Background and Purpose—Several cardiovascular risk factors are associated with cognitive disorders in older persons. Little is known about the association of the burden of coronary atherosclerosis with brain structure and function.

Methods—This is a cross-sectional analysis of data from the Age, Gene, Environment Susceptibility (AGES)-Reykjavik Study cohort of men and women born 1907 to 1935. Coronary artery calcification (CAC), a marker of atherosclerotic burden, was measured with CT. Memory, speed of processing, and executive function composites were calculated from a cognitive test battery. Dementia was assessed in a multistep procedure and diagnosed according to international guidelines. Quantitative data on total intracranial and tissue volumes (total, gray matter volume, white matter volume, and white matter lesion volume), cerebral infarcts, and cerebral microbleeds were obtained with brain MRI. The association of CAC with dementia (n=165 cases) and cognitive function in nondemented subjects (n=4085), and separately with MRI outcomes, was examined in multivariate models adjusting for demographic and vascular risk factors. Analyses tested whether brain structure mediated the associations of CAC to cognitive function.

Results—Subjects with higher CAC were more likely to have dementia and lower cognitive scores, more likely to have lower white matter volume, gray matter volume, and total brain tissue, and to have more cerebral infarcts, cerebral microbleeds, and white matter lesions. The relations of cognitive performance and dementia to CAC were significantly attenuated when the models were adjusted for brain lesions and volumes.

Conclusions—In a population-based sample, increasing atherosclerotic load assessed by CAC is associated with poorer cognitive performance and dementia, and these relations are mediated by evidence of brain pathology. (Stroke. 2010; 41:891-897.)

Key Words: atherosclerosis ■ calcinosis ■ cognitive function ■ coronary artery disease ■ dementia ■ radiography
Materials and Methods
The AGES-Reykjavik was initiated in 2002 to examine environmental factors, genetic susceptibility, and gene/environment interaction in relation to disease and disability in the elderly. Subjects (n=5764; age, 66–98 years) recruited for the AGES-Reykjavik cohort came from the population-based Reykjavik Study cohort composed of men and women born 1907 to 1935 and living in Reykjavik at the time the study was initiated in 1967 by the Icelandic Heart Association. As described previously, all eligible AGES-Reykjavik subjects participated in a comprehensive clinical evaluation, including cognitive testing, brain MRI, and a CT cardiac scan. All participants signed an informed consent. The study was approved (VSN00-063) by the National Bioethics Committee in Iceland and the Institutional Review Board of the Intramural Research Program of the National Institute on Aging.

Coronary Artery Calcifications
The heart was imaged with Siemens Somatom Sensation 4 multidetector CT (Siemens Medical Solutions) with prospective electrocardiographic triggering. CT scans were analyzed with a calcium scoring software, previously described as a part of the Multi-Ethnic Study of Atherosclerosis study. CAC, quantified according to the Agatston method, was the sum of all 4 coronary artery scores. Based on the reanalysis of 200 scans, the interreader agreement was r=0.99 and the interobserver Spearman correlation of measure made by the 5 readers compared to an expert reader from the Multi-Ethnic Study of Atherosclerosis study was r=0.94.

Assessment of Cognition and Dementia
A battery of 6 different cognitive tests was administered to all participants. From these tests, 3 cognitive domain composite scores were calculated: (1) the memory composite score included the immediate and delayed recall of a modified version of the California Verbal Learning Test; (2) the speed of processing composite included the Figure Comparison Test, the Digit Symbol Substitution Test, and the Stroop Test part 1 and 2; and (3) the executive function composite included a short version of the Cambridge Neuropsychological Test Automated Battery Spatial Working Memory test, the Digits Backward test, and the Stroop Test part 1 and 2. Gender-specific composite measures were computed by converting raw scores on each test to standardized Z-scores separately by gender and averaging the Z-scores across the tests in each composite. Inter-rater reliability for all tests was excellent (Spearman correlations range, 0.96–0.99).

