Arterial Stiffness and \( \beta \)-Amyloid Progression in Nondemented Elderly Adults

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**Importance** Recent studies show that cerebral \( \beta \)-amyloid (A\( \beta \)) deposition is associated with blood pressure and measures of arterial stiffness in nondemented individuals.

**Objective** To examine the association between measures of arterial stiffness and change in A\( \beta \) deposition over time.

**Design, Setting, and Participants** Deposition of A\( \beta \) was determined in a longitudinal observational study of aging by positron emission tomography using the Pittsburgh compound B twice 2 years apart in 81 nondemented individuals 83 years and older. Arterial stiffness was measured with a noninvasive and automated waveform analyzer at the time closest to the second positron emission tomography scan. All measures were performed under standardized conditions. Pulse wave velocity (PWV) was measured in the central (carotid-femoral and heart-femoral PWV), peripheral (femoral-ankle PWV), and mixed (brachial-ankle PWV) vascular beds.

**Main Outcomes and Measures** The change in A\( \beta \) deposition over 2 years was calculated from the 81 individuals with repeat A\( \beta \)-positron emission tomography.

**Results** The proportion of A\( \beta \)-positive individuals increased from 48% at baseline to 75% at follow-up. Brachial-ankle PWV was significantly higher among A\( \beta \)-positive participants at baseline and follow-up. Femoral-ankle PWV was only higher among A\( \beta \)-positive participants at follow-up. Measures of central stiffness and blood pressure were not associated with A\( \beta \) status at baseline or follow-up, but central stiffness was associated with a change in A\( \beta \) deposition over time. Each standard deviation increase in central stiffness (carotid-femoral PWV, \( P = .001 \); heart-femoral PWV, \( P = .004 \)) was linked with increases in A\( \beta \) deposition over 2 years.

**Conclusions and Relevance** This study showed that A\( \beta \) deposition increases with age in nondemented individuals and that arterial stiffness is strongly associated with the progressive deposition of A\( \beta \) in the brain, especially in this age group. The association between A\( \beta \) deposition changes over time and generalized arterial stiffness indicated a relationship between the severity of subclinical vascular disease and progressive cerebral A\( \beta \) deposition.
Hypertension is linked to cognitive impairment and the pathologic features of Alzheimer disease (AD), including neurofibrillary tangles and β-amyloid (Aβ) plaques, as well as cerebrovascular disease and white matter hypointensities (WMHs) in the brain. Arterial stiffness appears to play a major role in the relationship between hypertension and its consequences in the brain. Mounting evidence implicates arterial stiffness in the pathogenesis of brain aging, cerebrovascular disease, impaired cognitive function, and dementia in the elderly.

Recent studies using radiolabeled Aβ ligands (eg, Pittsburgh compound B) in positron emission tomography (PET) imaging demonstrated that more than half of nondemented adults older than 80 years have significant fibrillar Aβ deposition. With the exception of the apolipoprotein E4 (ApoE4) genotype and aging, the risk factors and determinants of Aβ deposition in the brain are poorly understood. Recent studies report that brain Aβ deposition is associated with blood pressure and that arterial stiffness may play a central role. We recently showed that greater arterial stiffness (measured as higher pulse wave velocities [PWVs]) was associated with the amount of Aβ deposition in the brain. Interestingly, this association was independent of standard covariates and systolic blood pressure. However, it is unknown if arterial stiffness or other modifiable vascular factors are associated with the accumulation of Aβ deposition in the brain over time.

In this study, we evaluated the relationship between arterial stiffness and change in Aβ deposition, measured twice, 2 years apart, in a longitudinal observational study of nondemented older adults. We hypothesized that greater systemic arterial stiffness would be associated with the extent of Aβ accumulation in the brain during 2 years of follow-up.

