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Carotid Atherosclerosis and Cognitive Function in midlife: the Beaver Dam Offspring Study

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Abstract

Background—Atherosclerosis may be associated with cognitive function; however the studies are few, especially among midlife adults.

Methods—Participants in the Beaver Dam Offspring Study who had cognitive test data and gradable carotid artery ultrasound scans were included (n=2794, mean age: 49 years). Atherosclerosis was measured by carotid intima-media thickness (IMT) and presence of plaque. Cognitive function was measured by the Trail Making Test (TMT), Grooved Pegboard Test (GPT) and Mini-Mental State Examination (MMSE). Generalized cognitive function was defined by a summary score calculated from the TMT and GPT. Linear regression was used to evaluate the associations between carotid atherosclerosis and cognitive function tests.

Results—Larger IMT was associated with lower GPT, MMSE and the summary score adjusting for multiple factors, the coefficients were: 13.8 seconds ($p<0.0001$), −0.6 ($p=0.007$), and 0.47 ($p=0.01$), respectively for 1 mm increase in IMT. Plaque scores were significantly associated with TMT-B, GPT, MMSE, and the summary score adjusting for age, sex and education. The associations remained statistically significant after further adjustments except for the association with TMT-B, which was attenuated and no longer significant.

Conclusions—Our results show significant associations between markers of carotid atherosclerosis and cognitive function in a cohort of persons aged 21 to 84 years. Longitudinal studies are needed to further examine these associations.

Keywords

atherosclerosis; cognitive function; epidemiology

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Introduction

Recent studies have shown that carotid atherosclerosis may be associated with cognitive function and dementia, but associations have been inconsistent [1–5]. In addition, most studies have been conducted among older adults, and there are few studies of this relationship in younger adults. It has been suggested that carotid atherosclerosis may cause cerebral ischemia and hypo-perfusion, which may contribute to brain atrophy and cause impairment in cognitive function [6]. Though atherosclerosis may begin earlier in life, even in childhood [7], it is not clear when it might begin to affect cognitive function. Therefore, it is important to examine the relationship between atherosclerosis and cognitive function in a relatively younger population.

Our study investigated the associations between carotid atherosclerosis and cognitive function in a large cohort of adults aged 21–84 years. We hypothesize that carotid atherosclerosis measurements are associated with worse cognitive function, although the effect size may be small in middle-aged adults.

Methods

Study population

The Beaver Dam Offspring Study (BOSS) is a cohort study of age-related sensory disorders in the adult offspring of the participants in the population-based Epidemiology of Hearing Loss Study (EHLS) [8, 9]. In brief, the adult children (aged 21 years or older) of EHLS participants were invited to participate in the BOSS examination in 2005–08. A total of 3,285 adults participated in the study, 45% of whom were men. More than 99% of participants were non-Hispanic white. Participants with gradable carotid ultrasound images and cognitive test data were included in the analyses (n=2794).

The BOSS was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board, and all participants provided informed consent.

Data collection

Carotid atherosclerosis—Carotid artery ultrasound scans were obtained with a Biosound AU4 (Indianapolis, IN, USA) and a 7.5 MHZ probe (LA13A) using a slightly modified protocol from the Atherosclerosis Risk in Communities (ARIC) study [10]. The intima-media thickness (IMT) was measured on the left and right sides of the near and far walls of the common carotid artery (CCA), the bifurcation and the internal carotid artery (ICA). The mean IMT of the measurements from 12 sites was calculated.

The presence of plaque at six sites (CCA, ICA and the bifurcation, both sides) was determined. Plaque was assessed as present if: acoustic shadowing was present and there was a change in wall shape, such as a protrusion into the lumen, a change in wall texture (seen as walls echoing brighter than adjacent boundaries), or the IMT at the maximum point in that location was greater than or equal to 1.5 mm; or, in the absence of acoustic shadowing, two of the three wall characteristics (shape, texture and thickness) were observed [11]. The number of sites was counted and a plaque score (0, 1 and 2) was created by categorizing the number of sites with plaque into 3 groups: 0 site (plaque score 0), 1–3 sites (plaque score 1) and 4–6 sites (plaque score 2).

