Aortic Pulse Wave Velocity Predicts Focal White Matter Hyperintensities in a Biracial Cohort of Older Adults

Caterina Rosano, Nora Watson,* YueFang Chang,* Anne B. Newman, Howard J. Aizenstein, Yan Du, Vijay Venkatraman, Tamara B. Harris, Emma Barinas-Mitchell, Kim Sutton-Tyrrell

Abstract—Although the cross-sectional relationship of arterial stiffness with cerebral small vessel disease is consistently shown in middle-aged and young-old adults, it is less clear whether these associations remain significant over time in very old adults. We hypothesize that arterial stiffness is longitudinally associated with white matter characteristics, and associations are stronger within watershed areas. Neuroimaging was obtained in 2006–2008 from 303 elderly (mean age 82.9 years, 59% women, 41% black) with pulse wave velocity (PWV) measures in 1997–1998. Multivariable regression models estimated the coefficients for PWV (cm/sec) in relationship to presence, severity, and spatial distribution of white matter hyperintensities (WMH), gray matter volume, and fractional anisotropy from diffusion tensor, adjusting for demographic, cardiovascular risk factors, and diseases from 1997–1998 to 2006–2008. Higher PWV in 1997–1998 was associated with greater WMH volume in 2006–2008 within the left superior longitudinal fasciculus (age and total brain WMH adjusted, P=0.023), but not with WMH in other tracts or with fractional anisotropy or gray matter volume from total brain (P>0.2). Associations were stronger in blacks than in whites, remaining significant in fully adjusted models. Elderly with WMH in tracts related to processing speed and memory are more likely to have had higher PWV values 10 years prior, before neuroimaging data being available. Future studies should address whether arterial stiffness can serve as an early biomarker of covert brain structural abnormalities and whether early arterial stiffness control can promote successful brain aging, especially in black elderly. *(Hypertension. 2013;61:160-165.)* ● Online Data Supplement

Key Words: pulse wave velocity ▪ small vessel disease ▪ longitudinal ▪ fractional anisotropy ▪ community-dwelling elderly

Stiffness of the central arteries is an important determinant of microvascular injury in aging and hypertension.1,2 Potential cognitive and renal consequences of arterial stiffness3,4 may reflect gradual loss of the cushioning capacity of the aorta and subsequent transmission of damaging flow pulsations to the fragile microvasculature of the target organs.5,6 Moreover, lower cerebral blood flow secondary to stiffening can also contribute to parenchymal damage and white matter hyperintensities (WMH).6

The brain is one of the organs preferentially susceptible to small vessel injury secondary to arterial stiffness because its low-impedance vascular system is exposed to highly pulsatile flow throughout the cardiac cycle.2 Initial studies suggest that central arterial stiffness may potentially exacerbate age-associated changes in brain connectivity. However, with the exception of 1 prospective study of incident stroke,2 most of the evidence to date is correlational. Previous studies have applied lower resolution neuroimaging methods to examine the cross-sectional association with arterial stiffness in exceptionally well-functioning and racially homogeneous cohorts of young elderly6-17 or of middle-aged patients with overt vascular disease.18-24 Overall, strongest evidence exists for a cross-sectional association between pulse wave velocity (PWV), a measure of aortic stiffness, and semiquantitative visual ratings of WMH, a crude marker of small vessel disease (SVD). Studies examining other measures of arterial stiffness, including pulse pressure, also found cross-sectional associations with visual ratings of WMH,25,26 small brain infarcts,27 and with lower fractional anisotropy (FA), a marker of microstructural white matter abnormalities.28

It is not clear whether arterial stiffness would be more strongly related with abnormalities affecting specific networks, or whether these associations would remain significant over long period of times in community-dwelling older adults. Understanding the longitudinal relationship of arterial stiffness with neuroimaging markers of brain networks can help identify precise biomarkers of brain abnormalities early in the neurodegenerative process. Early identification of subclinical brain abnormalities, and specifically of WMH, can have public health implications because these markers are...
important prognostic factors for functional decline, disability, and dementia and may be amenable to intervention.