Methods

Participants were recruited from the Ginkgo Evaluation of Memory Study (GEMS, September 2000 through April 2008), a multisite, placebo-controlled, double-masked, randomized clinical trial of the daily use of Ginkgo biloba in 3069 community-dwelling participants aged 72 to 96 years at baseline. In 2009, approximately 10 months following the GEMS drug close-out visit, 190 nondemented participants from the Pittsburgh site underwent brain magnetic resonance imaging (MRI) and PET using Aβ ligands (Aβ-PET) as part of the GEMS Imaging Sub-Study, detailed by Mathis et al. In 2011, approximately 2 years following neuroimaging, 91 of 190 (48%) of these nondemented GEMS Imaging Sub-Study participants returned to the clinic for measures of arterial stiffness. From July 2010 through November 2012, a total of 81 of these participants who remained nondemented returned for a second neuroimaging assessment. The mean (SD) follow-up time between baseline and follow-up Aβ-PET was 1.8 (0.5) years. Participants with repeat Aβ-PET were no different from those who did not return with respect to age, sex, antihypertensive medication use, ApoE4 status, body mass index, or cognitive status in 2009.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received local institutional review board approval from the University of Pittsburgh before study initiation. All participants completed the informed consent process before any study procedures.

PET Imaging of the Brain

Details of Aβ-PET data acquisition have been described previously. Recent advances in determining Aβ positivity show improved classification using a sparse k-means approach (SKM, averaged over 6 regions, standardized uptake value ratio of >1.67), as opposed to the iterative outlier method (IO, averaged over 5 regions, standardized uptake value ratio of >1.57), which we used in our baseline study. We conducted all analyses using both classification approaches and found them to be similar. Results from the IO method are presented herein in accordance with our baseline study. Results from the more conservative SKM approach are presented in eTables 2, 3, 4, and 5 in the Supplement.

MRI Protocol

Magnetic resonance imaging data were collected at the same time as PET imaging (July 2010 through November 2012) with a 3-T Siemens Trio TIM scanner (Siemens Healthcare). Visual assessment of WMHs was performed using T2-weighted fluid-attenuated inversion recovery (repetition time, 9160 ms; echo time, 90 ms [effective]; inversion time, 2500 ms; and number of excitations, 1) using an interleaved acquisition (48 slices, 3-mm slice thickness, no gap). The automated assessment of WMHs followed the method developed and validated by Wu and colleagues. This automated WMH segmentation method is an iterative algorithm that involves automated selection of “seeds” of possible WMH lesions and then makes use of a “fuzzy connectedness” approach to segment WMH lesions around the seeds. The segmented WMH voxels are then localized to the different white matter tracts using the Automated Labeling Pathway, also developed by Aizenstein et al and Rosano et al. The visual identification of MRI-defined infarcts was conducted by consensus by 2 raters (O.L.L. and W.E.K.).

Clinical Assessments

Just before PET imaging and MRI of the brain, participants underwent a cognitive evaluation, the 10-question Center for Epidemiologic Studies—Depression scale, a timed walk, and an inventory of their prescription and over-the-counter medications. Cognitive adjudication was performed masked to neuroimaging results by the Cognitive Diagnostic Center, taking into account historic serial cognitive assessments from the parent GEMS, as described in detail by Snitz et al. Criteria for mild cognitive impairment included 1 to 3 tests impaired at cutoffs of 1.5 SD below age- and education-adjusted means. Assessment for a history of cardiovascular disease, as well as the identification and classification of incident vascular outcomes, was based on methods previously published in GEMS. Cardiovascular outcomes were assessed again in the program project grant just before the PET scan between July 2010 and...
November 2012. A summary measure indicating a history of cardiovascular disease was created from baseline GEMS to follow-up PET and included angina pectoris, myocardial infarction, congestive heart failure, peripheral vascular disease, and a history of coronary revascularization procedures. Electrocardiographic abnormalities included ventricular conduction defects, major Q or QS with ST segment or T wave abnormalities, left ventricular hypertrophy, isolated major ST segment or T wave changes, atrial fibrillation, or first-degree atrial-ventricular block.

Arterial Dynamics
Arterial stiffness was measured by PWV using a noninvasive and automated waveform analyzer (VP2000; Omron Co). All measures were performed under standardized conditions as described previously. Pulse wave velocity was calculated as the distance (in centimeters) between arterial sites of interest over time (in seconds) that the pressure waveforms traveled from the heart to the respective arterial sites. Site-specific measurements were detailed previously. The mean of 2 runs was calculated to determine the mean PWV. For baPWV, the mean PWV of the left and right sides was used in the analysis. Validity and reliability of the PWV assessment with this device have been reported. Reproducibility of PWV measures was determined using the intraclass correlation coefficient, which was higher for baPWV (0.97) and faPWV (0.96) compared with cfPWV (0.75). Blood pressures were obtained at the same time using a conventional manual mercury sphygmomanometer. Pulse pressure was calculated as the difference between systolic and diastolic blood pressures.

