RESEARCH ARTICLE

Carotid Intima-Media Thickness and Midlife Cognitive Function

Impact of Race and Social Disparities in the Bogalusa Heart Study

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Abstract

Background and Objectives

Carotid intima-media thickness (c-IMT) is a measurement of atherosclerosis, a progressive disease that develops as early as childhood and has been linked with cognitive impairment and dementia in the elderly. However, the relationship between c-IMT and midlife cognitive function and the race and social disparities in this relationship remain unclear. We examined the association between c-IMT and cognitive function in midlife among Black and White participants from a semirural community-based cohort in Bogalusa, Louisiana.

Methods

In this cross-sectional analysis of participants from the Bogalusa Heart Study, linear regression models were used to determine the association between c-IMT dichotomized above the 50th percentile (>0.87 mm), an a demographically standardized global cognitive score (GCS), and individual cognitive domain–based *z* scores. Stratified analyses were performed to evaluate the impact of race and the individual's education status.

Results

A total of 1,217 participants (age 48 ± 5.28 years) were included; 66% (804) self-identified as White, and 34% (413) self-identified as Black. Of those, 58% (708) were women, and 42% (509) were men. Having a c-IMT ≥50th percentile was inversely associated with GCS (B ± SE −0.39 ± 0.18, $p = 0.03$), independently of cardiovascular risk factors (CVRFs) and achieved education. The effect remained significant in Black and White participants after adjustment for CVRFs (Black participants: B ± SE −1.25 ± 0.45, $p = 0.005$; White participants: B ± SE −0.92 ± 0.35, $p = 0.008$) but not for education. The interaction between c-IMT ≥50th percentile and education was significant ($p = 0.03$), and stratified analysis showed an association with GCS among those with lower achieved education (B ± SE −0.81 ± 0.33, $p = 0.013$) independently of major CVRFs.

Discussion

Subclinical atherosclerosis, measured as c-IMT, was associated with worse midlife cognitive function, independently of major CVRFs. The association was buffered by education and may be stronger among Black than White participants, likely due to corresponding structural and social determinants. These findings underscore the importance of establishing preventive measures in midlife and suggest subclinical atherosclerosis as a potential target to prevent cognitive decline.

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eReferences e1–e3 at links.lww.com/WNL/B843.

Glossary

AD = Alzheimer disease; **ADRD** = AD and related dementias; **BHS** = Bogalusa Heart Study; **BMI** = body mass index; **BP** = blood pressure; **c-IMT** = carotid intima-media thickness; **CARDIA** = Coronary Artery Risk Development in Young Adults; **CVRF** = cardiovascular risk factors; **DBP** = diastolic BP; **GCS** = global cognitive *z* score; **HDL** = high-density lipoprotein; **LCC** = left common carotid; **LIC** = left internal carotid; **NP** = neuropsychological; **RCB** = right carotid bulb; **RCC** = right common carotid; **SBP** = systolic BP; **WAIS-IV** = Wechsler Adult Intelligence Scale 4th edition; **WRAT** = Wide Range Achievement Test.

For decades, the leading cause of morbidity and mortality in the United States has been heart disease. As life expectancy increases, age-related diseases, including Alzheimer disease (AD) and AD-related dementias (ADRD), are increasing in prevalence.[1-3] The vascular hypothesis provides substantial evidence supporting its essential role in understanding the development of AD and ADRD.[4] Therefore, identifying modifiable risk factors shared by these conditions in a race-specific fashion and determining the critical time windows to prevent and delay the onset of ADRD are important.

The human brain can be affected by vascular dysfunction through diverse mechanisms.[5] Changes in arterial structure, including arterial stiffening and atherosclerosis of large arteries, can alter the normal blood flow to the brain.[6,7] As a consequence, microvascular ischemic disease and cerebral hypoperfusion are accompanied by a cascade of inflammatory response and endothelial dysfunction with subsequent alterations to the permeability of the blood-brain barrier.[5,6] These mechanisms have been shown to cause neuronal damage and neurodegeneration and thus can serve as markers for pathologic events in the chronological ordering of emergence of AD and ADRD.[4] A growing body of evidence shows that in late life, atherosclerosis of brain-supplying arteries, particularly the carotid arteries, is associated with subclinical injury of white matter, cognitive impairments, and dementia.[7-10]

Carotid intima-media thickness (c-IMT) is a subclinical indicator of atherosclerosis, a disease recognizable as early as childhood.[11] Assessed by noninvasive ultrasound, c-IMT has been established as a robust predictor of subsequent vascular events[12] and has been associated with cognitive performance in older adults.[10,13] Recent evidence suggests that midlife increased c-IMT is associated with worse cognitive performance and dementia diagnoses later in life.[14,15] However, the c-IMT–related effects on midlife cognitive function have not been well studied. Moreover, social and behavioral factors have been major drivers of inequalities in cardiovascular disease and dementia prevalence, and previous studies have shown higher dementia incidences among Black populations.[16,17]

This study examines the relationship between subclinical atherosclerosis, represented by c-IMT, and cognitive function among Black and White participants from a rural community-based cohort of middle-aged adults located in the southern city of Bogalusa, Louisiana. We hypothesized that individuals with lower c-IMT would have better cognitive performance in midlife.