The aim of this study was to quantify the contribution of exposure to PWV with presence of covert brain abnormalities in very old adults several years later. We hypothesize that these associations are independent of hypertension and other risk factors and intervening vascular events. We further hypothesize that associations are most evident in frontal-subcortical tracts and specifically in superior longitudinal tracts related to processing speed and memory, because of previous evidence that PWV is longitudinally associated with cognitive impairment in these cognitive domains. These tracts may be selectively vulnerable to central arterial stiffening because of their geographic localization within “watershed” areas perfused by arterioles with few interconnections and their selective vulnerability to vascular insults. Last, we test the hypothesis that these associations are stronger in black compared with white participants.

Methods

Study Population

Participants were recruited from the Health, Aging, and Body Composition (Health ABC) Study, an ongoing study that began in 1997–1998. See details at [http://hyper.ahajournals.org](http://hyper.ahajournals.org). Of the 1455 participants with arterial PWV measures at study entry in 1997–1998 at the Pittsburgh site, 739 returned for an in-person assessment in 2006–2008. Of these, 622 completed eligibility interviews to participate in the Healthy Brain Project, a neurological study of mobility control. A total of 322 participants with PWV measurements were included in the Healthy Brain Project. Of these, 303 (mean age 82.9 years, 59% women, 41% blacks) had WMH measured at 3 Tesla and were included in this analyses. Of these 303 elderly, 273 (82.9 years, 56% women, 42% blacks) had also diffusion tensor imaging data at 3 Tesla and were included in the analysis of diffusion tensor imaging data. The analyses of WMH data were also repeated in the n=273 subsample. The University of Pittsburgh institutional review board approved this study. All participants gave informed consent.

Pulse Wave Velocity

PWV was measured in cm/sec noninvasively and with high reliability via simultaneous Doppler-recorded carotid and femoral pulse waveforms (model 810A, 9.0 to 10-MHz probes, Parks Medical Electronics, Inc.). See details previously published at [http://hyper.ahajournals.org](http://hyper.ahajournals.org).

Magnetic Resonance Image Acquisition

Participants were scanned with a Siemens 12-channel head coil on a 3T Siemens Tim Trio MR scanner at the Magnetic Resonance Research Center of the University of Pittsburgh, using a previously published protocol. Details on measurements of WMH, gray matter, and intracranial volume and diffusion tensor have been previously published and reported at [http://hyper.ahajournals.org](http://hyper.ahajournals.org). Tracts included in the analysis (Figure S1 in the online-only Data Supplement) consisted of those known to be associated with executive control and processing speed (superior longitudinal fasciculus), as well as tracts known to be associated with memory (longitudinal fasciculus) and mobility (anterior thalamic radiation, corticospinal tract), in addition to interhemispheric connections (corpus callosum, frontal and occipital portions). The cingulum bundle was examined as a whole and separately for the lower (posterior) and upper (antero-dorsal) portions for the left and right hemisphere.

The diffusion-weighted images were preprocessed using the FMRIB’s Diffusion Toolbox to remove unwanted distortions resulting from eddy current; the tensors were computed and diagonalized to determine the eigen values from which the FA and MD maps were computed as previously described.

Other Measures of Interest

In addition to demographic variables (age, race, sex, and education), body mass index (BMI), systolic and diastolic blood pressure and pulse pressure, stroke, hypertension, cardiovascular disease, and diabetes mellitus were obtained from the in-person visit in 1996–1997 until time of magnetic resonance imaging (MRI) in 2006–2008 at regular intervals (yearly with the exception of years 4 and 7). Current smoking, drinking habit (number of drinks per week in previous 12 months), and physical activity (kcal, kg/week) were obtained at study entry and time of MRI as previously described and were also considered as potential lifestyle covariates. Systolic blood pressure (SBP) was measured twice per visit, and results were averaged. Participants’ reports of diagnosis and use of specific medications or procedures were used to identify vascular events. Antihypertensive medication use (having taken these medications at least 50% of the time between study entry and time of MRI) was considered a covariate of interest because of potential effects on PWV and brain health. Finally, to evaluate whether cognitive performance concurrent with PWV might explain the association between PWV and brain integrity after 10 years of follow-up, scores on the modified minimental state examination and the Digit Symbol Substitution Test (DSST) were obtained at study entry and at time of MRI. We chose the DSST because it is a test of attention and psychomotor speed that is sensitive to cerebral SVD, and because we previously found it was associated with PWV.