Potential Covariates
Age, height, and weight were assessed at the same time as arterial measures and used to calculate body mass index (BMI) by standard means. ApoE4 carrier genotyping and medication assessments were made during the GEMS. Antihypertensive medication use was assessed at each study visit in the GEMS between September 2000 and April 2008. For the purpose of this analysis, participants were categorized as ever using antihypertensive medication during the GEMS (2000-2008).

Statistical Analysis
Correlations between baseline and follow-up measures of Aβ deposition as well as between PWV measures were calculated using Spearman rank correlation coefficients. Differences in participant characteristics by Aβ status at follow-up were assessed using t tests, χ² tests, and Fisher exact tests where appropriate, as well as multivariable models using logistic regression adjusting for age and sex. Exact logistic regression was used to calculate adjusted P values for categorical variables with low cell counts. Vascular measures were converted to z scores with a mean (SD) of 0 (1). Multivariable logistic regression models were constructed to determine the odds of being Aβ positive per a 1-SD increase in measures of arterial stiffness and pressure. Multivariable modeling made adjustments for age, sex, BMI, and antihypertensive medication use. Change in Aβ deposition was calculated as the difference in global Aβ deposition (standardized uptake value ratio) between baseline Aβ-PET in 2009 and follow-up in 2010 through 2012. The relationship between vascular measures and the amount of change in Aβ deposition over 2 time points (baseline and follow-up) was assessed in separate models using analysis of variance, adjusting for potential covariates. We also analyzed these data with repeated-measures analysis of variance, taking into account each participant’s baseline and follow-up Aβ deposition, and found nearly identical results (data not shown). In a separate sensitivity analysis, we removed the 9 participants with negative changes in Aβ deposition to assess only the individuals with increases in Aβ deposition over time.

Results
PWV and Aβ Deposition at Follow-up
Using the IO classification approach, 44 of 91 participants (48%) were Aβ positive at baseline compared with 61 of 81 (75%) at follow-up. Ten participants did not return for follow-up Aβ-PET and did not significantly differ from the 81 who did, based on sample characteristics. As previously reported, Aβ status at baseline was significantly associated with the ApoE4 allele and marginally correlated with BMI and having a diagnosis of mild cognitive impairment. Aβ status at follow-up in 2010 through 2012 was associated with the ApoE4 allele (Table 1) independent of age and sex. All ApoE4 allele carriers became Aβ positive by the follow-up. Aβ status at the follow-up was not linked with having a history of heart disease, an abnormal electrocardiogram, or the presence of cerebrovascular disease (eg, myocardial infarcts and white matter lesions) assessed at follow-up in this cohort (eTable 1 in the Supplement).

At follow-up, continuous measures of Aβ deposition were significantly correlated with baPWV (R = 0.32; P = .001), cfPWV (R = 0.22; P = .049), hfPWV (R = 0.29; P = .01), faPWV (R = 0.20; P = .008), and systolic blood pressure (R = 0.26; P = .02), which were similar to those reported at baseline. Measures of arterial stiffness, including baPWV and faPWV, were significantly higher among Aβ-positive participants at follow-up (Table 2) in unadjusted and multivariable models. In multivariable models, each 1-SD increase in stiffness was associated with more than a 3-fold increase in the odds of being Aβ positive at follow-up for baPWV (odds ratio, 4.06; 95% CI, 1.83-9.01) and faPWV (1.64; 1.46-9.08) after adjustment for age, BMI, and antihypertensive medication use. Additional adjustment for pulse pressure did not attenuate the associations between Aβ status for baPWV and faPWV (P < .01 for both). Other vascular measures were not associated with Aβ status at follow-up (Table 2).