Methods

Study Design and Population

The Bogalusa Heart Study (BHS) is a longitudinal cohort dedicated to the study of the natural history of cardiovascular disease among White and Black individuals in the rural city of Bogalusa, Louisiana.[18] Between 1973 and 2016, the BHS has conducted 9 child and 11 adult examinations of participants enrolled from childhood, prospectively collecting repeated, longitudinal measurements.[18] Details of the study have been previously published.[11,19] A total of 1,298 individuals participated during the 2013–2016 examination; the current cross-sectional analysis includes 1,217 BHS participants with a complete neuropsychological (NP) evaluation and c-IMT B-mode ultrasound testing who were free of major cardiac events.

Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Review Board of Tulane University Health Sciences Center approved the study, and all participants provided written informed consent.

Carotid Ultrasound Measurements

Consistent with previously described protocols, far-wall carotid intima-media measurements were obtained by a single trained sonographer using a Toshiba SonoLayer SSH 160A ultrasound system (Toshiba Medical, Tokyo, Japan) and a 7.5-MHz linear-array transducer.[19] Recorded locations included the right carotid bulb (RCB), right common carotid (RCC), right internal carotid, left carotid bulb, left common carotid (LCC), and left internal carotid (LIC). Right- and left-sided maximum far-wall measurements defined segmental maximum c-IMT. The c-IMT composite was defined as the average of the segmental maximum c-IMT. For statistical analysis, the c-IMT composite was dichotomized at the 50th percentile on the basis of previous literature identifying higher c-IMT measures as clinically concerning.[20,21]

Cognitive Assessment

In accordance with recommendations from the NIH toolbox, the BHS cognitive assessment was conducted by a trained staff

in a private, distraction-free setting.[22] The NP protocol included a total of 9 tests assessing attention/information processing speed, executive control, and verbal episodic memory. Attention and processing speed were tested with the Digit Span Forward subtest (Wechsler Adult Intelligence Scale 4th edition [WAIS-IV]) and the Trail-Making Test Part A. Episodic memory was tested with the Wechsler Memory Scale 4th edition delayed free recall and delayed recognition subtests. Executive function was tested using the Trail-Making Test Part B and the Digit Symbol Coding subtest (WAIS-IV). Language was tested with the word and the letter reading tests (Wide Range Achievement Test [WRAT] 4th edition) and vocabulary subtest (WAIS-IV). Because NP test performance is highly influenced by cultural constructs, resulting in overrepresentation of lower scores among Black individuals and overrepresentation of higher scores in White individuals, demographically standardized NP test scores were obtained.[23-25] Individual participant scores for each cognitive test were age, sex, and race standardized by computing *z* scores with a mean of zero and an SD of 1.0 to enhance comparability of results. Age was standardized in 1-year increments. Reversed scores were calculated for Trail-Making Tests so that higher scores were consistent indicators of better performance. A global cognitive *z* score (GCS) was computed by averaging all scores.

Demographic, Socioeconomic, and Lifestyle Factors

Participant information on sociodemographic, lifestyle, and cardiometabolic characteristics has been collected in accordance with rigorous protocols to ensure replicability of information and following the standards of the BHS, which began in 1973.[18] Information for each study examination is obtained through validated questionnaires. Sex, age, and race, and socioeconomic status (education, employment, income, housing and, health access) are self-identified by participants.

Education and Additional Covariates

Measurement of education by years alone has been shown to be insufficient in comparisons of racial groups because race, income, geography, and other social determinants affect the quality of education and therefore the performance on NP tests. When additional indicators of education are not taken into consideration, this can result in below-average scores on NP tests for people from traditionally marginalized racial groups.[26-28] Therefore, the language cognitive domain *z* score was used as an indicator for achieved education and premorbid (before examination or before the onset of any brain dysfunction) cognitive abilities.[27,28]

Additional relevant covariates included fasting glucose, high-density lipoprotein (HDL) cholesterol, and triglycerides, measured at a centralized laboratory following standard protocols.[29] The calculated arithmetic average of blood pressure (BP) triplicate measures was used in analyses. Duplicate measures of height and weight for each study participant were used to calculate body mass index (BMI). Non-HDL cholesterol was computed from the lipid profile. Cognitive test scores were standardized for age, sex, and race; therefore, they were not included again as covariate terms in the regression models. Data on covariates were missing for 0.08% to 1.07% as follows: n = 1 for BMI, n = 1 for BP, n = 13 for triglycerides, and n = 21 for fasting glucose.

Statistical Analysis

Analyses were performed with Stata software (Stata/IC 15.1, StataCorp, College Station, TX). With the use of a complete case approach, 73 participants were excluded because of missing c-IMT measurements, and 8 participants were excluded because of missing GCS data (eFigure1 and eTable1, links.lww.com/WNL/B843). Descriptive and inferential statistics are provided for study sample characteristics by race with the use of a complete case approach. For continuous variables, means and SDs were reported and compared by analysis of variance and the Kruskal-Wallis test. For categorical variables, frequencies and percentages were compared by the Pearson χ^2 test.

Univariable and multivariable linear regression models were used to assess the association between c-IMT measures and GCS, individual cognitive tests scores, and cognitive domain *z* scores. Beta coefficients (*B*) and standard errors (SE) were reported. Multivariable models included the following selected covariates based on a priori knowledge of drivers for atherosclerosis and cognitive decline. Modifiable risk factors for atherosclerosis and dementia include systolic BP (SBP) levels, fasting glucose levels, smoking status, atherogenic cholesterol (non-HDL) levels, and triglyceride levels.[30,31] In addition, we adjusted for the use of hypertension medication because previous evidence has suggested potential effects of medications reducing atherosclerosis and dementia.[30,32] Last, a model adjusting for the language domain *z* score as an indicator for achieved education was performed. Effect modification was assessed by interaction terms for each analysis. All statistical tests were 2 tailed, and *p* values were considered significant if <0.05.

