Coronary Artery Calcium and Risk of Dementia in MESA (Multi-Ethnic Study of Atherosclerosis)

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Background—Studies suggest a link between vascular injuries and dementia. Only a few studies, however, examined a longitudinal relation of subclinical vascular disease with dementia. We tested whether baseline coronary artery calcium (CAC), a biomarker of subclinical vascular disease, is associated with incident dementia independent of vascular risk factors and APOE-ε4 genotype in a community-based sample.

Methods and Results—We analyzed 6293 participants of MESA (Multi-Ethnic Study of Atherosclerosis), aged 45 to 84 years at baseline (2000–2002), initially free of cardiovascular disease and noticeable cognitive deficit. Dementia cases were identified using hospital and death certificate International Statistical Classification of Diseases and Related Health Problems codes. Cox models were used to obtain hazard ratios according to CAC category, or per 1 SD log2[CAC+1], adjusted for vascular risk factor, APOE-ε4, with or without exclusion of interim stroke or cardiovascular disease. We observed 271 dementia cases in a median follow-up of 12.2 years. Baseline CAC had a graded positive association with dementia risk. Compared with no CAC, CAC score of 1 to 400, 401 to 1000, and ≥1001 had increased risk of dementia by 23%, 35%, and 71%, respectively, (P=0.026) after adjustment. 1 SD higher log2[CAC+1] was associated with 24% (95% confidence interval, 8%–41%; P=0.002) increase in dementia risk. Although the association was partially explained by interim stroke/cardiovascular disease, it remained significant even after excluding the interim events, or regardless of baseline age.

Conclusions—Higher baseline CAC was significantly associated with increased risk of dementia independent of vascular risk factor, APOE-ε4, and incident stroke. This is consistent with a hypothesis that vascular injuries play a role in the development of dementia. (Circ Cardiovasc Imaging. 2017;10:e005349. DOI: 10.1161/CIRCIMAGING.116.005349.)

Key Words: atherosclerosis • cohort • coronary artery calcium • dementia • epidemiology • stroke

Vascular risk factors predict cognitive decline and dementia. Coronary artery calcium (CAC) is a subclinical vascular disease and can be viewed as marking biological response to cumulative vascular injuries and may predict dementia independently of baseline vascular risk factors. Only a few longitudinal studies, however, reported on dementia and subclinical vascular disease.

See Editorial by Lu
See Clinical Perspective

Our primary aim is to examine the association of CAC with dementia risk in a community-based sample. We hypothesize that baseline CAC predicts future dementia independently of conventional vascular risk factors and Apolipoprotein E-ε4 genotype (APOE4). We also examine whether the association is attenuated by accounting for interim stroke or cardiovascular disease (CVD) because such clinical vascular manifestations increased future risk of dementia.

Methods

Study Population

Participants were from MESA (Multi-Ethnic Study of Atherosclerosis), a study of the prevalence, risk factors, and progression of subclinical CVD in a multiethnic cohort in the United States. In brief, 6814 participants aged 45 to 84 years who identified themselves as white, black, Hispanic, or Chinese, free of clinically apparent CVD and other

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serious illness, were recruited from 6 US communities in 2000 to 2002. Cognitive inability in the screening interview was an exclusion criterion (an interviewer judged whether the respondent was cognitively able to participate in the study). For this study, we used follow-up and events data through 2013. All participants in the analyses gave informed consent, and the study protocol was approved by the Institutional Review Board at each site.

CAC Score
Detailed methods for computed tomographic (CT) scan technique and interpretation were previously described. Computed tomographic scans were performed twice per participant at baseline and read centrally at the Harbor-University of California, Los Angeles Research and Education Institute to identify and quantify coronary calcium. We analyzed the baseline total Agatston score (CAC score) averaged across the 2 computer tomographic scans. Agreement for the presence of coronary calcium was high (k statistic 0.90–0.93 between and within readers), and the intraclass correlation coefficient for CAC score between readers was 0.99.9

