Subclinical Carotid Artery Atherosclerosis and Cognitive Function in Older Adults

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Abstract

Background

The combined effects of increased life expectancy and the considerable number of persons reaching old age will magnify the dementia epidemic in the United States. Demonstration that subclinical atherosclerosis precedes and is associated with cognitive impairment suggests a modifiable risk factor for age-associated cognitive impairment and dementia. The purpose of this study is to determine whether subclinical atherosclerosis as measured by carotid artery intima-media thickness (CIMT) is associated with changes in cognitive function over time in older adults.

Methods

This cohort study combined longitudinal data from three clinical trials conducted between 2000-2013: the B-Vitamin Atherosclerosis Intervention Trial (BVAIT), the Women's Isoflavone Soy Health (WISH) trial, and the Early versus Late Intervention Trial with Estradiol (ELITE). Participants were recruited from the general population in the Greater Los Angeles area and were free of cardiovascular disease and diabetes; no cognitive or psychiatric exclusion criteria were specified. The same standardized protocol for ultrasound image acquisition and measurement of CIMT was used in all trials. CIMT measurements performed at baseline were used in these analyses. Cognitive function was assessed at baseline and at 2.5 years using a battery of 14 standardized cognitive tests. All clinical trials were conducted at the University of Southern California Atherosclerosis Research Unit, Los Angeles and had at least 2.5 years of cognitive follow-up.

Results

308 men and 1,187 women, mean age of 61 years, were included in the combined longitudinal dataset for the primary analysis. No associations were found between CIMT and cognitive function at baseline. There was a weak inverse association between CIMT at baseline and change in global cognition assessed over 2.5 years (β (SE)=-0.056 (0.278) units per 0.1 mm CIMT, SE: 0.278, 95% CI: -0.110, -0.001, $p=0.045$). No associations between CIMT at baseline and changes in executive function, verbal memory, or visual memory were found.

Conclusions

In this sample of healthy older adults, our findings suggest an association between subclinical atherosclerosis and change in global cognitive function over 2.5 years. Subclinical atherosclerosis of the carotid artery may be a modifiable predictor of cognitive decline in middle and older age.

Trial Registration

BVAIT (NCT00114400), WISH (NCT00118846), ELITE (NCT00114517)

Background

Although Alzheimer's disease and related dementias are major public health concerns, the recognition of modifiable risk factors has elucidated new avenues for dementia risk reduction. Indeed, evidence of a decline in the prevalence of dementia in the United States may be attributed in part to an increased awareness about controlling cardiovascular risk factors, particularly in middle-aged adults(1).

Previous studies have shown a clear association between carotid artery atherosclerosis, a modifiable risk factor, and cognitive impairment(2). Greater amounts of carotid arterial plaque have been linked to an increased risk of developing dementia(3). Even mild carotid artery atherosclerosis, or subclinical atherosclerosis, has been shown to be associated with poorer cognitive function in middle-aged adults, even after adjusting for other vascular risk factors(4, 5).

Carotid artery intima-media thickness (CIMT), a measurement of the thickness of the two inner layers of the carotid artery, is a commonly used and validated research measure of atherosclerosis in the subclinical stages(6). Past cross-sectional research has shown that thicker CIMT is associated with poorer cognitive performance generally, and in certain cognitive domains. However, with regards to global cognition, the findings have been inconsistent. For example, while a few cross-sectional studies have failed to find an association between thicker CIMT and global cognition(5, 7, 8), one longitudinal study found an inverse association(9).

There are several possible reasons for the lack of consistency in the findings. One is that the various instruments used to evaluate the same cognitive domain differ in their sensitivity. In addition, some studies used a single instrument while others employ multi-test batteries to assess cognitive function. Differences in study populations and the image acquisition and measurement methods for subclinical atherosclerosis may also contribute to the lack of consistency in the findings. Finally, many previous studies have only examined cross-sectional associations between CIMT and cognitive function.

