Original Research Article

VASCULAR MEDICINE

Vascular Medicine
2026, Vol. 31(1) 28–34

DOI: 10.1177/1358863X251396507
journals.sagepub.com/home/vmj
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Carotid artery ultrasound grayscale median and incident dementia: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Introduction: Vascular contributions to cognitive impairment and dementia are potentially modifiable. Early detection of reversible arterial injury may improve risk stratification and provide treatment monitoring. We hypothesized that carotid ultrasound grayscale median (GSM), a novel imaging biomarker of early arterial injury, would predict incident all-cause dementia in the Multi-Ethnic Study of Atherosclerosis (MESA). **Methods:** The MESA enrolled adults free of atherosclerotic cardiovascular disease. Common carotid GSM was measured at baseline. Incident all-cause dementia events were identified by hospital and death records. Cox proportional hazards models with natural cubic splines investigated the association of baseline GSM and all-cause dementia. **Results:** The 1788 participants were a mean (SD) 63.1 (10.3) years old and 53% were women. Over a median 13.7 years, 157 all-cause dementia events occurred. In fully adjusted models, with additional adjustment for carotid intima–media thickness, lower (worse) GSM independently predicted incident all-cause dementia (hazard ratio, 1st to 3rd tertile, 1.45 [95% CI, 1.11–1.90], $p = 0.021$). **Conclusions:** Lower GSM independently predicts all-cause dementia, beyond traditional arterial injury measures, suggesting it may serve as an early marker of dementia risk.

Keywords

cardiovascular disease, dementia, epidemiology, vascular ultrasound, carotid ultrasound

Introduction

Arterial health is a well-recognized risk factor for the development of dementia and cognitive impairment.[1] Structural arterial changes such as arterial stiffening and plaque deposition represent late-stage, irreversible signs of arterial injury and are associated with cognitive decline and incident dementia.[1–3] These structural changes, however, are preceded by earlier arterial changes which may be reversible.[4,5] Arterial grayscale texture and echogenicity measures represent preclinical, early arterial injury, which predict future cardiovascular disease events[5,6] and are modified by exercise,[7] smoking cessation,[8] and antiinflammatory therapies.[4] Given the growing interest of arterial health in the paradigm of the vascular contributions to cognitive impairment and dementia, novel methods to identify arterial injury in its earlier forms can provide enhanced patient risk stratification, identify potential upstream treatment interventions, and better characterize the impact and overlap of arterial injury on the development of cognitive decline and dementia. We hypothesized that the carotid artery grayscale median (GSM) predicts incident all-cause dementia in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Participants

The MESA study is a diverse cohort of 6814 healthy participants recruited from six field centers located in Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; New York, New York; and St Paul, Minnesota. The baseline recruitment