Statistical Analysis

PWV was highly skewed and was used as log transformed in all main analyses. However, results are reported using quartiled PWV (with cut-offs from this study population and also from the parent population) or standardized untransformed PWV to ease interpretability of results. WMH volumes were also highly skewed and were dichotomized using the median as a cut-off. The ratio of total gray matter volume by intracranial volume was computed and interpreted as a marker of brain atrophy.

Associations between neuroimaging marker and PWV that were significant above the Sidak correction factor for multiple comparisons (P=0.0028 for n=18 comparisons) were retained in further analyses. Logistic models with WMH=median in each tract as dependent variable and PWV (as continuous or quartiles), age, and WMH from total brain as main independent variables were used. Age- and total WMH-adjusted partial correlation coefficients were used to evaluate the associations of PWV with FA, gray matter volume, and brain atrophy. Adjustment for WMH from total brain was applied to examine whether associations of WMH or FA from a given tract were specific for that tract or were explained by overall WMH burden. MRI measures that were associated with PWV at P<0.05 after adjustment for age and for total WMH entered multivariable regression models further adjusted for selected covariates. Covariates were selected if they were associated with the outcome in univariate analyses. Models were also adjusted for hypertension, incident stroke, incident vascular events, and slope of SBP, diastolic blood pressure, pulse pressure and of BMI, computed using the values of the risk factors measured at the in-person visits between study entry and time of MRI. Additionally, a stepwise model predicting the brain MRI measure of interest (P-entry=0.1; P-out=0.5) was run to identify the most parsimonious model. Analyses were repeated for men and women and for blacks and whites separately. All analyses were performed with SAS 9.1 and SPSS 19.0.

Results

The analysis cohort (n=303) ranged in age from 79–89 years at the time of the MRI (mean age 82.9 years, 59% women, 41% blacks), walked at a gait speed close to 1.0 m/sec, and had cognitive scores in the higher range for adults of similar age,
both for the DSST\textsuperscript{45} and 3MSE score\textsuperscript{45} (Table S1). The average number of antihypertensive medication used was 2.34 (1.92).

Compared with the parent cohort (Table S2), these participants had lower PWV, similar BMI, blood pressure, and lifestyle habits (data not shown), and they were also less likely to have cardiovascular diseases, stroke, hypertension, or diabetes mellitus. Higher PWV at study entry was significantly associated with higher DSST score measured at time of brain MRI ($P$=0.04). Cross-sectional associations of PWV with demographics, cognitive test scores, and health-related measures were overall similar to those previously published in the larger Health ABC cohort.\textsuperscript{46} Of note, higher PWV was not associated with older age in this cohort. WMH volume was similar in the right and left hemisphere for each of the tracts (Table S3) except for the anterior thalamic radiation and uncinate fasciculus (right>left) and the inferior longitudinal fasciculus (left>right).

Higher PWV was correlated above the Sidak threshold with greater WMH volume from total brain and less strongly with lower FA from total brain (age-adjusted $P<0.0001$ and $P=0.047$). After adjustment for WMH volume from total brain, the association of PWV with FA from total brain was no longer significant ($P=0.2$). Adjusted correlations with total brain atrophy and with total gray matter volume were $P=0.5$ and $P=0.7$, respectively.

Differences in PWV between those with WMH>median as compared with those without were in the expected direction for all tracts bilaterally. However, age-adjusted between-group differences in PWV were significant above the Sidak threshold only for the left superior longitudinal fasciculus (total fasciculus: $P=0.001$; temporal portion: $P=0.0003$) and not for the other tracts ($P>0.2$). Associations of PWV with WMH>median in the left longitudinal fasciculus were similar after adjustment for age and in men and women (data not shown), although they were larger in blacks as compared with whites (Table 1). Of note, associations were no longer statistically significantly different after stratifying the sample by race.

To better appreciate the size of the association of PWV with presence of WMH>median, unadjusted logistic models were obtained after stratifying by PWV quartiles (Table 2). The probability of having WMH>median followed the expected trend across increasing PWV quartiles, with a steep increase in odds ratios for the fourth quartile. Compared with those with PWV<575.30 cm/sec, the probability of having WMH>median was almost 3 times as high for those with PWV>966.00 cm/sec. Results were similar when using quartiles from the parent population and in the subsample of n=273.

