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ORIGINAL RESEARCH

Association of Carotid Intima-Media Thickness and Other Carotid Ultrasound Features With Incident Dementia in the ARIC-NCS

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BACKGROUND: Increased carotid intima-media thickness, interadventitial diameter, presence of carotid plaque, and lower distensibility are predictors for cardiovascular disease. These indices likely relate to cerebrovascular disease, and thus may constitute a form of vascular contributions to dementia and Alzheimer disease–related dementia. Therefore, we assessed the relationship of carotid measurements and arterial stiffness with incident dementia in the ARIC (Atherosclerosis Risk in Communities) study.

METHODS AND RESULTS: A total of 12 459 ARIC participants with carotid arterial ultrasounds in 1990 to 1992 were followed through 2017 for dementia. Dementia cases were identified using in-person and phone cognitive status assessments, hospitalization discharge codes, and death certificate codes. Cox proportional hazards models were used to estimate the hazard ratios (HRs) for incident dementia. Participants were aged 57±6 at baseline, 57% were women, and 23% were Black individuals. Over a median follow-up time of 24 years, 2224 dementia events were ascertained. After multivariable adjustments, the highest quintile of carotid intima-media thickness and interadventitial diameter in midlife was associated with increased risk of dementia (HR [95% CIs], 1.25 [1.08–1.45]; and 1.22 [1.04–1.43], respectively) compared with its respective lowest quintile. Presence of carotid plaque did not have a significant association with dementia (HR [95% CI], 1.06 [0.97–1.15]). Higher distensibility was associated with lower risk of dementia (HR [95% CI] highest versus lowest quintile, 0.76 [0.63–0.91]).

CONCLUSIONS: Greater carotid intima-media thickness, interadventitial diameter, and lower carotid distensibility are associated with an increased risk of incident dementia. These findings suggest that both atherosclerosis and carotid stiffness may be implicated in dementia risk.

Key Words: carotid intima-media thickness ■ dementia ■ epidemiology ■ risk factors

The burden of dementia is a public health concern, particularly as the US population ages.[1] By midcentury, the number of individuals with dementia in the United States is expected to increase to 13.8 million.[1] Preclinical changes in the brain can occur long before dementia develops. Therefore, identifying markers for dementia early in the condition's natural history is a priority.

Elevated carotid intima-media thickness (cIMT), interadventitial diameter (IAD), presence of carotid plaque, and low carotid distensibility have all been established as predictors for cardiovascular disease.[2,3] Plaque or elevated cIMT can disrupt or reduce cerebral blood flow or could rupture,[4] which may lead to silent brain infarctions,[5] a precursor to cognitive

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CLINICAL PERSPECTIVE

What Is New?

- In this large, community-based cohort, elevated carotid intima-media thickness and interadventitial diameter and lower carotid distensibility in midlife are associated with an increased risk of incident dementia in later life.
- Our findings suggest that markers of atherosclerosis and carotid stiffness may be independent risk factors for dementia.

What Are the Clinical Implications?

- A noninvasive ultrasound procedure may be a valuable screening tool in identifying who is at an increased risk for dementia.

Nonstandard Abbreviations and Acronyms

AD	Alzheimer disease
ARIC	Atherosclerosis Risk in Communities
ARIC-NCS	Atherosclerosis Risk in Communities–Neurocognitive Study
cIMT	carotid intima-media thickness
DC	distensibility coefficient
IAD	interadventitial diameter

decline.[6] Furthermore, if part of an unstable carotid plaque embolizes, it can cause a clinical stroke and may ultimately lead to dementia.[7,8] Elevated cIMT levels have also been cross-sectionally associated with silent brain infarctions in Black individuals in a prior ARIC (Atherosclerosis Risk in Communities) study analysis.[9] Plaque can still often be present even when cIMT is not elevated, indicating the importance of assessing both cIMT and plaque measurements during carotid ultrasounds.[10] Additionally, risk factors, such as smoking, hypertension, and diabetes mellitus, are related to increased cIMT and IAD.[11] Individuals with an enlarged IAD are less able to maintain levels of shear stress, making the artery more vulnerable to atherosclerotic development.[12] Alternatively, cIMT and carotid plaque may simply be markers of cumulative exposure to vascular risk factors throughout the life course.[13]

Arterial stiffening occurs during the aging process and is associated with arteriosclerosis.[14,15] It has been suggested that this stiffening affects the natural cushioning function of the arterial system, which contributes to the development and progression of cerebral small-vessel disease and could eventually affect brain function.[14,16] The association between pulse wave velocity and dementia was previously assessed, but results are mixed.[17–20] More recently, it was shown that higher pulse wave velocity is cross-sectionally associated with an increased risk of dementia in White participants in ARIC,[19] though this association was not noted in a Swedish cohort.[20] However, the prospective relationship between the stiffness of the common carotid artery, measured as the distensibility coefficient, and dementia is not well documented.

