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Research Article

Cerebral White Matter and Slow Gait: Contribution of Hyperintensities and Normal-appearing Parenchyma

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Abstract

Background. White matter hyperintensities (WMH), a common marker of cerebral small vessel disease, and lower microstructural integrity of normal-appearing white matter are associated with slower gait. How these cerebral measures interact in relation to slower gait is unknown. We assessed whether microstructural integrity of normal-appearing white matter, measured by fractional anisotropy (FA), moderates the association of higher WMH with slower gait.

Methods. WMH, FA, and gait speed were acquired for 265 community-dwelling older adults (average age = 82.9 years).

Results. The inverse association between WMH and gait was robust to adjustment for age, gender, muscle strength, obesity, stroke, and hypertension (fully adjusted model: $\beta_s = -0.19$, $p = .001$). The interaction between WMH and FA was significant; analyses stratified by FA showed that the inverse association between WMH and gait speed was significant only for those with low FA (FA < median, fully adjusted model: $\beta_s = -0.28$, $p = .001$). Voxel-based results were similar for participants with FA less than median, there was an inverse association between gait speed and WMH which extended throughout the white matter (genu and body of corpus callosum, anterior limb of internal capsule, corona radiata, and superior longitudinal and fronto-occipital fasciculus). In contrast, for participants with FA \geq median, the association was limited to the genu of corpus callosum, the cingulum, and the inferior longitudinal fasciculus.

Conclusions. Microstructural integrity is a moderating factor in the association between WMH and gait. Future studies should examine whether higher microstructural integrity represents a source of compensation in those with greater WMH burden to maintain function in late life.

Keywords: White matter hyperintensities—Fractional anisotropy—Normal-appearing white matter—DTI—Gait speed

An extensive body of evidence suggests that in older adults without overt neurologic disease (1–4), radiologically overt abnormalities of the white matter predict lower mobility. Emerging evidence also suggests that higher microstructural integrity of the normal-appearing white matter, measured by fractional anisotropy (FA), is related to higher mobility (5,6). However, most studies examined FA and mobility in clinical populations such as Parkinson's disease and hydrocephalus (7). The evidence from community-dwelling healthy older adults is sparse and contradictory (8). Studies have generally

examined only a single neuroimaging measure of white matter integrity (5,6) or used broad measures of mobility (eg, Tinetti scale) (6,9). Our aim was to examine the interrelationships between radiologically overt abnormalities of the white matter, microstructural characteristics of the normal-appearing white matter, and gait speed.

Gait speed is a robust indicator of mobility, health, and function with aging, and there is consistent evidence that slow gait speed increases risk for mortality, morbidity, and disability (10–13). Strategies to improve gait speed could potentially reduce negative

health outcomes but require a greater understanding of the contributing factors to gait speed. We hypothesize that higher integrity of the normal-appearing white matter could offset the association of radiologically overt abnormalities of the white matter with slow gait. This would indicate that novel intervention strategies could focus on promotion of microstructural integrity of normal-appearing white matter, in addition to reducing burden of overt abnormalities.

We utilized multimodal 3T imaging and voxel-based analyses, allowing us to precisely assess associations between white matter hyperintensities (WMH), a radiological marker of overt white matter, FA, a marker of microstructural integrity of normal-appearing white matter, and gait speed. We examined whether FA is a moderating factor in the association between WMH and gait speed. Lower FA via diffusion tensor is a marker of more subtle or earlier brain parenchymal abnormalities than those seen with other imaging measures such as WMH (14). Higher integrity of the normal-appearing white matter may act as a buffer to the detrimental effect of WMH on slower gait. Therefore, we hypothesize that the association between WMH and gait would be stronger for those with lower FA.

Materials and Methods

Study Population

Data are from the Health, Aging and Body Composition (Health ABC) study, a prospective study of older adults that began in 1997–1998 to examine contributors to physical functioning. The present analyses use the ancillary Healthy Brain Project conducted at the Pittsburgh site from 2006 to 2008. Of the initial 1,527 participants enrolled at the Pittsburgh site in 1997–1998, 819 participants were seen in 2006–2008, and 314 of these completed gait speed assessments and magnetic resonance imaging (MRI) at 3.0 Tesla. Individuals with MRI were not different from the remainder of the Pittsburgh cohort (15). Of these 314 participants, 265 had complete measures of WMH, diffusion tensor imaging (DTI), and covariate data. The study protocol was approved by the Institutional Review Board. All participants provided informed consent. The details about eligibility criteria are included in the [Supplementary Material](#).