Other Measures at Baseline
Standardized questionnaires were used to obtain information at baseline, including highest level of education attained, possession of health insurance, physical activity, smoking history, and medical history. Height and weight were measured in light clothing and no shoes. Physical activity level was quantified as average metabolic equivalent minutes per week of moderate or vigorous activity using the MESA Typical Week Physical Activity Survey.11 Body mass index (BMI) was calculated as weight divided by height squared (kg/m²). Obesity was defined as body mass index ≥30 kg/m². Seated resting blood pressure was measured 3x with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon). The average of the last 2 measurements was used in analysis.12 Total and high-density lipoprotein cholesterol, triglycerides, and glucose concentrations were measured from blood samples obtained after a 12-hour fast. Non–high-density lipoprotein cholesterol was calculated by subtracting high-density lipoprotein cholesterol from total cholesterol. Diabetes mellitus was defined as fasting glucose >6.99 mmol/L (126 mg/dL) or use of hypoglycemic medication. APOE4 isoforms were estimated from single nucleotide polymorphisms rs429358 and rs741 using the algorithm reported previously.13 It was categorized here according to carriage of APOE4 as homozygous, heterozygous, or null/zygous (noncarrier).

Ascertainment of Clinical Events
In MESA, telephone interviews inquired about interim hospital admissions and deaths every 9 to 12 months. Copies of death certificates were obtained for the potential cases identified with the ICD codes F03, F04, G30, G31 (excluding G31.2), I69.91, and R41. A physi¬

Statistical Analyses
The participants were categorized according to the baseline CAC score of 0, 1 to 400, 401 to 1000, and ≥1001. To test a graded relation of baseline characteristics across CAC categories, P values were obtained with linear regression for continuous and Mantel–Haenszel χ² test for categorical variables.

In secondary analyses to study mediation of the association, we additionally adjusted for time-dependent stroke or CVD (myocardial infarction, resuscitated cardiac arrest, or stroke) occurring before dementia diagnosis. We also ran models excluding such interim events. In sensitivity analyses, we used a competing risk model using the proportional subdistribution hazards model14 with otherwise the same set of adjusting covariates. In this model, we treated death without dementia diagnosis as the risk competing with dementia. To address possible residual confounding by age and birth cohort effect, we conducted a model using age as the time scale with stratification by 3 birth cohorts: <1925 (n=626, [age range at baseline, 77–84 years], 1925 to <1935 (n=1688, [67–76 years]), and 1935 or after (n=3979, [45–66 years])). This model may be preferred when age at event may have a larger effect on the hazard (ie, dementia) than follow-up time because age is a strong risk factor for dementia and CAC. Finally, we ran the full adjustment model according to the baseline age (<75 versus ≥75 years). The age cutoff was chosen so that number of dementia cases was approximately halved for each age group. Interactions by sex, race/ethnicity, and baseline age (<75 or ≥75 years) on the relation between CAC and dementia were tested by inserting a product term in the full adjustment model. All adjusting covariates except interim stroke and CVD were assessed at baseline.

Because an interaction between atherosclerosis and APOE4 genotype was suggested in some studies,20,21 we examined whether the association of CAC with dementia differed by APOE4 status (carrier/ noncarrier) inserting a product term in the full adjustment model. Statistical significance was at P <0.05 (2-sided P value). SAS software (version 9.4; SAS Institute, Inc, Cary, NC) was used for all statistical analyses.

Results
We analyzed 6293 participants (47.5% men, 12.2% Chinese, 26.1% black, 22.5% Hispanic, and 39.2% white) and observed 271 dementia cases, 173 interim strokes, and 385 interim CVD events during the median follow-up of 12.2 years (interquartile range, 11.6–12.7 years). The proportions with baseline CAC score of 0, 1 to 400, 401 to 1000, and ≥1001 were 49.8% (n=3132), 40.3% (2539), 6.1% (384), and 3.8% (238), respectively. Those with higher baseline CAC tended to be older, white, male, less physically active, former smoker, user of antihypertensive and lipid-lowering medications, having higher systolic blood pressure, and diabetics (Table 1). Crude
dementia rates in both sexes increased steeply with age (Table I in the Data Supplement). Table 2 shows mutually adjusted HRs for the covariates in the full adjustment plus interim stroke. Interim stroke had the greatest magnitude of association with dementia risk (HR, 5.66) followed by older age. Male sex, current smoker, and CAC were positively associated with dementia, whereas physical activity was inversely associated. Chinese participants had lower dementia risk than white participants. APOE4 genotype had a graded association with dementia; HRs of heterozygous and homozygous compared with noncarriers were 1.33 and 2.20, respectively. Interim CVD was also strongly associated with dementia (HR, 5.08; Table II in the Data Supplement).