As current knowledge gaps exist, we aimed to identify the prospective association of carotid measurements and arterial stiffness indices with incident dementia in the ARIC study, a large, population-based cohort. We hypothesized that greater cIMT, presence of carotid plaque, increased IAD, and lower carotid distensibility are associated with an increased risk for dementia.

METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure in accordance with ARIC study policies. Data from the ARIC study can be accessed, with appropriate approvals, through the National Heart, Lung, and Blood Institute's Biospecimen and Data Repository Information Coordinating Center (https://biolincc.nhlbi.nih.gov/home/) or by contacting the ARIC Coordinating Center.

Study Population and Design

The ARIC study is a population-based cohort of predominantly Black and White adults recruited from 4 US communities: Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi. The ARIC study recruited 15 792 men and women aged 45 to 64 who underwent a baseline examination (visit 1) in 1987 to 1989.[21] After the initial examination, participants were examined 6 additional times: 1990 to 1992 (visit 2), 1993 to 1995 (visit 3), 1996 to 1998 (visit 4), 2011 to 2013 (visit 5), 2016 to 2017 (visit 6), and 2018 to 2019 (visit 7). In addition to the clinic visits, participants were contacted by telephone (annually before 2012; twice yearly since). Hospitalization *International Classification of Diseases* (*ICD*) codes were obtained through regular cohort surveillance,[22] with record abstraction and adjudication of clinical cardiovascular events. National and state death indices were used to identify mortality, and informant interviews were conducted.

Visit 2 served as the baseline since this was when the arterial indices were measured. Participants whose race was not Black or White, as well as

non-White individuals in the Minneapolis and Washington County centers were excluded because of low numbers (n=92). Additionally, those with prevalent cardiovascular events (heart failure, stroke, or coronary heart disease) at visit 2 (n=1005), prevalent dementia at visit 2 (n=1), missing carotid plaque or cIMT measurements at visit 2 (n=579), and missing covariate information (n=212) were excluded from this analysis. Of the 14 348 ARIC participants who attended visit 2, 12 459 participants were included in this analysis after exclusions.

The institutional review boards at each participating center approved the ARIC protocol, and all participants provided written informed consent.

Exposure Measurements

cIMT, IAD, and Carotid Plaque

The ARIC ultrasound measurements were conducted by trained technicians, and scans were read centrally at the ARIC Ultrasound Reading Center, as has been previously described.[23] Briefly, Biosound 2000 II duplex scanners were used to acquire all images. cIMT was assessed in 3 segments of the right and left extracranial carotid arteries: the distal common carotid artery (1 cm proximal to dilation of the carotid bulb), the carotid artery bifurcation (1 cm proximal to the flow divider), and the proximal internal carotid arteries (1 cm section in the internal branch distal to the flow divider).[24] A total of 11 measurements of the far wall were attempted at each of these segments in 1-mm increments; the mean of these measurements was calculated. The site-specific reliability coefficients for the mean carotid far wall intima-media thickness at the carotid bifurcation, internal carotid arteries, and the common carotid artery were estimated as 0.77, 0.73, and 0.70, respectively.[25] Consistent with the European Society of Cardiology definition, we considered a cIMT >0.90 mm to be "abnormal."[26] The IAD was defined as the distance from the near border of the media of the near wall to the far border of the media on the far wall.[11]

Trained readers indicated the presence of plaque if located in any of the 6 artery segments of the right and left carotid arteries (common carotid, area of bifurcation, and internal carotid).[27] Carotid plaque was recorded as present if 2 of the following 3 criteria were met: abnormal wall thickness (>1.5 mm), abnormal shape (protrusion into the lumen, loss of alignment with adjacent arterial wall boundary), or abnormal wall texture (brighter echoes than adjacent boundaries). The intrareader agreement for carotid plaque had a κ statistic of 0.76 and an interreader agreement of 0.56.[27]

Carotid Distensibility

B-mode ultrasound scans of the left common carotid artery with electrocardiographic gating and echo tracking of the arterial diameter were used to assess carotid distensibility. B-mode ultrasound scans with electrocardiographic gating and echo tracking methods were done as previously described.[21] Starting the night before the ultrasound, participants were asked to refrain from smoking, vigorous exercise, and beverages containing caffeine. Arterial wall characteristics were determined using an average of 5.6 cardiac cycles of adequate quality for readers to measure arterial diameter changes through the cardiac cycle. Readers at the ARIC Ultrasound Reading Center used a standardized protocol to assess the arterial diameter variation.[28] The cross-sectional arterial wall distensibility coefficient (DC) was calculated on the basis of the following equation: $DC=2\Delta D/(D\times\text{pulse pressure})$ (10^{-3}/kPa), where ΔD is defined as the absolute change in diameter during systole and D is the end-diastolic diameter. The reliability coefficient, which is defined as the between-person variance over the total variance, for carotid distensibility is 0.67.[28] A lower distensibility coefficient indicates less carotid distensibility (ie, arterial stiffness).