Dementia case ascertainment was a 3-step process described previously. Briefly, all subjects were screened on cognitive function with the Mini-Mental State Examination and Digit Symbol Substitution Test. Those with positive screen results were administered a diagnostic battery of neuropsychological tests and, among them, those with positive screen results were examined by a neurologist and a proxy interview was administered. A consensus diagnosis, according to international guideline, was made by a panel that included a geriatrician, neurologist, neuropsychologist, and neuroradiologist.

Brain MRI Measures
All participants without contraindications were eligible for a brain MRI performed on a study-dedicated 1.5-T Signa Twinspeed system (General Electric Medical Systems). The image protocol, described previously, included an axial T1-weighted 3-dimensional, T2*-weighted gradient echo-type echo planar (T2*), a proton density/T2-weighted fast-spin echo (T2), and a fluid-attenuated inversion recovery sequences. The intracranial volume and the brain parenchyma compartments were segmented automatically with an AGES-Reykjavik Study-modified algorithm based on the Montreal Neurological Institute pipeline. The volumes of gray matter, white matter, lesion, and cerebrospinal fluid were estimated for each subject and divided by total intracranial volume, yielding a percent tissue volume. Total brain tissue volume was defined as the sum of gray matter volume, white matter volume, and white matter lesion volume. Cerebral infarcts (CI) were identified by trained radiographers as defects in the brain parenchyma with associated hyperintensity on T2 and fluid-attenuated inversion recovery images with a maximal diameter of at least 4 mm. For infarcts in the cerebellum and brain stem or infarcts with cortical involvement, no size criterion was required. Cerebral microbleeds (CMB) were defined as focal areas of signal void within the brain parenchyma that met the following criteria: visible on T2* images and smaller or invisible on T2 images, not abutting a parenchymal defect, and not showing any other structure in the signal–void area. The average inter-rater reliability (weighted kappa) was 0.7 for both CI and CMB (presence/absence) and intrarater reliability scores were 0.9 and 1.0, respectively, in 5% of all scans reread without knowledge of the previous reading.

Potential Confounders
Analyses were adjusted for demographic, health, and vascular risk factors associated with both CAC and cognitive function or dementia. Presence of depressive symptoms was defined as a score of ≥6 on the Geriatric Depression Scale. Education level (college or university vs lower education) and smoking history (never, ever) were assessed by questionnaire. Diabetes was defined as a history of diabetes, use of glucose-modifying medication, or a fasting blood glucose of ≥7 mmol/L. Hypertension was defined as measured systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg, or self-reported doctor’s diagnosis of hypertension, or using antihypertensive medications. Prevalent coronary heart disease was defined as self-reported history of coronary artery disease or coronary artery bypass surgery or angioplasty or angiina pectoris on the Rose Angina Questionnaire, or evidence on ECG of possible or probable myocardial infarction. We also adjusted the analyses for midlife systolic blood pressure and total cholesterol measured at the Reykjavik Study examination that occurred 25 years (SD=4.2) earlier, because these 2 variables were strongly associated with CAC and cognition.

Analytic Sample
Of the 5764 examined subjects, 453 did not have a CAC measure because of technical or medical reasons or refusal, leaving 5311 subjects with a measure of CAC. The 3 cognitive domains could be computed for 5215, of whom 4490 underwent brain MRI from which the brain volumes could be assessed. Complete data for this analysis therefore were available for 4250 subjects, including 165 with dementia diagnosed. Compared to the 4250 subjects with complete data, subjects with incomplete data (n=1514) were significantly older (76.3 [SD, 5.4] vs 79.5 [SD, 6.7]), had a higher rate of depressive symptoms, and were more likely to have diabetes and a history of smoking. At midlife they had higher systolic and diastolic blood pressures. The coronary artery calcium score, CI, and CMB, did not differ between the 2 groups after adjusting for age and gender.

