause and vascular risk on prospective cognition (β = 0.013, 95% CI 0.001–0.025, $p = 0.03$; Figure 1; eTable 5), whereby earlier age at menopause exacerbated the association of greater vascular risk with lower cognitive scores. In analyses stratified by age at menopause (based on tertile split), elevated vascular risk was significantly associated with lower cognitive scores in participants with earlier menopause (β = −0.044, 95% CI −0.066 to −0.022, $p < 0.001$), but not participants with average (β = −0.007, 95% CI −0.027 to 0.012, $p = 0.46$) or later menopause (β = 0.003, 95% CI −0.020 to 0.025, $p = 0.82$; eTable 6). For each tertile of age at menopause, beta coefficients represent the predicted change in cognition for a 1 SD increase in the vascular risk score.

To contextualize these associations, we also tested the associations of vascular risk with cognition in subgroups of male participants age-matched to female participants with earlier, average, or later menopause. In each age-matched male group, the average vascular risk score was higher relative to the corresponding group of female participants (vascular risk scores: mean [SD] = 1.67 [1.25] in female participants with earlier menopause vs 1.74 [1.21] in matched men; mean [SD] = 1.56 [1.23] in female participants with average menopause vs 1.77 [1.21] in matched men; mean [SD] = 1.69 [1.21] in female participants with later menopause vs 1.81 [1.23] in matched men). Vascular risk was significantly associated with lower cognitive scores at follow-up in each age-matched group of male participants (male participants matched to female participants with earlier menopause: β = −0.035, 95% CI −0.056 to −0.014, $p = 0.001$; male participants matched to female participants with average menopause: β = −0.035, 95% CI −0.054 to −0.016, $p < 0.001$; male participants matched to female participants with later menopause: β = −0.043, 95% CI −0.065 to −0.021, $p < 0.001$; eTable 7). Notably, when comparing the association of higher vascular risk with lower cognitive scores in female participants with earlier menopause to that of age-matched male participants, the effect size was larger in female participants with earlier menopause. Specifically, for each 1 SD increase in vascular risk scores, female participants with earlier menopause showed a 0.044 SD decrease in cognitive scores, whereas age-matched male participants showed a 0.035 SD decrease in cognitive scores.

Modifying Effects of HT

eTable 8 summarizes participant characteristics for female participants included in HT analyses (n = 7,314 total). We included 2,322 participants who reported a history of HT containing estrogens and 4,992 participants with no HT.

The 3-way interaction between HT containing estrogens, age at menopause, and vascular risk on cognition was not significant (β = −0.005, 95% CI −0.032 to 0.021, $p = 0.69$; eTable 9). There was also no 2-way interaction between HT containing estrogens and vascular risk on cognition (β = 0.009, 95% CI −0.018 to 0.037, $p = 0.51$; eTable 9). However, we observed a trend toward a 2-way interaction between history of HT and age at menopause on cognition (β = −0.026, 95% CI −0.052 to 0.001, $p = 0.06$, Figure 2; eTable 9). Specifically, the association of earlier menopause with lower cognitive scores was attenuated in female participants who took HT relative to those who did not take HT.

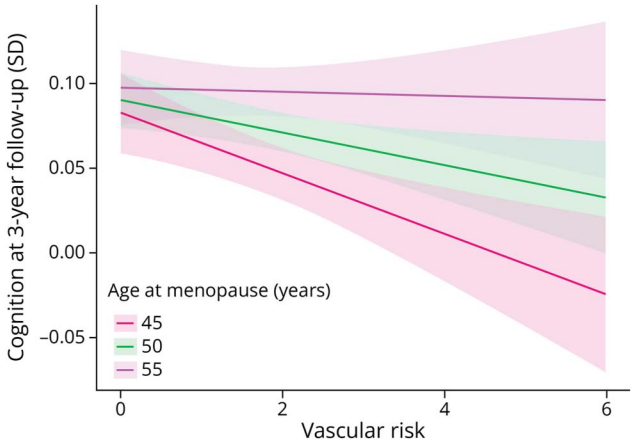
Sensitivity Analyses

In sensitivity analyses, we found similar results when we repeated the main models after adjusting for additional relevant covariates (eTable 10) and when using the modified vascular risk score that excluded smoking status (eTable 11). Analyses testing the interactive associations of age at menopause and each individual vascular risk factor with cognition showed that elevated blood pressure and smoking had the strongest effects (eTable 12).