The reproducibility of IMT and plaque assessment was good. In a 10% sample (n=280) of participant scans that were re-graded the mean difference in IMT was 0.0019 mm and kappa statistics for plaque assessment ranged from 0.58 (ICA) to 0.71(bifurcation) with 97.3% agreement within +/−1 for the number of sites with plaque.

Cognitive function tests—The Trail Making Test, part A (TMT-A) and part-B (TMT-B), and the Grooved Pegboard Test (GPT) were administered to the participants [12]. The TMT measures executive, attention and psychomotor function, and the GPT measures executive, and psychomotor function (eye-hand coordination and motor speed). The TMT requires a subject to connect 25 consecutive targets as fast as possible on a sheet of paper, within five minutes. Two versions were used: TMT-A, in which the targets are all numbers (1, 2, 3, etc.), and TMT-B, in which the subject alternates between numbers and letters (1, A, 2, B, etc.). The GPT consists of a metal board with a matrix of 25 holes with randomly positioned slots. Pegs have a ridge along one side and must be rotated to match the hole before they can be inserted. The subject's task is to insert metal pegs as quickly as possible into the slots in sequence within five minutes. The score for each task is the time (seconds) taken to complete the test within five minutes, and a score of 301 was given if the subject had not completed the task within 5 minutes. The Mini-Mental State Examination (MMSE) is a measure of general cognitive function which measures orientation to time and place, attention and calculation, language, and memory [13]. The test was only administered to participants aged 50 years or older, as it was suggested to be relatively insensitive in younger persons [14]. The MMSE score was used as the outcome in our analyses in individuals aged 50 years or older.

Covariates—Data on demographics, current medications, lifestyle and the SF-36 mental score were obtained during the interview. Height, weight and seated blood pressures were measured. Blood samples were obtained and assayed for the glycated hemoglobin A1C, serum total cholesterol and high density lipoprotein (HDL) levels. APOE genotyping was performed at the Center for Applied Genomics, the Children's Hospital of Philadelphia among participants 45 years and older.

Besides age, sex and education, other CVD factors were considered as potential confounders if they were found to be associated with carotid atherosclerosis and cognitive function, and if their inclusion in the statistical models resulted in a moderate change in the estimates of the effect of atherosclerosis.

Statistical Analysis

Ordinary linear regression models were used with each original individual test score as an outcome in separate models. Because participants who did not complete the TMT or GPT in the allotted time were older, had lower income and less education than those who did complete the tasks (data not shown), a sensitivity analysis was conducted excluding those participants. Analyses with the TMT and GPT were repeated among participants < 60 years old.

A principal component analysis (PCA) was performed for the three tests (TMT-A, TMT-B and GPT) to get a summary score, which combines information from the three individual tests and measures the common aspect of cognition that was captured by each test. Analysis with this score reduces multiple testing for each individual test score, and it also provides an answer to whether there is an association between atherosclerosis and the common aspect of cognitive function measured by these tests, in addition to the results from individual tests. All the analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Among the 2794 participants, 46% were men. The mean age was 49 years (s.d.: 9.8 years), and the quartiles of age distribution were 42, 48, and 56 years for the 25th, 50th and 75th percentile, respectively. The mean carotid IMT was 0.65 mm (s.d : 0.15 mm), and the quartiles of IMT distribution were 0.56, 0.62, and 0.70 mm for the 25th, 50th and 75th percentile, respectively. Two percent of the cohort had a plaque score of 2 (plaque presented in 4–6 sites), and 22% had a plaque score of 1 (plaque presented in 1–3 sites). Fourteen participants and two participants failed to complete the TMT-B and the GPT in five minutes. The characteristics of the study population are presented in Table 1.

The associations between carotid atherosclerosis and TMT and GPT are shown in Table 2. After adjusting for multiple potential confounders, carotid IMT was associated with the GPT performance. Plaque scores were associated with TMT-A, TMT-B and GPT after adjusting for age, sex and education. The associations between plaque score and TMT were attenuated and lost significance in the multivariable model. However, in the sensitivity analysis (excluding those who scored 301s), plaque score was significantly associated with TMT-B after multiple adjustments, with coefficients 1.7s (se: 1.3, p=0.2) and 7.4s (se: 3.6, p=0.04) for plaque score 1 and 2, respectively.