Statistical Analyses
Because CAC load differed significantly between men and women, quartiles of distribution of CAC were calculated separately by gender and then pooled (thresholds for men: 60, 584, and 1498; thresholds for women: 12, 136, and 521). This ensures women are ranked and compared to other women and, similarly, men are compared to other men. White matter lesion volume was highly skewed so the measure was log-transformed; for clarity, we report the means of white matter lesion volume as antilogs.

General characteristics and cardiovascular risk factors of the sample were examined among subjects with and without dementia for each cognitive domain and across the quartiles of CAC. Logistic regression was used to evaluate the association with dichotomized variables and analysis of covariance was used to evaluate the association with continuous variables. Analysis of covariance was used to calculate the adjusted means (and 95% confidence intervals) of the 3 cognitive domains for each...
The median Agatston score of CAC was 278 among the 4250 subjects; median score was higher among men than women (584 vs 136). Increasing CAC quartile was associated with older age, presence of depressive symptoms, higher midlife systolic and diastolic blood pressures, and more hypertension treatment (Table 1). Older subjects in the higher quartiles of CAC were more likely to have hypertension and diabetes and were more likely to be smokers or former smokers.

Lower scores on each cognitive domain were strongly associated with older age, lower educational level, presence of depressive symptoms, and more cardiovascular risk factors and disease. Low scores were also associated with CI, CMB, lower brain volumes, and higher white matter lesion volume.

**Table 1. Cohort Characteristics Across the Gender-Specific Quartiles of Coronary Artery Calcium:**

<table>
<thead>
<tr>
<th>Late life variables</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Quartile</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Quartile</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Quartile</th>
<th>4&lt;sup&gt;th&lt;/sup&gt; Quartile</th>
<th>P&lt;sup&gt;†&lt;/sup&gt; Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.5 (4.9)</td>
<td>75.8 (5.2)</td>
<td>77.1 (5.5)</td>
<td>78.0 (5.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Men, % (N)</td>
<td>25.0 (444)</td>
<td>25.0 (444)</td>
<td>25.0 (444)</td>
<td>25.0 (444)</td>
<td>0.53</td>
</tr>
<tr>
<td>Higher education, % (N)</td>
<td>24.9 (284)</td>
<td>26.8 (304)</td>
<td>23.9 (272)</td>
<td>24.3 (276)</td>
<td>0.49</td>
</tr>
<tr>
<td>Hypertension, % (N)</td>
<td>21.9 (746)</td>
<td>24.7 (841)</td>
<td>25.9 (883)</td>
<td>27.5 (938)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes, % (N)</td>
<td>16.5 (77)</td>
<td>23.8 (111)</td>
<td>25.1 (117)</td>
<td>34.7 (162)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ever smoker, % (N)</td>
<td>21.5 (521)</td>
<td>24.8 (601)</td>
<td>26.2 (635)</td>
<td>27.5 (668)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m&lt;sup&gt;2&lt;/sup&gt;, mean (SD)</td>
<td>26.1 (4.1)</td>
<td>25.9 (4.3)</td>
<td>25.9 (4.3)</td>
<td>26.0 (4.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Presence of depressive symptoms, % (N)</td>
<td>24.4 (72)</td>
<td>23.4 (69)</td>
<td>22.7 (67)</td>
<td>29.5 (87)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Prevalent coronary heart disease, % (N)</td>
<td>7.6 (67)</td>
<td>14.6 (128)</td>
<td>27.1 (238)</td>
<td>50.7 (446)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Dementia</td>
<td>10.3 (17)</td>
<td>21.8 (36)</td>
<td>29.1 (48)</td>
<td>38.8 (64)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Midlife variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure, mm Hg, mean (SD)</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg, mean (SD)</td>
</tr>
<tr>
<td>Cholesterol, mg/100 mL, mean (SD)</td>
</tr>
</tbody>
</table>