Data Availability

Data not provided in the article and additional information on methods and materials can be shared on responsible request.

Results

Demographic, Socioeconomic, and Lifestyle Factors

A total of 1,217 participants were included in the analysis. The mean age of participants was 48 (SD 5.28) years, and 58% (708) were women. From the total sample, 66% (804) self-identified as White and 34% (413) as Black. There were no significant differences in smoking behavior between races. Among Black participants, men had a higher proportion of current (35.4%) and former (18.4%) smoking behavior compared to women ($p < 0.05$). Compared to White participants, Black women and

men had significantly lower educational level ($p < 0.001$), less annual income ($p < 0.001$), lower rates of homeownership, and lower rates of private health insurance ($p < 0.05$). White men reported higher rates of employment (71.2%) compared to Black men (46.2%) ($p < 0.001$) (Table 1).

Cardiometabolic Risk Factors

Race and sex differences were found for BP, cholesterol, and triglyceride levels. The mean SBP and diastolic BP (DBP) were significantly higher in Black participants (SBP $p < 0.05$, DBP $p < 0.05$); SBP was also higher in men (White men $p < 0.001$, Black men $p < 0.05$). Atherogenic lipoprotein, the non-HDL level, was significantly higher in White men compared to Black men ($p = 0.018$). Triglyceride levels were significantly higher in White participants. Among White participants, men had higher triglyceride levels than women ($p < 0.05$). Black women reported more hypertension medication use compared to White women and Black men (Table 1).

c-IMT Measurements

Far-wall c-IMT measurements are displayed in full detail in eTable 2, links.lww.com/WNL/B843. Black participants had higher RCC and LCC thickness compared to White participants. Black women had thicker LCC, LIC, RCB, RCC, and c-IMT composite measures compared to White women. Significant sex differences were found among White participants, with men having greater intima-media thickness in all carotid sections (Figure 1).

c-IMT Measurements and Cognitive Function

After adjustment for cardiovascular risk factors (CVRFs) and achieved education, our results show that c-IMT composite ≥50th percentile (0.87 mm) was inversely associated with GCS (standardized $B \pm SE$ -0.39 ± 0.18, $p = 0.03$). In subgroup analyses by race, after adjustment for CVRFs, we found a larger point estimate in Black participants ($B \pm SE$ -1.25 ± 0.45, $p = 0.005$) compared to White participants ($B \pm SE$ -0.92 ± 0.35, $p = 0.008$). However, the effect was not persistent after adjustment for achieved education (Black individuals: $B \pm SE$ -0.40 ± 0.30, $p = 0.187$; White individuals: $B \pm SE$ -0.39 ± 0.23, $p = 0.09$) (Table 2). The interaction between c-IMT composite ≥50th and the achieved education indicator (language cognitive domain z score) was significant ($p = 0.03$), and stratified analysis by achieved education showed a significant association between c-IMT composite and GCS among those in the 2 lower quartiles of language cognitive domain z score ($B \pm SE$ -0.81 ± 0.33, $p = 0.013$) independently of major CVRFs. Additional analysis using self-reported educational level instead of other education indicators is shown in eTable 3, links.lww.com/WNL/B843. Analysis excluding language from the GCS did not change the interpretation of results (eTable 4).

Greater c-IMT had the most impact on executive function and episodic memory. The c-IMT composite ≥50th percentile (0.87 mm) was independently associated with poorer cognitive performance in episodic memory ($B \pm SE$ -0.23 ± 0.10, $p = 0.015$) and with poorer performance in executive function ($B \pm SE$ -0.33 ± 0.06, $p < 0.001$) (Table 3). In subgroup analyses, the effect on episodic memory performance remained significant in Black and White participants after adjustment for CVRFs (Black participants: $B \pm SE$ -0.45 ± 0.17, $p = 0.008$; White participants: $B \pm SE$ -0.29 ± 0.13, $p = 0.028$) but not after adjustment for achieved education. The effects on executive function remained significant among Black participants after adjustment for CVRFs ($B \pm SE$ -0.35 ± 0.12, $p = 0.026$) but not after adjustment for achieved education ($B \pm SE$ -0.16 ± 0.14, $p = 0.272$). In White participants, the association was independent of CVRFs and achieved education ($B \pm SE$ -0.40 ± 0.11, $p < 0.001$) (eTable 5, links.lww.com/WNL/B843).

Discussion

Our results show that midlife c-IMT is an independent predictor of global cognitive function in midlife. This finding extends from previous studies examining these relationships in late life, when the pathophysiologic processes that lead to dementia may have already been well established. The association between c-IMT composite and GCS was independent of major risk factors (age, sex, race, SBP, glucose level, BMI, smoking status, non-HDL cholesterol, triglycerides, use of hypertension medication, and achieved education). Achieved education appeared to buffer the effect of c-IMT on midlife cognitive function; however, the strength of this buffering effect may differ by race. We also found differences based on the cognitive domain tested, with executive function having the strongest association. These findings support the hypothesis that subclinical atherosclerosis is associated with cognitive performance as early as midlife and raise the possibility of preventing atherosclerotic disease to maintain cognitive function.

