Published in final edited form as:

Neuroepidemiology. 2018 ; 51(1-2): 57–63. doi:10.1159/000490351.

Regional Subclinical cerebrovascular disease is associated with balance in an elderly multi-ethnic population

Joshua Z Willey, MD,

Department of Neurology, Columbia University, New York NY

Yeseon P Moon, MS,

Department of Neurology, Columbia University, New York NY

Mandip S Dhamoon, MD,

Department of Neurology, Mount Sinai School of Medicine, New York NY

Erin R Kulick, MPH,

Department of Epidemiology, Columbia University, New York, NY

Ahmet Bagci, PhD,

Evelyn McKnight Brain Institute, University of Miami, Miami FL

Noam Alperin, PhD,

Evelyn McKnight Brain Institute, University of Miami, Miami FL

Ying K. Cheung, PhD,

Department of Biostatistics, Columbia University, New York, NY

Clinton B Wright, MD,

National Institutes of Health, NINDS

Ralph L Sacco, MD, and

Evelyn McKnight Brain Institute, University of Miami, Miami FL; Department of Neurology, University of Miami, Miami FL

Mitchell SV Elkind, MD

Department of Neurology, Columbia University, New York NY; Department of Epidemiology, Columbia University, New York, NY

Joshua Z Willey: jzw2@columbia.edu; Yeseon P Moon: ypm2102@columbia.edu; Mandip S Dhamoon: mandip.dhamoon@mssm.edu; Erin R Kulick: erk2140@columbia.edu; Ahmet Bagci: abagci@med.miami.edu; Noam Alperin: nalperin@med.miami.edu; Ying K. Cheung: yc632@columbia.edu; Clinton B Wright: Clinton.wright@nih.gov; Ralph L Sacco: rsacco@med.miami.edu; Mitchell SV Elkind: mse13@columbia.edu

Corresponding author: Joshua Z Willey; 710 West 168th street, New York, NY 10032; jzw2@columbia.edu.

Financial Disclosure: Dr. Willey has received royalties as an author for the American College of Physicians for MKSAP-18 and as a reviewer for Uptodate. Dr. Willey has served as a consultant for Heartware Inc (subsidiary of Medtronic). The authors report no other financial disclosures.

Author contributions:

Study concept and design: Drs. Willey, Cheung

Acquisition of Data: Drs. Willey, Bagci, Alperin, Wright

Analysis and Interpretations: Dr. Cheung, Ms. Kulick and Moon

Critical revisions of the manuscript for intellectual content: Drs. Dhamoon, Wright, Sacco, Elkind

Study Supervision: Drs. Willey, Wright, Elkind, Sacco

Abstract

Introduction—White matter hyperintensity volume (WMHV) and subclinical brain infarcts (SBI), are associated with impaired mobility but less is known about the association of WMHV in specific brain regions. We hypothesized that anterior WMHV would be associated with lower scores on the Short Physical Performance Battery (SPPB), a well-validated mobility scale.

Methods—The SPPB was measured a median of 5 years after enrollment into the Northern Manhattan MRI sub study. Volumetric distributions for WMHV in 14 brain regions as a proportion of total cranial volume were determined. Multi-variable linear regression was performed to examine the association of SBI and regional log-WMHV with the SPPB score.

Results—Among 668 participants with SPPB measurements (mean 74±9 years, 37% male and 70% Hispanic) the mean SPPB score was 8.2±2.9. Total (beta = −0.3 per SD, p=0.001), anterior periventricular (beta= −0.4 per SD, p=0.001), parietal (beta = −0.2 per SD, p=0.02) and frontal (beta=−0.3 per SD, p=0.002) WMHVs were associated with SPPB; other WMHV and SBI were not associated with the SPPB

Conclusions—WMHV, especially in the anterior cerebral regions, are associated with a lower SPPB. Prevention of subclinical cerebrovascular disease is a potential target to prevent physical decline in the elderly.

Keywords

magnetic resonance imaging; white matter hyperintensities; balance

Introduction

The contributions of cardiovascular disease risk factors and subclinical cerebrovascular disease to abnormal aging have been increasingly recognized¹. The impact of subclinical cerebrovascular disease, as demonstrated on magnetic resonance imaging (MRI) by white matter hyperintensity volumes (WMHV) and subclinical brain infarcts (SBI), on gait and balance decline has been well established². WMHV and SBI are associated with slower gait speed, poorer balance and mobility^{3,4}, and risk of falls⁵. Prevention of subclinical cerebrovascular disease therefore poses a potential therapeutic target for the prevention of abnormal physical decline.