Discussion

In a large cohort of postmenopausal female adults, earlier age at menopause and elevated vascular risk burden were synergistically associated with lower cognitive scores at 3-year follow-up. Vascular risk burden was more strongly associated with lower cognitive scores in female participants with earlier menopause than in age-matched male participants, suggesting that age at menopause and vascular risk burden may together contribute to sex differences in cognitive outcomes. History of HT did not modify the combined impact of age at menopause and vascular risk on prospective cognition. However, female

Figure 1 Two-Way Interaction Between Age at Menopause and Vascular Risk Burden on Cognition at 3-Year Follow-Up in Postmenopausal Female Participants



The plot depicts marginal effects, showing model estimates of the association of vascular risk burden score with follow-up cognition (standardized score) in participants with menopausal ages of 45, 50, and 55 years. Age at menopause is modeled as a continuous variable, and model estimates for the median age at menopause for each tertile (i.e., earlier, average, and later menopause) are shown for visualization purposes. The models are adjusted for baseline cognition, baseline age, years of education, test language, and history of HT containing estrogens. Shaded regions represent 95% CIs. HT = hormone therapy.

participants with a history of HT containing estrogens exhibited an attenuated association between earlier age at menopause and lower cognitive scores, regardless of level of vascular risk burden. Together, these findings underscore the importance of considering the combined impact of hormonal and vascular risk factors in investigations of female AD risk.

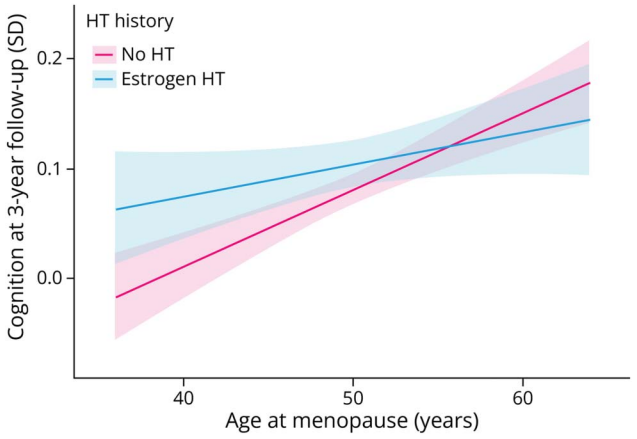
Separate studies suggest that both earlier menopause[3,12-16] and greater vascular risk[4-6] increase the risk of AD and dementia. Our findings build on this evidence by suggesting that earlier menopause may worsen the adverse effects of elevated vascular risk on cognitive decline. Of interest, we found a significant association between vascular risk and cognition in participants with earlier menopause (i.e., menopausal age 35–48 years), which was not observed in women with average or later menopause. By contrast, the association of greater vascular risk with lower cognitive scores was significant across all age-matched groups of male participants. However, the effect size was notably larger in female participants in the earliest tertile of age at menopause compared with their age-matched male counterparts. This suggests that endocrine processes may modify sex differences in associations of vascular risk factors with cognitive outcomes, highlighting the need to include female-specific factors in the evaluation of sex differences in dementia risk.

The mechanisms underlying the interactive association of age at menopause and vascular risk on cognition are unclear. Estrogens have a wide range of beneficial properties including protecting the vasculature of the brain.[38] Declining estradiol during the menopause transition may increase female susceptibility to the detrimental effects of vascular risk on brain and cognitive health. This hypothesis is supported by human and animal studies demonstrating that female individuals are more susceptible to vascular brain changes (e.g., white matter hyperintensities, myelin degeneration) after menopause.[39,40] Additional support for this hypothesis comes from a recent study that used a mouse model of vascular cognitive impairment and found that induced menopause led to more severe metabolic dysfunction and cognitive impairments compared with nonmenopausal mice.[41] One possibility is that the depletion of ovarian hormones may exacerbate the influence of vascular factors in promoting AD pathology, potentially through mechanisms such as reduced Aβ clearance.[42] This process may be especially salient in female individuals who undergo menopause at younger ages because they experience an earlier loss of estradiol-related neuroprotection.

The interactive association of age at menopause and vascular risk with cognition was not modified by history of HT. However, we observed a pattern where HT containing estrogens attenuated the association of earlier age at menopause with cognitive decline after adjusting for vascular risk, though the interaction did not reach statistical significance ($p = 0.06$). These findings are consistent with studies showing that HT is associated with lower AD risk, especially if initiated in midlife and/or proximal to menopause.[22-24] However, our study was limited by self-reported medication data and lacked details about HT types, doses, and regimens. In addition, we used a prevalent user design, and therefore, we cannot establish a causal link between HT and cognition.