Change in Aβ Deposition
The amount of Aβ deposition at baseline and follow-up was highly correlated with each other (R = 0.88; P < .001). Changes in Aβ deposition were significantly correlated with Aβ deposition at follow-up (R = 0.53, P < .001) but unrelated to base-
Table 1. Baseline Sample Characteristics of 81 Participants by Aβ Status at Follow-up (July 2010 Through November 2012)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follow-up</th>
<th>P Valueb</th>
<th>Model 1c per 1 SD, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aβ Positive (n = 61)</td>
<td>Aβ Negative (n = 20)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>87.6 (2.9)</td>
<td>86.7 (2.6)</td>
<td>.25</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>26.6 (4.5)</td>
<td>25.6 (5.2)</td>
<td>.41</td>
</tr>
<tr>
<td>Female sex</td>
<td>20 (32.8)</td>
<td>7 (35.0)</td>
<td>.53</td>
</tr>
<tr>
<td>ApoE4 allele (n = 76)</td>
<td>12 (21.0)</td>
<td>0 (0.0)</td>
<td>.03</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>45 (73.8)</td>
<td>11 (55.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Antihypertensive medication use</td>
<td>45 (73.8)</td>
<td>11 (55.0)</td>
<td>.10</td>
</tr>
<tr>
<td>Mild cognitive impairment</td>
<td>10 (16.4)</td>
<td>3 (15.0)</td>
<td>.60</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; ApoE4, apolipoproteinE4; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

a Values are presented as number (percentage) unless otherwise indicated. Aβ status was determined using the iterative outlier method (standardized uptake value ratio of >1.57).

b Unadjusted P value from Fisher exact test. P value from logistic regression model was adjusted for age and sex.

d The results from multivariable models of Aβ status were also similar when using the more conservative SKM approach to define Aβ deposition (eTables 2-5 in the Supplement). Overall, baPWV showed strong independent associations with Aβ status regardless of the classification scheme. In contrast to the consistent baPWV results, measures of central vascular disease (eg, cfPWV, faPWV, and having a history of heart disease) were significantly associated with Aβ status only when defined by the SKM method (eTables 3-5 in the Supplement). Results from multivariable models of longitudinal change, including Aβ repeated-measures analysis of variance models, were nearly identical to those using a simple change variable reported earlier. As part of additional sensitivity analyses, we also removed the 9 individuals who experienced declines in Aβ over follow-up and found similar results (data not shown).

Table 2. Measures of Arterial Stiffness and Aβ Status in 81 Participants at Follow-up (July 2010 Through November 2012)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Follow-up, Mean (SD)</th>
<th>P Value for Unadjustedb</th>
<th>Model 1c per 1 SD, OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV, cm/s</td>
<td>1888 (293)</td>
<td>1610 (218)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>cfPWV, cm/s</td>
<td>1618 (642)</td>
<td>1393 (451)</td>
<td>.17</td>
</tr>
<tr>
<td>hfPWV, cm/s</td>
<td>1389 (266)</td>
<td>1304 (297)</td>
<td>.25</td>
</tr>
<tr>
<td>faPWV, cm/s</td>
<td>1109 (196)</td>
<td>989 (117)</td>
<td>.002</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>60 (12)</td>
<td>60 (10)</td>
<td>.92</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>136 (17)</td>
<td>129 (26)</td>
<td>.27</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>71 (11)</td>
<td>68 (11)</td>
<td>.32</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>66 (14)</td>
<td>61 (17)</td>
<td>.25</td>
</tr>
</tbody>
</table>

Abbreviations: Aβ, β-amyloid; baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; DBP, diastolic blood pressure; faPWV, femoral-ankle pulse wave velocity; hfPWV, heart-femoral pulse wave velocity; OR, odds ratio; PP, pulse pressure; SBP, systolic blood pressure.

* Aβ status was determined using the iterative outlier approach (standardized uptake value ratio of >1.57).

b Unadjusted P value from χ2 test.

c Model 1 adjusted for age, sex, body mass index, and antihypertensive medications.

Discussion

These data showed that measures of arterial stiffness were strongly associated with the extent of Aβ deposition and the accumulation of Aβ in the brain over 2 years in nondemented elderly adults. Each standard deviation increase in baPWV was associated with a 4-fold increase in the odds of being Aβ positive at follow-up, which was higher than the 2-fold increase observed at baseline.8 Measures of central stiffness were not associated with Ol-defined Aβ status at baseline or follow-up. The accumulation of Aβ over follow-up was significantly associated with greater central measures of arterial stiffness (cfPWV and hfPWV), having a history of cardiovascular disease, and carrying the ApoE4 allele; it was not significantly related to age, sex, BMI, cognitive status, and antihypertensive medication use. During the 2 years of follow-up, the amount of Aβ deposition in the brain increased in 90% of the cohort of nondemented older adults.