Gait Speed Measurement

Gait speed was assessed at usual pace on the *GaitMat II*, an instrumented, computerized 8-m walkway. The first two and last two meters were inactive to allow acceleration and deceleration. Gait speed was calculated as the distance between the first switch closure of the first and last steps divided by the time between them in meters/seconds (m/s). For participants not assessed in the lab, 3-, 4- or 6-m in-home hallway walk was used ($n = 10$).

Imaging

MRI scanning was performed at the MR Research Center of the University of Pittsburgh using a 3 T Siemens Tim Trio MR scanner with a Siemens 12-channel head coil as previously described (16). Specific details about MRI scanning are included in the [Supplementary Material](#).

White Matter Hyperintensities

WMH volumes were obtained from T2-weighted fluid-attenuated inversion recovery (FLAIR) images using a semi-automated method for quantification and localization of WMH (17). A trained rater reviewed each image and adjusted the threshold for choosing the seed WMH voxels, to ensure that the WMH were accurately segmented. Total brain WMH volume was obtained for each participant and

normalized to brain volume. For the volumetric analyses, the WMH from the right anterior thalamic radiation and the corpus callosum frontal were summed; these tracts were selected among all 21 tracts of interest because of previously shown association with slower gait in this sample (4). Log transformation of WMH volume reduced the skewness of this variable (skewness: 2.26 and -0.60 before and after log transformation).

The WMH maps were segmented from each individual's T2-weighted FLAIR image. These segmented maps were transformed using a common space by aligning each individual subject's FLAIR image to their nondiffusion B0 DTI image and aligned across subjects using functional MRI of the Brain Software Library FNIRT (18).

Diffusion Tensor Imaging

DTI is a useful tool for characterizing microstructural integrity of the white matter tracts by quantifying on directionality of water diffusion (FA) (14). The values for FA range from 0 to 1 where higher values suggest highly oriented water diffusion (ie, anisotropic diffusion), and therefore highly organized white matter structure (14).

DTI data were preprocessed using the FMRIB's Diffusion Toolbox (19) to remove distortions due to eddy current. The tensors were computed and diagonalized to determine the eigen values from which FA maps were computed (20). The FA maps were registered to the FMRIB58_FA template (19) using the FMRIB's Non-linear Image Registration Tool (FNIRT) (14). Then, using the segmentation obtained from the T2-weighted FLAIR images, the FA maps were restricted to normal-appearing white matter. Total brain volume measures for FA were calculated for all normal-appearing white matter.

Covariates

Key contributors to gait speed were identified based on prior work (21). Age, gender, race, and education were self-reported. Body mass index (BMI) was calculated using a standard formula (weight in kilograms)/(height in meters)². Diabetes was determined by self-report, use of hypoglycemia medication, a fasting glucose of ≥ 126 mg/dL, or 2-h glucose tolerance test >200 mg/dL at baseline or during follow-up until time of MRI. Prevalent hypertension and history of stroke were determined based on self-report of physician diagnoses and recorded medications. Global cognitive function was tested by the Modified Mini-Mental Status Exam (3MS). The 3MS ranges from 0 to 100 and a score of 80 or below indicates poor cognitive function (22). Depressive symptoms were assessed by the short-form Center for Epidemiologic Studies-Depression (CES-D) scale and reported as number of symptoms. Four individuals were missing data on CES-D.

Muscle strength was measured as the peak torque from isokinetic knee extension on a dynamometer (model 125 AP, Kin-Com, Chattanooga, TN). The right leg was measured unless contra-indicated due to prior surgery, injury, or pain. Some individuals were missing data on muscle strength at the time of MRI ($n = 38$). For these participants, muscle strength from the year prior to MRI ($n = 10$) or the next year ($n = 14$) was used where available.

