Aortic Stiffness and the Risk of Incident Mild Cognitive Impairment and Dementia

Matthew P. Pase, PhD; Alexa Beiser, PhD; Jayandra J. Himali, PhD; Connie Tsao, MD; Claudia L. Satizabal, PhD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD*; Gary F. Mitchell, MD*

Background and Purpose—Aortic stiffening increases the transfers of high pressure and flow pulsatility to small cerebral vessels potentially causing the accumulation of vascular brain injury. Our aim was to investigate the prospective association of aortic stiffness with the risks of incident mild cognitive impairment and dementia.

Methods—We studied 1101 dementia-free Framingham Offspring study participants (mean age, 69±6 years; 54% women). Aortic stiffness was measured as carotid–femoral pulse wave velocity using applanation tonometry and modeled as a linear variable and the top 2 quintiles (>11.4 m/s). Outcomes were the 10-year risk of incident mild cognitive impairment and dementia, including clinically characterized Alzheimer disease. We observed 106, 77, and 59 events of mild cognitive impairment, all-cause dementia, and clinical Alzheimer disease, respectively.

Results—After adjustment for age and sex, higher continuous aortic stiffness predicted an increased risk of mild cognitive impairment (hazard ratio, 1.40 [95% confidence interval, 1.13–1.73]), all-cause dementia (hazard ratio, 1.45 [95% confidence interval, 1.13–1.87]), and Alzheimer disease (hazard ratio, 1.41 [95% confidence interval, 1.06–1.87]). In risk factor–adjusted statistical models, aortic stiffness remained a significant predictor of mild cognitive impairment but not incident dementia. In nondiabetic patients, the top 2 quintiles of aortic stiffness were associated with a higher risk of incident all-cause dementia across all statistical models.

Conclusions—Aortic stiffness was an independent predictor of incident mild cognitive impairment in the whole sample and with incident dementia in nondiabetic patients. Our findings suggest aortic stiffness as a potentially modifiable risk factor for clinical cognitive impairment and dementia. (Stroke. 2016;47:2256-2261. DOI: 10.1161/STROKEAHA.116.013508.)

Key Words: Alzheimer disease ■ brain ■ dementia ■ risk factors ■ vascular stiffness
Methods
The FHS Offspring cohort is a prospective, community-based cohort study conducted in the town of Framingham, MA. Enrollment commenced in 1971 with the recruitment of 5124 participants. The cohort has been examined 9 times, with the latest examination concluding in 2014. For the present study, we used the seventh examination cycle (1998–2001) as a baseline, from which we calculated the prospective risk of incident MCI and dementia in adults ≥60 years. Applanation tonometry on the study cohort began after the commencement of the seventh examination cycle; hence, carotid–femoral pulse wave velocity (CFPWV) was not measured on approximately the first third of participants who completed the seventh examination. There were 3539 participants who attended examination 7, of whom 1928 participants were ≥60 years. Of these 1928 participants, 1206 had CFPWV measured. For the analysis of incident dementia, we excluded 13 participants who had prevalent dementia at baseline and 92 participants who had no follow-up for dementia, leaving a sample of 1101 participants. For the analysis of incident MCI, we excluded 30 participants with dementia or MCI at baseline and a further 108 participants who did not have follow-up for MCI, leaving a sample of 1068. All participants provided written informed consent, and the study was approved by the Institutional Review Board and Boston University Medical Center.

Assessment of Aortic Stiffness
The primary exposure was CFPWV, the reference standard noninvasive measure of aortic stiffness. Measurements were obtained in the morning, fasting, and after a supine rest period of ≈5 minutes. Trained research assistants used a commercially available tonometer (Millar Instruments, Houston, TX) to applanate the brachial, radial, femoral, and carotid arteries. Using body surface measurements, path length was calculated by subtracting the distance between the carotid measurement site and the suprasternal notch from the distance between the suprasternal notch and the femoral measurement site. This subtraction method adjusts for parallel transmission of the arterial pulse wave in the aortic arch and brachiocephalic artery. A simultaneous ECG was obtained to synchronize pressure waveforms to the ECG R wave for the purpose of signal averaging. CFPWV was calculated by dividing the path length by the pulse wave transit time (from the carotid to femoral sites), with values expressed in meters per second. Mean arterial pressure was calculated as the mean of the signal-averaged brachial pressure waveform. Carotid pressure tracings were calibrated with diastolic and integrated mean brachial blood pressures (BPs) and used to estimate central pulse pressure (PP), a surrogate marker of aortic stiffness. Brachial PP was also calculated during the tonometry assessment. Prevalent hypertension was defined as a physician-measured BP ≥140/90 mm Hg at examination 7 or treatment with BP-lowering drugs. The reproducibility of CFPWV in the FHS has been examined in a random sample of 50 participants that were blindly reanalyzed by a second observer (correlation coefficient, r=0.972).