These findings confirm and extend our initial results8 showing that Aβ deposition is strongly related to the severity of peripheral vascular stiffness and that this relationship

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differs by arterial bed measured. Taken together, the results from these 2 studies show that the degree of systemic arterial stiffness, measured by baPWV, is strongly associated with the extent of Aβ deposition at both baseline and follow-up. In contrast, measures of central stiffness (eg, cfPWV) are more strongly associated with the progression of Aβ accumulation in the brain over time. Therefore, the longitudinal accumulation of Aβ deposition in the brains of older adults may be driven by greater central arterial stiffening, while the cross-sectional extent of Aβ accumulation is better reflected by greater systemic stiffness, a composite of central elastic and peripheral muscular arteries.21 Our findings provide interesting analogies to the central progression of arterial stiffening across the age range. Our findings suggest that arterial stiffness is a better marker of Aβ deposition and accumulation than measures of blood pressure may decline late in life,23-25 there is evidence that arterial stiffness increases26 without reversal across the age range. Our findings suggest that arterial stiffness is a better marker of Aβ deposition and accumulation than blood pressure in this group of nondemented elderly adults. Recent amyloid imaging studies suggested that Aβ deposition has a long, protracted development in sporadic AD.27 However, to our knowledge, no studies have determined whether these two processes develop simultaneously or whether the vascular factors determine progression to dementia. Here we propose a conceptual model of vascular and brain aging that ties arterial stiffness to Aβ deposition in the brain (Figure).

Although we determined that Aβ deposition and vascular stiffness are associated, the pathophysiologic mechanisms involved in this process are not well established. Large artery stiffness has a direct effect on microvascular structure and function28 in the brain, resulting in cerebral hypoperfusion, which can lead to cognitive impairments.29 Alternatively, microvascular dysfunction may also lead to protein leakage, edema formation, and damage to brain tissue,29 which may contribute to Aβ deposition. The mechanisms linking arterial stiffness and Aβ deposition may be explained from a vascular perspective. It is possible that increased arterial stiffening has a direct influence on penetrating arterioles of the brain, leading to altered structure and function, with subsequent effects on Aβ clearance from the brain via cerebrospinal fluid drainage along the perivascular space.30 This may contribute to a disruption of vascular dynamics, weakness of the arterioles, insufficient brain perfusion, increased small-vessel pulsatility, and wave reflections, all mechanisms that could

### Table 3. Standardized β-Coefficients for Each Vascular Measure With Change in Aβ Deposition Over 2 Years of Follow-up (July 2010 Through November 2012)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Model 1a</th>
<th>Model 2b</th>
<th>Model 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P Value</td>
<td>β</td>
</tr>
<tr>
<td>Cardiovascular measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baPWV, cm/s</td>
<td>.196</td>
<td>.07</td>
<td>.206</td>
</tr>
<tr>
<td>cfPWV, cm/s</td>
<td>.595</td>
<td>.001</td>
<td>.572</td>
</tr>
<tr>
<td>hfPWV, cm/s</td>
<td>.467</td>
<td>.003</td>
<td>.452</td>
</tr>
<tr>
<td>faPWV, cm/s</td>
<td>.052</td>
<td>.34</td>
<td>.053</td>
</tr>
<tr>
<td>Pulse rate, beats/min</td>
<td>.032</td>
<td>.46</td>
<td>.029</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>.016</td>
<td>.61</td>
<td>.015</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>.000</td>
<td>.96</td>
<td>.000</td>
</tr>
<tr>
<td>PP, mm Hg</td>
<td>.029</td>
<td>.48</td>
<td>.031</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 2; ellipses, adjustment for pulse pressure is not appropriate for blood pressure measures.

a P value adjusted for age, sex, antihypertensive medication use, body mass index, time between Aβ scans, and history of cardiovascular disease.

b P value adjusted for age, sex, antihypertensive medication use, body mass index, time between Aβ scans, and PP.
Arterial Stiffness and Aβ Progression