In the elderly population, epidemiologic studies have linked atherosclerosis indicators such as c-IMT at baseline with subsequent cognitive decline and increased risk for mild cognitive impairment and dementia.[8,10] Recently, c-IMT progression has also been correlated with decreased hippocampal volume and white matter hyperintensities, brain changes linked to both vascular dementia and AD.[13,33,34] These changes are characteristic of late-life dementia syndromes and are thought to occur, in part, as a result of chronic hypoperfusion and endothelial damage to the capillaries of the brain, leading to blood-brain barrier dysfunction.[35,36] Such changes are known to develop in the early stages of ADRD, further supporting the contribution of vascular pathophysiology and the exposure-length component of CVRFs; i.e., prolonged exposure increases the risk for AD/vascular dementia spectrum dementia.[6] Our results extend previous findings into midlife, a less studied and critical time window for the initiation of early dementia pathology.

Of the few studies that have examined this relationship in midlife, the Coronary Artery Risk Development in Young

Table 1 Participant Characteristics at Time of Cognitive Assessment by Sex and Race

Participant characteristics	All (N = 1,217)	White participants		Black participants		Race difference, *p* value[c]	
		Female (n = 453)	Male (n = 351)	Female (n = 255)	Male (n = 158)	Female	Male
Sociodemographic and lifestyle							
Age, y	48.16 (5.28)	48.16 (5.10)	48.90 (4.98)	47.65 (5.42)	47.36 (5.99)	NS	0.01
Education level, n (%)						<0.001	<0.001
Less than college	694 (57.03)	199 (43.9)	201 (57.3)	171 (67.1)	123 (77.8)		
College and above	523 (42.97)	254 (56.1)	150 (42.7)	84 (32.9)	36 (22.2)		
Employment, n (%)						0.06	<0.001
Yes	768 (63.1)	300 (66.2)	250 (71.2)	145 (56.9)	73 (46.2)		
Mean annual income, n (%)						<0.001	<0.001
<$25,000	463 (38.04)	158 (34.9)	83 (23.6)[a]	141 (55.3)	81 (51.3)		
>$25,000	574 (47.2)	239 (52.8)	230 (65.5)[a]	66 (25.9)	39 (24.7)		
Unknown	180 (14.79)	56 (12.36)	38 (10.8)	48 (18.8)	38 (24.1)		
Homeownership, n (%)						<0.001	<0.001
Owned	874 (71.8)	383 (84.5)	272 (77.5)	135 (52.9)	84 (53.2)		
Rented	211 (17.3)	40 (8.8)	42 (12.0)	87 (34.1)	42 (26.6)		
Other	132 (10.9)	30 (6.6)	37 (10.5)	33 (12.9)	32 (20.3)		
Health insurance, n (%)						0.031	0.015
Governmental	302 (24.8)	65 (14.3)	68 (19.4)	99 (38.8)	70 (44.3)		
Private	631 (51.8)	305 (67.3)	201 (57.3)	83 (32.5)	42 (26.6)		
Self-pay	209 (17.2)	57 (12.6)	61 (17.4)	56 (22.0)	35 (22.2)		
More than 1	75 (6.2)	26 (5.7)	21 (6.0)	17 (6.7)	11 (7.0)		
Smoking behavior, n (%)						NS	0.15
Never	772 (63.4)	305 (67.3)	217 (61.8)	177 (69.4)	73 (46.2)[a]		
Current	247 (20.3)	78 (17.2)	70 (19.9)	43 (16.9)	56 (35.4)[a]		
Former	198 (16.3)	70 (15.5)	64 (18.2)	35 (13.7)	29 (18.4)[a]		
Cardiometabolic risk factors							
BMI, kg/m^2	31.32 (7.69)	30.02 (7.14)	30.55 (6.16)	34.88 (8.81)	31.05 (8.63)[b]	<0.001	NS
MAP, mm Hg	123.57 (16.85)	89.44 (11.08)	94.96 (11.08)[b]	95.96 (14.87)	99.08 (12.97)	<0.001	0.003
SBP, mm Hg	93.65 (12.69)	117.59 (14.64)	125.88 (14.02)[b]	126.28 (20.89)	131.21 (15.86)[a]	<0.001	0.004
DBP, mm Hg	78.70 (11.54)	75.36 (10.26)	79.48 (10.55)[b]	80.88 (12.90)	83.02 (12.32)	<0.001	0.006
Total cholesterol, mg/dL	193.08 (40.69)	198.95 (39.02)	190.73 (40.17)[a]	189.63 (42.16)	187.11 (42.36)	0.026	NS
Non-HDL cholesterol, mg/dL	141.70 (41.85)	143.03 (41.19)	147.79 (40.56)	134.80 (42.63)	135.48 (43.39)	0.076	0.018
HDL, mg/dL	51.38 (16.33)	55.85 (16.39)	42.94 (12.86)[b]	54.83 (15.62)	51.63 (17.06)	NS	<0.001
LDL, mg/dL	115.01 (35.84)	116.12 (34.27)	116.93 (34.14)	113.46 (38.15)	110.38 (39.51)	NS	0.43
Triglycerides, mg/dL	135.91 (100.59)	135.96 (97.31)	159.54 (119.17)[a]	110.42 (86.87)	122.82 (67.55)	0.008	0.001
Serum glucose level, mg/dL	107.56 (37.02)	105.13 (38.31)	109.57 (31.38)	109.21 (44.16)	107.48 (31.57)	NS	NS

Continued

Table 1 Participant Characteristics at Time of Cognitive Assessment by Sex and Race *(continued)*