Crude rate ratio of dementia, relative to CAC score zero, for those with CAC score of 1 to 400, 401 to 1000, and ≥1001 were 3.12, 5.05, and 8.44, respectively, (Table 3). In the minimal adjustment and the full adjustment models, results were attenuated, but the graded positive trend remained (Table 4). The HR associated with 1 SD higher log2[CAC+1] (1 SD=3.634, equivalent to multiplying CAC score by 12.4) was 1.24 (95% confidence interval, 1.08–1.41; \( P=0.002 \)) in the full adjustment model. Further adjustment for interim stroke or the competing risk model attenuated the relation, but the overall association lost statistical significance only in a mediation model, adjusting for interim CVD (\( P=0.084 \)). The model using age as time scale, stratified by 3 birth cohorts, yielded
We observed no statistical evidence supporting interaction by younger and older group, respectively, (data not tabulated). P = 0.035) in the 1.21 (95% confidence interval, 1.01–1.45; P = 0.038) and were 1.24 (95% confidence interval, 1.01–1.51; P = 0.128) with full adjustment. The HRs per 1 SD higher log2[CAC+1] a positive association remained significant in both age groups events), the association was attenuated in the older group, but 75 years (n = 905, 154 ≥75 years (n = 5388, 117 events) versus cant using log2[CAC+1]. In stratified analysis by baseline age or CVD, the associations were decreased but remained significant after excluding interim stroke/CVD.

With some inconsistency,22 vascular risk factors have been shown to predict subsequent cognitive decline or dementia,1–3 perhaps depending on when risk factors were measured over the life course, as some risk factors such as blood pressure and smoking habits change over time. CAC, in contrast, is a cumulative, quantitative biomarker of vascular injury. To our knowledge, this is the first population-based study that prospectively showed a positive graded association of CAC with dementia risk not only independent of vascular risk factors and APOE4, but also in the absence of clinical CVD. Our finding is consistent with the conjecture that vascular injury plays an important pathogenetic role in dementia because CAC may correlate well with subclinical vascular changes in the brain.23,24 A few longitudinal studies4,5,7 have reported an association of carotid atherosclerosis with dementia. In many of those, only higher levels of IMT (eg, >80th percentile) were associated with (total) dementia with no clear dose–response relation.4,5,7 In longitudinal analysis of a subgroup of the CHS (Cardiovascular Health Study), the participants with CAC score of ≥400 at baseline had higher dementia risk than those with low score of 0 to 10.6 However, the average age of the participants was much older (80 years), and the sample size was smaller (n = 532) than our study.

We observed remarkably elevated dementia risk among those who developed interim stroke or CVD. Exclusion of those participants attenuated the association between CAC and dementia. Certainly, stroke increases the risk of vascular-related

either sex, race/ethnicity, or age (<75 or ≥75 years) regardless of representation of CAC as categories or log2[CAC+1] (P for interaction >0.5 in all models tested). There was no indication supporting interaction by APOE4 on the association between CAC and dementia (P values for product term were ≥0.14 whether CAC was in categories or log2[CAC+1]).

Discussion

In this community-based multiethnic cohort sample, we found that baseline CAC was associated with future dementia risk independent of baseline vascular risk factors and APOE4 genotype. Although the positive association was attenuated to nonsignificance by adjustment for interim CVD, it remained significant after excluding interim stroke/CVD. Similar results to the full adjustment model. In secondary analyses excluding the participants who developed interim stroke or CVD, the associations were decreased but remained significant using log2[CAC+1]. In stratified analysis by baseline age <75 years (n = 5388, 117 events) versus ≥75 years (n = 905, 154 events), the association was attenuated in the older group, but a positive association remained significant in both age groups with full adjustment. The HRs per 1 SD higher log2[CAC+1] were 1.24 (95% confidence interval, 1.01–1.51; P = 0.038) and 1.21 (95% confidence interval, 1.01–1.45; P = 0.035) in the younger and older group, respectively, (data not tabulated). We observed no statistical evidence supporting interaction by

Table 3. Crude Rates of Dementia According to Coronary Artery Calcium Score at Baseline (n = 6293, From 2000 Through 2013)