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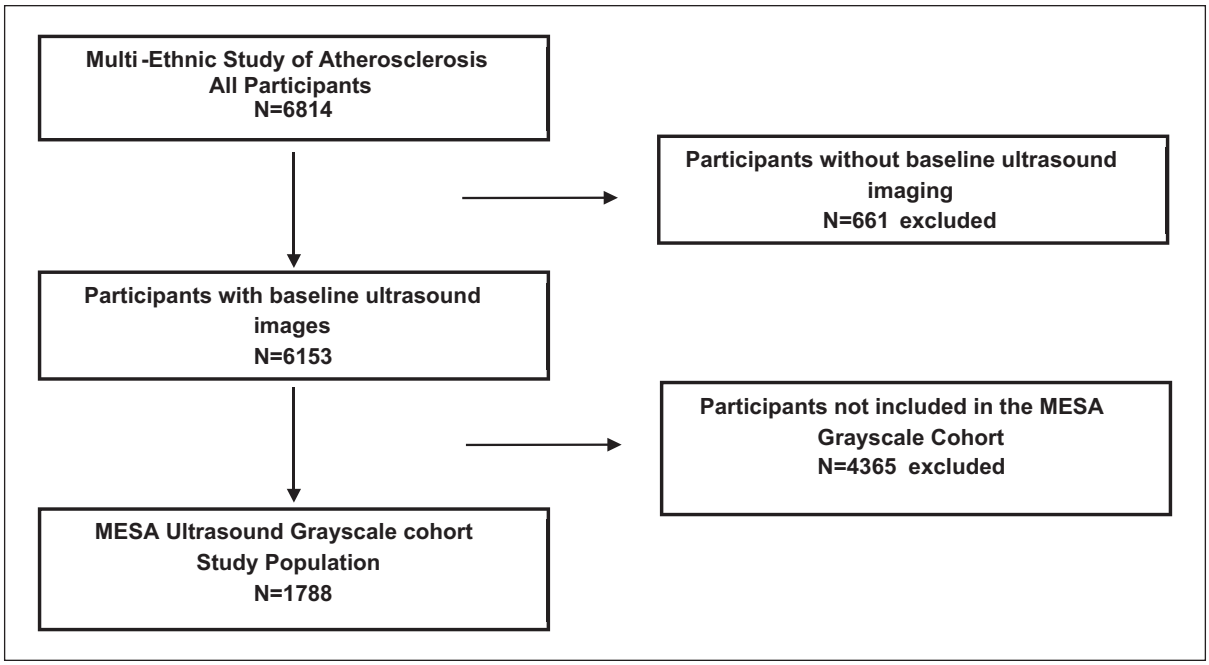

Figure 1. Flow diagram of included Multi-Ethnic Study of Atherosclerosis (MESA) participants.

occurred in 2000–2002. Participants were aged 45–84 years old and free of atherosclerotic cardiovascular disease (ASCVD) at study entry. This study was approved by the institutional review boards of all participating centers. All participants provided informed consent. Details of the MESA design have been published previously.[9] Our analysis was restricted to participants at four field centers (Baltimore, Chicago, Los Angeles County, and New York), which acquired baseline ultrasound images using the same grayscale map[5] (Figure 1). The analytic sample was derived from the original MESA GSM case-cohort, which included participants free of ASCVD at baseline with available GSM measurements.[5] Of these, 491 individuals subsequently developed incident ASCVD, and the remainder represented a randomly selected subcohort from the same four field centers ($N = 1788$).[5]

Carotid ultrasound

The carotid imaging protocol for the MESA has been described previously. B-mode ultrasound longitudinal scans of the right and left common, bifurcation, and internal carotid artery segments were captured on Super-VHS videotape using a Logiq 700 ultrasound system equipped with the M12L transducer (General Electric Medical Systems, Waukesha, WI, USA; common carotid artery (CCA) frequency 13 MHz) at exam 1 (baseline exam). The video recordings were then digitized at high resolution and frame rates using a medical digital recording device (PacsGear, Pleasanton, CA, USA) and transformed into DICOM-compatible digital format. Digitized images were imported into syngo Ultrasound Workplace 3.5B reading stations loaded with Arterial Health Package software (Siemens Medical, Malvern, PA, USA) for carotid intima–media thickness (IMT) measurement and plaque scoring. The ultrasound images were analyzed and interpreted by the MESA Carotid Ultrasound Reading Center (University of Wisconsin Atherosclerosis Imaging Research Program, Madison, WI, USA). To measure carotid artery GSM, the DICOM files were converted to BITMAP images using Access Point (Freeland Systems) for grayscale analysis, with normalization assigning a grayscale value of 0 to the darkest blood region and 190 to the brightest adventitia (LifeQ Medical, Nicosia, Cyprus).[5] The distal 1.0 cm of the far wall of the CCA was traced, and the median gray level (GSM) of the intima–media complex was calculated using standardized images (20 pixels/mm) and plaque texture analysis software (Figure 2). Carotid ultrasound GSM was measured in 1788 participants at exam 1 as described in previous studies.[5] To evaluate the relationship between GSM and incident all-cause dementia, we assessed the regression function at three specific values corresponding to the 25th percentile (1st quartile), 50th percentile (median or 2nd quartile), and 75th percentile (3rd quartile) of the GSM distribution.