There are several limitations to prior studies examining the association of WMHV and SBI with physical performance in aging, however. Though prior investigators have examined the association of WMHV with performance scales, such as the Tinetti scale⁶, most studies have been cross-sectional^{7,8}. Fewer studies have examined whether WMHV in certain brain regions have more impact than others on physical performance or have adjusted for important confounders such as arthritis⁹. Among prospective studies, there are few with a significant proportion of participants over the age of 75 or including a large proportion of Hispanics and African-Americans, limiting generalizability to these groups. In this study we examined the associations of cardiovascular disease risk factors and regional WMHV with a commonly obtained geriatric gait and balance scale, the Short Physical Performance Battery (SPPB), in an elderly race/ethnically diverse cohort. We hypothesized that cardiovascular

disease (CVD) risk factors, SBI, total WMHV, and specifically anterior WMHV due to the involvement of motor pathways would be associated with lower scores on the SPPB.

Methods

Recruitment and baseline evaluation of the cohort

The Northern Manhattan Study (NOMAS) (n=3298) is a population-based prospective cohort study designed to examine risk factors for CVD in diverse community cohort¹⁰. Baseline recruitment and assessment protocols are summarized in prior publications.¹¹ Leisure time physical activity (LTPA) was captured with a questionnaire adapted from the National Health Interview Survey of the National Center for Health Statistics; activity was dichotomized as any versus none¹².

An MRI sub-study recruited participants during annual follow-up to undergo a brain MRI and neuropsychological examination if they were free of clinical stroke, aged >50, and had no contraindications to MRI. Recruitment occurred from 2003 to 2008. A sample of household members of NOMAS participants (n=199) were enrolled using the same criteria from 2006-2008 to increase sample size, creating a final MRI cohort of 1,290.

MRI measurements of subclinical brain infarction, global and regional white matter hyperintensity volume

Imaging for subclinical cerebrovascular disease was performed on a 1.5T MRI system (Philips Medical Systems, Best, Netherlands) at the Hatch Research Center. Total WMHV measurement and SBI were performed as previously described¹³. The interpretation of MRI's and quantification of WMHV and SBI was performed by readers blinded to baseline assessments. A tailored protocol using tools from the FSL software package (<http://www.fmrib.ox.ac.uk/fsl>) was developed to automatically measure total WMHV and its regional distribution over 14 lobar, deep brain, and periventricular regions (4 cerebral lobes in each of the 2 hemispheres, cerebellum, brain stem and 4 periventricular regions). Steps for segmentation of hyper-intense pixels include removal of the skull region using the FSL-BET tool¹⁴ followed by a two-class segmentation of the whole brain into CSF and brain tissue region using the FSL-FAST segmentation algorithm after correction for image non-uniformity¹⁵. The mean (μ) and standard deviation (σ) of intensity values of the brain tissue voxels were derived. White matter hyperintensity voxels were then defined as voxels having intensity greater than $\mu+3.5*\sigma$. Finally, the regional WMHV were calculated, using as a reference the Montreal Neurological Institute structural atlas, by nonlinearly registering the subject images to the atlas template and then mapping the regions delineated on the atlas onto the subject images using the FSL-FNIRT tool. The periventricular regions are defined as voxels within 1 cm distance from the lateral ventricles¹⁶. Total WMHV was obtained by summation of the volumes in each of the 14 sub-regions. The reliability of the WMHV method was previously established using repeated measurements of the same subjects¹⁷.

Physical performance measurements

A mean of five years after the initial MRI, participants were invited for a follow-up visit starting in 2008. Physical performance measures were added in 2011 in the NOMAS-MRI

cohort and were performed on all participants who were returning for a second neuropsychological examination. Recruitment into the gait and balance sub-study has been previously published¹⁸. In brief we collected the SPPB by examining the following: gait speed, timed 5 chair stands, and stance (standing, semi-tandem, tandem)¹⁹. All assessments were performed by a physician with specific training in geriatric gait and balance assessments who was blinded to baseline risk factors and imaging. Gait speed was measured using a 5-meter straight space free of obstacles, and participants were given three trials to walk at their “normal pace” without the use of an assist device unless they were at high risk of falling. Participants were asked to arise and sit from a chair for a total 5 times as quickly as possible without the use of arms; participants deemed unsafe or who could not complete all 5 were coded as unable. Participants were then asked to stand without an assistive device with the feet together, and then in a semi-tandem and tandem stance for up to 10 seconds; participants unable or felt to be unsafe were coded as zero. The scoring of the SPPB is summarized in supplemental table 1. A hand dynamometer was used to measure grip strength and the mean from 3 trials was used²⁰. Participants were also asked if they had been diagnosed with osteoarthritis by a physician. Participants did not complete testing if: 1) it was medically unsafe, or 2) there was inadequate space for home-bound participants examined at home or nursing home. The study was approved by the Columbia University and University of Miami Institutional Review Boards; all participants had capacity and provided informed consent.