<table>
<thead>
<tr>
<th>Coronary Artery Calcium Score at Baseline</th>
<th>0</th>
<th>1 to 400</th>
<th>401 to 1000</th>
<th>≥1001 Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk (baseline)</td>
<td>3132</td>
<td>2539</td>
<td>384</td>
<td>238</td>
</tr>
<tr>
<td>Follow-up period, person-years</td>
<td>36231</td>
<td>27618</td>
<td>3880</td>
<td>2251</td>
</tr>
<tr>
<td>Dementia, n</td>
<td>61</td>
<td>145</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Dementia rate, per 1000 person-years</td>
<td>1.68</td>
<td>5.25</td>
<td>8.50</td>
<td>14.22</td>
</tr>
<tr>
<td>Crude rate ratio for dementia</td>
<td>1.0 (ref)</td>
<td>3.12</td>
<td>5.05</td>
<td>8.44</td>
</tr>
</tbody>
</table>
dementia, and CAC is known to predict stroke.25 Beyond that, our results suggest that overall CVD is a risk factor for dementia, conceivably related to subclinical cerebrovascular changes, which is consistent with the CHS report of elevated dementia risk among those with prevalent CVD, other than stroke.3 The pathway via clinical stroke to dementia is known to be only the tip of the iceberg. Recent evidence suggests an important role of cerebral small vessel disease, manifested as lacunes, microbleeds, and white matter hyperintensities in magnetic resonance imaging, for both vascular and neurodegenerative dementia.26,27 From this perspective, previous studies give insights into potential mechanisms linking CAC and dementia. The AGES (Age, Gene, Environment Susceptibility)–Reykjavik Study, a cross-sectional study in Iceland, for example, reported not only a positive association of CAC with dementia/cognitive performance, but also an association between CAC and cerebral pathologies (infarcts, microbleeds, white matter lesions, and lower brain volume) assessed with brain magnetic resonance imaging. Interestingly, in their analysis, the relation of dementia/cognitive performance to CAC was significantly attenuated after adjustment for those brain findings.23 Similarly, the Rotterdam study and the CHS reported cross-sectional associations of CAC with (subclinical) brain pathologies and abnormal cognitive status.24,28,29 In our model, adjustment for interim CVD attenuated the association of CAC with dementia to non-significance. This may be because those with interim CVD had more advanced atherosclerosis in the brain at the CAC measurement than those without, providing a mechanism for the relationship and attenuating the overall association. Although exclusion of interim events may result in a biased estimate, that estimate is more conservative than in the full adjustment model. Therefore, the existing literature, together with our findings, suggests that CAC indicates the presence of the coexisting brain pathologies that increase dementia risk.23,24,28,29

MESA previously found a positive association of continuous CAC with dementia risk, one of the multiple outcomes evaluated in that report.17 Compared with the earlier report, our dementia ascertainment was more thorough and validated,15 using not only hospital records used in the previous study but also death certificates and more inclusive dementia-defining codes, which enabled us to almost double the number of cases. Other novel findings shown in our study but not in the previous one include a clear dose–response relation of CAC with dementia in multivariable adjustment, including APOE4, and persistent association of CAC with dementia after excluding or adjustment for interim stroke events, supporting the importance of subclinical vascular injury in occurrence of dementia.

APOE4 is an established risk factor for Alzheimer’s disease. Effect size of APOE4 carriers observed in our study seems to be weaker than other cohort studies.30,31 Because those previous reports studied only on Alzheimer disease, our estimate is likely diluted because of inclusion of other type of

### Table 4. HRs of Dementia According to CAC Score at Baseline (n=6293, From 2000 Through 2013)

<table>
<thead>
<tr>
<th>CAC Category</th>
<th>0</th>
<th>1 to 400</th>
<th>401 to 1000</th>
<th>≥1001</th>
<th>Continuous CAC per 1 SDI Higher CAC (log2[CAC+1])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal adjustment</td>
<td>1.0 (ref)</td>
<td>1.27 (0.93, 1.74)</td>
<td>0.127</td>
<td>1.37 (0.89, 2.13)</td>
<td>0.157</td>
</tr>
<tr>
<td>Full adjustment</td>
<td>1.0 (ref)</td>
<td>1.13 (0.82, 1.56)</td>
<td>0.245</td>
<td>1.21 (0.77, 1.90)</td>
<td>0.412</td>
</tr>
<tr>
<td>Full adjustment+interim stroke† adjusted</td>
<td>1.0 (ref)</td>
<td>1.07 (0.78, 1.48)</td>
<td>0.664</td>
<td>1.06 (0.67, 1.67)</td>
<td>0.799</td>
</tr>
<tr>
<td>Full adjustment+interim CVD† adjusted</td>
<td>1.0 (ref)</td>
<td>1.18 (0.86, 1.62)</td>
<td>0.310</td>
<td>1.23 (0.78, 1.95)</td>
<td>0.364</td>
</tr>
<tr>
<td>Competing risk model (full adjustment)‡</td>
<td>1.0 (ref)</td>
<td>1.22 (0.89, 1.67)</td>
<td>0.226</td>
<td>1.33 (0.85, 2.08)</td>
<td>0.220</td>
</tr>
<tr>
<td>Interim stroke excluded (n=6120, case=241)</td>
<td>1.0 (ref)</td>
<td>1.11 (0.81, 1.54)</td>
<td>0.513</td>
<td>1.16 (0.72, 1.87)</td>
<td>0.553</td>
</tr>
<tr>
<td>Interim CVD excluded (n=5908, case=220)</td>
<td>1.0 (ref)</td>
<td>1.10 (0.79, 1.53)</td>
<td>0.569</td>
<td>0.96 (0.57, 1.63)</td>
<td>0.883</td>
</tr>
</tbody>
</table>