ASCVD risk factors

Laboratory samples were taken at baseline following a 12-hour fast. Lipid analyses were performed at the University

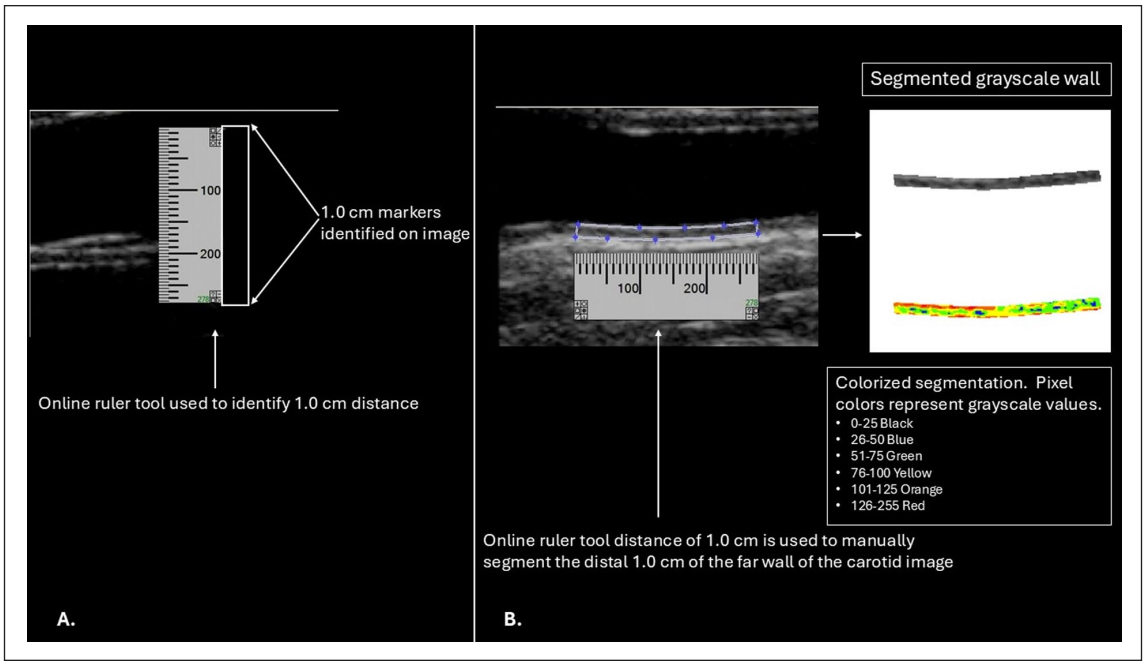

Figure 2. (A) Demonstrates identification and segmentation of the distal 1-cm segment of the far wall of the common carotid artery. The white rectangle represents the region of interest. **(B)** The arterial wall segmented in grayscale, followed by a color overlay applied by the software based on grayscale intensity values.
The grayscale values are colorized with the software as follows: 0–25 = black, 26–50 = blue, 51–75 = green, 76–100 = yellow, 101–125 = orange, 126–255 = red.

of Minnesota as previously reported.[9] Total and high-density lipoprotein cholesterol levels were measured in EDTA plasma using a cholesterol oxidase method on a Roche COBAS FARA centrifugal analyzer (Roche Diagnostics, Indianapolis, IN, USA), with coefficients of variation (CV) of 1.6% and 2.9%, respectively. Serum glucose was measured via rate reflectance spectrophotometry on a Vitros analyzer (Johnson & Johnson Clinical Diagnostics, Rochester, NY, USA), demonstrating a CV of 1.1%. Diabetes mellitus was defined according to the American Diabetes Association consistent with prior MESA investigations (use of hypoglycemic medications and/or fasting serum glucose $\geqslant$ 126 mg/dL at baseline).[10,11] Systolic blood pressure was measured using a Dinamap PRO Monitor 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL, USA) after the participant had rested for 5 minutes. Three readings were obtained and the average of the last two readings was used for analysis. Smoking was classified as 'never', 'former', or 'current' users. Education was classified as the highest level completed.