Statistical Analysis

Total brain measures

Descriptive statistics, including frequencies and percentages, mean and standard deviation were computed for baseline characteristics, total brain measures, and gait speed. Simple linear regression analyses determined the association between each covariate or MR measure (independent variable) and gait (dependent variable). Pearson's correlation coefficient was computed to determine the association between WMH volume and total brain FA. Wilcoxon–Mann–Whitney and Chi-square

tests compared WMH burden and cognitive function frequencies between the FA groups. In addition, multivariable linear regression analyses determined the association between WMH volume (independent variable) and gait (dependent variable) before and after adjustment for age, gender, muscle strength, body mass index, diabetes, hypertension, stroke, or FA. Total brain FA volume was dichotomized at the median for the sample (less than, or above or equal to 0.3580030); the interaction term between this variable and WMH was computed before and after adjustment for other covariates. Variance inflation factors were estimated from regression models to assess potential multicollinearity. Regression diagnostics (ie, unusual and influential data), such as studentized deleted residuals greater than 2 and Cook's distance greater than 0.02, were assessed for all models. All statistical analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC) and all *p* values were two sided with a significance level of .05.

Voxel-based Analyses

A linear regression analysis was applied to determine voxel-based associations between WMH and gait speed separately for each FA group (FA above/below the median) and for the total group. Analyses were performed before and after adjustment by age and gender. Voxel-based statistical analyses were performed using a permutation-based nonparametric testing approach (randomize) as part of FMRIB Software Library. The number of permutations was set to 5,000. All statistical analyses were performed using the threshold-free cluster enhancement corrected for multiple comparisons (familywise error rate correction). The resulting statistics maps were thresholded at significance level *p* less than .05.

Results

Participants included in these analyses did not differ by demographic or health characteristics from individuals without DTI measures (all *p* ≥ .10). Excluded individuals did not have significantly different WMH volume than included individuals (*p* > .20).

Older age, lower muscle strength, higher body mass index, lower 3MS, higher CES-D score, being a male, being black, and having diabetes, hypertension, and stroke were associated with slower gait speed (Table 1). The Pearson's correlation coefficient between WMH burden and total FA was $r(263) = -0.45$ ($p < .0001$). The median (range) WMH burden for low and high FA group were 0.001504 (0.000035–0.008989) and 0.000701(0.000026–0.004962), respectively ($p < .0001$). Of the participants, 7% and 8% had poor cognitive function based on the 3MS for low and high FA groups, respectively ($p = .6545$). The median (interquartile range) CES-D scores for low and high FA group were 6 (9) and 5 (6), respectively.

Higher WMH were associated with slower gait in unadjusted models and remained similar after adjustment for FA and in fully adjusted models (Table 2). The interaction between FA group and WMH volume on gait speed was statistically significant before ($\beta_s = 1.06$, $p = .0250$) and after adjustment by each covariate at a time (β_s range = 0.87–1.15, p range = .0132–.0610) and also after exclusion of potential influential points ($n = 10$, $\beta_s = 1.49$, $p = .0015$). After full adjustment, the interaction was not statistically significant ($\beta_s = 0.57$, $p = .1923$).

In further analyses stratified by FA group, the association of WMH volume with gait was not significant in unadjusted or fully adjusted models for those with high FA ($p > .1367$). By contrast, the association of WMH volume with gait was significant in unadjusted ($\beta_s = -0.34$, $p < .0001$) and fully adjusted models ($\beta_s = -0.17$, $p = .0376$) for those with low FA. Figure 1 summarizes these patterns.

Table 1. Baseline Demographic, Health, and Functional Characteristics of Participants

| Characteristic | Total Sample | Association With Gait Speed |
|--------------------------|--------------------|-----------------------------|
| | Mean (SD) or N (%) | β_s (<i>p</i> Value) |
| | <i>n</i> = 265 | |
| Age (years) | 82.9 (2.7) | -0.22 (.0004) |
| Gait speed (m/s) | 0.9 (0.2) | |
| Muscle strength (N*m) | 81.5 (30.3) | 0.31 (<.0001) |
| BMI (kg/m ²) | 27.5 (4.4) | -0.23 (.0002) |
| 3MS score | 92.8 (6.8) | 0.27 (<.0001) |
| CES-D score | 7.0 (6.4) | -0.19 (.0017) |
| Female | 152 (57%) | -0.17 (.0064) |
| White | 158 (60%) | -0.26 (<.0001) |
| Education < high school | 39 (15%) | 0.10 (.1024) |
| Diabetes | 73 (28%) | -0.22 (.0003) |
| Hypertension | 180 (68%) | -0.19 (.0020) |
| Stroke | 20 (8%) | -0.13 (.0347) |
| Total brain MR measure | | |
| WMH (median, IQR) | 0.0033 (0.0074) | -0.25 (<.0001) |
| Fractional anisotropy | 0.358 (0.014) | 0.16 (.0110) |
| Gray matter atrophy* | 0.280 (0.023) | 0.07 (.2505) |

Notes: 3MS = Modified Mini-Mental Status Examination; β_s = standardized beta; BMI = body mass index; CES-D = Center for Epidemiologic Studies-Depression; IQR = interquartile range; MR = magnetic resonance; WMH = white matter hyperintensities.