To further elucidate the association between subclinical atherosclerosis and cognitive function in older age, this current study combined data from three clinical trials and examined cognitive change over time. Participants in each of these clinical trials completed an extensive battery of standardized neuropsychological tests at baseline and at follow-up visits, allowing for examination of longitudinal associations. All trials used a well-characterized measure of subclinical atherosclerosis, CIMT of the right common carotid artery; ultrasound imaging and CIMT measurement were completed using the same standardized protocol in all three trials. Additionally, we controlled for a number of potential confounding effects of cardiovascular, genetic and demographic risk factors. We hypothesized that thicker CIMT is associated with greater declines in cognitive function.

Methods

Study Design

This longitudinal cohort study combined data from three clinical trials: B-Vitamin Atherosclerosis Intervention Trial (BVAIT, NCT00114400), Women's Isoflavone Soy Health (WISH, NCT00118846), and Early versus Late Intervention Trial with Estradiol (ELITE, NCT00114517). Participants in all three trials were of similar cardiovascular health and did not have diabetes or clinical signs/symptoms of cardiovascular disease. Cognitive function was measured using the same battery of 14 neuropsychological tests at baseline and 2.5 years in all three trials.

BVAIT Design

BVAIT was a randomized, double-blinded, placebo-controlled trial conducted from November 2000 to June 2006. The trial was designed to examine whether B-vitamin supplementation would reduce the progression of early subclinical atherosclerosis in individuals over 40 years of age with higher levels of total homocysteine. Eligible men and women had fasting total homocysteine $\geq 8.5 \mu\text{mol/L}$. A total of 506 participants were randomized to daily high-dose vitamin B supplementation (folic acid 5 mg + vitamin B₁₂ 0.4 mg + vitamin B₆ 50 mg) or matching placebo in a 1:1 ratio within two strata of baseline CIMT thickness ($<0.75 \text{ mm}$, $\geq 0.75 \text{ mm}$).

WISH Design

WISH was a randomized, double-blinded, placebo-controlled, randomized trial conducted from April 2004 to March 2009. WISH was designed to determine whether isoflavone-rich soy protein supplementation had any effect on the progression of subclinical atherosclerosis in healthy post-menopausal women. A total of 350 women were randomized to treatment (25 g soy protein) or matching placebo in a 1:1 ratio within two strata of baseline CIMT thickness ($<0.75 \text{ mm}$, $\geq 0.75 \text{ mm}$).

ELITE Design

ELITE was a randomized, double-blinded, placebo-controlled trial conducted from July 2005 to February 2013. ELITE was designed to examine the effects of oral 17 β -estradiol on the progression of subclinical atherosclerosis and cognitive decline in healthy postmenopausal women. A total of 643 women were randomized to treatment (oral 17 β -estradiol 1 mg/day) or placebo in a 1:1 allocation ratio within strata defined by length of time since menopause (early postmenopause, <6 years past menopause and late postmenopause, ≥ 10 years past menopause).

Participants for these clinical trials were recruited from the general population in the Greater Los Angeles area mainly through media advertisements. The WISH and ELITE clinical trials included women only. Due to similar exclusion criteria for cardiovascular risk factors, all participants were of comparable cardiovascular health. All studies had CIMT measurements performed every 6 months and had at least 3 years of follow-up. No cognitive or psychiatric exclusion criteria were specified.

The final study sample included 1,495 men and women. Four other participants were excluded due to missing baseline cognitive data.

CIMT Assessment

In each of the trials, high-resolution B-mode ultrasound images of the right distal common carotid artery were obtained as previously described at baseline and every 6 months during follow-up(10). From the images, CIMT was measured using software that was developed at the University of Southern California (USC) for longitudinal measurements of atherosclerosis changes(11, 12). CIMT was calculated as the average of multiple individual measurements between the intima-lumen and the media-adventitia interfaces along a 1 cm length of the right common carotid artery far wall(5). This method standardized the location and distance over which CIMT was measured and ensured that the same measurements were obtained for each participant in all trials(12).