Incident all-cause dementia

The primary outcome of the study was incident all-cause dementia. Incident all-cause dementia in the MESA was identified through hospital and death records using International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10) codes identified during telephone follow-up calls with participants at intervals of 9–12 months.[12] This definition is consistent with previous MESA studies for the definition of incident dementia.[12]

Statistical analysis

Baseline descriptive statistics are reported as means (SDs) for continuous variables and percentages for categorical variables. To assess the association of carotid GSM and incident all-cause dementia, we employed Cox proportional hazards models with natural cubic splines allowing for nonlinear effects, adjusted for biologic confounders. The proportional hazards assumption was evaluated using Schoenfield's test. A series of models adjusting for biological confounders was constructed: Model 1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity, total and high-density lipoprotein cholesterol, systolic blood pressure, smoking status, body mass index, diabetes mellitus, and education. Model 3 additionally adjusted for carotid IMT to ascertain whether carotid GSM added predictive information beyond standard measures of arterial injury. Although our study outcome was incident dementia rather than ASCVD, the analytic sample was derived from a previously established case-cohort design. To account for potential bias related to this sampling structure, we conducted a sensitivity analysis that included adjustment for case status (ASCVD event vs random subcohort) in the fully adjusted model. Statistical significance was set at a two-sided p-value less than 0.05. Analyses were performed in R, version 4.4.0 (R Foundation for Statistical Computing).

Table 1. Participant characteristics.

Characteristic	MESA GSM subcohort $N = 1788$	MESA non-GSM cohort $N = 5026$
Age, years	63 (10)	62 (10)
Sex, *n* (%)		
Female	940 (53)	2661 (53)
Male	848 (47)	2365 (47)
Race/ethnicity, *n* (%)		
Black	497 (28)	1395 (28)
Chinese	301 (17)	503 (10)
Hispanic	416 (23)	1080 (21)
White	574 (32)	2048 (41)
Total cholesterol, mg/dL	196 (37)	193 (35)
High-density lipoprotein cholesterol, mg/dL	52 (15)	51 (15)
Systolic blood pressure, mmHg	127 (22)	127 (21)
Smoking status, *n* (%)		
Never	931 (52)	2487 (50)
Former	634 (35)	1853 (37)
Current	221 (12)	666 (13)
Body mass index, kg/m^2	27.7 (5.4)	28.5 (5.5)
Diabetes mellitus, *n* (%)		
Normal	1275 (72)	3,17 (74)
Impaired fasting glucose	258 (14)	681 (14)
Untreated diabetes	51 (2.9)	128 (2.6)
Treated diabetes	199 (11)	481 (9.6)
Education, *n* (%)		
Less than high school	374 (21)	851 (17)
High school	740 (41)	2433 (49)
College	312 (17)	859 (17)
Graduate or professional	359 (20)	863 (17)
Interleukin-6, pg/mL	1.54 (1.22)	1.56 (1.23)
C-reactive protein, mg/L	3.8 (6.7)	3.8 (5.6)

Values are mean (SD) unless otherwise noted.
The number of participants for each category may not add to the total number in the cohort if missing data are present.
GSM, grayscale median; MESA, Multi-Ethnic Study of Atherosclerosis.

Results

Descriptive characteristics

At baseline, the final cohort of 1788 participants were a mean (SD) 63.1 (10.3) years old, 53% were women, 32% White, 28% Black, 23% Hispanic, and 17% Chinese (Table 1). Overall, participants in the GSM cohort were similar to participants of MESA ($N = 5026$) not in the GSM cohort (Table 1). There were slight differences with participants in the GSM cohort being slightly older with higher total cholesterol and lower body mass index (Table 1). Over a median 13.7 years of follow up, a total of 157 incident all-cause dementia events occurred.