Assessment of Incident MCI and Dementia
Using examination 7 as a baseline, we calculated the 10-year risks of incident MCI, all-cause dementia, and clinical AD, which were measured through active surveillance of the cohort as described previously.

A diagnosis of dementia was made in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition. A diagnosis of clinical AD was based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the AD and Related Disorders Association for definite, probable, or possible AD. Those with possible or probable AD dementia and concomitant vascular dementia were also classified as having AD. A diagnosis of MCI was made in accordance with the criteria defined by Petersen et al.

Statistical Analysis
Consistent with our previous publications, CFPWV was inverse transformed to approximate normality, with higher scores indicating a stiffer aorta. We also modeled CFPWV as a categorical variable, according to the top 2 quintiles (CFPWV >11.4 m/s). We used SAS Software (SAS Institute, Cary, NC) to examine the association between CFPWV and the outcomes using Cox proportional hazard regression models. Results were expressed as a hazard ratio and 95% confidence interval. Analyses were conducted according to 4 statistical models, with each including additional adjustment. The models were designed to adjust for known competing risk factors for vascular brain injury and other important confounding factors. The covariates included age at baseline and sex (model 1); education and apoE ε4 allele status (model 2); mean arterial pressure, prevalent diabetes mellitus, and high-density lipoprotein-cholesterol (model 3); prevalent atrial fibrillation, current smoking, prevalent cardiovascular disease, heart rate, total cholesterol, depressive symptoms (Center for Epidemiologic Studies Depression Scale score ≥16), central adiposity defined by the highest sex-specific quartile of waist-to-hip ratio, and treatment for hypertension (model 4). We explored possible interactions with sex, apoE ε4 allele status, prevalent diabetes mellitus, and prevalent hypertension. We also repeated the regression models with prevalent hypertension, brachial PP, and central PP as the predictors (for models 1 and 2). The threshold for statistical significance was P<0.1 for tests of interaction and P<0.05 for all other analyses.

Results
The sample demographics are displayed in Table 1. Over 10 years of surveillance, we observed 106 (10%) cases of MCI and 2257 (20%) cases of all-cause dementia. The highest risk was for clinical AD, with 418 (38%) cases. The sample demographics are displayed in Table 1. Characteristics of the Baseline Study Sample

Table 1. Characteristics of the Baseline Study Sample

<table>
<thead>
<tr>
<th></th>
<th>MCI Analysis Sample (n=1068)</th>
<th>Dementia Analysis Sample (n=1101)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>69 (6)</td>
<td>69 (6)</td>
</tr>
<tr>
<td><strong>Men, n (%)</strong></td>
<td>486 (46)</td>
<td>504 (46)</td>
</tr>
<tr>
<td><strong>Education, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school degree</td>
<td>348 (34)</td>
<td>359 (34)</td>
</tr>
<tr>
<td>College graduate</td>
<td>341 (33)</td>
<td>347 (33)</td>
</tr>
<tr>
<td><strong>Waist/hip ratio, median (Q1, Q3)</strong></td>
<td>0.97 (0.92, 1.01)</td>
<td>0.97 (0.92, 1.01)</td>
</tr>
<tr>
<td><strong>Heart rate, min⁻¹</strong></td>
<td>64 (11)</td>
<td>64 (11)</td>
</tr>
<tr>
<td><strong>Systolic BP, mm Hg</strong></td>
<td>127 (18)</td>
<td>127 (18)</td>
</tr>
<tr>
<td><strong>Diastolic BP, mm Hg</strong></td>
<td>69 (11)</td>
<td>69 (11)</td>
</tr>
<tr>
<td><strong>Brachial PP, mm Hg</strong></td>
<td>58 (15)</td>
<td>58 (15)</td>
</tr>
<tr>
<td><strong>Central PP, mm Hg</strong></td>
<td>56 (17)</td>
<td>56 (17)</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>618 (58)</td>
<td>645 (59)</td>
</tr>
<tr>
<td><strong>Hypertension treatment, n (%)</strong></td>
<td>462 (43)</td>
<td>486 (44)</td>
</tr>
<tr>
<td><strong>Total cholesterol, mg/dL</strong></td>
<td>200 (37)</td>
<td>200 (37)</td>
</tr>
<tr>
<td><strong>HDL-cholesterol, mg/dL</strong></td>
<td>54.4 (17.4)</td>
<td>54.3 (17.3)</td>
</tr>
<tr>
<td><strong>Diabetes mellitus, n (%)</strong></td>
<td>158 (15)</td>
<td>171 (16)</td>
</tr>
<tr>
<td><strong>Prevalent CVD, n (%)</strong></td>
<td>206 (19)</td>
<td>220 (20)</td>
</tr>
<tr>
<td><strong>Current smoker, n (%)</strong></td>
<td>85 (8)</td>
<td>87 (8)</td>
</tr>
<tr>
<td><strong>Apolipoprotein E ε4 presence, %</strong></td>
<td>238 (23)</td>
<td>249 (23)</td>
</tr>
</tbody>
</table>