Cognitive Function Assessment

The same battery of cognitive and neuropsychological assessments was administered by a single trained psychometrist in a standardized order to participants. The battery included the following 14 assessments(5, 13):

- Symbol Digit Modalities Test
- Trail Making Test, Part B
- Judgment of Line Orientation, Form H
- Block Design, Wechsler Adult Intelligence Scale, 3rd Edition
- Letter-Number Sequencing, Wechsler Memory Scale, 3rd Edition
- Category Fluency (animal naming, 60 seconds)
- Boston Naming Test, 30-item version
- Shipley Institute of Living Scale, Abstraction Scale
- California Verbal Learning Test, 2nd Edition, 3-trial immediate recall and delayed recall
- Logical Memory, immediate recall and delayed recall
- Faces I (immediate recall) and Faces II (delayed recall), Wechsler Memory Scale, 3rd Edition

The assessments were selected for sensitivity to age-related changes in cognitive function and representation of different cognitive functions and abilities with a focus on executive function and verbal and visual memory. Results from the 14 assessments were used to generate composite scores for executive function, verbal memory, visual memory and global cognition. The executive function composite score was calculated as a weighted average of the following cognitive tests: Symbol Digit Modalities Test, Trail Making Test, Part B, Shipley Institute of Living Scale, Abstraction Scale, Letter-Number Sequencing, and Category fluency (animal naming, 60 seconds). The verbal memory composite score was calculated as a weighted average of the California Verbal Learning Test, 2nd Edition (immediate and delayed recall) and Logical Memory (immediate and delayed recall). The visual memory composite score was calculated as a weighted average of the Faces I (immediate recall) and Faces II (delayed recall) tests. Global cognition composite score was calculated as a weighted average of all 14 assessments. For each participant, all test scores were converted to a standardized Z score at baseline and 2.5 years for all trials. The Z scores were calculated using the study-specific baseline mean and

standard deviation of each test. To calculate the composite scores, the Z scores for the appropriate cognitive test were summed and then weighted by the inter-test correlation matrix(5, 14–16).

Covariates

At the baseline visit for each clinical trial, demographic information (age, sex, race, education level, income level and marital status), laboratory values (low-density lipoprotein- (LDL) and high-density lipoprotein- (HDL) cholesterol, glucose), lifestyle factors (smoking status, alcohol consumption and physical activity summary measures), use of anti-hypertensive and lipid-lowering medications, body mass index (BMI), and blood pressure were collected. Genotyping for three isoforms ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$) of the apolipoprotein E (ApoE) gene was also performed (TaqMan Assay-on-Demand Genotyping Service; Applied Biosystems). In addition, participants completed the Center for Epidemiological Studies Depression (CES-D) scale.

Statistical Methods

Because some CIMT and cognitive data were not captured exactly at the 2.5- and 5-year visits (primarily due to missed study visits), follow-up CIMT and cognitive measures were defined over a range of visits for the two time points; the 2.5-year variable encompassed visit months 24-36, and the 5-year variable (ELITE only) encompassed visit months 52-66.

Baseline Cross-Sectional Associations between CIMT and Cognition

Multivariable linear regression models were used to examine the baseline cross-sectional association between CIMT and cognitive function. Covariates that were evaluated as potential confounders included age, sex, race, education, income, marital status, ApoE4 genotype, current smoking status, CES-D score, systolic blood pressure (SBP), and HDL. In models where height or weight were found to be confounders, they were replaced with BMI as it incorporates both height and weight and is a better indicator of body composition. To account for differences between clinical trials, indicator variables for study were included in all models. Product terms were used to test for interactions between CIMT and ApoE4 genotype as well as between CIMT and sex, and between CIMT and age group (participants <65 years old and participants ≥ 65 years old). CIMT was assessed as a continuous variable. Because BMI, systolic blood pressure, and HDL-cholesterol are potential determinants of CIMT in the cognitive function pathway, the association was also examined without adjustment for these variables. Associations with CIMT were reported per 0.1 mm, the approximate standard deviation from the study population.

Longitudinal Associations between CIMT and Cognition

A change variable was created for each dependent cognitive variable as the difference between the 2.5 year and baseline scores. Associations between baseline CIMT and the cognitive change variables were tested in models adjusting only for baseline cognitive scores and in multivariable linear regression

models. Potential confounders were re-evaluated in the final models. Modeling procedures were completed as described above with the change in cognitive measure as the dependent variable.