APOE indicates Apolipoprotein E; CAC, coronary artery calcium; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and MET, metabolic equivalent.

*1 SD of log2(CAC+1)=3.634, equivalent to multiplying CAC score by 12.4. The corresponding HRs (95% CIs) per doubling [CAC+1] in models from the top to the bottom rows were 1.06 (1.02, 1.10), 1.06 (1.02, 1.10), 1.05 (1.01, 1.09), 1.03 (1.00, 1.07), 1.05 (1.01, 1.09), 1.06 (1.02, 1.10), 1.05 (1.01, 1.09), and 1.04 (1.00, 1.09).

†Adjusting covariates in minimal adjustment: age (y), sex, and race (White/Black/Chinese/Hispanic). Full adjustment further included education level (to high school/associate degree/bachelor’s degree or higher), having health insurance (yes/no), physical activity (MET min/wk, log-transformed), smoking (current/former/never), obesity (yes/no), hypertension (yes/no), medication(s) for hypertension or dyslipidemia (yes/no), systolic blood pressure (mm Hg), non-high-density lipoprotein cholesterol (mg/dL), diabetes mellitus (yes/no), APOE ε4 genotype (homo/hetero/none).

‡Interim stroke and interim CVD were treated as time-dependent variables.

§In the competing risk model, death without dementia diagnosis was treated as the competing risk to dementia.

The results were based on Cox regression model stratified with 3 birth cohorts (1917 to <1925, 1925 to <1935, and thereafter).
dementia. Our results did not support interaction by APOE4 on the association of atherosclerosis (CAC) with dementia in contrast with some,20,21 but not all,4,7 previous studies. This question, therefore, warrants further investigation.

**Validity of ICD-Based Code**

Because we used ICD codes from hospitalization and death certificate in identifying dementia cases, and given that dementia is a nonprimary event of interest in MESA, we may have missed cases from nonhospitalized and or less advanced dementia (false negatives).32,33 Our estimate is, therefore, likely more applicable to advanced cases of dementia. Nevertheless, our findings were generally consistent with other population-based studies that used more clinically oriented case ascertainment (ie, cognitive screening tests on the entire cohort followed by clinical assessment as indicated).3,4 In addition, our model found multiple factors associated with dementia, directionally consistent with the current literature: increased risk with current smoking,35 less physical activity,35 and inability to diagnose cognitive decline from their baseline.13,14 Hence, our hypothesis because vascular injuries have been related not only to vascular-type dementia, but also to Alzheimer types,4,5,7,38 and these 2 subtypes can be viewed as a continuum (ie, mixed-type dementia).20,27

Importantly, we are unable to isolate the potential independent contribution of CAC from that of cerebral small vessel disease26 with which it is known to be related. This does not, however, diminish the important strong predictive value of the CAC measure we demonstrated. An advantage of the ICD-based approach compared with cognitive function testing alone is that the former is based on a clinical diagnosis.26,27

We were unable to study the association of CAC with major dementia subtypes: Alzheimer and vascular type. These subtypes may be difficult to differentiate as necropsy studies have shown that each neuropathological feature commonly coexists in demented elderly adults.36,37 We think that such differentiation is of interest, but not necessarily crucial in examining our hypothesis because vascular injuries have been related not only to vascular-type dementia, but also to Alzheimer types,4,5,7,38 and these 2 subtypes can be viewed as a continuum (ie, mixed-type dementia).20,27