The analyses with TMT and GPT were repeated among participants less than 60 years old. In these relatively younger participants, IMT remained associated with GPT in the multivariable model, and plaque score was significantly associated with TMT-A, TMT-B and GPT in the multivariable models (data not shown).

The PCA yielded one eigenvalue greater than 1 which accounted for 67% of the variance of the three tests. This component was retained as the summary score. The coefficients of this score for TMT-A, TMT-B and GPT were 0.60, 0.60, and 0.54, respectively. Carotid IMT and plaque score were both associated with this summary score after multiple adjustments, and the coefficients were 0.47 (s.e.: 0.19, p=0.01) for 1mm IMT, and 0.11 (s.e.: 0.06, p=0.04), 0.37 (s.e.: 0.15, p=0.02) for plaque score 1 and 2, respectively.

Of the 1262 participants (mean age: 57.6 yrs) who completed the MMSE, 9 were cognitively impaired (total score < 24 out of 30). Carotid IMT and plaque were both associated with the MMSE score (Table 3).

Discussion

While controlling for other risk factors, we found carotid atherosclerosis to be significantly associated with measures of cognitive function. It has been hypothesized that sub-clinical atherosclerosis may cause cerebral ischemia and hypoperfusion, which may in turn cause brain dysfunction [6]. It has also been hypothesized that sub-clinical atherosclerosis may be a marker for other pathogenic pathways such as inflammation and endothelial dysfunction, and these pathways may contribute to atrophy in the brain leading to cognitive decline [15–16]. Another hypothesis has suggested that unstable carotid plaque may cause cerebral emboli, which manifests as silent strokes, and thus cause cognitive function impairment [17]. A recent study using proton magnetic resonance spectroscopy found that sub-clinical atherosclerosis (IMT levels below clinically significant threshold) was associated with compromised neuronal viability in middle-aged adults [18], which provided further support for the association between atherosclerosis and cognitive function in midlife.

In our study, carotid IMT was not associated with either TMT test, which might be due to the lack of statistical power. The associations found between carotid plaque and both TMT tests after adjusting for age, sex and education may suggest that a more severe form of atherosclerosis is associated with TMT in this relatively young population. The results of the sensitivity analysis with TMT-B suggests that including those who were unable to complete the task within allotted time might introduce bias. Because their assigned score of 301s underestimated the time they needed to complete the test, the association may be biased toward null. Inclusion of cardiovascular disease risk factors, present in the causal pathway between atherosclerosis and cognitive function may have led to an over-adjustment in the multivariable models limiting our ability to find an association.

In addition to the associations found for the individual TMT, a measure of executive function, psychomotor speed, and attention, and GPT, a measure of eye-hand coordination, motor speed and attention, we also found the association with the summary score. This suggests there is an association between atherosclerosis and the generalized cognitive function measured by these individual tests.

Significant associations were found between carotid atherosclerosis and the MMSE score in the subset of participants who were 50 years of age or older. Because few participants had cognitive impairment, we did not analyze the dichotomized outcome. The small effect size of the association is also most likely due to the young age of participants (mean age: 57.6 years).

Previous studies have found inconsistent associations between atherosclerosis and cognitive function. For example, carotid IMT was associated with cognitive decline among adults without CVD in one study [5], while another study reported IMT was not associated with cognitive tests scores changes [4]. Conflicting findings of associations of atherosclerosis with cognitive domains have also been reported. For example, some studies found that IMT was associated with memory [5, 19], but another study found that IMT was associated with other cognition domains but not with memory [20]. These discrepancies may be due to differences in sample populations, choice of cognitive tests, treatment of potential confounders and analytical approaches.

One distinct feature of our study is that most participants were middle-aged, with a mean age of 49 years. There have been few studies conducted among middle-aged adults [4, 20]. We repeated the analyses with the TMT and GPT performance among participants less than 60 years old, and the associations remained in the younger participants, which suggested that the associations were not driven by the older participants. Strengths of our study include a large sample size, multiple measurements of cognitive function, and multiple adjustments of potential confounders. However, since it was a cross-sectional study, a temporal inference cannot be made from this study.