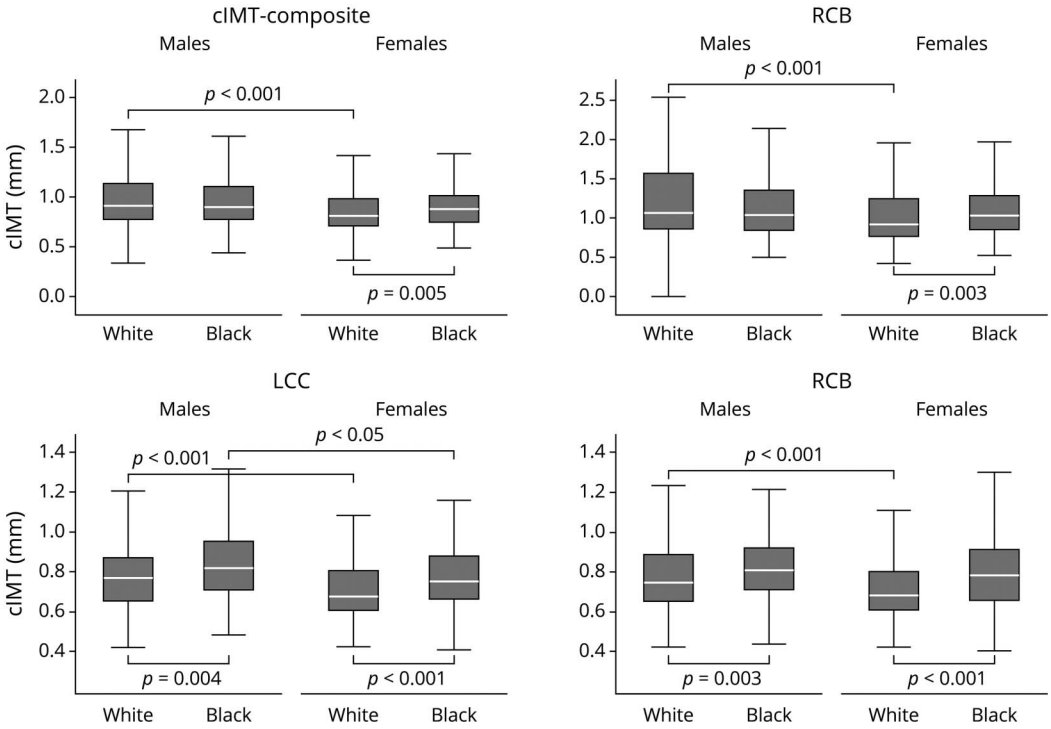
Participant characteristics	All (N = 1,217)	White participants		Black participants		Race difference, *p* value[c]	
		Female (n = 453)	Male (n = 351)	Female (n = 255)	Male (n = 158)	Female	Male
Hypertension medication	426 (35.0%)	124 (27.4%)	103 (29.3%)	135 (52.9%)	64 (40.5%)[a]	<0.001	0.065
Diabetes medication	142 (11.7%)	52 (11.5%)	31 (8.8%)	39 (15.3%)	20 (12.7%)	0.629	0.962
Cholesterol medication	174 (14.3%)	56 (12.4%)	69 (19.7%)[a]	27 (10.6%)	22 (13.9%)	1.0	0.7

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAP = mean arterial pressure; NS = nonsignificant; SBP = systolic blood pressure.
Data are presented as mean (SD) for continuous measures and number (percent) for categorical measures unless otherwise specified. Missing data as follows: n = 1 for BMI, n = 1 for SBP, n = 1 for DBP, n = 13 for triglycerides, n = 13 for Non-HDL, and n = 21 for serum glucose level.
[a] Sex difference $p < 0.05$.
[b] Sex difference $p < 0.001$.
[c] Bonferroni-adjusted *p* values.

Adults (CARDIA) study showed that greater c-IMT was associated with worse global cognitive performance later in life, and this relationship was attenuated after adjustment for education and CVRFs, with greater impairment on executive tests.[14] Among international studies, the Malmo Diet and Cancer Study[15] and the Brazilian Longitudinal Study of Adult Health found that midlife stroke-free participants with higher c-IMT had worse cognitive function even after adjustment for major CVFRs.[37] Our results extend these findings to a younger cohort with greater burden of cardiometabolic conditions. Regardless of these characteristics, adjustment for major CVRFs such as age, history of smoking, BMI, triglycerides, and BP levels did not eliminate the association between c-IMT and midlife cognitive function.

Our results also showed a buffered association between c-IMT and global cognitive function after adjustment for achieved education. Education has always played a key role in understanding the potential mechanisms of protection from dementia and drivers of racial disparities in ADRD prevalence.[30,38,39] Previous studies showed modified effects by education when looking at the association between certain risk factors and AD prevalence.[40] Indeed, recent literature suggests that higher education levels may increase cognitive reserve, the

Figure 1 c-IMT Ultrasound Measurements by Sex and Race



c-IMT = carotid intima-media thickness; LCC = left common carotid; RCB = right carotid bulb; RCC = right common carotid.