A strength of our study was verification of cases by review on the association of atherosclerosis (CAC) with dementia in the Framingham vascular risk scores.6 We used ICD codes from hospitalization and death certificate in identifying dementia cases, and given that dementia is a nonprimary event of interest in MESA, we may have missed cases from nonhospitalized and or less advanced dementia (false negatives).32,33 Our estimate is, therefore, likely more applicable to advanced cases of dementia. Nevertheless, our findings were generally consistent with other population-based studies that used more clinically oriented case ascertainment (ie, cognitive screening tests on the entire cohort followed by clinical assessment as indicated).3,4 In addition, our model found multiple factors associated with dementia, directionally consistent with the current literature: increased risk with current smoking,35 less physical activity,35 and inability to diagnose cognitive decline from their baseline.13,14 Hence, our hypothesis because vascular injuries have been related not only to vascular-type dementia, but also to Alzheimer types,4,5,7,38 and these 2 subtypes can be viewed as a continuum (ie, mixed-type dementia).20,27

**Limitations and Strengths**

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Importantly, we are unable to isolate the potential independent contribution of CAC from that of cerebral small vessel disease26 with which it is known to be related. This does not, however, diminish the important strong predictive value of the CAC measure we demonstrated. An advantage of the ICD-based approach compared with cognitive function testing alone is that the former is based on a clinical diagnosis.26,27

Any type of cognitive function test administered at 1x has an inherent limitation, influenced by fluctuation of concentration, and inability to diagnose cognitive decline from their baseline. A strength of our study was verification of cases by review on medical records to minimize false positives.

In conclusion, our study showed a positive graded association between baseline CAC score and future dementia risk independent of baseline vascular risk factors, APOE4 genotype, and interim stroke events in a community-based sample of men and women. The results support the important role of vascular injuries in pathogenesis of dementia, although whether CAC indicates presence of dementia-related pathologies in the brain warrants further investigation.

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**Disclosures**

None.

**References**


Coronary Artery Calcium and Dementia


CLINICAL PERSPECTIVE

Although studies suggest that vascular injuries play a role in pathogenesis of dementia, only a few studies examined a longitudinal relation of subclinical vascular disease with dementia. We examined whether baseline coronary artery calcium (CAC), a quantitative biomarker of subclinical vascular disease, is associated with incident dementia independent of vascular risk factors measured at baseline and APOE-ε4 genotype in a community-based sample. We analyzed 6293 participants of MESA (Multi-Ethnic Study of Atherosclerosis), aged 45 to 84 years at baseline (2000–2002), initially free of cardiovascular disease (stroke included) and noticeable cognitive deficit. Two-hundred seventy-one dementia cases were observed during a median follow-up of 12.2 years. Baseline CAC had a positive association with dementia risk in multivariable adjustment: CAC score of 1 to 400, 401 to 1000, and ≥1001 had elevated risk of dementia by 23%, 35%, and 71%, respectively, compared with no CAC; doubling of CAC score was associated with 6% (95% confidence interval, 2%–10%; P=0.002) higher dementia risk. The association remained significant regardless of baseline age (<75 versus ≥75 years) or after excluding those who developed cardiovascular disease during the follow-up. The results are consistent with the vascular injury to dementia hypothesis, suggesting that prevention of vascular injury may reduce future dementia risk. However, more study is needed to prove this hypothesis.
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Title
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Number of Supplement: 2 tables
Online Supplementary Table 1.
Crude incident dementia rates by sex and age during the median follow-up of 12.2 years.
MESA study (n=6293), baseline 2000-2002.

<table>
<thead>
<tr>
<th>Age at baseline</th>
<th>Participants at baseline, no.</th>
<th>Incident dementia, no.</th>
<th>Rate per 1,000 person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-64 years</td>
<td>1,859</td>
<td>10</td>
<td>0.46</td>
</tr>
<tr>
<td>65-69 years</td>
<td>556</td>
<td>15</td>
<td>2.40</td>
</tr>
<tr>
<td>70-74 years</td>
<td>418</td>
<td>21</td>
<td>4.64</td>
</tr>
<tr>
<td>75-79 years</td>
<td>319</td>
<td>45</td>
<td>14.41</td>
</tr>
<tr>
<td>80 years or older</td>
<td>151</td>
<td>32</td>
<td>23.42</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-64 years</td>
<td>1661</td>
<td>10</td>
<td>0.52</td>
</tr>
<tr>
<td>65-69 years</td>
<td>504</td>
<td>29</td>
<td>5.37</td>
</tr>
<tr>
<td>70-74 years</td>
<td>390</td>
<td>32</td>
<td>7.82</td>
</tr>
<tr>
<td>75-79 years</td>
<td>314</td>
<td>47</td>
<td>15.83</td>
</tr>
<tr>
<td>80 years or older</td>
<td>121</td>
<td>30</td>
<td>31.64</td>
</tr>
</tbody>
</table>
Online Supplementary Table2.
Multivariable adjusted hazard ratio (HR) and 95% confidence interval (95%CI) for dementia risk with adjustment for interim CVD‡ (N=6293, from 2000 through 2013, MESA)