*Adjusted for age.
†Overall difference between the 4 quartiles of combined gender-specific quartiles.
When the brain volumes and brain lesions were entered into the models, the relation of CAC to speed of processing and executive function was strongly attenuated and the overall difference between the CAC quartiles and the linear relation was no longer significant (Tables 3 and 4). Similarly, the relation of CAC and dementia was dramatically weakened when MRI brain volumes and brain lesions were added into the model (Tables 3 and 4).}

Finally, in models only adjusted for age and gender, taking into the model each brain characteristic separately (ie, CI, CMB, and MRI brain volumes), we found that the magnitude and significance of the associations of CAC to cognitive domain and dementia were dramatically reduced by the addition of brain volumes and marginally reduced by the addition of CI or CMB (Supplemental Table I, available online at http://stroke.ahajournals.org).

**Discussion**

We found that increasing calcification of the coronary arteries, a robust cumulative measure of atherosclerosis, was associated with decreased cognitive speed of processing, executive function, and increase risk of dementia in a large, well-described cohort of men and women with an average age of 76 years. We also found that these relations were mediated by brain volumes and lesions.

The strength of this study lies in the large number of participants and the quality and reproducibility of assessment of the different outcomes. Cognitive function was assessed with a robust battery of tests that allowed us to develop more stable measures of 3 different cognitive domains: memory, speed of processing, and executive function.

This study has some limitations that should be taken into account when interpreting the results. Subjects not included in this analysis were older, more often had diabetes, and had higher levels of systolic blood pressure at midlife. Furthermore, they had significantly lower cognitive performance and lower brain volumes. Therefore, the proportion of people with low cognitive performance, as well as lower brain volumes and higher CAC, may be underrepresented in this analysis. However, there is no reason to suggest a differential association of CAC to cognitive function between subjects included or not from the analysis.

The magnitude of the association of CAC with speed of processing and executive function did not diminish after adjustment for cardiovascular risk factors. This likely reflects
the fact that CAC is a measure of lifetime exposure to these risk factors, which lead to atherosclerosis. Before adjusting for brain structure, CAC was significantly associated with speed of processing and executive function, but not with memory. In addition, increasing CAC was associated with an increased risk for dementia. These results are consistent with other published studies showing memory is not significantly associated with atherosclerosis burden.7,29

Table 3. Association of Gender-Specific Quartiles of Coronary Artery Calcium With MRI-Detected Brain Characteristics and Pathology: The AGES-Reykjavik Study

<table>
<thead>
<tr>
<th>Brain Characteristics</th>
<th>Coronary Artery Calcium Gender-Specific Quartiles</th>
<th>Odds ratios (95% confidence intervals)</th>
<th>P*</th>
<th>P Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cerebral infarcts</td>
<td>Adjusted for age</td>
<td>1 (reference)</td>
<td>1.09 (0.89–1.07)</td>
<td>1.21 (0.99–1.47)</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>1 (reference)</td>
<td>0.99 (0.80–1.21)</td>
<td>1.00 (0.82–1.23)</td>
</tr>
<tr>
<td>Cerebral microbleeds</td>
<td>Adjusted for age</td>
<td>1 (reference)</td>
<td>1.28 (0.81–2.02)</td>
<td>1.00 (0.62–1.62)</td>
</tr>
<tr>
<td></td>
<td>Adjusted model</td>
<td>1 (reference)</td>
<td>1.25 (0.79–1.98)</td>
<td>0.97 (0.59–1.58)</td>
</tr>
</tbody>
</table>

*Overall difference between the 4 quartiles.
†Relative to intracranial volume.
‡Subjects with dementia (N=165) excluded.