Dementia Ascertainment

Dementia was ascertained 3 ways[22]: (1) Adjudicated dementia cases were identified from in-person cognitive testing at ARIC–Neurocognitive Study (NCS) visits 5 and 6. Information available to adjudicators included data from longitudinal evidence of cognitive decline based on cognitive assessments from prior visits, complete neuropsychological battery at the ARIC-NCS visits, and informant interviews.[22] (2) Among participants who did not attend the ARIC-NCS clinic visits, the Telephone Instrument of Cognitive Status–Modified was used to determine cognitive status, or an informant telephone interview was conducted.[22] (3) Additional dementia cases were identified from *ICD* hospitalization discharge codes or death certificate codes.[29] Etiologic dementia diagnoses were available for participants who completed neurocognitive assessments at visit 5. Reviewers were required to assign a primary diagnosis but were allowed to diagnose >1 etiology.[22] The diagnosis of Alzheimer disease (AD)-related dementia followed criteria from the National Institute of Aging–Alzheimer's Association,[30,31] while vascular dementia diagnosis was based on the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria.[32] For our analysis, dementia etiology was categorized as AD-related dementia if the primary diagnosis was AD and as vascular dementia if cerebrovascular disease was the primary or secondary diagnosis.

Covariate Measurements

Covariates in this analysis were assessed at visit 2 and included age, sex, race, ARIC field center, apolipoprotein

E ε4 genotype (≥1 allele, 0 alleles), body mass index, systolic blood pressure, antihypertensive medications (yes, no), smoking status (current, former, never), pack-years of smoking, and diabetes mellitus status (yes, no). Education level (less than high school education, high school graduate or high school equivalent or vocational school, college or above) was assessed at visit 1. A 5-level race/center variable (White participants from Minneapolis, Minnesota; White participants from Washington County, Maryland; Black participants from Jackson, Mississippi; Black participants from Forsyth County, North Carolina; White participants from Forsyth County, North Carolina) was used in all analyses. Participants self-reported their race category, education level, smoking status, and amount smoked. Pack-years of smoking was calculated. Technicians recorded current medication use via review of medication bottles, which included antihypertensive agents. Apolipoprotein E ε4 genotyping was done as previously described using the TaqMan assay (Applied Biosystems, Foster City, CA).[33] Technicians also measured height and weight to derive body mass index and measured sitting blood pressure 3 times via a random-zero sphygmomanometer after a 5-minute rest. The final 2 blood pressure measurements were averaged. Diabetes mellitus was defined as a fasting serum glucose of ≥126 mg/dL, nonfasting serum glucose of ≥200 mg/dL, a self-reported physician diagnosis of diabetes mellitus, or use of antidiabetic medication in the past 2 weeks. Stroke was defined as a self-reported physician diagnosis of a stroke before visit 1; following visit 1, stroke was adjudicated from diagnosis codes indicative of cerebrovascular disease using criteria adapted from the National Survey of Stroke.[34]

Statistical Analysis

Baseline characteristics, stratified across cIMT quintiles, were described using frequencies and percentages for categorical variables and means and SDs for continuous variables. cIMT, IAD, and carotid distensibility were also categorized in quintiles for the primary analyses.

Using Cox proportional hazards models, we estimated the hazard ratios (HRs) and 95% CIs for incident dementia per 1-SD increment and per quintile of arterial index (cIMT, IAD, and DC), as well as for presence of carotid plaque or abnormal cIMT. Follow-up time was defined as time from visit 2 to the occurrence of incident dementia, death, loss to follow-up, or December 31, 2017, whichever occurred first. When assessing dementia etiology, logistic regression was used to estimate odds ratios and 95% CIs. Model 1 was adjusted for age, sex, race/center (5 levels), education, and apolipoprotein E ε4 genotype. Model 2 was additionally adjusted for body mass index, systolic blood pressure, smoking status, and pack-years of smoking. Model 3 further adjusted for antihypertensive medications and diabetes mellitus status. Model 4 further adjusted for stroke as a time-varying covariate.

Multiplicative interactions by sex, race, and apolipoprotein E ε4 were analyzed by including cross-product terms in the model. All analyses were conducted using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

RESULTS

Participants had a mean age of 57 years, 57% were women, and 23% were Black individuals. Those in the highest cIMT quintile were more likely to be men, older, current and heavier smokers, have diabetes mellitus, carry ≥1 apolipoprotein E ε4 allele, and have lower educational attainment (Table 1). Over a median follow-up time of 24 years, 2224 participants developed dementia. Among those who developed dementia, 23% were diagnosed via in-person cognitive assessments at ARIC-NCS visits, 45% were diagnosed from Telephone Instrument of Cognitive Status–Modified telephone interviews or informant interview, and 32% were diagnosed on the basis of hospitalization discharge codes or death certificates.