In conclusion, our study found significant associations between carotid atherosclerosis and cognitive function. The associations were small but consistent, which suggests that early cognitive decline may start in middle age and may worsen as atherosclerosis develops. Future longitudinal studies with sensitive cognitive tests are needed to accurately assess the role of atherosclerosis in cognitive decline early in life.

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Table 1

Description of the study population

Variables	n	Mean (sd) or %
Education yrs	2779	
<12		3
12		29
12–15		34
16+		34
Family income (1000 $)	2708	
−39.9		22
40–59.9		23
60–74.9		19
75–99.9		16
100+		20
Married	2791	74
HDL-Cholesterol (mg/dl)	2730	50.0 (14.7)
Smoking	2792	
Past smokers		28
Current smokers		18
Heavy drinking*	2788	
Past heavy drinkers		16
Current heavy drinkers		2
Regular exercise*	2790	61
SF-36 mental score	2792	53.9 (8.0)
Diabetes prevalence*	2793	6
CVD history	2787	3
Hypertension*	2793	36
Hypertension medications	2788	22
Current use of Statins	2793	15
GPT (second)	2789	72.7 (18.3)
TMT-A (second)	2794	28.0 (10.5)
TMT-B (second)	2789	67.6 (33.0)
MMSE score	1261	28.7 (1.3)

*Hypertension: diagnosed hypertension with current medications or a measured blood pressure ≥140/90 mmHg; diabetes: diagnosed diabetes or A1C>6.5; heavy drinking: four or more drinks daily; regular exercise: exercise enough to sweat at least once a week.

Table 2

Associations between carotid atherosclerosis and the TMT, GPT scores

	TMT-A				TMT-B				GPT			
	N	Coef. (s.e.)	t-value	P	N	Coef. (s.e.)	t-value	P	N	Coef. (s.e.)	t-value	P
Carotid IMT (mm)												
Simple model[#]	2779	2.6 (1.5)	1.7	0.09	2775	4.0 (4.7)	0.9	0.4	2775	17.3 (2.6)	6.6	<.0001
Multivariable model[*]	2610	1.0 (1.5)	0.7	0.5	2606	0.2 (4.7)	0.04	0.9	2607	13.8 (2.7)	5.1	<.0001
Plaque score (0 is the reference group)												
Simple model[#]	2665				2661				2661			
Plaque score 1		1.0 (0.5)	0.7	0.03		3.0 (1.4)	2.1	0.04		1.9 (0.8)	2.4	0.02
Plaque score 2		2.5 (1.3)	1.9	0.06		8.9 (4.0)	2.2	0.03		9.9 (2.2)	4.5	<.0001
Multivariable model[*]	2505				2501				2502			
Plaque score 1		0.6 (0.5)	1.2	0.2		1.7 (1.4)	1.2	0.2		1.1 (1.8)	0.6	0.07
Plaque score 2		1.2 (0.4)	3.0	0.4		4.9 (4.0)	1.2	0.2		7.4 (2.3)	3.2	0.001

[#] adjusted for age, sex, and education

[*] Confounders included were: marital status, family income, hypertension, CVD, diabetes, smoking and heavy drinking status, regular exercise, SF-36 mental score, HDL cholesterol, anti-hypertensive medications and use of statins.

Table 3

Associations between carotid atherosclerosis and the MMSE score

	N	Coefficient (s.e.)	t-value	P
Carotid IMT (mm)				
Simple model#	1251	−0.4 (0.2)	−1.9	0.057
Multivariable model*	1164	−0.6 (0.2)	−2.7	0.007
Plaque score (0 is the reference group)				
Simple model#	1192			
Plaque score 1		−0.1 (0.1)	−1.5	0.1
Plaque score 2		−0.4 (0.2)	−2.4	0.02
Multivariable model*	1111			
Plaque score 1		−0.1 (0.1)	−1.6	0.1
Plaque score 2		−0.4 (0.2)	−2.3	0.02

#adjusted for age, sex, and education

*adjusted for the same confounders in table 2