Table 2 Association Between c-IMT and GCS

Exposure	Model	All		White participants		Black participants	
		β (SE)	*p* Value	β (SE)	*p* Value	β (SE)	*p* Value
c-IMT composite dichotomous[b]	Unadjusted	−1.32 (0.28)	<0.001	−1.06 (0.32)	0.001	−1.21 (0.43)	0.005
	Only CVRFs	−1.08 (0.29)	<0.001	−0.92 (0.35)	0.008	−1.25 (0.45)	0.005
	Only education indicator[a]	−0.38 (0.18)	0.03	−0.43 (0.22)	0.05	−0.26 (0.29)	0.371
	Education indicator[a] + CVRFs	−0.39 (0.18)	0.03	−0.39 (0.23)	0.09	−0.40 (0.30)	0.187

Abbreviations: c-IMT = carotid intima-media thickness; CVRF = cardiovascular risk factor; GCS = global cognitive *z* score.
CVRFs: systolic blood pressure, glucose level, smoking status, non–high-density lipoprotein cholesterol, triglyceride level, and hypertension medication use. A model including c-IMT in addition to interaction terms between c-IMT and race was nonsignificant.
[a] Indicator for achieved education and premorbid cognitive abilities.
[b] Above the 50th percentile (0.87 mm).

adaptability to sustain better cognitive function despite brain pathology, and therefore buffer the association between known CVRFs and brain pathology.[41-44] Furthermore, it is recognized that the quality of education and literacy differs across geographic regions and is a potential explanation for racial disparities in cognitive performance.[45] Individuals from segregated racial and rural communities in the southern United States are likely exposed to poorer quality of education.[39,46] As a result, self-reported years of education may overestimate the achieved learning. Thus, the use of language domain tests as indicators of education is proposed as a method to obtain more accurate results.[26,27,47] Consistent with this concept, our findings suggest that a higher education offers a protective effect on cognitive performance as early as midlife. We found that independently of major CVRFs, the association between c-IMT and GCS was significant only among those with lower language cognitive domain *z* score, our indicator for achieved education. In addition, we found that independently of major CVRFs, the point estimate was larger in Black participants and was more attenuated by education compared to White participants.

Driven by an array of social and behavioral determinants, health disparities are one of the primary causes of the high burden of cardiovascular disease among Black Americans and, in conjunction with educational level, are some of the most robust risk factors accounting for race and ethnic differences for the risk of ADRD.[48,49] In line with this model, our subgroup analyses showed that Black participants had higher levels of CVRFs, including SBP and triglycerides, poorer educational level, income, homeownership, and health access. They also had greater intima-media thickness in bilateral common carotids, regions that have been shown to be more affected by the hypertensive hypertrophic response. In comparison, we did not find racial differences in carotid bulb segments, regions exposed to constant turbulent flow and more prone to atherosclerotic plaque formation.[50] These findings are important given that studies have shown associations between upper quintiles of c-IMT thickness and Alzheimer dementia but not with carotid plaque.[8]

After the GCS was disaggregated into specific underlying cognitive domains, our results showed a stronger effect of subclinical atherosclerosis on executive function and verbal episodic memory. These results are in line with previous findings of c-IMT as a predictor of poorer memory, a common preclinical deficit in AD,[e2] independently of other significant risk factors in late life.[e1] We also found a negative association between c-IMT and executive function that was independent of achieved education and CVRFs. As a whole, the data described above suggest that measurable cognitive

Table 3 Association Between c-IMT and Cognitive Domains *z* Scores

Exposure	Model	Attention and processing speed		Episodic memory		Executive function	
		β (SE)	*p* Value	β (SE)	*p* Value	β (SE)	*p* Value
c-IMT composite dichotomous[b]	Unadjusted	−0.38 (0.08)	0.001	−0.37 (0.10)	<0.001	−0.56 (0.09)	<0.001
	Only CVRFs	−0.34 (0.09)	<0.001	−0.36 (0.11)	0.001	−0.49 (0.09)	<0.001
	Only education indicator[a]	−0.20 (0.08)	0.014	−0.19 (0.09)	0.038	−0.34 (0.08)	<0.001
	Education indicator[a] + CVRFs	−0.21 (0.09)	0.016	−0.23 (0.10)	0.015	−0.33 (0.09)	<0.001

Abbreviations: c-IMT = carotid intima-media thickness; CVRF = cardiovascular risk factor.
CVRFs: systolic blood pressure, glucose level, smoking status, non–high-density lipoprotein cholesterol, triglyceride level, and hypertension medication use.
[a] Indicator for achieved education and premorbid cognitive abilities.
[b] Above the 50th percentile (0.87 mm).

decline, perhaps linked to the eventual emergence of dementia, may begin in midlife rather than late life.[e3]

Our study has several strengths that underpin confidence in our findings. Given the nature of the BHS, it provides a one-of-a-kind opportunity to study the effects of CVRFs, subclinical atherosclerotic disease, and cognition among a diverse, community-based cohort of midlife individuals followed up from childhood. We were able to examine the relationship between c-IMT and cognitive function among both Black and White participants. Furthermore, due to socioeconomic factors, the quality of educational attainment may differ by race. To address this issue, we adjusted for achieved education using performance on the WRAT-4 and the WAIS-IV Vocabulary subtest. Previous findings have shown that NP tests such as the WRAT-3 and the National Adult Reading Test are more sensitive indicators of achieved education than traditional grade-level cutoffs.[27] Although this approach has been shown to be consistent, additional research is needed to accurately depict and assess the crucial role of education in the association between CVRFs and cognitive function. Moreover, even when NP tests measure the same construct across racial/ethnic groups, cultural experiences of people from less socially advantaged environments affect their NP performance, leading to misclassification with their overrepresentation in low average scores.[23,25] We addressed this issue by demographically standardizing NP test scores because this method has been strongly supported as a measure to maintain consistency in test scores across different groups.[25]

Our work also has some limitations. As with any observational study, the potential for residual confounding due to measurement error cannot be eliminated. Given the cross-sectional design of the study, we cannot assess causality or the temporal relationship in these associations. We also acknowledge that to thoroughly address racial disparities and to better understand their health consequences, it would be necessary to further characterize aspects of social disadvantage beyond what is currently available in our historical cohort. Participants in the BHS are relatively young and from a semirural community, which may limit the generalizability of our findings. However, this is one of the few epidemiologic studies to assess the relationship between subclinical atherosclerosis and cognitive function in early midlife, a critical and understudied period during which subclinical disease may begin. We expect to continue repeated longitudinal collection of both atherosclerotic and cognitive data that will allow continued evaluation of this association in the future.