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 1SD* higher</td>
<td>4.81</td>
<td>3.94</td>
<td>5.87</td>
</tr>
<tr>
<td>Female gender</td>
<td>0.65</td>
<td>0.50</td>
<td>0.84</td>
</tr>
<tr>
<td>Race/Ethnicity (ref. White)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1.24</td>
<td>0.91</td>
<td>1.69</td>
</tr>
<tr>
<td>Chinese</td>
<td>0.50</td>
<td>0.30</td>
<td>0.83</td>
</tr>
<tr>
<td>Hispanic</td>
<td>0.82</td>
<td>0.57</td>
<td>1.17</td>
</tr>
<tr>
<td>Higher education level attained †</td>
<td>0.88</td>
<td>0.75</td>
<td>1.03</td>
</tr>
<tr>
<td>No health insurance</td>
<td>1.37</td>
<td>0.72</td>
<td>2.59</td>
</tr>
<tr>
<td>Physical activity, per 1 SD higher *</td>
<td>0.88</td>
<td>0.80</td>
<td>0.97</td>
</tr>
<tr>
<td>Smoking habit (ref. never)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>current</td>
<td>1.84</td>
<td>1.23</td>
<td>2.73</td>
</tr>
<tr>
<td>former</td>
<td>0.81</td>
<td>0.62</td>
<td>1.07</td>
</tr>
<tr>
<td>Obesity (BMI ≥ 30kg/m²)</td>
<td>0.88</td>
<td>0.66</td>
<td>1.17</td>
</tr>
<tr>
<td>Systolic blood pressure, per 1SD* higher</td>
<td>1.08</td>
<td>0.97</td>
<td>1.22</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>0.97</td>
<td>0.75</td>
<td>1.26</td>
</tr>
<tr>
<td>Non HDL-cholesterol, per 1SD* higher</td>
<td>0.99</td>
<td>0.87</td>
<td>1.13</td>
</tr>
<tr>
<td>Lipid-lowering medication</td>
<td>0.81</td>
<td>0.60</td>
<td>1.11</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.22</td>
<td>0.87</td>
<td>1.71</td>
</tr>
<tr>
<td>APOEε-4 genotype (ref. non-carrier)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>heterozygous</td>
<td>1.33</td>
<td>1.02</td>
<td>1.73</td>
</tr>
<tr>
<td>homozygous</td>
<td>2.26</td>
<td>1.18</td>
<td>4.33</td>
</tr>
<tr>
<td>Interim CVD‡</td>
<td>5.08</td>
<td>3.80</td>
<td>6.79</td>
</tr>
<tr>
<td>Log2[CAC+1], per 1SD* higher</td>
<td>1.13</td>
<td>0.98</td>
<td>1.29</td>
</tr>
</tbody>
</table>

All the above factors were adjusted simultaneously in Cox model with 271 dementia cases over the median follow-up of 12.2 years. * 1 standard deviation (SD) for each variable was as follows: age, 10.3 years; physical activity (in log[MET-min/week]), 1.34; systolic blood pressure, 21.5mmHg; non HDL-cholesterol, 36.0 mg/dL; log2[CAC+1], 3.63 which approximates 12.4-times greater CAC-score. † Education level was categorized into the following three groups and treated as an ordinal variable: 0=up to high school, 1= up to associate degree, 2= bachelors’ degree or higher. ‡ CVD was defined as either myocardial infarction, resuscitated cardiac arrest, or stroke. Interim CVD was treated as a time-dependent variable.
Abbreviations: SD, standard deviation; BMI, body mass index; HDL, high-density lipoprotein; APOE, Apolipoprotein E; CAC, coronary artery calcium; MET, metabolic equivalent, CVD, cardiovascular disease.