While we found significant interactive associations of age at menopause and vascular risk with prospective cognition, the effect sizes were small. This is in line with the observation that cognitively unimpaired adults generally experience only small changes in cognition over a 3-year period.[43] It is possible that our findings represent subtle cognitive changes that could serve as early signs of risk for cognitive impairment. Future studies should test whether cognitive trajectories by menopause age and vascular risk level continue to diverge over longer follow-up periods. It is also worth noting that we did not use sex-specific thresholds in our calculation of vascular risk burden. While there is evidence that male and female individuals should have different cutoffs for many biomarkers used to diagnose cardiovascular conditions, there are currently not established sex-specific clinical recommendations.[44] Furthermore, existing sex-specific algorithms for predicting vascular risk, such as the Framingham Risk Score, are strongly driven by age and lack validation in older adults (i.e., older than 74 years),[45] complicating their use in studies of cognitive decline that involve a wide age range, such as this study. It is also important to note that most clinical tools and research methodologies used to assess vascular risk fail to consider female-specific factors that may influence cardiovascular outcomes, such as adverse pregnancy outcomes, hormonal contraception, and menopause.[46]

Figure 2 Two-Way Interaction Between HT Containing Estrogens and Age at Menopause on Cognition at 3-Year Follow-Up



The plot depicts marginal effects, showing estimates of the association of age at menopause with follow-up cognition (standardized score) in female participants with history of HT containing estrogens vs female participants with no history of HT. The model is adjusted for baseline cognition, baseline age, vascular risk burden score, years of education, test language, and cumulative HT exposure. Shaded regions represent 95% CIs. HT = hormone therapy.

There are several other limitations to note. Given that age at menopause was retrospectively self-reported, temporality between menopause and vascular risk factors could not be established. Moreover, we relied on self-reported data to determine age at menopause and HT history. This methodology may introduce inaccuracies, especially given that, for many participants, menopause had occurred several years to decades before the study. Previous research has found that data on self-reported age at menopause may be less accurate when collected long after menopause,[47] although the discrepancy between menopause age reported proximal to menopause vs long after menopause is small.[48] Future research should leverage longitudinal medical records or objective hormone levels to ascertain age at menopause. To minimize the potential influence of menopause symptoms on cognitive test performance, we excluded female participants <2 years post menopause at baseline. However, we acknowledge that this cutoff is somewhat arbitrary, given the variability in the duration of menopause symptoms.[26] Future studies would benefit from collecting data on menopause symptoms to perform analyses that account for their influence. In addition, 22.7% of female participants who took systemic HT containing estrogens (n = 526) in our analytic sample reported starting HT before their self-reported age at menopause. Self-reported age at menopause may be less accurate in these participants, given that some types of HT may cause uterine bleeding that could be confused with a menstrual period.[49]

While we excluded female participants who self-reported hysterectomy, a substantial proportion of participants in our sample reported history of estrogens-only HT (presumably unopposed), which is typically prescribed only to people without uteruses due to the risk of endometrial cancer.[50] It is possible that hysterectomy status and/or type of HT were misclassified in some of these participants. Furthermore, the CLSA does not collect data on history of oophorectomy, so we could not confirm whether menopause was spontaneous or surgical among participants who did not report a hysterectomy. It is possible that participants with earlier menopause were more likely to have had an oophorectomy, which may contribute to the observed associations between earlier menopause and greater cognitive decrements. Due to small sample sizes, we did not investigate the effects of HT initiated in late life and/or more than 10 years after menopause, which might further influence cognitive outcomes.

This study could not follow participants from the onset of menopause and/or HT initiation, which may lead to selection bias in HT use and residual confounding. As such, causation cannot be inferred, and HT findings should be cautiously interpreted. During manuscript preparation, cognitive data from the CLSA were available only for the baseline and the 3-year follow-up visit, limiting our ability to detect cognitive changes beyond this period. Finally, the CLSA is racially/ethnically homogenous, with the overwhelming majority of participants identifying as White. This limits the generalizability of our findings and highlights the need for greater diversity in AD research.

In this study, we showed that earlier menopause and elevated vascular risk synergistically drive lower cognitive scores at 3-year follow-up in postmenopausal female adults. The interactive association of age at menopause and vascular risk on prospective cognition was not modified by a history of HT. However, female participants with a history of HT containing estrogens showed an attenuated association between earlier menopause and lower cognitive scores at follow-up. Considering that female individuals with earlier menopause and higher vascular risk may be at greater risk of dementia, both factors should be considered when developing sex-specific interventions to slow cognitive decline.

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