Our study shows that subclinical atherosclerosis is associated with worse cognitive function in midlife independently of major CVRFs. The association is buffered by education, and this effect may be stronger among Black compared to White participants. These findings reinforce the importance of establishing primary preventive measures as early as midlife, a critical time window for the initiation of early dementia pathology, and suggest that subclinical atherosclerosis may be a potential target in efforts to prevent cognitive decline.

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Camilo Fernandez Alonso, MD	Tulane University School of Medicine, New Orleans, LA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
David J. Libon, PhD	Rowan University, Stratford, NJ	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
Owen T. Carmichael, PhD	Louisiana State University's Pennington Biomedical Research Center, Baton Rouge, LA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
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Continued

Appendix *(continued)*

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References

1. Kochanek KD. Mortality in the United States, 2019. NCHS Data Brief, no 395. Hyattsville, MD: National Center for Health Statistics. 2020.
2. Wimo A, Prince M. World Alzheimer report 2010: the global economic impact of dementia: executive summary. Accessed April 4, 2022. https://www.alzint.org/resource/world-alzheimer-report-2010/
3. Zahodne LB, Manly JJ, Azar M, Brickman AM, Glymour MM. Racial disparities in cognitive performance in mid- and late adulthood: analyses of two cohort studies. *J Am Geriatr Soc.* 2016;64(5):959-964.
4. Emrani S, Lamar M, Price CC, et al. Alzheimer's/vascular spectrum dementia: classification in addition to diagnosis. *J Alzheimers Dis.* 2020;73(1):63-71.
5. Scheffer S, Hermkens DMA, van der Weerd L, de Vries HE, Daemen MJAP. Vascular hypothesis of Alzheimer disease: topical review of mouse models. *Arterioscler Thromb Vasc Biol.* 2021;41(4):1265-1283.
6. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2011;42(9):2672-2713.
7. Moroni F, Ammirati E, Magnoni M, et al. Carotid atherosclerosis, silent ischemic brain damage and brain atrophy: a systematic review and meta-analysis. *Int J Cardiol.* 2016;223:681-687.
8. Wendell CR, Waldstein SR, Ferrucci L, O'Brien RJ, Strait JB, Zonderman AB. Carotid atherosclerosis and prospective risk of dementia. *Stroke.* 2012;43(12):3319-3324.
9. Moneta GL. Reduced neuropsychological test performance in asymptomatic carotid stenosis: the Tromsø study. *Yearb Vasc Surg.* 2006;2006:292.
10. Sander K, Bickel H, Förstl H, et al. Carotid- intima media thickness is independently associated with cognitive decline. The INVADE study. *Int J Geriatr Psychiatry.* 2010;25(4):389-394.
11. Li S, Chen W, Srinivasan SR. Childhood cardiovascular risk factors and carotid vascular changes in adulthood: the Bogalusa Heart Study. *ACC Curr J Rev.* 2004;13(2):63-64.
12. Polak JF, O'Leary DH. Carotid intima-media thickness as surrogate for and predictor of CVD. *Glob Heart.* 2016;11(3):295.
13. Baradaran H, Demissie S, Himali JJ, et al. The progression of carotid atherosclerosis and imaging markers of dementia. *Alzheimers Dement Transl Res Clin Interv.* 2020;6(1).
14. Al Hazzouri AZ, Vittinghoff E, Sidney S, Reis JP, Jacobs DR, Yaffe K. Intima-media thickness and cognitive function in stroke-free middle-aged adults: findings from the Coronary Artery Risk Development in Young Adults study. *Stroke.* 2015;46(8):2190-2196.
15. Gustavsson A, Westen D, Stomrud E, Engström G, Nägga K, Hansson O. Midlife atherosclerosis and development of Alzheimer or vascular dementia. *Ann Neurol.* 2020;87(1):52-62.
16. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. *Alzheimers Dement.* 2016;12(3):216-224.
17. Mazimba S, Peterson PN. *JAHA* spotlight on racial and ethnic disparities in cardiovascular disease. *J Am Heart Assoc.* 2021;10(17):e023650.
18. Berenson GS. Bogalusa Heart Study: a long-term community study of a rural biracial (Black/White) population. *Am J Med Sci.* 2001;322(5):267-274.
19. Urbina EM, Srinivasan SR, Tang R, Bond MG, Kieltyka L, Berenson GS. Impact of multiple coronary risk factors on the intima-media thickness of different segments of carotid artery in healthy young adults (the Bogalusa Heart Study). *Am J Cardiol.* 2002;90(9):953-958.
20. Stein JH, Douglas PS, Srinivasan SR, et al. Distribution and cross-sectional age-related increases of carotid artery intima-media thickness in young adults: the Bogalusa Heart Study. *Stroke.* 2004;35(12):2782-2787.
21. Nagai Y, Metter EJ, Earley CJ, et al. Increased carotid artery intimal-medial thickness in asymptomatic older subjects with exercise-induced myocardial ischemia. *Circulation.* 1998;98(15):1504-1509.
22. Gershon RC, Cella D, Fox NA, Havlik RJ, Hendrie HC, Wagster MV. Assessment of neurological and behavioural function: the NIH toolbox. *Lancet Neurol.* 2010;9(2):138-139.