While past research has found that greater CIMT is longitudinally associated with cognitive decline in adults aged 65 years and older, results have been mixed for middle-aged adults(17). To examine the CIMT-cognition association by age, analysis of associations between baseline CIMT and the cognitive change variables were also stratified by age group (<65 and $\geq$ 65 years old).

Results

Study participant characteristics at baseline are summarized in Table 1. Since ELITE and WISH enrolled only women, most (79%) study participants were women. The majority were non-Hispanic White (66%) and married (59%). Study participants had an average age of 61 years, were highly educated (mean 16 years of education), had an average annual income of \$66,700, and were overweight (mean BMI 27 kg/m²). Over a quarter of participants (27%) carried the ApoE4 genotype. The average CES-D score at baseline was low, and only 13% scored above the cut-off score of 16 indicating concern for clinical depression(18). The average CIMT at baseline was highest in the WISH trial but was otherwise comparable across all three clinical trials (overall mean=0.77 $\pm$ 0.12 mm).

Table 1
Baseline characteristics for study participants by clinical trial (n = 1,495).

Variable	BVAIT (n = 504) ^a	WISH (n = 349) ^a	ELITE (n = 642) ^a	Combined
Mean ± SD or Number (%)				
Age (years)	61.5 ± 9.9	61.4 ± 7.1	60.6 ± 6.9	61.1 ± 8.1
Sex				
Male	308 (61.1%)	0 (0%)	0 (0%)	308 (20.6%)
Female	196 (38.9%)	349 (100%)	642 (100%)	1,187 (79.4%)
Race				
Non-Hispanic White	326 (64.7%)	222 (63.6%)	439 (68.4%)	987 (66.0%)
Non-Hispanic Black	75 (14.9%)	21 (6.0%)	60 (9.3%)	156 (10.4%)
Hispanic	55 (10.9%)	55 (15.8%)	90 (14.0%)	200 (13.4%)
Asian or Pacific Islander	45 (8.9%)	38 (10.9%)	53 (8.3%)	136 (9.1%)
Other	3 (0.6%)	13 (3.7%)	0 (0%)	16 (1.1%)
Education (# of years)	15.7 ± 2.0 ^b	15.8 ± 2.0	16.0 ± 1.9	15.9 ± 2.0
Income	\$64.6k ± \$29.7k ^b	\$65.3k ± \$31.3k ^b	\$69.0k ± \$31.0k ^b	\$66.7k ± \$30.7k
Marital status				
Single, never married	45 (8.9%) ^b	33 (9.5%)	50 (7.8%)	128 (8.6%)
Married	323 (64.1%) ^b	197 (56.4%)	368 (57.3%)	888 (59.4%)
Separated	5 (1.0%) ^b	7 (2.0%)	12 (1.9%)	24 (1.6%)
Divorced	89 (17.7%) ^b	80 (22.9%)	171 (26.6%)	340 (22.8%)

a. 2 participants in BVAIT and 1 participant in both WISH and ELITE each did not complete the baseline cognitive exam.

b. Differing sample sizes: Education, BVAIT: n = 503. Income, BVAIT: n = 472, WISH: n = 319, ELITE: n = 597. Marital status, BVAIT: n = 503. Current smoker, BVAIT: n = 503. BMI, ELITE: n = 641. Blood pressure, ELITE: n = 640. ApoE4 genotype, BVAIT: n = 463, WISH: n = 334, ELITE: n = 637. CES-D score, WISH: n = 348.

c. A score of 16 or higher on the CES-D indicates concern for clinical depression.