In multivariable-adjusted logistic regression models, each SD of PWV was associated with a 40% greater probability of having WMH>median in the left superior longitudinal fasciculus independent of demographics (age, race, gender, education; Table 3, Model 1). This effect was minimally attenuated after adjustment for demographics and for SBP, BMI, smoking, and prevalence of diabetes and cardiovascular disease measured at study entry (Table 3, Model 2). Results were similar after adjustment for these variables measured at time of MRI (Table 3, Model 3) and also after adjustment for changes in vascular markers between study entry and time of MRI, including incident stroke, incident myocardial infarction, incident cardiovascular events, and slope of change in SBP, diastolic blood pressure, pulse pressure, and BMI (data not shown). Models adjusted for hypertension, antihypertensive medication use, smoking, physical activity, or drinking yielded similar results (data not shown). In stepwise models with all covariates (Table 3, Model 4), PWV was the only variable, among those measured at study entry, to be associated with presence of focal WMH>median. SBP and stroke prevalence (odds ratio, 1.495; 95% confidence interval, 1.088–2.054; and odds ratio, 5.207; 95% confidence interval, 1.626–16.674, respectively) at time of MRI were the only other variables retained in the model. Of note, the cross-sectional association of 1 SD of SBP with presence of WMH was similar to that estimated between PWV measured 10 years prior.

### Discussion

In this cohort of community-dwelling older adults, greater arterial stiffness was associated with greater volume of WMH localized within the left superior longitudinal fasciculus as measured 10 years later. Our results suggest selective spatial vulnerability of the white matter to long-term cerebrovascular consequences of central arterial stiffness in aging.

### Table 1. Mean PWV for Those With as Compared With Those Without WMH in the Left Superior Longitudinal Fasciculus

<table>
<thead>
<tr>
<th>Race</th>
<th>WMH=0</th>
<th>WMH&gt;0</th>
<th>Between-Group Difference in PWV</th>
<th>Adjusted P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean SD Med</td>
<td>n</td>
<td>Mean SD Med</td>
</tr>
<tr>
<td>All</td>
<td>139</td>
<td>759.54 349.4 683.3</td>
<td>164</td>
<td>908.76 449.33 793.5</td>
</tr>
<tr>
<td>White</td>
<td>88</td>
<td>747.96 361.01 682.5</td>
<td>92</td>
<td>865.38 422.97 760.5</td>
</tr>
<tr>
<td>Black</td>
<td>51</td>
<td>779.52 330.93 683.3</td>
<td>72</td>
<td>964.2 478.19 843.5</td>
</tr>
</tbody>
</table>

PWV indicates pulse wave velocity; WMH, white matter hyperintensities.

*From age- and WMH-adjusted models of PWV predicting WMH ≥0.

### Table 2. Results of Univariate Logistic Regression Models According to Quartiles of PWV for WMH>Median in the Left Superior Longitudinal Fasciculus

<table>
<thead>
<tr>
<th>Quartiles</th>
<th>Odds Ratio (95% CI) of Having WMH&gt;Median</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st, PWV&lt;575.30 cm/s</td>
<td>Referent</td>
<td>1.08 (0.56, 2.06)</td>
<td>0.75 (0.39, 1.41)</td>
</tr>
<tr>
<td>2nd, 575.30≤PWV&lt;713.80</td>
<td></td>
<td>1.41 (0.74, 2.68)</td>
<td>0.92 (0.49, 1.75)</td>
</tr>
<tr>
<td>3rd, 713.80≤PWV&lt;966.00</td>
<td></td>
<td>2.84 (1.48, 5.48)</td>
<td>1.86 (0.97, 3.56)</td>
</tr>
</tbody>
</table>