**CFPWV, m/s, median (Q1, Q3)** 10.6 (9.0, 13.1) 10.7 (9.0, 13.2)

Data are displayed as mean (SD), unless specified otherwise. Continuous BP variables were measured during the CFPWV assessment. BP indicates blood pressure; CFPWV, carotid–femoral pulse wave velocity; CVD, cardiovascular disease; HDL, high-density lipoprotein; MCI, mild cognitive impairment; and PP, pulse pressure.
and 77 (7%) cases of dementia, 59 (5%) of which were clinically consistent with AD.

### Aortic Stiffness and MCI

As a continuous variable, higher aortic stiffness was associated with higher risk of incident MCI, across all statistical models (Table 2). Results were similar when aortic stiffness was modeled as the top 2 quintiles of CFPWV, with the exception that the association failed to reach statistical significance in model 3.

### Aortic Stiffness and Dementia

After adjustment for age and sex, aortic stiffness was associated with a higher risk of both all-cause dementia and AD (Table 2). Aortic stiffness remained a significant predictor of all-cause dementia after adjustment for apolipoprotein ε4 and education (model 2), whereas results were no longer statistically significant after adjusting for additional vascular risk factors (models 3 and 4). Aortic stiffness was only associated with AD in model 1. Results were similar regardless of whether aortic stiffness was modeled as a continuous or categorical variable.

#### Interactions

When all-cause dementia was the outcome, we observed an interaction between prevalent diabetes mellitus and the top 2 quintiles of aortic stiffness ($P=0.09$). We thus repeated the dementia analyses, stratifying by diabetes mellitus status at examination 7. In those without diabetes mellitus, the top 2 quintiles of aortic stiffness were associated with a $>2$-fold increase in the risk of incident all-cause dementia, across all statistical models (Table 3). There were no significant associations between aortic stiffness and dementia in people with diabetes mellitus. No other interactions were observed.

#### Comparisons With PP and Prevalent Hypertension

Brachial PP was associated with a marginal increase in the risk of all-cause dementia, in model 1 only, but with neither MCI nor AD. Central PP and prevalent hypertension were not associated with the risks of MCI, all-cause dementia, or AD (Table 4).

### Discussion

This prospective, community-based cohort study confirms an association between aortic stiffness and the development of dementia, and the top 2 quintiles of aortic stiffness were associated with a $>2$-fold increase in the risk of incident all-cause dementia, across all statistical models (Table 3). There were no significant associations between aortic stiffness and dementia in people with diabetes mellitus. No other interactions were observed.