Figure. A Conceptualized Trajectory of Vascular Factors Related to Arterial Stiffness and β-Amyloid Deposition in the Brain Across Adulthood

Figure represents the proposed relationships between factors related to arterial stiffness and age. Arterial stiffness is measured by blood pressure and pulse wave velocity. Joas et al. 23 and others 24,25 show that blood pressure begins to decline late in life, at least partly explaining why middle age blood pressure is a risk factor for dementia and late-life measures are not. In contrast, pulse wave velocity, a surrogate measure for arterial stiffness, does not appear to decline in late life and continues to increase with age. 26 A recent prospective study of β-amyloid deposition suggests that its progression occurs in a protracted manner over several decades before the diagnosis of dementia. 27 Interestingly, these data also suggest that the rate of β-amyloid deposition slows and may level off as deposition approaches a saturation point.

alter the perivascular clearance of Aβ, 31 leading to plaque formation. 32 Our data suggest that arterial stiffness may play a central and potentially unifying role in the development of both white matter disease and Aβ deposition and provide interesting insight to the ongoing debate that Aβ and WMHs have complementary 33 or dissociable effects 34 on the presentation and conversion to AD. Future research needs to assess the role of brain vascular dynamics in the development and progression of Aβ deposition in the brain. Plaque formation in the vascular wall and perivascular space may also affect vascular dynamics. This alternate hypothesis also deserves attention.

The associations between arterial stiffness and Aβ deposition are independent of several potential confounders, and arterial stiffness is a strong indicator of change in Aβ accumulation over time. However, this study is not without limitations. This is a small study, and the limited sample size may inhibit the statistical power to observe between-group differences, particularly regarding differences by ApoE4. Our data show that IO and SKM classification schemes result in different proportions of Aβ-positive individuals and alter the relationships between Aβ status, central arterial stiffness, and history of cardiovascular disease. These relationships should be studied further in greater detail. It is also important to note that arterial stiffness was assessed in 2011 at the time of follow-up PET; it would have been desirable to have baseline measures and to assess change in arterial stiffness as well. These arterial markers provide insight into the role of vascular stiffness and the brain, but they do not assess the cerebrovascular structure or function directly. Techniques that assess vascular dynamics in the brain as well as cerebral blood flow may be more direct factors related to Aβ deposition in the brain. Despite these limitations, these data make an interesting case that peripheral markers of arterial stiffness are novel risk factors for Aβ deposition and accumulation over time.

Conclusions

This study shows that arterial stiffness, as measured by PWV, is associated with the amount of Aβ in the brain and is an independent indicator of Aβ progression among nondemented elderly adults. With the advent of amyloid imaging, Aβ deposition in the brain is becoming an established hallmark of brain aging, yet the causes remain unknown. Arterial stiffness is likely a driving factor connecting hypertension, cerebrovascular disease, and Aβ deposition in the brains of non-demented older adults. The exact mechanism linking arterial stiffness and Aβ deposition in the brain needs to be elucidated.

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Author Contributions: Dr Hughes had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
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Acquisition, analysis, or interpretation of data: Kuller, Barinas-Mitchell, McDade, Klunk, Cohen, Mathis, Price, Lopez.
Drafting of the manuscript: Hughes, Lopez.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Hughes.
Obtained funding: DeKosky, Lopez.
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Study supervision: Hughes, Kuller, DeKosky, Lopez.
Conflict of Interest Disclosures: Dr Klunk reported being a coinventor of Pittsburgh compound B, a technology described in this study. As such, he has a financial interest in the license agreement, which GE Healthcare holds with the University of Pittsburgh. He reported serving as a consultant to GE Healthcare, Janssen, Pfizer, Lilly, AstraZeneca, Wyeth, Roche, and Elan. Dr Mathis reported being a coinventor of Pittsburgh compound B, a technology described in this study. As such, he has a financial interest in the license agreement, which GE Healthcare holds with the University of Pittsburgh. He reported serving as a consultant for GE Healthcare, Elan/Wyeth, Novartis, Janssen, Genzyme, Pfizer, Bristol Myers Squibb, IBA, and Baxter Bioscience. Dr Lopez reported serving as a consultant for Lilly, Lundbeck, Merz, and Baxter. No other disclosures are reported.

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REFERENCES