PWV indicates pulse wave velocity; WMH, white matter hyperintensities.
Our study extends previous cross-sectional findings in racially homogeneous cohorts of adults ranging in age from late 50s to mid-70s in 2 ways. First, we examined longitudinal associations in a racially diverse cohort of older adults living in the community, and second, we examined the spatial distribution of objective measures of white matter abnormalities, including hyperintensities and FA. Most neuroimaging studies have relied on semiquantitative ratings of hyperintensities combined across 2 large brain areas: periventricular and deep. Among the reports of a spatial distribution of brain abnormalities in relationship with arterial stiffness, results have been discordant. Although Shresta et al found a cross-sectional association between higher PWV and hyperintensities in periventricular and deep white matter, Ohmine et al found a cross-sectional association only in the periventricular areas. Another cross-sectional investigation applied FA to study the spatial distribution of white matter abnormalities in relationship to pulse pressure, in a small sample of 52 healthy normotensive adults. Similar to our longitudinal findings, this work found a cross-sectional association of pulse pressure with FA in the total brain. However, associations with individual tracts were not significant. Of note, in our study, the association of PWV with FA was no longer significant after adjustment for total WMH. Although it has been shown that WMH can impact the spatial distribution of FA, ours is the first report to indicate that the total burden of WMH can affect the association of pulse pressure with FA. More longitudinal work is needed to examine the interaction of arterial stiffness on macro- as compared with microstructural characteristics of brain connectivity.

Although we found larger PWV differences in blacks as compared with whites, this analysis did not have adequate power to further investigate these relationships stratified by race.

Our results also extend our knowledge of the relationship between arterial stiffness and brain abnormalities observed in the context of overt vascular disease. We found that the longitudinal association of PWV with WMH remained statistically significant after adjustment for blood pressure (including pulse and diastolic blood pressure), diabetes mellitus, incident vascular events, and other markers of vascular conditions. Thus, our data implicate underlying central arterial stiffness as a potential novel predictor of focal SVD, beyond these other well-established risk factors for white matter abnormalities in older adults.

The association of PWV with WMH was stronger for the left than the right hemisphere. We did not find significant differences in the volume of WMH in the left as compared with the right superior longitudinal fasciculus (P=0.3). Future studies relating SVD burden with vascular architectural differences between hemispheres are needed to explain these observed differences in relationship with risk factors.

The results of our study support previous findings that higher PWV in community-dwelling older adults is associated with selected cognitive domains, namely processing speed and memory. The superior longitudinal tract, containing bundles critical for processing speed (parietal portion) and memory (temporal portion), might be particularly vulnerable to arterial stiffening and to microvascular alterations in aging and hypertension because it travels across fronto-parietal “watershed” regions. These regions are perfused by arterioles with few interconnections available to preserve the blood supply in the presence of ischemic injury. It is biologically plausible that the structural characteristics of the prefronto-parietal connecting tracts in adults with higher PWV could explain the association of higher PWV with accelerated decline in processing speed. A recent cross-sectional study found neuroimaging data attenuate the association of PWV with cognitive tests. Future studies with follow-up measures of cognitive function are needed to explore this potential mechanism. We could not test this hypothesis because, at the present time, cognitive measurements for the time after the brain MRI acquisition are unavailable.

The association of PWV with WMH and not with gray matter volume supports the notion that the white matter is a brain tissue particularly sensitive to vascular-related insults. Gradual decline in cerebral volume observed throughout adulthood is consistent with relative sparing of gray matter from vascular insult in aging. Another study in patients with type 1 diabetes mellitus also did not find association with gray matter volume.

Several limitations should be considered. PWV data were not available at follow-up or concurrent with neuroimaging measurement to demonstrate a temporal association of aortic stiffness with incident brain structural abnormalities. However, associations of baseline PWV with subsequent neuroimaging indices were not explained by slope of change in vascular risk factors or interim events, suggesting a potential prognostic value of PWV in assessment of cerebrovascular risk after extended follow-up. Furthermore, neuroimaging measures were not available at time of the PWV measurement; thus we cannot infer the predictive values of PWV independently of baseline values of WMH. However, adjustment for DSST measured at study entry, a correlate of volume of WMH, did not modify these relationships. Our results indicate that very old adults with WMH are more likely to have had higher PWV values 10 years prior, at a point in time when MRI data were not available. Although this study cannot address temporality or mechanistic relationships linking PWV and WMH because of the lack of concurrent PWV and MRI data, these risk estimates warrant future studies to examine such mechanisms.

Strengths of this study include the large, community-dwelling population of very old adults, detailed brain MRI assessment, and evaluation of central arterial stiffness by PWV, which is a valid and noninvasive measure of central arterial stiffness. Although these adults appeared to have overall stable values of subclinical vascular risk factors and function, the prevalence of overt vascular events is comparable...
with that of elderly of similar age, thus indicating that this is not an exceptionally healthy or selected sample.