Carotid GSM and incident all-cause dementia events

In risk-factor adjusted models, lower (worse) carotid GSM independently predicted incident all-cause dementia (hazard ratio [HR], 1st to 3rd tertile, 1.39 [95% CI, 1.08–1.80], $p = 0.04$) (Table 2, Figure 3). In analyses adjusting additionally for carotid IMT, there was no attenuation of the association of GSM and incident all-cause dementia (HR 1.45 [95% CI, 1.11–1.90], $p = 0.021$) (Table 2), suggesting that the GSM provides additional, independent prediction beyond carotid wall thickness. In our sensitivity analysis, adjusting for case status (ASCVD event) in our fully adjusted model, we found no difference in effect sizes (HR 1.48 [95% CI, 1.13–1.93], $p = 0.016$).

Discussion

In a large, multiethnic cohort with over 13 years of follow up, baseline carotid GSM, a novel, early marker of arterial injury, independently predicted incident all-cause dementia. Importantly, carotid GSM provided additional predictive data beyond carotid IMT, which is an established arterial injury predictor of incident cognitive decline and dementia.[3,13]

Table 2. Association of carotid grayscale median and incident all-cause dementia.

Model	75th Percentile (Ref.) (68.1 units)	Median (52.9 units)	25th Percentile (38.2 units)	*p*-value
Model 1 (Unadjusted)	Ref.	1.28 (1.07–1.54)	1.61 (1.27–2.05)	< 0.001
Model 2 (Fully adjusted)	Ref.	1.23 (1.02–1.49)	1.39 (1.08–1.80)	0.040
Model 3 (Fully adjusted + IMT)	Ref.	1.29 (1.05–1.58)	1.45 (1.11–1.90)	0.021

Values are HR (95% CI).
Model 2 (Fully adjusted): Adjusted for age, sex, race/ethnicity, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, smoking status, body mass index, diabetes mellitus, education.
Model 3: Additionally adjusted for carotid IMT.
HR, hazard ratio; IMT, intima–media thickness.