*Volume of atrophy is calculated as gray matter volume divided by intracranial volume.

Table 2. Results From the Multivariable Linear Regression Analyses for the Effect of White Matter Hyperintensities on Gait Speed

| | β_s (<i>p</i> Value) | | |
|----------------|-----------------------------|---------------|----------------|
| | Model 1 | Model 2 | Model 3 |
| WMH | -0.27 (<.0001) | -0.24 (.0001) | -0.38 (<.0001) |
| FA group | | 0.10 (.1177) | 1.10 (.0149) |
| WMH × FA group | | | 1.06 (.0250) |

Notes: FA = fractional anisotropy; WMH = white matter hyperintensities.

Logarithm-based WMH volume (right anterior thalamic radiation and the corpus callosum frontal were summed) was used for analyses.

Model 1: Effect of WMH volume on gait speed.

Model 2: Effect of WMH volume on gait speed, controlling for FA group (FA dichotomized at the median).

Model 3: Effect of WMH volume on gait speed, including FA group and the interaction between WMH and FA group.

The voxel-based analyses of WMH in relation to gait showed that slower gait speed was associated with greater WMH in many of the white matter tracts among participants with low FA (Figure 2A) but not among the participants with high FA (Figure 2B). For those with low FA, the peaks of the inverse associations between gait and WMH were found in the anterior and superior corona radiata and included corona radiata, superior longitudinal fasciculus (L), superior fronto-occipital fasciculus (R), anterior limb of internal capsule (R), and genu and body of corpus callosum. By contrast, among participants with high FA, slower gait was associated with greater WMH only in the inferior longitudinal fasciculus, the cingulum and

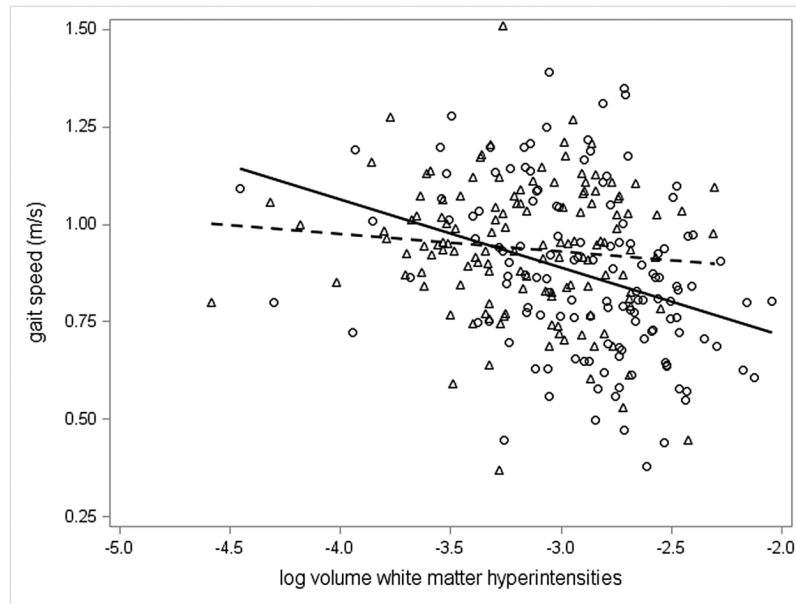


Figure 1. Association of white matter hyperintensities (WMH) and gait speed. Scatterplot of gait speed (m/s, y-axis) by volume of WMH (log-transformed, x-axis) stratified by low (circles, solid line) or high (triangles, dashed line) fractional anisotropy, defined as below or above and equal to the median.