Carotid Atherosclerosis and Incident Dementia

For both cIMT and IAD, there was evidence of a dose-response association, with higher values associated with greater dementia risk. After model 1 adjustments, participants in the highest quintile of cIMT (>0.85 mm) had a 1.48-fold increased risk of incident dementia (95% CI, 1.28–1.71) compared with the lowest quintile (Table 2). This association remained in model 3 (HR [95% CI], 1.33 [1.15–1.54]). For IAD, the highest (versus lowest) quintile was associated with a higher risk of incident dementia in model 1 (HR [95% CI], 1.49 [1.28–1.73]) and model 3 (HR [95% CI], 1.24 [1.06–1.46]). When all vessel measures were included in model 3, cIMT (per 1-SD increment) was found to be an independent predictor for dementia (HR [95% CI], 1.08 [1.03–1.14]), while IAD (per 1-SD increment) was not (HR [95% CI], 1.02 [0.95–1.09]). In addition, greater cIMT was associated with higher odds of vascular dementia in model 1 (HR [95% CI], 2.16 [1.13–4.12]); however, after accounting for vascular risk factors, this association was attenuated (eg, model 2 HR [95% CI], 1.84 [0.95–3.55]); Table S1). No significant association between cIMT and AD-related dementia (Model 1 HR [95% CI], 1.50 [0.72–3.12]), though precision was poor (Table S2). IAD was not associated with and either dementia subtype (Tables S1 and S2).

Table 1. Baseline Characteristics According to cIMT Quintiles: the ARIC study, 1990 to 1992*

	cIMT Quintile				
	1	2	3	4	5
No.	2491	2492	2492	2492	2492
cIMT median, mm	0.56	0.64	0.70	0.79	0.96
cIMT range, mm	0.38–0.60	0.60–0.67	0.67–0.74	0.74–0.85	0.85–2.98
Carotid plaque	269 (10.8)	455 (18.3)	627 (25.2)	922 (37.0)	1849 (74.2)
Demographics					
Age, y	54.4 (5.2)	55.9 (5.5)	56.9 (5.6)	57.6 (5.7)	59.4 (5.3)
Male sex	669 (26.9)	877 (35.2)	1073 (43.1)	1259 (50.5)	1449 (58.2)
Black race	402 (16.1)	549 (22.0)	659 (26.4)	621 (24.9)	586 (23.5)
Education, < high school degree	360 (14.5)	435 (17.5)	498 (20.0)	539 (21.6)	697 (28.0)
Physiologic indicators					
Body mass index, kg/m^2	26.6 (5.0)	27.7 (5.4)	28.2 (5.2)	28.2 (5.1)	28.1 (5.1)
Systolic blood pressure, mm Hg	115.2 (16.1)	118.9 (17.1)	121.2 (17.8)	123.2 (19.1)	126.7 (19.7)
Use of antihypertensive medication	527 (21.2)	659 (26.4)	711 (28.5)	839 (33.7)	917 (36.8)
Diabetes mellitus	179 (7.2)	269 (10.8)	356 (14.3)	362 (14.5)	491 (19.7)
>1 Apolipoprotein E ε4 allele	680 (27.3)	716 (28.7)	726 (29.1)	750 (30.1)	802 (32.2)
Behavioral characteristics					
Smoking status					
Current smoker	508 (20.4)	488 (19.6)	503 (20.2)	541 (21.7)	705 (28.3)
Former smoker	791 (31.8)	869 (34.9)	888 (35.6)	958 (38.4)	1043 (41.9)
Never smoker	1192 (47.9)	1135 (45.6)	1101 (44.2)	993 (39.9)	744 (29.9)
Pack-years smoking	21.6 (38.4)	22.2 (38.6)	25.0 (41.5)	29.0 (46.2)	40.7 (51.6)

ARIC indicates Atherosclerosis Risk in Communities; and cIMT, carotid intima-media thickness.
*Continuous variables are expressed as mean (SD), while categorical variables are n (%).

Abnormal cIMT (>0.9 mm) was associated with greater risk of incident dementia throughout all models (Table 3; model 1 HR, 1.32 [1.18–1.48]; model 3 HR, 1.22 [1.09–1.36]). Participants with carotid plaque had a 1.10 (95% CI, 1.00–1.20) times higher risk of incident dementia than those without plaque in model 1. However, this association attenuated with further adjustment (Table 3). There were no significant interactions with sex, race, or apolipoprotein E ε4.

