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White matter hyperintensity volume and impaired mobility among older adults

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Abstract

Gait speed is associated with multiple adverse outcomes of aging. White matter hyperintensities (WMH) on magnetic resonance imaging (MRI) have been associated with gait speed, though few studies have examined changes in gait speed over time in population-based studies comprising participants from diverse cultural backgrounds. The purpose of this study was to examine the association between a decline in gait speed and total and regional WMH volumes in a community-based study of aging. Participants (n=701) in a community-based study of older adults underwent gait speed measurement via a 4-meter walk test at the time of initial enrollment and MRI at a second time interval (mean 4.7[SD=0.5] years apart). Logistic regression was used to examine the association between large WMH volume and regional WMH volume with gait speed < 0.5 m/s (abnormal speed), and a transition to abnormal gait speed. Analyses were adjusted for demographic and clinical factors. Large WMH volume was associated with a transition to abnormal gait speed between the two visits, but not after adjustment for modifiable vascular disease risk factors. In adjusted models increased frontal lobe WMH volume was not associated with a transition to abnormal gait speed.

WMH are associated with slowing of gait over time. Prevention of WMH presents a potential strategy for the prevention of gait speed decline.

Introduction

Successful aging involves a constellation of cognitive, physical, and physiological stability [1]. Multiple neurological abnormalities that emerge with aging are associated with poor outcomes, including parkinsonism and decline in mobility[2]. In the United States alone, one

of the fastest growing age groups of the population are those aged greater than 85, in whom gait abnormalities are present in close to half[3]. Decline in gait speed is a common component of many definitions of abnormal physical aging.

Gait speed, measured by tasks such as the 4 meter walk test, has been commonly used in epidemiological studies to measure gait dysfunction. Slow gait speed correlates with decline in activities of daily living and falls[4, 5], as well as independence and fitness[6], and may be particularly important for urban dwelling individuals who need to walk in busy streets or cross intersections[7]. Slow gait speed is also associated with mild cognitive impairment[8], incident vascular dementia[9], new onset stroke[10], and mortality[11]. Risk factors for abnormal gait speed include mostly risk factors for vascular disease[12-15]; white matter hyperintensities (WMH) on magnetic resonance imaging (MRI) are also commonly implicated[16-18]. Previous studies have examined cross-sectional associations where the MRI and gait speed are measured concomitantly, but few have examined the association between MRI findings and a decline in gait speed[19]. Furthermore, few studies have used quantitative volumetric methods for measuring total WMH volumes[20], or used such methods to examine the regional distribution of WMH. Lastly, few studies have included urban dwelling community cohorts, Hispanics and African Americans, and high proportions of participants over the age of 80. The current study aimed to examine whether total and regional WMH volume is associated with gait speed in a racially and ethnically diverse community cohort of older adults residing in upper Manhattan. We hypothesized that larger WMH volumes would be associated with slower gait speeds.

Methods

Participants

Participants for this study were in the Washington Heights Inwood Columbia Aging Project (WHICAP), a prospective cohort study of Medicare recipients aged 65 or older in northern Manhattan examining aging and dementia. A total of 2776 participants were initially enrolled and then followed every 18-24 months. Recruitment of the cohort has been described in detail previously [21]. Starting in 2004, participants were asked to return for high resolution magnetic resonance imaging (MRI) scans; the current analyses are focused on the subset of WHICAP participants who received MRI scans. Detailed description of the derivation of the imaging sample has been reported elsewhere. Briefly, participants were eligible for MRI scanning if they did not meet criteria for dementia at the follow-up visit previous to the planned MRI scan. Those who were enrolled in the MRI cohort were 1 year older and less likely to be women and African American versus those who did not receive MRI scans but were otherwise eligible; we found no other clinical differences between those who underwent MRI and those who did not[22]. The study received institutional ethics review and approval.