Variable	BVAIT (n = 504) ^a	WISH (n = 349) ^a	ELITE (n = 642) ^a	Combined
Widowed	41 (8.1%) ^b	32 (9.2%)	41 (6.4%)	114 (7.6%)
Current smoker	17 (3.4%) ^b	8 (2.3%)	22 (3.4%)	47 (3.2%)
Alcohol	221 (43.8%)	152 (43.6%)	313 (48.8%)	686 (45.9%)
Use of anti-hypertensives at baseline	190 (37.7%)	117 (33.5%)	220 (34.3%)	527 (35.3%)
Use of cholesterol lowering medication at baseline	81 (16.1%)	72 (20.6%)	126 (19.6%)	279 (18.7%)
BMI (kg/m ²)	28.1 ± 4.9	26.6 ± 5.2	27.2 ± 5.4 ^b	27.4 ± 5.2
Blood pressure (mmHg)				
Systolic	127.0 ± 15.6	117.9 ± 13.9	116.5 ± 13.7 ^b	120.4 ± 15.2
Diastolic	78.7 ± 8.9	75.0 ± 8.6	74.5 ± 8.4 ^b	76.0 ± 8.8
ApoE4+	103 (22.2%) ^b	86 (25.7%) ^b	197 (30.9%) ^b	386 (26.9%)
CES-D score	6.2 ± 6.6	7.3 ± 6.8 ²	8.3 ± 8.6	7.4 ± 7.6
CES-D score ≥ 16 ^c	44 (8.7%)	40 (11.5%)	113 (17.6%)	197 (13.2%)
Average CIMT (mm, over 1 cm segment)	0.75 ± 0.15	0.81 ± 0.10	0.77 ± 0.11	0.77 ± 0.12
Executive function composite score	-0.012 ± 1.369	-0.005 ± 1.323	-0.002 ± 1.360	-0.006 ± 1.353
Verbal memory composite score	-0.005 ± 1.317	-0.006 ± 1.357	0.001 ± 1.348	-0.003 ± 1.339
Visual memory composite score	0.001 ± 1.108	0.001 ± 1.107	0 ± 1.103	0.001 ± 1.105
Global cognition composite score	0.014 ± 1.745	0.002 ± 1.715	-0.001 ± 1.827	0.05 ± 1.773
a. 2 participants in BVAIT and 1 participant in both WISH and ELITE each did not complete the baseline cognitive exam.				
b. Differing sample sizes: Education, BVAIT: n = 503. Income, BVAIT: n = 472, WISH: n = 319, ELITE: n = 597. Marital status, BVAIT: n = 503. Current smoker, BVAIT: n = 503. BMI, ELITE: n = 641. Blood pressure, ELITE: n = 640. ApoE4 genotype, BVAIT: n = 463, WISH: n = 334, ELITE: n = 637. CES-D score, WISH: n = 348.				
c. A score of 16 or higher on the CES-D indicates concern for clinical depression.				

Baseline and 2.5 Year Cross-Sectional Associations between CIMT and Cognition

CIMT was not associated with any of the cognitive function composite scores after adjustment for various confounders either at baseline or at 2.5 years (Table 2).

Table 2
Cross-sectional associations between CIMT and cognitive function at baseline and at 2.5 years from multivariable linear regression models.

	Baseline		2.5 years		
Cognitive Domain	β (95% CI) ^a	p-value	β (95% CI) ^a	p-value	Model covariates
Executive function	0.0227 (-0.0325, 0.0778)	0.42	-0.0302 (-0.1022, 0.0419)	0.41	Age, sex, race, education, income, marital status, ApoE genotype, BMI, SBP, HDL, study
Verbal memory	0.0088 (0.0507, 0.0684)	0.77	-0.0620 (-0.1389, 0.0149)	0.11	Age, sex, race, education, income, ApoE genotype, current smoking status, CES-D score, BMI, study
Visual memory	0.0489 (-0.0031, 0.1001)	0.07	0.0220 (-0.0413, 0.0854)	0.50	Age, sex, race, education, income, marital status, SBP, HDL, study
Global cognition	0.0445 (-0.0297, 0.1187)	0.24	-0.0347 (-0.1299, 0.0605)	0.47	Age, sex, race, education, CES-D score, BMI, SBP, HDL, study
a. Beta estimates are reported in units per 0.1 mm of CIMT.					