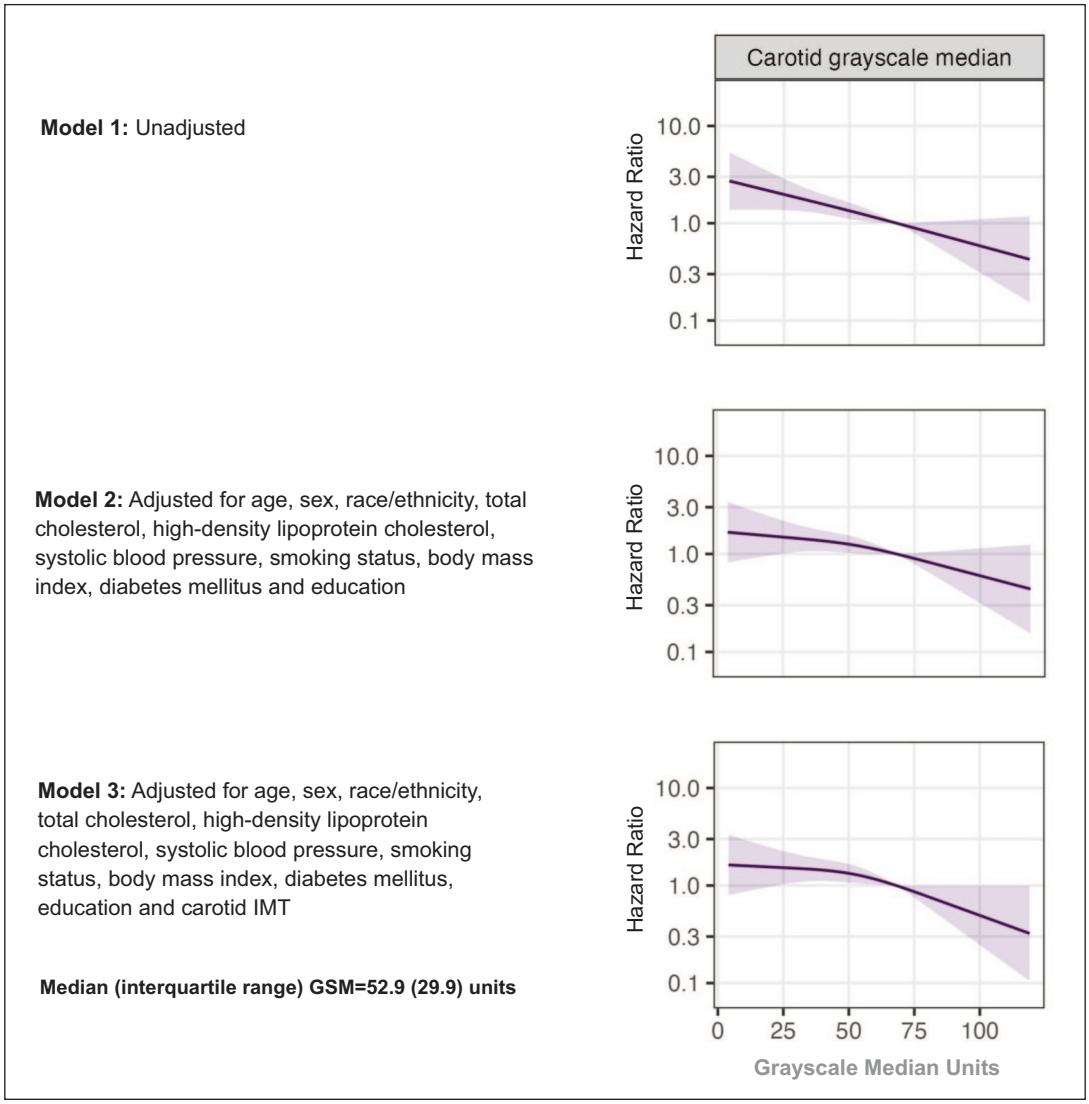

Figure 3. Association of carotid artery grayscale median (GSM) and incident dementia in the Multi-Ethnic Study of Atherosclerosis.
The *x*-axis shows units of GSM; the *y*-axis shows the hazard ratio for incident dementia.
Shaded areas represent 95% CIs.
IMT, intima–media thickness.

The vascular contributions to the development of cognitive decline and dementia remain an important and fundamental modifiable risk factor in the prevention of the disease.[1,14–17] Previous studies have established strong associations between carotid IMT, arterial stiffness, and incident dementia. A recent study from the Atherosclerosis Risk in Communities (ARIC) found several arterial injury ultrasound measures indicative of structural remodeling of the carotid artery (carotid IMT,