Clinical Assessments

At the initial evaluation participants underwent in-person interviews about general health and functioning, as well as a medical history. Details of vascular disease assessment have been described elsewhere[23]. A complete medical and neurological examination was carried out; a neuropsychological battery was performed and used to define mild cognitive impairment based on previously published criteria[24]. Dementia was diagnosed based on review of all the available clinical data (apart from neuroimaging results) by neuropsychologists and neurologists at a consensus conference following standard research criteria and a neuropsychological battery paradigm as previously described [24, 25].

Physical performance measures

Gait speed was assessed at two time points: at the initial enrollment period starting in 1999, and repeated when participants returned for their first MRI, beginning in 2004. Gait speed at each visit was calculated by obtaining the mean of two trials of a 4-meter straight line course.

Magnetic Resonance Imaging

MRI was performed at Columbia University on a 1.5T Philips Intera scanner. T1-weighted anatomical images (TR=20 ms, TE = 2.1 ms, FOV 240 cm, 256×160 matrix with 1.3 mm slice thickness) and T2-weighted fluid attenuated inverse recovery (FLAIR) images (TR=11,000ms, TE=144.0ms, inversion time=2800, FOV 25cm, 2 nex, 256×192 matrix with 3mm slice thickness) were acquired axially for derivation of regional WMH volume following procedures that have been previously described[26, 27]. Briefly, each subject's T1-weighted image was realigned into a standard anatomical atlas and segmented into grey matter, white matter, and cerebrospinal fluid tissue classes, which were used for brain extraction. A Gaussian curve was fit to voxel intensities on the FLAIR images and WMH seeds were defined as voxels that were above 3.0 SD of the image mean. Each seed was passed into a mean intensity-based region growing algorithm, using a 10-point connectivity scheme, which labeled adjacent voxels that fell within 5% of the mean intensity value for the seed. This process continued iteratively, such that labeled voxels were added to the image and a new seed mean was created. White matter hyperintensity volume was derived by adding the number of labeled voxels and multiplying by voxel dimensions. To derive regional volumes, frontal, temporal, parietal, and occipital lobes were defined on a standard "lobar" atlas were spatially normalized to each subject's labeled FLAIR image using the inverse transform matrix generated from the tissue class segmentation of the T1-weighted image[28]. Regions of interest were defined by a unique identification number for each region and the intersection of the labeled WMH with the anatomical label defined the regional WMH volume. Total WMH volume was defined as the summation of all frontal, parietal, temporal, and occipital volumes and then corrected for total cranial volume (TCV).

A binary definition of large WMH volume normalized for age was used as the primary exposure to define a clinically interpretable quantity of "large given the patient's age" based on previously used methods in the Framingham Offspring Study. Given the strong association between age and WMH volume, total WMH volume/TCV was regressed on age and participants with residuals that were more than one standard deviation above the expected mean were defined as having large WMH volume[29]. Regional WMH volumes were used as continuous variables given no accepted categorical definitions.

Silent brain infarcts (SBI) were defined based on previously published methods[30]. In brief, SBI were lesions greater than 3 mm in diameter with similar intensity to CSF on T1- and T2-weighted images, and separated from the circle of Willis.

Statistical methods

Population based studies have shown an association between a speed of < 0.5 m/s with several adverse health outcomes[31], while other studies have shown association between speeds of 0.4 m/s, 0.6m/s, 0.8 m/s, and a decline by 0.1 m/s with disability and mortality [31, 32]. We therefore defined the main outcomes in our study as (1) gait speed at the time of MRI of < 0.5 m/s (abnormal gait speed), and (2) transition from a gait speed of > 0.5 m/s to a speed of < 0.5 m/s between the two physical performance measures. We carried out further supplemental analyses using different categorical definitions of gait speed as the outcome including 0.4, 0.6, and 0.8 m/s, as well as for the clinically meaningful decline of 0.1 m/s. Baseline characteristics were compared between those with and without large