In models without BMI, SBP or HDL, CIMT was also not associated with any of the cognitive function composite scores. No significant interaction by ApoE4 genotype was found between CIMT associations with cognition (all interaction p-values ≥ 0.19). Similarly, no significant interaction by age group was found (all interaction p-values ≥ 0.32). There was a significant interaction by sex for the association between CIMT and verbal memory composite score ($p=0.019$). When the analysis was stratified by sex, the CIMT association was in opposite directions, but was not significantly associated with verbal memory composite score among men ($\beta=-0.071$ units per 0.1 mm CIMT, 95% CI: -0.156, 0.013, $p=0.10$) or among women ($\beta = 0.059$ units per 0.1 mm CIMT, 95% CI: -0.021, 0.139, $p=0.15$).

Longitudinal Associations between CIMT and Cognition

Higher CIMT at baseline was weakly associated with a decrease in global cognition composite score assessed over 2.5 years ($\beta=-0.056$ units per 0.1 mm CIMT, 95% CI: -0.110, -0.001, $p=0.045$) after adjusting for baseline global cognition composite score, age, sex, race, education, baseline CES-D, baseline BMI, baseline SBP, baseline HDL-cholesterol and the three clinical trials. There were no significant associations between CIMT at baseline and other cognitive domains over 2.5 years (Table 3). There were no significant interactions by ApoE4 genotype, sex, or age group in the longitudinal models (all p-values ≥ 0.21).

Table 3

Associations between baseline CIMT and change in cognitive function assessed over 2.5 years from multivariable linear regression models.

Cognitive Domain	β (95% CI) ^a	p-value	Model Covariates
Executive function	-0.0173 (-0.0542, 0.0196)	0.36	Baseline executive function composite score, age, sex, race, education, income, marital status, ApoE4 genotype, baseline BMI, baseline SBP, baseline HDL, study
<65 years old	-0.0193 (-0.0631, 0.0246)	0.39	
≥65 years old	-0.0131 (-0.0844, 0.0581)	0.72	
Verbal memory	-0.0245 (-0.0795, 0.0304)	0.38	Baseline verbal memory composite score, age, sex, race, education, income, ApoE4 genotype, current smoking status, baseline CES-D score, baseline BMI, study
<65 years old	-0.0208 (-0.0853, 0.0438)	0.53	
≥65 years old	-0.0387 (-0.1461, 0.0688)	0.48	
Visual memory	-0.0209 (-0.0617, 0.0199)	0.32	Baseline visual memory composite score, age, sex, race, education, income, marital status, baseline SBP, baseline HDL, study
<65 years old	-0.0324 (-0.0798, 0.0150)	0.18	
≥65 years old	-0.0148 (-0.0962, 0.0667)	0.72	
Global cognition	-0.0558 (-0.1104, -0.0012)	0.045	Baseline global cognition composite score, age, sex, race, education, baseline CES-D score, baseline BMI, baseline SBP, baseline HDL, study
<65 years old	-0.0354 (-0.1006, 0.0297)	0.29	
≥65 years old	-0.1061 (-0.2080, -0.0043)	0.0412	
a. Beta estimates are reported in units per 0.1 mm of CIMT.			

In analysis stratified by age group, the weak inverse association between baseline CIMT and change in global cognition composite score assessed over 2.5 years remained significant only for participants aged 65 years and older (Table 3). The interaction by age group for the association between baseline CIMT and change in global cognition composite score was not significant ($p=0.21$). No other associations between baseline CIMT and change in cognitive domain composite scores assessed over 2.5 years were observed for either age category.

The average CIMT at 2.5 years across all three clinical trials (0.79 ± 0.12 mm) increased by 0.01 mm from average CIMT at baseline. There were no significant associations between change in CIMT and change in cognition in models adjusting only for baseline cognitive function scores.

Discussion

In this post hoc analysis of three randomized trials, longitudinal analysis revealed a weak inverse association between CIMT at baseline and change in global cognition composite score assessed 2.5 years later. The global cognition composite score includes cognitive tests comprising the executive function, visual memory, and verbal memory composite scores, strengthening the overall association between CIMT at baseline and change in global cognition composite score from baseline to 2.5 years.