Statistical analysis

Baseline characteristics were summarized in proportions for categorical variables and means ($\pm$ standard deviation) for continuous variables. The primary outcome was the total SPPB and secondary outcomes were individual components of SPPB (chair stands, gait speed, tandem-semi tandem stance). The primary exposure, WMHV was calculated as a proportion of total cranial volume (TCV)(WMHV/TCV*100), and log-transformed to achieve linearity for analysis. SBI was defined as a cavitation on the FLAIR sequence of at least 3mm in size, and distinct from a vessel due to the lack of signal void on T2 sequence, and without focal neurological deficits²¹; SBI were categorized as any versus none. We performed multivariable linear regression models to examine the association of log-WMHV and SBI with total SPPB. Model 1 was adjusted for age, sex, education, insurance status, and modifiable vascular risk factors (physical activity, smoking, moderate alcohol consumption, cardiac disease, waist circumference, low density lipoprotein cholesterol, high density lipoprotein cholesterol, hypertension, and diabetes). Model 2 adjusted for grip strength and diagnosis of arthritis. Since the time between initial MRI and the SPPB varied by each individual, this time difference was taken into account in analyses as a co-variate in all models. A p-value of < 0.05 was considered significant in all our analyses. All analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Baseline demographics

The baseline characteristics of the sample are summarized in table 1. Among 668 stroke-free participants with SPPB measurements, mean age at the time of assessment was 74 ± 9 years,

37% were male and 70% Hispanic; the mean SPPB score was 8 ± 3 , interquartile range 7-10 (supplemental table S1). There were 616 participants with MRI regional WMHV and SPPB measures: mean total WMHV was 0.55 ± 0.75 cc, mean anterior WMH volume 0.18 ± 0.24 cc, and 12% of participants had SBI.

Association of baseline cardiovascular disease risk factors with SPPB

Several modifiable CVD risk factors were associated with SPPB in our cohort, including hypertension, diabetes, and waist circumference. In adjusted models, diabetes (beta = -0.5 , $p=0.04$) and waist circumference (beta per standard deviation = -0.5 , $p<0.0001$) were associated with a lower SPPB, while hypertension was associated with a paradoxically increased SPPB (beta = 0.5 , $p=0.02$). Among baseline demographics, only age was associated with the SPPB (beta per standard deviation of age = 1.0 , $p<0.0001$), while sex and race-ethnicity were not. A diagnosis of arthritis (beta = -0.4 , $p = 0.05$) and grip strength measured by dynamometry (beta per standard deviation = 0.9 , $p<0.0001$) were also associated with SPPB.

Association of total and regional WMHV with SPPB

In multi-variable models, total log-WMHV was associated with a lower SPPB (beta per SD = -0.3 , $p=0.004$), while SBI was not (beta = -0.1 , $p=0.7$) (table 1). For regional log-WMH volumes, anterior periventricular (beta per SD = -0.4 , $p=0.001$), parietal (beta per SD = -0.2 , $p=0.02$) and frontal (beta per SD = -0.3 , $p=0.002$) log-WMHV were associated with SPPB (table 2).

Association of regional WMHV with components of the SPPB

We carried out further analyses to examine whether regional WMHV was associated with individual components of the SPPB (table 2). The time to complete chair stands in seconds was associated with log-WMHV in the frontal (beta per SD = 0.5 , $p = 0.02$) and parietal lobes (beta per SD = 0.6 , $p=0.01$) but not in other regions. Gait speed in meters per second on the other hand was associated with temporal (beta per SD = -0.02 , $p=0.002$) and anterior (beta per SD = -0.02 , $p = 0.03$) log-WMHV. We found the same cerebral regions associated with categorical cut-offs of chair stands and gait speed used in SPPB scoring (supplemental table S2). The categorical scores of the balance sub-scales (0-4) were associated with frontal (beta per SD = -0.1 , $p = 0.03$) and anterior (beta per SD = $-$, $p = 0.005$) log-WMHV.