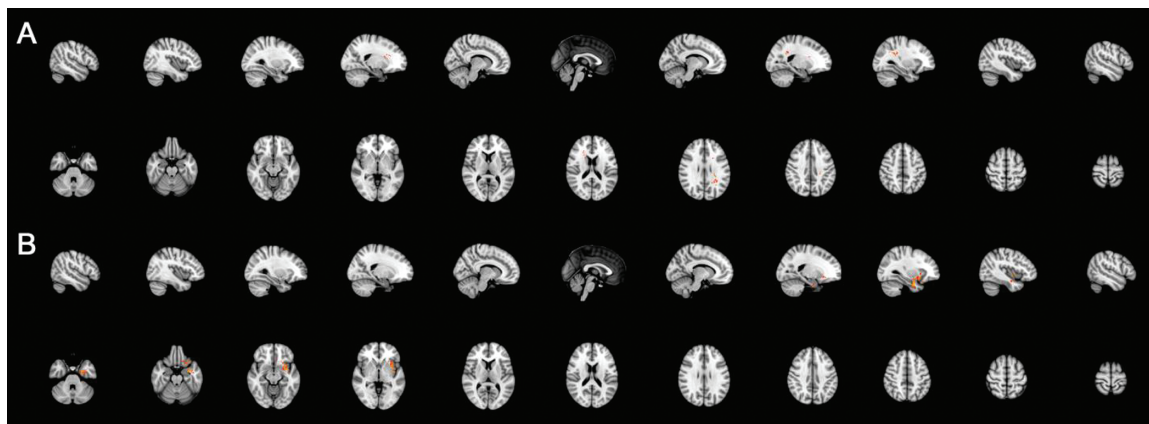


Figure 2. Voxel-based analysis of white matter hyperintensities (WMH) and gait speed stratified by low and high fractional anisotropy. Voxel-based analysis of WMH and its association with gait speed for participants with (A) low and (B) high fractional anisotropy after adjustment by age and gender. Results show brain patterns of significant associations for sagittal and axial views. Red and yellow areas denote significant voxels after threshold-free cluster enhancement. All results are thresholded at $p < .05$ using familywise error rate correction. The statistical map is overlaid on the Montreal Neurological Institute standard template.

genu of corpus callosum. Table 3 shows local maximums of the significant clusters ($p < .05$, familywise error rate corrected).

The voxel-wise analyses of WMH and gait for the full group after adjustment by age and gender showed that slower gait was significantly associated with greater WMH (Supplementary Figure 1 and Supplementary Table 1). Associations were strongest ($p < .001$) in the anterior corona radiata and the superior longitudinal fasciculus and included corona radiata, superior longitudinal and fronto-occipital fasciculus, uncinate fasciculus, anterior limb of internal capsule, posterior limb of internal capsule and retrolenticular part of internal capsule (L), posterior thalamic radiation, external capsule (R) and corpus callosum.

Discussion

We found that FA was a moderator of the association between WMH and gait speed such that WMH were more strongly associated with gait in those with low FA compared with those with high FA. This finding suggests that in those with greater microstructural integrity

of the white matter, WMH may play less of a role in determining gait speed. In addition, in older adults with low microstructural integrity of the normal-appearing white matter, greater WMH throughout all white matter tracts of the brain was related to slower gait. In contrast, for those with high microstructural integrity, the associations of WMH and gait were restricted to the cingulum, genu of corpus callosum, and inferior longitudinal fasciculus. These findings suggest that greater microstructural integrity of the normal-appearing white matter may be a candidate factor to maintain function in the presence of small vessel disease related neurologic abnormalities. Our finding is consistent with a very recent report that patients with stroke who also have better white matter microstructural integrity, measured by FA, are more likely to display better motor recovery (23).

Hyperintensities in the cingulum and the corpus callosum may be of particular importance in control of gait speed, as denoted by the presence of a significant association with gait in both high and low FA groups. The role of interhemispheric tracts in the control of gait has been previously shown for older adults (24). Other tracts may

Table 3. Brain Patterns of Associations Between White Matter Hyperintensities and Gait Speed for Participants With Low and High Total Brain Fractional Anisotropy After Adjustment by Age and Gender