WMH volumes using a χ^2 statistic for categorical variables and 2-sided t-tests for continuous variables. Multivariable logistic regression models were calculated for the main independent variables: (1) large total WMH volume and (2) regional (frontal, temporal, parietal, occipital) WMH volumes. We first carried out univariate analyses (model 1), which were then followed by a model adjusting for baseline characteristics (age, race/ethnicity, sex, mild cognitive impairment or dementia, the length of time between the two physical performance measures, and the initial gait speed measure) (model 2). Additional models (model 3) were adjusted for modifiable vascular disease risk factors (model 2 plus history of clinical stroke, hypertension, diabetes and body mass index). An additional analysis controlled for risk factors that may be in the causal pathway (mediation analysis) was also carried out (model 4) including only large WMH volumes and modifiable vascular disease risk factors (clinical stroke, hypertension, diabetes and body mass index). We tested for interactions between the primary independent variables and age, sex, race/ethnicity, and education. Stratified models were planned only if the p-value for the interaction term was < 0.05 . All analyses were carried out with SAS version 9.2 (Cary, NC). Results were considered significant if the p-value was < 0.05 .

Results

Baseline demographics

A total of 701 participants had volumetric MRI data and physical performance measures available. The baseline demographics and clinical characteristics of the sample are outlined in Table 1. The mean time interval between the first physical performance measure and MRI was 4.7 years (SD=0.5), and 95% of the sample had the MRI done within 6 months of the second physical performance measure. Participants who had large total WMH volume were more likely to be African American or Hispanic, have hypertension and a clinical stroke, and be diagnosed with mild cognitive impairment; there were no differences in age or BMI. Gait speed at the time of MRI was slower in participants with large WMH volumes (0.75 m/s versus 0.86 m/s).

Association of WMH with gait speed

Table 2 outlines the results examining the associations between physical performance measures and large WMH volume. In univariate analysis there was an association between large WMH volume and abnormal gait speed at the time of MRI, which was no longer present after adjusting for demographics (model 2) and modifiable vascular disease risk factors (model 3). In model 4 however large WMH volume remained associated with abnormal gait speed. Large WMH volume on the other hand was not associated with the outcome of transition to an abnormal gait speed in adjusted models.

We examined whether regional WMH volumes were associated with abnormal gait speeds (Table 3). Frontal WMH volumes were associated with abnormal speed at the time of MRI in univariate analysis and in model 4, but not after adjusting for baseline socio-demographic factors (models 2 and 3). Similar results were noted for a transition to an abnormal gait speed.

Other regional volumes (temporal, parietal, occipital) were not associated with any of the outcomes. None of the interactions terms between large WMH volume or regional WMH volumes with age, sex, race/ethnicity, or education was statistically significant.

Association between WMH volumes and additional gait speed cut offs

In supplementary analyses we explored different gait speed cut-offs at the time of MRI, and transition to those speeds, as the outcomes. We examined the association of gait speeds of

0.4 m/s, 0.6 m/s, 0.8 m/s, and a decline by 0.1 m/s with large WMH volume, and regional WMH volumes (supplemental tables 1 and 2). Large WMH volumes were associated in univariate models and adjusted models with a transition to each cut-off in gait speed except for 0.8 m/s. Consistent findings were not found for the gait speed at the time of MRI. We found no association between large WMH volumes and a decline of gait speed of 0.1 m/s. Frontal, but not other regional volumes, were associated with gait speed cut-offs at the time of MRI, though not with a transition to each gait speed cut-off.

Association between WMH volumes and gait speed adjusted for silent brain infarcts

In univariate analyses there was a strong association between large WMH volume and SBI (OR 3.33, 95% CI 2.20-5.02). We carried out further analyses including SBI as a covariate in our final models and all of the measures of association were not appreciably different (data not shown). In addition we found no evidence of effect modification by SBI in any of our analyses (p-value for interaction terms all greater than 0.2).