When analysis was stratified by age group, the weak inverse association held for participants aged 65 years and older. Age was inversely associated with decline in global cognition at 2.5 years in our data (Pearson's $r = -0.19$), and older-aged adults typically exhibit greater levels of cognitive decline compared with their middle-aged counterparts(17). Increasing age is also known to be associated with higher CIMT(19), and is evident in our data (Pearson's $r = 0.37$). It is possible that associations between CIMT and cognition become evident once CIMT reaches a certain thickness, as in the older participants in this sample.

Stronger associations of cognition with CIMT were observed longitudinally over 2.5 years than cross-sectionally at baseline. In this population of healthy middle- to older-aged adults, changes in cognition may be a more sensitive indicator of vulnerability to vascular health than a single measure of cognition. The cross-sectional associations between CIMT and cognitive functions at baseline were not observed. In a previous cross-sectional analysis from the BVAIT, baseline measures showed that thicker CIMT was weakly associated with lower verbal learning abilities, but not with global cognition(5). Because of clinical trial inclusion/exclusion criteria and the demands of participation, persons with higher levels of cognitive impairment would not have been enrolled despite possibly having cardiovascular disease risk factors. This may have created a healthy-bias selection that reduced cross-sectional baseline associations.

Atherosclerosis may adversely affect cognition through several mechanisms, including cerebral hypoperfusion, as blood vessel stenosis may result in reduced blood flow and oxygen supply to the brain. Reduced intracerebral perfusion can damage brain tissue and lead to declines in cognitive function. Indeed, low cerebral blood flow velocity has been found to be associated with cognitive decline(20).

Higher CIMT is a risk factor for subclinical brain infarcts, or silent strokes, which are in turn associated with declines in cognitive function and an increased risk for dementia(21–23). Silent strokes may not have noticeable symptoms and are thought to be common among older people, with the estimated prevalence ranging from 5-62% in populations with mean ages 54 to 79 years old, respectively(24). This mechanism is entirely plausible in this study population of otherwise healthy middle- to older-aged adults. Although this study did not directly measure cerebrovascular stenosis through methods such as brain MRI or transcranial Doppler, carotid artery atherosclerosis serves as a surrogate marker for intracerebral atherosclerosis(17).

Limitations of this study include inclusion of more women than men due to convenience of available data from three clinical trials, two of which only enrolled post-menopausal women. Because of the focus on postmenopausal women in the WISH and ELITE studies, the study sample included few individuals who were middle-age or elderly. In addition, given clinical trial selection criteria, individuals with a history of cardiovascular disease and diabetes were excluded. As such, the findings of this study may not be generalized to individuals with cardiovascular disease, premenopausal women or elderly individuals >80 years.

Conclusions

In this longitudinal study of 1,495 healthy adults with a mean age of 61 years, greater carotid artery intima-media thickness at baseline had a weak, statistically significant inverse association with change in global cognition assessed over 2.5 years. This study provides evidence that subclinical atherosclerosis of the carotid artery may be a modifiable predictor of cognitive decline in middle-and older age. Further research is needed to expand and support these findings in more representative samples. Given that the number of people with dementias is expected to increase in the coming decades, early detection and management of cardiovascular disease could reduce the risk for cognitive impairment in older age.

Abbreviations

ApoE

apolipoprotein E

BMI

body mass index

BVAIT

B-Vitamin Atherosclerosis Intervention Trial

CES-D

Center for Epidemiological Studies Depression scale

CIMT

carotid intima-media thickness

ELITE

Early versus Late Intervention Trial with Estradiol

HDL
high-density lipoprotein
LDL
low density lipoprotein
SBP
systolic blood pressure
USC
University of Southern California
WISH
Women's Isoflavone Soy Health trial

Declarations

Ethics approval and consent to participate: BVAIT, WISH, and ELITE were approved by the Institutional Review Board of the University of Southern California. All participants provided written informed consent before trial-related procedures were performed.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: FL analyzed the data and interpreted the results. HNH, VWH, and WJM designed and conducted the trials. JAS performed all cognitive assessments. All authors advised and reviewed analyses and provided critical review and edits for the final manuscript.

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