| Peak | Cluster Size (mm ³) | 1 - <i>p</i> value | MNI Coordinates (mm) | | | Tracts JHU White Matter Labels and Tractography Atlases |
|------------------------------------|---------------------------------|--------------------|----------------------|----------|----------|--|
| | | | <i>x</i> | <i>y</i> | <i>z</i> | |
| Participants with low FA | | | | | | |
| Posterior corona radiata L | 1,115 | .979 | 115 | 98 | 103 | Information processing tracts (superior and posterior corona radiata L, superior longitudinal fasciculus L) Interhemispheric tracts (superior and posterior corona radiata L) |
| Anterior corona radiata R | 402 | .979 | 66 | 146 | 93 | Information processing tracts (anterior corona radiata R, superior fronto-occipital fasciculus R) Sensory-motor tracts (anterior limb of internal capsule R) Interhemispheric tracts (genu and body of corpus callosum, anterior corona radiata R) |
| Superior corona radiata L | 133 | .969 | 112 | 134 | 96 | Information processing tracts (anterior and superior corona radiata L, superior fronto-occipital fasciculus L) Interhemispheric tracts (anterior and superior corona radiata L) |
| Anterior corona radiata R | 18 | .960 | 64 | 161 | 79 | Information processing tracts (anterior corona radiata R) |
| Anterior corona radiata R | 14 | .962 | 68 | 151 | 77 | Information processing tracts (anterior corona radiata R) |
| Participants with high FA | | | | | | |
| Inferior longitudinal fasciculus L | 5,732 | .988 | 121 | 124 | 48 | Information processing tracts (anterior corona radiata L, inferior longitudinal fasciculus L, inferior fronto-occipital fasciculus L) Sensory-motor tracts (external capsule L) Interhemispheric tracts (genu of corpus callosum) |
| Cingulum L | 117 | .961 | 95 | 150 | 65 | Information processing tract (cingulum L) |
| Genu of corpus callosum | 78 | .961 | 94 | 149 | 73 | Interhemispheric tracts (genu of corpus callosum) |

Notes: FA = fractional anisotropy; MNI = Montreal Neurological Institute.

This table reports the spatial distribution of the associations including the size of the cluster, the corrected 1 - *p* value for the cluster and the location of the maximum *z*-statistic in MNI coordinates.

be of particular importance, as denoted by the stronger associations for tracts related to information processing (eg, superior longitudinal fasciculus and inferior and superior fronto-occipital fasciculus). Prior research has indicated associations between executive function and speed of processing, two domains served by these networks, and gait in older adults (25). Finally, associations were also found in sensory-motor tracts, including the anterior limb of the internal capsule and the external capsule. Preservation of microstructural integrity in normal-appearing white matter alone may not be sufficient to buffer the negative impact of WMH in these tracts on gait speed. Future work needs to consider other aspects of brain integrity, as well as other contributors to gait speed as potential compensatory factors for WMH.

The pathologic differences underlying WMH and FA are still not well characterized. Several processes are possible: WMH and low FA represent separate though related phenomena; low FA indicates early damage that may lead to WMH; low FA follows accumulation

of WMH; or, most likely, some combination of the above. Without further characterization from longitudinal studies, discussions are inherently speculative. If the pathologies underlying WMH and low FA are inherently linked, then our results may be related to severity or localization of white matter damage. In contrast, if WMH and low FA represent at least partially independent processes, then preserved microstructural integrity of the normal-appearing white matter may buffer against damage indicated by WMH.

Important limitations of the current study are the study-specific cutoffs for FA and the cross-sectional analysis. Future longitudinal analyses of WMH and FA, and their association with gait changes, are warranted. Several strengths should be noted. We utilized a multimodal neuroimaging approach, combining macro- and microstructural measures, which can provide a broader understanding of underlying mechanisms compared with a single imaging modality. We also considered the possible confounding effect of muscle strength

and other non-neurological factors which have not been typically assessed in neuroimaging studies of gait in older adults. Loss of muscle strength is a major contributor to slow gait speed (26) and may be more common in older adults with poor brain health (27).

Cerebral small vessel disease, as quantified by WMH, is common in older adults and is associated with poorer function (1,3,28). Understanding the underlying mechanisms by which older adults are able to compensate for WMH can improve our ability to design preventative and rehabilitative interventions. For example, cognitive training (29), physical exercise (30), and control of cardiovascular risk factors (31) can improve microstructural integrity of white matter tracts even among those with advanced small vessel disease. These interventions could be more aggressively targeted towards those with evidence of cerebral small vessel disease in order to prevent the functional losses that lead to loss of independence, increased morbidity, and earlier mortality.

Supplementary Material

Please visit the article online at <http://gerontologist.oxfordjournals.org/> to view supplementary material.

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Disclosure

No potential conflict of interest relevant to this article was reported.

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