Carotid Distensibility and Incident Dementia

Similar to cIMT and IAD, carotid distensibility showed evidence of a dose-response association, with greater DC indicating lower risk of dementia. This pattern persisted with further model adjustments (Table 2). Likewise, when the DC was modeled linearly (per 1-SD increment), higher distensibility was associated with lower risk of dementia across all models. Additionally, the DC (per 1-SD increment) was found to be an independent predictor of dementia when all vessel measures were included in the model (HR [95% CI], 0.89 [0.84–0.95]). When assessing dementia subtypes separately, greater DC had lower odds of vascular dementia in model 1, but associations were attenuated with further model adjustments (Table S1). No association with AD-related dementia were noted (Table S2). No significant interactions with sex, race, or apolipoprotein E ε4 were detected.

DISCUSSION

Elevated markers of atherosclerosis (cIMT and IAD) and lower carotid distensibility were associated with greater risk of incident dementia in this community-based study of participants followed for a median of 24 years. cIMT and carotid distensibility were also found to be independent predictors of dementia. No significant association with carotid plaque was noted. Because atherosclerosis can often be asymptomatic,[5] identifying its markers through a noninvasive ultrasound procedure[35] may be a useful screening tool in identifying who may be at an increased risk for developing dementia.

These findings add to the growing body of literature suggesting that atherosclerosis,[36–38] and particularly elevated cIMT,[37,38] is associated with increased dementia risk. Our results are consistent with prior studies, which have reported that the highest (versus lowest) quintile of cIMT was associated with dementia.[37,38] However,

Table 2. Hazard Ratios (95% CIs) of Incident Dementia by Quintiles or Per 1-SD Increment: the ARIC Study, 1990 to 2017

	cIMT Quintiles (mm)					cIMT Continuous per 1 SD (0.19)
	<0.60	0.60 to <0.67	0.67 to <0.74	0.74 to <0.85	>0.85	
Incident dementia, n	318	398	454	489	565	2224
Incidence rate (per 1000 PY)	5.66	7.35	8.65	9.54	12.32	8.55
N at risk	2491	2492	2492	2492	2492	12 459
HR (95% CI)						
Model 1	1 (ref)	1.07 (0.92–1.24)	1.19 (1.03–1.37)	1.20 (1.04–1.38)	1.48 (1.28–1.71)	1.15 (1.11–1.20)
Model 2	1 (ref)	1.03 (0.89–1.20)	1.15 (0.99–1.33)	1.14 (0.98–1.32)	1.38 (1.19–1.59)	1.12 (1.07–1.17)
Model 3	1 (ref)	1.03 (0.89–1.20)	1.13 (0.98–1.31)	1.12 (0.97–1.30)	1.33 (1.15–1.54)	1.11 (1.06–1.16)
Model 4	1 (ref)	1.01 (0.87–1.17)	1.12 (0.97–1.30)	1.09 (0.94–1.27)	1.25 (1.08–1.45)	1.08 (1.04–1.13)
	IAD Quintiles (mm)					IAD Continuous per 1 SD (0.92)
	<6.89	6.89–7.34	7.34–7.76	7.77–8.35	8.36–13.43	
Incident dementia, n	341	415	457	454	449	2116
Incidence rate (per 1000 PY)	6.33	7.96	8.99	9.44	10.33	8.52
N at risk	2377	2374	2380	2378	2378	11 887
HR (95% CI)						
Model 1	1 (ref)	1.18 (1.02–1.37)	1.23 (1.07–1.43)	1.29 (1.12–1.50)	1.49 (1.28–1.73)	1.13 (0.94–1.13)
Model 2	1 (ref)	1.14 (0.98–1.31)	1.15 (0.99–1.34)	1.16 (0.99–1.35)	1.25 (1.06–1.47)	1.06 (1.01–1.12)
Model 3	1 (ref)	1.14 (0.99–1.32)	1.17 (1.01–1.35)	1.16 (0.99–1.35)	1.24 (1.06–1.46)	1.06 (1.00–1.11)
Model 4	1 (ref)	1.12 (0.96–1.29)	1.13 (0.98–1.31)	1.12 (0.96–1.30)	1.22 (1.04–1.43)	1.05 (0.99–1.01)
	DC Quintiles (10^{-3}/kPa)					DC Continuous per 1 SD (6.80)
	<11.31	11.31–14.33	14.34–17.62	17.64–21.95	>21.95	
Incident dementia, n	461	358	339	274	213	1645
Incidence rate (per 1000 PY)	12.76	9.34	8.46	6.68	5.05	8.32
N at risk	1867	1869	1870	1861	1871	9338
HR (95% CI)						
Model 1	1 (ref)	0.81 (0.70–0.93)	0.82 (0.72–0.95)	0.72 (0.62–0.84)	0.65 (0.55–0.76)	0.87 (0.82–0.92)
Model 2	1 (ref)	0.83 (0.72–0.96)	0.87 (0.75–1.01)	0.78 (0.67–0.92)	0.71 (0.60–0.86)	0.90 (0.85–0.96)
Model 3	1 (ref)	0.84 (0.73–0.96)	0.89 (0.77–1.03)	0.80 (0.68–0.94)	0.73 (0.61–0.88)	0.91 (0.86–0.97)
Model 4	1 (ref)	0.85 (0.74–0.98)	0.88 (0.76–1.02)	0.81 (0.69–0.95)	0.76 (0.63–0.91)	0.92 (0.86–0.98)