### Table 2. Aortic Stiffness and the 10-Year Risk of Incident Mild Cognitive Impairment and Dementia

<table>
<thead>
<tr>
<th>Exposure Model</th>
<th>No. of Cases/Subj.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>No. of Cases/Subj.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
<th>No. of Cases/Subj.</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous CFPWV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>106/1068</td>
<td>1.40 (1.13–1.73)</td>
<td>0.002</td>
<td>77/1101</td>
<td>1.45 (1.13–1.87)</td>
<td>0.004</td>
<td>59/1101</td>
<td>1.41 (1.06–1.87)</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>104/1016</td>
<td>1.37 (1.10–1.69)</td>
<td>0.005</td>
<td>76/1047</td>
<td>1.35 (1.05–1.74)</td>
<td>0.02</td>
<td>59/1047</td>
<td>1.24 (0.93–1.65)</td>
<td>0.14</td>
</tr>
<tr>
<td>3</td>
<td>104/1000</td>
<td>1.31 (1.03–1.66)</td>
<td>0.03</td>
<td>76/1030</td>
<td>1.20 (0.90–1.60)</td>
<td>0.21</td>
<td>59/1030</td>
<td>1.17 (0.85–1.61)</td>
<td>0.34</td>
</tr>
<tr>
<td>4</td>
<td>98/976</td>
<td>1.41 (1.08–1.83)</td>
<td>0.01</td>
<td>73/1004</td>
<td>1.17 (0.85–1.61)</td>
<td>0.33</td>
<td>57/1004</td>
<td>1.17 (0.81–1.67)</td>
<td>0.41</td>
</tr>
<tr>
<td>Top 2 quintiles of CFPWV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>106/1068</td>
<td>1.71 (1.13–2.58)</td>
<td>0.01</td>
<td>77/1101</td>
<td>2.14 (1.29–3.56)</td>
<td>0.003</td>
<td>59/1101</td>
<td>2.03 (1.15–3.61)</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>104/1016</td>
<td>1.70 (1.11–2.58)</td>
<td>0.01</td>
<td>76/1047</td>
<td>2.02 (1.20–3.42)</td>
<td>0.008</td>
<td>59/1047</td>
<td>1.78 (0.99–3.20)</td>
<td>0.05</td>
</tr>
<tr>
<td>3</td>
<td>104/1000</td>
<td>1.52 (1.06–2.39)</td>
<td>0.07</td>
<td>76/1030</td>
<td>1.66 (0.94–2.92)</td>
<td>0.08</td>
<td>59/1030</td>
<td>1.61 (0.85–3.06)</td>
<td>0.14</td>
</tr>
<tr>
<td>4</td>
<td>98/976</td>
<td>1.69 (1.04–2.73)</td>
<td>0.03</td>
<td>73/1004</td>
<td>1.60 (0.87–2.93)</td>
<td>0.13</td>
<td>57/1004</td>
<td>1.69 (0.85–3.37)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Model 1 adjusts for age and sex. Model 2 includes additional adjustment for education and apolipoprotein ε4 allele status. Model 3 includes additional adjustment for mean arterial pressure, prevalent diabetes mellitus and high-density lipoprotein-cholesterol. Model 4 includes additional adjustment for atrial fibrillation, current smoking, prevalent cardiovascular disease, heart rate, total cholesterol, depressive symptoms, central adiposity, and treatment for hypertension. CFPWV indicates carotid–femoral pulse wave velocity; CI, confidence interval; and HR, hazard ratio.
MCI and incident dementia. Specifically, we report an association between higher aortic stiffness and an increased risk of incident MCI in the whole sample and with an increased risk of incident dementia in nondiabetic patients. Aortic stiffness was also associated with clinical AD independent of age and sex, although results were no longer significant after adjusting for the apoE ε4 allele and vascular risk factors. Prevalent hypertension was not associated with incident MCI or dementia in our sample.

A large body of previous work has demonstrated associations between high aortic stiffness, vascular brain injury, and cognitive decline. However, such work does not explain whether aortic stiffness is simply associated with normal brain aging, vascular brain injury because of small vessel disease, or the beginnings or a neurodegenerative process leading to clinical dementia. A cross-sectional study reported aortic stiffness to be higher in both MCI and dementia compared with healthy controls, although the temporal association between aortic stiffness and dementia could not be established. To our knowledge, only the Rotterdam study has investigated the prospective association between aortic stiffness and the risk of incident dementia. Whereas aortic stiffness was not associated with dementia, and MCI by Petersen criteria was not assessed in the Rotterdam study, the authors did find an association between aortic stiffness and poorer executive function. Other cohort studies have linked aortic stiffness to vascular brain injury because such individuals are at an increased risk of dementia. Aortic stiffening increases the transmission of pulsatile energy into small cerebral vessels, and numerous studies have associated aortic stiffness with a higher burden of vascular brain injury.