Discussion

In our study of elderly ethnically diverse community dwellers we demonstrated that a large WMH volume was associated with a clinically meaningful transition to a slower gait speed. The findings remained after adjusting for socio-demographic factors and modifiable vascular disease risk factors. Our results did not appreciably change in mediation analyses, suggesting that clinical modification of vascular disease risk factors alone would unlikely influence the effect of WMH's on gait speed. The pathological basis of WMH remains poorly characterized as there are few radiological and pathological correlation studies. In small case series WMH reflect arteriolar ischemic injury, though other pathologies such as venous sclerosis or oligodendrocytic free radical damage, have also been described [33, 34]. Further research will therefore be needed to identify the pathological basis of WMH, as well as subsequent modifiable risk factors that could exist in the causal pathway with gait impairment.

Others have also found that WMH's are associated with gait speed [16, 18, 20, 33], but few have demonstrated an association with decline in gait speed over two time points. We also found that a clinically interpretable definition of large WMH volume for a given age group was associated with gait speed impairment, and in exploratory analyses we noted the strongest effect with a transition to the slowest speeds (0.4 and 0.5 m/s)[31] that are most likely to have an impact on patient outcomes. In regional volumes analyses frontal WMH volume, but not other regional volumes, was associated in univariate analyses (and marginally in adjusted models) with change in gait speed. The mechanisms by which WMH can influence gait dysfunction and balance are multi-factorial. Frontal cortical and subcortical regions, including bilateral supplemental motor cortex have been associated with motor control of the lower limbs and gait control appears to rely on bilateral signals[35, 36]. These same structures lie within the frontal white matter.

Our study has some important strengths, including the high proportion of Hispanic and African American participants, who have been underrepresented in studies on gait speed and MRI. The cohort also has one of the oldest average ages, for whom the findings regarding impaired mobility may be most relevant. Measures for multiple potential confounders were carefully recorded and adjusted for in the analyses. In our study we explored clinically significant gait speeds which may be more easily interpreted than an absolute difference in gait speed, and noted an effect in the transition to the slowest gait speeds. We included a method for quantifying regional WMH that allowed us to further examine the potential role of regionally distributed pathology on impaired gait speed.

A limitation of our study is the lack of MRI data at both time intervals when gait speed was measured. Thus, we cannot address whether an increase in WMH volumes is also associated with a decline in gait speed. The MRI was obtained at the time of the second gait speed measure, and as such we cannot comment on whether WMH caused the decline, or whether decline preceded the formation of WMH (in this case increased WMH volumes could be the marker of reduced mobility). On the other hand several investigators have shown that WMH volume remains stable or worsens, so we would expect our findings to remain or be stronger had an MRI been done during the initial enrollment. In the Cardiovascular Health Study 28% of participants were found to have worsening of their WMH grade over an average of 5 years, with the increasing appearing greater among those with initially severe WMH grades[37]. We may have been underpowered to detect more subtle associations of frontal WMH volume with abnormal gait speed. On the other hand total burden of WMH may provide more information of maintenance of gait posture, which requires integration of motor and sensory inputs from multiple cerebral locations.

Our results indicate that large total WMH volume is associated with a transition into abnormal gait speed. Given the high prevalence of WMH, the findings could have important clinical implications. Modification of risk factors for the development of WMH could lead to a greater likelihood of preserved mobility in the elderly, highlighting the importance further research on the pathological basis and risk factors for WMH. Our findings identify potential targets for future intervention trials to prevent a decline in gait speed, and support the neuroanatomical literature implicating frontal subcortical circuits in the maintenance of preserved mobility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Newman AB, et al. "Successful aging": effect of subclinical cardiovascular disease. *Arch Intern Med.* 2003; 163(19):2315–22. [PubMed: 14581251]
2. Bennett DA, et al. Prevalence of parkinsonian signs and associated mortality in a community population of older people. *N Engl J Med.* 1996; 334(2):71–6. [PubMed: 8531961]
3. Odenheimer G, et al. Comparison of neurologic changes in 'successfully aging' persons vs the total aging population. *Arch Neurol.* 1994; 51(6):573–80. [PubMed: 8198468]
4. Guralnik JM, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. *J Gerontol A Biol Sci Med Sci.* 2000; 55(4):M221–31. [PubMed: 10811152]
5. Gill TM, et al. The development of insidious disability in activities of daily living among community-living older persons. *Am J Med.* 2004; 117(7):484–91. [PubMed: 15464705]
6. Scarmeas N, et al. Physical activity, diet, and risk of Alzheimer disease. *JAMA.* 2009; 302(6):627–37. [PubMed: 19671904]
7. Hoxie RE, Rubenstein LZ. Are older pedestrians allowed enough time to cross intersections safely? *J Am Geriatr Soc.* 1994; 42(3):241–4. [PubMed: 8120306]
8. Verghese J, et al. Gait dysfunction in mild cognitive impairment syndromes. *J Am Geriatr Soc.* 2008; 56(7):1244–51. [PubMed: 18482293]