Model 1: adjusted for age, sex, race/center, education, apolipoprotein E ε4. Model 2: adjusted for model 1 plus body mass index, systolic blood pressure, smoking status, and pack-years of smoking. Model 3: adjusted for model 2 plus antihypertensive medications and diabetes mellitus status. Model 4: adjusted for model 3 plus time-varying stroke. ARIC indicates Atherosclerosis Risk in Communities; cIMT, carotid intima-media thickness; DC, distensibility coefficient; HR, hazard ratio; IAD, interadventitial diameter.

a French multisite study found no association between cIMT and dementia over a mean follow-up period of 5.4 years,[39] which differed from our findings of a significant association between abnormal cIMT and dementia over a mean follow-up of 21 years. On the other hand, we found no significant association between presence of carotid plaque and incident dementia after adjustment for risk factors. Other studies have reported an association between carotid plaque and incident dementia; however, in these studies, mean follow-up time was relatively short (5.4 and 6.7 years, respectively) and carotid measurements were obtained in late life (mean age, 73 years for both studies).[38,39] Our study differed in that follow-up was on average 20.9 years and carotid measurements were taken in midlife (mean age, 57 years), which is a strength given the long natural history of dementia.

Plaque development can cause outward arterial remodeling.[40] As the IAD indirectly references wall remodeling on both sides,[41] plaque development can in turn affect the IAD. Because plaque is often reported as being

Table 3. Hazard Ratios (95% CIs) of Incident Dementia by Carotid Plaque and cIMT Status: the ARIC Study, 1990 to 2017

	Plaque Absent	Plaque Present	Normal cIMT	Abnormal cIMT (>0.9 mm)
Incident dementia, n	1420	804	1815	409
Incidence rate (per 1000 PY)	7.88	10.08	7.96	12.81
N at risk	8337	4122	10 681	1778
HR (95% CI)				
Model 1	1 (ref)	1.10 (1.00–1.20)	1 (ref)	1.32 (1.18–1.48)
Model 2	1 (ref)	1.07 (0.98–1.17)	1 (ref)	1.26 (1.12–1.40)
Model 3	1 (ref)	1.06 (0.97–1.15)	1 (ref)	1.22 (1.09–1.36)
Model 4	1 (ref)	1.02 (0.93–1.12)	1 (ref)	1.15 (1.03–1.29)

Model 1: adjusted for age, sex, race/center, education, apolipoprotein E ε4. Model 2: adjusted for model 1 plus body mass index, systolic blood pressure, smoking status, pack-years of smoking. Model 3: adjusted for model 2 plus antihypertensive medications, diabetes status. Model 4: adjusted for model 3 plus time-varying stroke. ARIC indicates Atherosclerosis Risk in Communities; cIMT, carotid intima-media thickness; HR, hazard ratio.

present or absent, the IAD may better reflect the severity of atherosclerotic disease[41] and potentially the progression of dementia. Currently, there is little research evaluating the association of IAD and incident dementia. Our study provided novel evidence that greater IAD was associated with a higher risk of dementia, suggesting that arterial remodeling may be associated with dementia.

Carotid stiffness, assessed by the distensibility coefficient, was also associated with greater risk of developing dementia. Prior ARIC publications have reported that carotid stiffness was cross-sectionally associated with white matter hyperintensity volume and prospectively associated with incident ischemic stroke, both of which are associated with impaired cognitive function and poor neurologic outcomes.[42,43] Although this suggests that there is potentially a direct link between carotid stiffness and dementia, prior studies analyzing this relationship are scarce and show mixed results.[14,18] Therefore, our results indicating that those with higher distensibility coefficients have a lower risk of dementia are an important finding.

An alternative explanation for our findings is that cIMT and IAD are not truly independent risk factors but are rather a reflection of atherosclerotic risk factor duration and severity across the life course. A single measure of cardiovascular risk factors, such as we adjusted for in the present analysis, does not fully capture the impact of past exposure to risk factors.[44] Elevated cIMT represents not only increased intimal thickening but also medial hypertrophy, which is a result of long-standing hypertension.[9,13] Additionally, there is a dose-response association between hypertension status and carotid atherosclerosis severity,[45] with increases in cIMT beginning before overt hypertension.[45,46] Prevalent metabolic syndrome has also been associated with increased IAD, cIMT, and Young's elastic modulus (a measure of carotid distensibility) over 6 years of follow-up.[47] These observations suggest that greater cIMT may represent the cumulative effect of both clinical and subclinical vascular risk factors.[48] In addition, a large meta-analysis reports reducing cIMT progression through interventions, such as antihypertensives or lipid-lowering medications, reduces cardiovascular disease event rates.[49] Regardless of whether the associations we observed between carotid markers and dementia are causal, cIMT and IAD were early markers of dementia risk, and our findings highlight the potential for optimal control of hypertension and other modifiable vascular risk factors in midlife to decrease dementia risk.