Perspectives

Although more work is needed to evaluate the hypothesized association of greater aortic stiffness with accelerated worsening in brain connectivity, the current interpretation of modifiable, vascular contributors to brain abnormalities in aging highlights an important potential to delay-associated cognitive and functional declines in late life. Longitudinal studies relating central arterial stiffness with subsequent measures of white matter integrity in older adults living in the community could inform future preventative strategies targeting central stiffness and help maintain function in late life.

Acknowledgments

We acknowledge the participants of the Health, Aging, and Body Composition Study.

Sources of Funding

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Disclosures

None.

References


Novelty and Significance

What Is New?

- Hyperintensities in tracts important for memory and processing speed are related to exposure to higher arterial pulse wave velocity 10 years prior.
- These associations were significant in very old adults living in the community.
- This association appears stronger in blacks as compared with whites.

What Is Relevant?

- Arterial pulse wave velocity may be used to estimate the future probability of having brain SVD many years later.

Summary

The association between arterial pulse wave velocity and focal WMH persists over a long period of time; it is independent of intervening cardiovascular events and appears stronger in blacks than in white.
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AORTIC PULSE WAVE VELOCITY PREDICTS FOCAL WHITE MATTER HYPERINTENSITIES IN A BIRACIAL COHORT OF OLDER ADULTS.

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Methods

Study Population

The cohort was followed prospectively to evaluate the relationship of changes in body composition, weight, and related health conditions to incident mobility disability. The cohort consisted of 3,075 well-functioning older black and white men and women living in Pittsburgh, PA and Memphis, TN. Eligible participants were 70-79 years of age and reported no difficulty walking a quarter of a mile (400 m), climbing 10 steps, or performing activities of daily living.

Pulse Wave Velocity

A minimum of ten beats were recorded for each simultaneous recording run. Three separate runs were recorded for each participant, and all usable runs were averaged to calculate the final PWV measure. The distance between the carotid and femoral recording sites was measured above the surface of the body with a tape measure. The distance was divided by the time delay between the foot of the pressure waves at each site to calculate PWV in cm/s.

Magnetic Resonance Image Acquisition

The magnetization-prepared rapid gradient echo T1-weighted images and fluid-attenuated inversion recovery images were acquired in the axial plane. Diffusion Weighted Images were acquired using single-shot spin-echo sequence. White matter hyperintensities volume was obtained from T2-weighted FLAIR image using an automated method and normalized for brain volume. FA was obtained from Diffusion weighted images, using previously published processing steps. Using the segmentation of white matter, gray matter, and WMH that were obtained from the T1-weighted and T2-weighted FLAIR images, the FA maps were restricted to normal appearing white matter.

The spatial distribution of white matter tracts was obtained using the JHU atlas. Volume of the gray matter was calculated by segmenting the skull-stripped T1-weighted image in native anatomical space using the FAST - FMRIB's Automated Segmentation Tool. Intracranial volume was measured using a T1-weighted image, BET with advanced option (−A) to extract additional skull and scalp surfaces.
References


Table S1. Population characteristics of this study cohort (n=303) measured at study entry in 1997-98 and concurrent with the MRI in 2006-08. Means and standard deviations (SD) are reported, unless otherwise noted.