9. Verghese J, et al. Abnormality of gait as a predictor of non-Alzheimer's dementia. *N Engl J Med*. 2002; 347(22):1761–8. [PubMed: 12456852]
10. McGinn AP, et al. Walking speed and risk of incident ischemic stroke among postmenopausal women. *Stroke*. 2008; 39(4):1233–9. [PubMed: 18292379]
11. Wilson RS, et al. Progression of gait disorder and rigidity and risk of death in older persons. *Neurology*. 2002; 58(12):1815–9. [PubMed: 12084882]
12. Okoro CA, et al. Association between the metabolic syndrome and its components and gait speed among U.S. adults aged 50 years and older: a cross-sectional analysis. *BMC Public Health*. 2006; 6:282. [PubMed: 17105659]
13. Soumare A, et al. Cross-sectional association between homocysteine and motor function in the elderly. *Neurology*. 2006; 67(6):985–90. [PubMed: 17000965]
14. Volpato S, et al. Comorbidities and impairments explaining the association between diabetes and lower extremity disability: The Women's Health and Aging Study. *Diabetes Care*. 2002; 25(4): 678–83. [PubMed: 11919124]
15. Arvanitakis Z, et al. Diabetes mellitus and progression of rigidity and gait disturbance in older persons. *Neurology*. 2004; 63(6):996–1001. [PubMed: 15452289]
16. Baezner H, et al. Association of gait and balance disorders with age-related white matter changes: the LADIS study. *Neurology*. 2008; 70(12):935–42. [PubMed: 18347315]
17. Longstreth WT Jr. et al. Incidence, manifestations, and predictors of brain infarcts defined by serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2002; 33(10):2376–82. [PubMed: 12364724]
18. Longstreth WT Jr. et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. *Stroke*. 1996; 27(8):1274–82. [PubMed: 8711786]
19. Zheng JJ, et al. Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke*. 2011; 42(7):2086–90. [PubMed: 21636821]
20. Srikanth V, et al. The location of white matter lesions and gait—a voxel-based study. *Ann Neurol*. 2010; 67(2):265–9. [PubMed: 20225293]
21. Tang MX, et al. Incidence of AD in African-Americans, Caribbean Hispanics, and Caucasians in northern Manhattan. *Neurology*. 2001; 56(1):49–56. [PubMed: 11148235]
22. Brickman AM, et al. Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Arch Neurol*. 2008; 65(8):1053–61. [PubMed: 18695055]
23. Reitz C, et al. Validity of self-reported stroke in elderly African Americans, Caribbean Hispanics, and Whites. *Arch Neurol*. 2009; 66(7):834–40. [PubMed: 19433651]
24. Stern Y, et al. Diagnosis of dementia in a heterogeneous population. Development of a neuropsychological paradigm-based diagnosis of dementia and quantified correction for the effects of education. *Arch Neurol*. 1992; 49(5):453–60. [PubMed: 1580806]
25. Scarmeas N, et al. Mediterranean diet and magnetic resonance imaging-assessed cerebrovascular disease. *Ann Neurol*. 2011; 69(2):257–68. [PubMed: 21387371]
26. Brickman AM, Muraskin J, Zimmerman ME. Structural neuroimaging in Alzheimer's disease: do white matter hyperintensities matter? *Dialogues Clin Neurosci*. 2009; 11(2):181–90. [PubMed: 19585953]
27. Brickman AM, et al. Quantitative approaches for assessment of white matter hyperintensities in elderly populations. *Psychiatry Research: Neuroimaging*. 2011 In press.
28. Admiraal-Behloul F, et al. Fully automatic segmentation of white matter hyperintensities in MR images of the elderly. *Neuroimage*. 2005; 28(3):607–17. [PubMed: 16129626]
29. Massaro JM, et al. Managing and analysing data from a large-scale study on Framingham Offspring relating brain structure to cognitive function. *Stat Med*. 2004; 23(2):351–67. [PubMed: 14716734]
30. Blum S, et al. Memory after silent stroke: hippocampus and infarcts both matter. *Neurology*. 2012; 78(1):38–46. [PubMed: 22201111]
31. Studenski S, et al. Gait speed and survival in older adults. *JAMA*. 2011; 305(1):50–8. [PubMed: 21205966]