Strengths of this study include the prospective design, large sample size, and number of dementia cases, long follow-up period, representation of Black and White men and women, and comprehensive cognitive assessments. However, this study also has limitations. Some dementia diagnoses were ascertained from hospitalization discharge codes (*International Classification of Diseases, Ninth Revision* [*ICD-9*]). *ICD* codes for dementia have been shown to have high specificities (cases identified are true) but lower sensitivities (true cases are missed).[22] We suspect that this misclassification would be nondifferential by cIMT, and therefore would most likely bias our results toward the null. Also, the date of dementia onset is difficult to verify. Therefore, because it is possible that some participants had dementia before their date of diagnosis, we subtracted 6 months from their estimated diagnosis date in a sensitivity analysis, and the results remained similar. There is also potential for missing dementia cases and survival bias because of attrition, as average follow-up time was >20 years. Misclassified cases would likely lead to an underestimation. Dementia etiology was available in a subset of our participants but was available for only a subset of dementia cases, and precision for those analyses were poor. Measurement error when assessing carotid plaque may have resulted in a lack of association given that the interreader agreement for presence of carotid plaque was considered fair. In addition, we

were unable to evaluate the volume of carotid plaque since B-mode ultrasounds were used in this study, which mainly indicates the presence or absence of carotid plaque. Furthermore, we are unable to assess the association between progression of cIMT, IAD, or DC with dementia, as repeat ultrasounds were not obtained. Finally, similar to other observational studies, residual confounding may exist.

CONCLUSIONS

In this large, cohort study, we have shown that greater cIMT and IAD and lower carotid distensibility are prospectively associated with an increased risk of incident dementia. No significant association with the presence of carotid plaque was observed. These associations remained after adjustment for traditional cardiovascular risk factors. Atherosclerosis and arterial stiffness may be independent risk factors for dementia, though it is also possible that they are simply robust markers of lifetime exposure to vascular risk factors, which are themselves linked to dementia.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Odds ratios (95% confidence intervals) of vascular dementia by quintiles or per 1-SD increment: the Atherosclerosis Risk in Communities (ARIC) study, 1990–2013.

	cIMT quintiles (mm)					cIMT continuous
	< 0.58	0.58 – 0.64	0.65 – <0.71	0.71 – <0.80	> 0.80	per 1 SD (0.15)
Vascular dementia, n	13	22	24	29	50	138
N at risk	1,163	1,164	1,164	1,164	1,164	5,819
OR (95% CI)						
Model 1	1 (ref)	1.38 (0.69, 2.79)	1.32 (0.66, 2.64)	1.44 (0.73, 2.83)	2.16 (1.13, 4.12)	1.21 (1.04, 1.41)
Model 2	1 (ref)	1.29 (0.63, 2.60)	1.25 (0.72, 2.50)	1.30 (0.66, 2.58)	1.84 (0.95, 3.55)	1.17 (0.99, 1.37)
Model 3	1 (ref)	1.30 (0.64, 2.64)	1.22 (0.61, 2.45)	1.28 (0.65, 2.55)	1.78 (0.92, 3.45)	1.15 (0.98, 1.35)
	IAD quintiles (mm)					IAD continuous
	< 6.77	6.77 – 7.18	7.19 – 7.57	7.58 – 8.10	> 8.11	per 1 SD (0.83)
Vascular dementia, n	23	15	26	22	46	132
N at risk	1,125	1,104	1,113	1,110	1,120	5,572
OR (95% CI)						
Model 1	1 (ref)	0.61 (0.32, 1.20)	0.92 (0.51, 1.67)	0.70 (0.37, 1.32)	1.32 (0.74, 2.33)	1.17 (0.98, 1.40)
Model 2	1 (ref)	0.59 (0.30, 1.16)	0.82 (0.45, 1.48)	0.60 (0.31, 1.13)	0.95 (0.52, 1.74)	1.04 (0.86, 1.27)
Model 3	1 (ref)	0.60 (0.31, 1.17)	0.83 (0.46, 1.51)	0.59 (0.31, 1.12)	0.94 (0.51, 1.73)	1.04 (0.85, 1.26)
	DC quintiles (10^{-3}/kPa)					DC continuous
	< 12.21	12.22 – 15.48	15.49 – 18.66	18.67 – 23.25	> 23.28	per 1 SD (6.97)
Vascular dementia, n	41	26	16	10	9	102
N at risk	908	910	906	909	910	4,543
OR (95% CI)						
Model 1	1 (ref)	0.86 (0.51, 1.44)	0.66 (0.36, 1.22)	0.46 (0.22, 0.95)	0.53 (0.25, 1.14)	0.75 (0.57, 0.97)
Model 2	1 (ref)	0.95 (0.56, 1.62)	0.83 (0.44, 1.56)	0.58 (0.27, 1.24)	0.73 (0.32, 1.65)	0.87 (0.65, 1.15)
Model 3	1 (ref)	0.94 (0.55, 1.60)	0.83 (0.44, 1.57)	0.59 (0.28, 1.26)	0.74 (0.33, 1.68)	0.87 (0.66, 1.16)