<table>
<thead>
<tr>
<th>Population Characteristics</th>
<th>Study entry</th>
<th>Time of MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV, cm/sec</td>
<td>840.31 (412.68)</td>
<td>27.27 (4.48)</td>
</tr>
<tr>
<td>BMI, m/kg^2</td>
<td>27.21 (4.54)</td>
<td>27.27 (4.48)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>137.08 (20.12)</td>
<td>135.14 (18.32)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>73.77 (9.66)</td>
<td>69.64 (9.65)</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>63.31 (16.53)</td>
<td>64.74 (16.28)</td>
</tr>
<tr>
<td>Current Smoker, N (%)</td>
<td>15 (5)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>DSST, points</td>
<td>42.54 (12.59)</td>
<td>38.50 (12.66)</td>
</tr>
<tr>
<td>MMSE, points</td>
<td>92.45 (6.24)</td>
<td>92.94 (8.29)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>36 (12)</td>
<td>83 (29)</td>
</tr>
<tr>
<td>Cardiovascular diseases, N (%)</td>
<td>49 (14)</td>
<td>83 (27)</td>
</tr>
<tr>
<td>Stroke, N (%)</td>
<td>12 (4)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>146 (48)</td>
<td>211 (70)</td>
</tr>
<tr>
<td>WMH volume, cm^3</td>
<td>6.00 (7.00)</td>
<td>0.91 (1.41)</td>
</tr>
<tr>
<td>Atrophy, cm^3</td>
<td>0.357 (0.014)</td>
<td></td>
</tr>
</tbody>
</table>
Table S2. Population characteristics of the parent cohort (N=1455) measured at study entry in 1997-98 and at follow-up in 2006-07. Means and standard deviations (SD) are reported, unless otherwise noted.

<table>
<thead>
<tr>
<th>Population Characteristics</th>
<th>Study entry 1997-98</th>
<th>Follow-up visit in 2006-07</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PWV, cm/sec</td>
<td>902.76</td>
<td>(393.77)</td>
</tr>
<tr>
<td>BMI, m/kg²</td>
<td>27.7</td>
<td>(4.8)</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>138.7</td>
<td>(21.1)</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>74.3</td>
<td>(10.5)</td>
</tr>
<tr>
<td>Pulse pressure, mmHg</td>
<td>64.5</td>
<td>(17.3)</td>
</tr>
<tr>
<td>Current Smoker, N (%)</td>
<td>147</td>
<td>(10.1)</td>
</tr>
<tr>
<td>DSST, points</td>
<td>37.8</td>
<td>(13.8)</td>
</tr>
<tr>
<td>MMSE, points</td>
<td>90.6</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Diabetes, N (%)</td>
<td>215</td>
<td>(15)</td>
</tr>
<tr>
<td>Cardiovascular diseases, N (%)</td>
<td>410</td>
<td>(28)</td>
</tr>
<tr>
<td>Stroke, N (%)</td>
<td>129</td>
<td>(10)</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>955</td>
<td>(67)</td>
</tr>
</tbody>
</table>

^N=325 missing; ²n=178 missing.
Table S3. Mean, 25th and 75th percentile of white matter hyperintensities volume for each tract of interest.

<table>
<thead>
<tr>
<th>Tract of Interest</th>
<th>Median, cm³</th>
<th>25th - 75th percentile cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superior Longitudinal Fasciculus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.001</td>
<td>0 - .014</td>
</tr>
<tr>
<td>Right</td>
<td>0.001</td>
<td>0 - .024</td>
</tr>
<tr>
<td>Anterior thalamic radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.033</td>
<td>.014-.071</td>
</tr>
<tr>
<td>Right</td>
<td>0.060</td>
<td>.027-.120</td>
</tr>
<tr>
<td>Cortico- spinal tracts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.001</td>
<td>0 - .006</td>
</tr>
<tr>
<td>Right</td>
<td>0.001</td>
<td>0 - .012</td>
</tr>
<tr>
<td>Inferior Longitudinal Fasciculus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.005</td>
<td>0 - .026</td>
</tr>
<tr>
<td>Right</td>
<td>0.002</td>
<td>0 - .009</td>
</tr>
<tr>
<td>Uncinate Fasciculus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.008</td>
<td>.002-.017</td>
</tr>
<tr>
<td>Right</td>
<td>0.012</td>
<td>.003 -.031</td>
</tr>
<tr>
<td>Cingulum^</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>0.003</td>
<td>0 - .130</td>
</tr>
<tr>
<td>Right</td>
<td>0</td>
<td>0 - .008</td>
</tr>
<tr>
<td>Corpus Callosum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal</td>
<td>.032</td>
<td>.014,.069</td>
</tr>
<tr>
<td>Occipital</td>
<td>.017</td>
<td>.001,.082</td>
</tr>
</tbody>
</table>

^Upper and lower portions of the Cingulum are reported combined.
Figure S1.

**Figure Legend**

Figure S1. Axial views of white matter tracts of interest are illustrated in color overlays on a T1-weighted MPRAGE in standard space (Montreal Neuroimaging Initiative).