32. Schmid A, et al. Improvements in speed-based gait classifications are meaningful. *Stroke*. 2007; 38(7):2096–100. [PubMed: 17510461]
33. Baloh RW, Vinters HV. White matter lesions and disequilibrium in older people. II. Clinicopathologic correlation. *Arch Neurol*. 1995; 52(10):975–81. [PubMed: 7575225]
34. Brown WR, et al. Venous collagenosis and arteriolar tortuosity in leukoaraiosis. *J Neurol Sci*. 2002; 203-204:159–63. [PubMed: 12417376]
35. Enzinger C, et al. Brain activity changes associated with treadmill training after stroke. *Stroke*. 2009; 40(7):2460–7. [PubMed: 19461018]
36. Luft AR, et al. Treadmill exercise activates subcortical neural networks and improves walking after stroke: a randomized controlled trial. *Stroke*. 2008; 39(12):3341–50. [PubMed: 18757284]
37. Longstreth WT Jr. et al. Incidence, manifestations, and predictors of worsening white matter on serial cranial magnetic resonance imaging in the elderly: the Cardiovascular Health Study. *Stroke*. 2005; 36(1):56–61. [PubMed: 15569873]

Table 1

Baseline demographics of the Washington Heights Inwood Columbia Aging Project Magnetic Resonance Imaging (MRI) cohort with gait speed measured (n= 701)

	All sampl (n = 701)	Present large white matter hyperinte nsity volume (n = 114)	Absent large white matter hyperinte nsity volume (n = 587)	p-value for differ ence
	Mean (+/- standard deviation), or n (proportion)			
Age	80.3 (5.6)	80.1 (5.7)	80.3 (5.6)	0.6
Women	471 (67.2 %)	79 (69.3%)	392 (66.8%)	0.6
Race ethnicity [†]	Hispanic 253 (36.1 %)	38 (33.3%)	215 (36.6%)	0.0005
	Non- Hispanic black 0247 (35.2 %)	58 (50.9%)	189 (32.2%)	
	Non- Hispanic white 189 (27.0 %)	17 (14.9%)	172 (29.3%)	
Vascul ar disease risk factors	Hyperten sion 474 (67.6 %)	88 (77.2%)	386 (65.7%)	0.02
	Diabetes 158 (22.5 %)	22 (19.3%)	136 (23.2%)	0.4
	Clinical stroke 80 (11.4 %)	23 (20.2%)	57 (9.7%)	0.001
	Body Mass Index 27.5 (5.6)	27.8 (5.5)	27.4 (5.6)	0.6