carotid distensibility, and inter-adventitial diameter) independently predicted incident dementia.[3] This finding is consistent with previous studies that focused on late arterial injury markers consistent with structural remodeling and/or development of plaque and risk of development and progression of dementia.[18–21] These late-stage structural changes, however, have limited capacity to substantially improve with therapy. Novel methods to identify early arterial injury, prior to irreversible structural remodeling changes, can serve as an early barometer of disease risk and facilitate therapeutic interventions at the early stages, which may have a greater impact on reducing or delaying the onset of deleterious late-stage arterial structural changes that have been associated with cognitive decline and increased cerebral β-amyloid (Aβ) deposition.[22–24] Common carotid GSM reflects arterial wall echogenicity and serves as a marker of early arterial injury and subclinical atherosclerosis.[5] Lower GSM values indicate increased echolucency, which, based on histopathological studies of carotid plaques, has been associated with lipid-rich, inflamed arterial walls containing macrophage infiltrate.[5,25,26] This arterial pathology may contribute to neurodegenerative processes through mechanisms such as endothelial dysfunction, impaired cerebral perfusion, blood–brain barrier dysfunction, and chronic inflammation.[27] These vascular insults are increasingly recognized as common contributors across multiple forms of dementia, including Alzheimer's disease, vascular dementia, and mixed dementias, often coexisting with neurodegenerative pathologies and influencing clinical outcomes.[28] Prior studies have demonstrated associations between systemic vascular dysfunction and elevated levels of neurodegeneration-related biomarkers in both plasma and cerebrospinal fluid.[29] Thus, GSM may serve as a noninvasive imaging marker of early arterial injury. Future studies integrating GSM with blood-based biomarkers of dementia will be essential to further elucidate these mechanisms and their relevance across dementia subtypes. Given the well-established role of vascular contributions to cognitive impairment and dementia, our findings support the hypothesis that lower GSM may reflect an early arterial injury process, such as cellular infiltration and vascular inflammation, that contributes to dementia risk. Our study further supports prior work highlighting the strong association of carotid arterial injury and the risk of incident dementia; however, it extends these findings by (i) establishing the association of incident dementia with a novel and early marker of arterial injury (GSM), (ii) highlighting that GSM predicts incident dementia independent of structural change such as carotid IMT, and (iii) establishing a potentially early, reversible imaging biomarker that can serve as an early, easily obtainable barometer for risk of incident dementia, which is especially important given the long latent period prior to onset of clinically significant dementia. This is the first study, to our knowledge, that has investigated the association of a novel, noninvasive ultrasound-based measure of early arterial injury to predict incident dementia in a large, ethnically diverse US population.

Limitations

Despite the large sample size, there were a small number of dementia subtype-specific events that prohibited our ability to further associate carotid artery grayscale measures with specific dementia subtypes, which suggests the need to study early arterial injury measures in large, well-characterized Alzheimer's disease-specific cohorts. Second, this study includes a subset of MESA participants with carotid GSM measures performed at baseline; however, this subset did not differ substantially compared to the MESA cohort. Ultrasound images were acquired using the GE Logiq 700 system, which, though ensuring consistency across participants, may limit generalizability as gray-scale measurements differ across ultrasound systems. Models were adjusted for biologic confounders; however, residual confounding due to unmeasured confounders cannot be excluded. Blood-based biomarkers specific to dementia subtypes were not widely available for a substantial portion of participants in the GSM cohort, limiting our ability to examine associations between these biomarkers and GSM. Finally, this is an observational study, and the results do not confirm causation.

Conclusions

Carotid artery GSM is an ultrasound imaging biomarker of early arterial injury which independently predicts incident all-cause dementia in a multiethnic population free of prevalent ASCVD at baseline. Arterial health is a key marker of vascular contributions to cognitive impairment and dementia. Our findings suggest a great need for validating imaging biomarkers that can identify arterial injury at an early, potentially reversible stage, providing important opportunities to identify, intervene, and longitudinally track arterial health to aid in risk assessment and treatment.

Acknowledgements

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of MESA investigators and institutions can be found at https://www.mesa-nhlbi.org/.

Data availability

Anonymized data and materials have been made publicly available at BioLINCC and can be accessed at https://biolincc.nhlbi.nih.gov/home/.

Declaration of conflicting interests

The authors disclosed the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article. Carol C. Mitchell receives research funding (to institution) from W. L. Gore & Associates and consulting fees from Acoustic Range Estimates. The remaining authors have no conflicting interests.

Funding

Dr Tattersall is in part supported by grants KL2TR002374 and UL1TR002373 awarded to UW Institute for Clinical and Translational Research through the National Center for Advancing Translational Sciences (NIHNCATS). The Multi-Ethnic Study of Atherosclerosis (MESA) was supported by contracts HHSN268 201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from the National Center for Research Resources.

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