Model 1: adjusted for age, sex, race/center, education, APOE ε4.
Model 2: adjusted for model 1 plus body mass index, systolic blood pressure, smoking status, pack-years of smoking.
Model 3: adjusted for model 2 plus antihypertensive medications, diabetes status.
Abbreviations: OR = odds ratio; SD = standard deviation; cIMT = carotid intima-media thickness; IAD = interadventitial diameter; DC = distensibility coefficient

Table S2. Odds ratios (95% confidence intervals) of Alzheimer's disease-related dementia by quintiles or per 1-SD increment: the Atherosclerosis Risk in Communities (ARIC) study, 1990–2013.

	cIMT quintiles (mm)					cIMT continuous
	< 0.58	0.58 – 0.64	0.65 – <0.71	0.71 – <0.80	> 0.80	per 1 SD (0.15)
AD-related dementia, n	11	17	23	21	31	103
N at risk	1,163	1,164	1,164	1,164	1,164	5,819
OR (95% CI)						
Model 1	1 (ref)	1.28 (0.59, 2.79)	1.53 (0.73, 3.22)	1.27 (0.59, 2.71)	1.50 (0.72, 3.12)	1.12 (0.94, 1.35)
Model 2	1 (ref)	1.25 (0.57, 2.72)	1.50 (0.72, 3.15)	1.22 (0.57, 2.62)	1.41 (0.67, 2.97)	1.11 (0.92, 1.34)
Model 3	1 (ref)	1.26 (0.58, 2.75)	1.50 (0.71, 3.14)	1.22 (0.57, 2.63)	1.40 (0.67, 2.96)	1.10 (0.91, 1.33)
	IAD quintiles (mm)					IAD continuous
	< 6.77	6.77 – 7.18	7.19 – 7.57	7.58 – 8.10	> 8.11	per 1 SD (0.83)
AD-related dementia, n	16	10	21	28	19	94
N at risk	1,125	1,104	1,113	1,110	1,120	5,572
OR (95% CI)						
Model 1	1 (ref)	0.60 (0.27, 1.35)	1.10 (0.56, 2.17)	1.28 (0.66, 2.49)	0.70 (0.34, 1.47)	0.97 (0.78, 1.21)
Model 2	1 (ref)	0.58 (0.26, 1.31)	1.05 (0.53, 2.08)	1.19 (0.60, 2.35)	0.60 (0.27, 1.30)	0.92 (0.73, 1.17)
Model 3	1 (ref)	0.59 (0.26, 1.32)	1.06 (0.53, 2.11)	1.21 (0.61, 2.39)	0.61 (0.28, 1.32)	0.92 (0.73, 1.17)
	DC quintiles (10^{-3}/kPa)					DC continuous
	< 12.21	12.22 – 15.48	15.49 – 18.66	18.67 – 23.25	> 23.28	per 1 SD (6.97)
AD-related dementia, n	31	13	12	10	8	74
N at risk	908	910	906	909	910	4,543
OR (95% CI)						
Model 1	1 (ref)	0.51 (0.26, 1.00)	0.57 (0.28, 1.15)	0.51 (0.24, 1.08)	0.49 (0.21, 1.11)	0.86 (0.64, 1.14)
Model 2	1 (ref)	0.52 (0.26, 1.02)	0.58 (0.28, 1.19)	0.52 (0.24, 1.14)	0.50 (0.20, 1.20)	0.89 (0.65, 1.21)
Model 3	1 (ref)	0.51 (0.26, 1.00)	0.57 (0.28, 1.18)	0.52 (0.24, 1.14)	0.50 (0.20, 1.21)	0.89 (0.65, 1.21)

Model 1: adjusted for age, sex, race/center, education, APOE ε4.
Model 2: adjusted for model 1 plus body mass index, systolic blood pressure, smoking status, pack-years of smoking.
Model 3: adjusted for model 2 plus antihypertensive medications, diabetes status.
Abbreviations: AD = Alzheimer's disease; OR = odds ratio; SD = standard deviation; cIMT = carotid intima-media thickness; IAD = interadventitial diameter; DC = distensibility coefficient