	All sample (n = 701)	Present large white matter hyperinte nsity volume (n = 114)	Absent large white matter hyperinte nsity volume (n = 587)	p-value for differ ence
Mild cognitive impairment	157 (25.5 %)	33 (35.9%)	124 (23.7%)	0.01
Dementia	48 (6.9%)	12 (10.5%)	36 (6.1%)	0.09
Gait speed at time of MRI (meters/second)	0.84 (0.28)	0.75 (0.25)	0.86 (0.28)	0.03
Gait speed less than 0.5 meters/second at time of MRI	52 (7.4%)	14 (12.3%)	38 (6.5%)	0.03
Transition from gait speed >0.5 meters/second to less than 0.5 meters/second	40 (5.7%)	13 (11.4%)	27 (4.6%)	0.001

[†] Missing or other race-ethnicity (n = 12)

Table 2

Association between large total white matter hyperintensity volume and an abnormal gait speed (< 0.5 meters/second) Odds ratios (OR) calculated via logistic regression

	Model 1[*] (OR, 95% confidence interval)	Model 2^{**} (OR, 95% confidence interval)	Model 3^{***} (OR, 95% confidence interval)	Model 4(Mediation analysis)^{****} (OR, 95% confidence interval)
Gait speed < 0.5 m/s at time of MRI (N = 107)	1.96, 1.16-3.31	1.92, 0.98-3.74	1.83, 0.93-3.60	1.85, 1.08-3.16
Transition from normal gait speed (> 0.5 m/s) to abnormal gait speed (< 0.5 m/s) (N = 40)	2.67, 1.33-5.35	2.66, 1.26-5.61	2.56, 1.20-5.48	2.66, 1.30-5.42

* Univariate analysis

** Adjusted for socio-demographic factors: age, race/ethnicity, gender, mild cognitive impairment or dementia, gait speed at enrollment, and time interval between second gait assessment and MRI

*** Model 2 additionally adjusted for modifiable cardiovascular disease risk factors (clinical stroke, hypertension, diabetes, body mass index)

**** Mediation analysis: univariate analysis additionally adjusted for modifiable cardiovascular disease risk factors (clinical stroke, hypertension, diabetes, body mass index)

Table 3

Association between regional white matter hyperintensity volumes and abnormal gait speed (< 0.5 meters/second) Odds ratios (OR) calculated via logistic regression

Outcome	Regional white matter hyperintensity location	Model 1* (OR, 95% confidence interval)	Model 2** (OR, 95% confidence interval)	Model 3*** (OR, 95% confidence interval)	Model 4 (mediation analysis) (OR, 95% confidence interval)
Gait speed < 0.5 m/s at time of MRI (N = 107)	Frontal lobe	1.20, 1.10-1.30	1.06, 0.96-1.17	1.05, 0.95-1.16	1.19, 1.09-1.30
	Temporal lobe	1.07, 0.37-3.15	1.89, 0.57-6.24	2.06, 0.62-6.86	1.35, 0.46-4.01
	Parietal lobe	0.88, 0.76-1.03	0.99, 0.84-1.19	1.00, 0.84-1.19	0.87, 0.74-1.03
Transition from normal gait speed (> 0.5 m/s) to abnormal gait speed (< 0.5 m/s) (N = 40)	Frontal lobe	1.14, 1.03-1.27	1.10, 0.98-1.23	1.10, 0.98-1.22	1.14, 1.02-1.26
	Temporal lobe	1.36, 0.38-4.90	1.79, 0.50-6.45	1.84, 0.51-6.62	1.45, 0.41-5.20
	Parietal lobe	1.01, 0.84-1.22	1.01, 0.83-1.23	1.01, 0.83-1.23	1.01, 0.84-1.23

* Univariate analysis

** Adjusted for socio-demographic factors: age, race/ethnicity, gender, mild cognitive impairment or dementia, gait speed at enrollment, and time interval between second gait assessment and MRI

*** Model 2 additionally adjusted for modifiable cardiovascular disease risk factors (clinical stroke, hypertension, diabetes, body mass index)

**** Mediation analysis: univariate analysis additionally adjusted for modifiable cardiovascular disease risk factors (clinical stroke, hypertension, diabetes, body mass index)