Meta-analysis of available studies has demonstrated relationships between aortic stiffness and evidence of cerebral small vessel disease, including white matter hyperintensities, silent brain infarcts, cerebral microbleeds, and cognitive impairment. Injury to deep white matter may follow from high aortic stiffness, given that such tissue is perfused by the short ascending branches arising from the circle of Willis, which are less able to dampen high pressure and flow pulsatility compared with the tortuous vessels that perfuse the cerebral cortex. Aortic stiffening is also related to impaired microvascular reactivity, reduced cerebral perfusion, BP variability, and incident hypertension, which are also related to vascular brain injury and cognitive impairment. Recent research showed that white matter hyperintensities and cerebrovascular remodeling explained 41% of the observed association between aortic stiffness and memory function. Finally, the arterial pulse wave is also thought to propel the movement of cerebrospinal fluid along perivascular spaces. Changes in pulsatile flow dynamics, following from aortic stiffening, may alter this process potentially disrupting the clearance of metabolic waste from the brain.

Because dementia involves the irreversible loss of neurons, it is important to find ways to prevent dementia before onset. The characterization of those with MCI has been advocated because such individuals are at an increased risk of dementia and may be ideal candidates for intervention. Importantly, aortic stiffness can be lowered through appropriate pharmacological therapy, dietary change, and lifestyle intervention. Because CFPWV is not routinely used in clinical care, the lowering of aortic stiffness is generally achieved indirectly and incidentally, as a consequence of efforts to lower brachial BP. However, it remains unclear whether lowering aortic stiffness can reduce the risk of developing MCI and dementia. We are unlikely to have an answer to this question in the near future, given the difficulties in designing appropriate clinical trials. As with exposure to hypertension, high aortic stiffness likely leads to the insidious accumulation of cerebrovascular injury, with clinical dementia only becoming apparent decades after sustained exposure. It is thus extremely challenging for

Table 4. Association of Prevalent Hypertension and PP With the 10-Year Risk of Incident Mild Cognitive Impairment and Dementia

<table>
<thead>
<tr>
<th>Event</th>
<th>Mild Cognitive Impairment</th>
<th>All-Cause Dementia</th>
<th>Alzheimer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases/Subjects</td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Prevalent hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>106/1068</td>
<td>1.14 (0.76–1.70)</td>
<td>0.54</td>
</tr>
<tr>
<td>2</td>
<td>104/1016</td>
<td>1.10 (0.73–1.67)</td>
<td>0.64</td>
</tr>
<tr>
<td>Brachial PP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>106/1068</td>
<td>1.00 (0.99–1.02)</td>
<td>0.71</td>
</tr>
<tr>
<td>2</td>
<td>104/1016</td>
<td>1.00 (0.99–1.01)</td>
<td>0.93</td>
</tr>
<tr>
<td>Central PP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>106/1068</td>
<td>1.00 (0.99–1.01)</td>
<td>0.997</td>
</tr>
<tr>
<td>2</td>
<td>104/1016</td>
<td>1.00 (0.99–1.01)</td>
<td>0.86</td>
</tr>
</tbody>
</table>

Model 1 adjusts for age and sex. Model 2 includes additional adjustment for education and apoE ε4 allele status. CI indicates confidence interval; HR, hazard ratio; and PP, pulse pressure.
clinical trials to ascertain whether treating aortic stiffness can lower the risks of MCI and dementia. Nevertheless, reducing vascular risk factors such as aortic stiffness, through healthy lifestyle choices and possible pharmacological treatments, is already encouraged for the purpose of preventing heart disease and stroke. On the basis of the results of numerous cohort studies, the benefits of maintaining normal arterial stiffness may extend to lowering the risk of clinical cognitive impairment and dementia.

Interactions revealed that aortic stiffness was associated with an increased risk of all-cause dementia, but only in those without diabetes mellitus. Individuals with type II diabetes mellitus have been shown to be at an increased risk of dementia, although the mechanisms linking diabetes mellitus to dementia remain uncertain. It is possible that those with diabetes mellitus are at an increased risk of dementia through largely metabolic rather than hemodynamic mechanisms, stemming from insulin resistance, disrupted insulin signaling, and hyperglycemia. As an alternative explanation, those with diabetes mellitus and high aortic stiffness may have been at an increased risk of dying from competing illness, before dementia onset.

Our study was limited by the observational design, which precludes conclusions on the causal link between aortic stiffness and outcome. Next, our sample was composed mostly of whites, limiting the applicability of our findings to other ethnic groups. We observed interactions between CFPWV and diabetes mellitus status when predicting incident dementia of whites, limiting the applicability of our findings to other ethnic groups. We observed interactions between CFPWV and diabetes mellitus status when predicting incident dementia, perhaps owing to time constraints, the need for specialized diabetes mellitus status when predicting incident dementia—Reykjavik study. Brain. 2011;134(pt 11):3398–3407. doi: 10.1093/brain/awr253.


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