23. Werry AE, Daniel M, Bergström B. Group differences in normal neuropsychological test performance for older non-Hispanic White and Black/African American adults. *Neuropsychology.* 2019;33(8):1089-1100.
24. Manly JJ, Miller SW, Heaton RK, et al. The effect of African-American acculturation on neuropsychological test performance in normal and HIV-positive individuals. *J Int Neuropsychol Soc.* 1998;4(3):291-302.
25. Norman MA, Moore DJ, Taylor M, et al. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test–Revised, Brief Visuospatial Memory Test–Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-card version. *J Clin Exp Neuropsychol.* 2011;33(7):793-804.
26. Sisco S, Gross AL, Shih RA, et al. The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. *J Gerontol B Psychol Sci Soc Sci.* 2015;70(4):557-567.
27. Ahl RE, Beiser A, Seshadri S, Auerbach S, Wolf PA, Au R. Defining MCI in the Framingham Heart Study offspring: education versus WRAT-based norms. *Alzheimer Dis Assoc Disord.* 2013;27(4):330-336.
28. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. *J Int Neuropsychol Soc.* 2002;8(3):341-348.
29. Burke GL, Webber LS, Srinivasan SR, Radhakrishnamurthy B, Freedman DS, Berenson GS. Fasting plasma glucose and insulin levels and their relationship to cardiovascular risk factors in children: Bogalusa Heart Study. *Metabolism.* 1986;35(5):441-446.
30. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet.* 2020;396(10248):413-446.
31. Pollock BD, Stuchlik P, Harville EW, et al. Life course trajectories of cardiovascular risk: impact on atherosclerotic and metabolic indicators. *Atherosclerosis.* 2019;280:21-27.
32. Hodis HN. Reduction in carotid arterial wall thickness using lovastatin and dietary therapy: a randomized, controlled clinical trial. *Ann Intern Med.* 1996;124(6):548.
33. Della-Morte D, Dong C, Markert MS, et al. Carotid intima-media thickness is associated with white matter hyperintensities: the Northern Manhattan Study. *Stroke.* 2018;49(2):304-311.
34. Altamura C, Scrascia F, Quattrocchi CC, et al. Regional MRI diffusion, white-matter hyperintensities, and cognitive function in Alzheimer's disease and vascular dementia. *J Clin Neurol.* 2016;12(2):201.
35. Nation DA, Sweeney MD, Montagne A, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nat Med.* 2019;25(2):270-276.
36. Ivanidze J, Mackay M, Hoang A, et al. Dynamic contrast-enhanced MRI reveals unique blood-brain barrier permeability characteristics in the hippocampus in the normal brain. *AJNR Am J Neuroradiol.* 2019;40(3):408-411.
37. Suemoto CK, Santos IS, Bittencourt MS, et al. Subclinical carotid artery atherosclerosis and performance on cognitive tests in middle-aged adults: baseline results from the ELSA-Brasil. *Atherosclerosis.* 2015;243(2):510-515.
38. Lövdén M, Fratiglioni L, Glymour MM, Lindenberger U, Tucker-Drob EM. Education and cognitive functioning across the life span. *Psychol Sci Public Interest.* 2020;21(1):6-41.
39. Farina MP, Hayward MD, Kim JK, Crimmins EM. Racial and educational disparities in dementia and dementia-free life expectancy. *J Gerontol Ser B.* 2020;75(7):e105-e112.
40. Letenneur L, Gilleron V, Commenges D, Helmer C, Orgogozo JM, Dartigues JF. Are sex and educational level independent predictors of dementia and Alzheimer's disease? Incidence data from the PAQUID project. *J Neurol Neurosurg Psychiatry.* 1999;66(2):177-183.
41. Stern Y, Arenaza-Urquijo EM, Bartrés-Faz D, et al. Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. *Alzheimers Dement.* 2010;16(9):1305-1311.
42. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve. *Trends Cogn Sci.* 2013;17(10):502-509.
43. Pettigrew C, Soldan A. Defining cognitive reserve and implications for cognitive aging. *Curr Neurol Neurosci Rep.* 2019;19(1):1.
44. Zahodne LB, Mayeda ER, Hohman TJ, et al. The role of education in a vascular pathway to episodic memory: brain maintenance or cognitive reserve? *Neurobiol Aging.* 2019;84:109-118.
45. Liu SY, Glymour MM, Zahodne LB, Weiss C, Manly JJ. Role of place in explaining racial heterogeneity in cognitive outcomes among older adults. *J Int Neuropsychol Soc.* 2015;21(9):677-687.
46. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. *Neuropsychol Rev.* 2008:18(3):223-254.
47. Rentz DM, Huh TJ, Faust RR, et al. Use of IQ-adjusted norms to predict progressive cognitive decline in highly intelligent older individuals. *Neuropsychology.* 2004;18(1):38-49.
48. Babulal GM, Quiroz YT, Albensi BC, et al. Perspectives on ethnic and racial disparities in Alzheimer's disease and related dementias: update and areas of immediate need. *Alzheimers Dement.* 2019;15(2):292-312.
49. Carnethon MR, Pu J, Howard G, et al. Cardiovascular health in African Americans: a scientific statement from the American Heart Association. *Circulation.* 2017;136(21):e393-e423.
50. Arntzen KA, Mathiesen EB. Subclinical carotid atherosclerosis and cognitive function: subclinical carotid atherosclerosis and cognitive function. *Acta Neurol Scand.* 2011;124:18-22.