---

Table 4. Association of Gender-Specific Quartiles of Coronary Artery Calcium With Cognition and Dementia Adjusted for Brain Characteristics and Lesions: AGES-Reykjavik Study

<table>
<thead>
<tr>
<th>Cognitive domains‡</th>
<th>Coronary Artery Gender-Specific Calcium Quartiles</th>
<th>Odds ratios (95% confidence intervals)</th>
<th>P*</th>
<th>P Linear Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1&lt;sup&gt;st&lt;/sup&gt;</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;</td>
<td>3&lt;sup&gt;rd&lt;/sup&gt;</td>
<td>4&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Memory</td>
<td>−0.01 (−0.08–0.06)</td>
<td>−0.003 (−0.07–0.07)</td>
<td>−0.009 (−0.08–0.06)</td>
<td>−0.01 (−0.08–0.06)</td>
</tr>
<tr>
<td>Speed of processing</td>
<td>0.007 (−0.06–0.07)</td>
<td>−0.005 (−0.07–0.06)</td>
<td>−0.04 (−0.10; 0.02)</td>
<td>−0.05 (−0.11–0.02)</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.05 (−0.02–0.12)</td>
<td>0.03 (−0.04–0.10)</td>
<td>−0.01 (0.08–0.06)</td>
<td>0.005 (−0.07–0.08)</td>
</tr>
<tr>
<td>Dementia</td>
<td>1 (reference)</td>
<td>1.55 (0.84–2.85)</td>
<td>1.72 (0.95–3.11)</td>
<td>1.56 (0.86–2.83)</td>
</tr>
</tbody>
</table>

*Overall difference between the 4 quartiles.
†Adjustment for age, education level, presence of depressive symptoms, ever smoker, prevalent coronary heart disease, current hypertension and diabetes, midlife systolic pressure and total cholesterol, cerebral infarct, cerebral microbleeds, white matter volume, white matter lesion volume, and total brain tissue volume.
‡Subjects with dementia (N=165) excluded.
Speed of processing and executive function involve the subcortical network, which is particularly susceptible to ischemic damage. Compared to patients with Alzheimer disease, patients with cerebrovascular cognitive impairment have characteristically more impaired test results on speed and executive functions than on memory.

CAC was associated with CI, CMB, and brain tissue volumes in a linear dose–response relation. The increased risk for CI as CAC increases has been reported in other large, population-based cohorts. Other atherosclerotic markers such as carotid intima-media thickness or ankle–brachial index have also been reported to be associated with brain lesion and atrophy, but these studies have little or no measures of brain function.

Finally, the relations of increasing CAC with dementia and with decreasing scores on tests of speed of processing and executive function were most strongly mediated by brain volumes and less so by CI or CMB. This analysis suggests that the association of dementia with CAC was not independent of brain atrophy and white matter lesion volume. The association of CAC to cognitive function was not assessed in that study.

**Conclusion**

Overall, this study shows that coronary atherosclerosis, measured with the CAC, is associated with pathological changes in the brain that have functional consequences ranging in severity from mild to severe cognitive function. Additional research is needed to understand how atherosclerosis interacts with other factors, such as hemodynamic changes, to damage the brain. On a practical basis, these findings highlight the chances that individuals who present with high CAC may also have concomitant cerebral damage that should be investigated.

**Acknowledgments**

The authors thank the participants of the study and the Icelandic Heart Association clinic staff for their invaluable contribution.

**Sources of Funding**

This study was supported by a grant from the National Institutes of Health (N01-AG-1-2100), National Institute on Aging Intramural Research Program, the Hjartaværing (the Icelandic Heart Association), and the Althingi (the Icelandic Parliament).

**Disclosures**

None.

**References**


Coronary Artery Calcium, Brain Function and Structure: The AGES-Reykjavik Study
Jean-Sébastien Vidal, Sigurdur Sigurdsson, Maria K. Jonsdottir, Gudny Eiriksdottir, Gudmundur Thorgeirsson, Olafur Kjartansson, Melissa E. Garcia, Mark A. van Buchem, Tamara B. Harris, Vilmundur Gudnason and Lenore J. Launer

*Stroke*. 2010;41:891-897; originally published online April 1, 2010;
doi: 10.1161/STROKEAHA.110.579581

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/41/5/891

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/