Discussion

In the NOMAS gait and balance sub-study we found that total WMHV was associated with a lower SPPB score, but that the results were mostly driven by the effect of volumes in white matter that are associated with motor control, namely frontal and anterior WMHV. The magnitude of the effect on the SPPB is equivalent to that of other predictors of a lower SPPB and falls such as arthritis and grip strength²²²³. We also found that several cardiovascular disease (CVD) risk factors were also associated with a lower SPPB, with the largest effect size for diabetes and waist circumference. As expected based on previous studies we also found that age and grip strength were the strongest predictors of the SPPB, though adjustment for both did not eliminate the association of CVD risk factors with SPPB.

The SPPB is a well-validated geriatric assessment scale that has been strongly associated with several adverse health events in the elderly including falls, fractures, and mortality²⁴. The association between subclinical cerebrovascular disease and the SPPB has been the subject of several cohort studies in the elderly⁷⁸²⁴²⁵. It is hypothesized that white matter hyperintensities and SBI may damage descending corticospinal tracts and ascending proprioceptive and sensory pathways leading to difficulty with the examination maneuvers of the SPPB⁴. Fewer studies, however, have examined regional patterns of white matter hyperintensities as they relate to balance scales such as the SPPB. We found that anterior white matter hyperintensities, which in functional studies carry motor control information²⁶, were most strongly associated with lower SPPB. Since the findings on anterior WMHV were independent of grip strength, a potential surrogate marker of sarcopenia²⁰, there is likely to be a cerebral contribution to the gait and balance as captured by the SPPB. Interestingly, in our study we found that larger anterior WMHV were associated with lower scores in the balance and gait speed components but not the chair stands. The balance and gait speed tasks in the SPPB require sensory integration of proprioceptive signals, along with feedback information from the cerebellum, to maintain posture and balance; these pathways are located in the anterior white matter and connect to the frontal lobe to create a feedback loop²⁷. Conversely, chair stands, which are independently associated with falls²⁸, were not associated with anterior WMHV. This task may require less sensory integration due to the use primarily of larger muscle groups. Chair stands were associated with frontal and parietal WMHV, the former important for generating motor commands and the latter with cognitive and visual-spatial processing which may be relevant in being able to use visual inputs to carry out the task²⁹. The results of our analysis may therefore suggest that in order to maintain balance and prevent falls, special focus during therapy interventions should be placed on motor strengthening and dynamic motor control exercises to prevent falls. Such intervention in conjunction with other modalities of therapy has already been emphasized to prevent sarcopenia and thus falls³⁰, but may also help overcome the cerebral contributions to loss of balance.

We also found that modifiable cardiovascular disease risk factors, particularly diabetes and a larger waist circumference, were associated with a lower SPPB. Our results on CVD risk factors, however, may be limited by having only a single assessment several years before the SPPB, and therefore we may be underestimating the true prevalence of the exposure. In prior studies we have found that over follow-up in the NOMAS cohort a substantial proportion of the population developed new onset diabetes³¹. On the other hand by measuring the exposures (CVD risk factors and MRI) a mean of five years before the outcome (SPPB) we have the benefit of temporality in assessing a potential causal link. The results of CVD risk factors being independent of WMHV and SBI additionally argue against a true mediation effect and suggest that, independently of any impact of cerebral ischemic injury, control of these risk factors will also prevent a decline in balance and potentially falls. A surprising finding in our study is that hypertension was independently associated with a higher SPPB score. The explanation for this finding could be several, though given the very high prevalence of hypertension in our cohort, this finding should be interpreted with caution. In our definition of hypertension we included those who are under treatment and we did not collect information on whether it was adequately controlled. It is possible that the treatment

of hypertension, which is associated with a lower prevalence of subclinical disease³³², thereby paradoxically explains our results. We have previously shown a similar phenomenon when we found a paradoxical association of LDL-C with risk of stroke which was explained after considering treatment with statins and the subsequent decline in LDL-C³³. Unfortunately we do not have repeated measures of blood pressure to be able to explore this as a possible explanation.

Our study has several strengths including a high proportion of participants who are Hispanic and non-Hispanic black, with a high proportion of cardiovascular disease risk factors, in whom there is less known about predictors of gait and balance impairment. We were also able to examine the specificity of which regions in the brain may be contributing the most to the impairment of gait and balance, which may have future therapeutic interventions in terms of understanding which components of dynamic balance control can be targeted best. Our study does have several limitations that should be noted including not capturing important confounders such as pain. We only collected one measure of both the MRI and SPPB, and additional measures showing changes in both would be more informative to establish any potential causal link. We did not collect more advanced MRI measures such as diffusion tensor imaging, tractography, or connectivity which in recent studies have been associated with gait and balance scales^{34–36}. Our sample size was smaller compared to other studies, which may have limited our ability to detect more subtle effects of SBI, as well as any statistical interactions by race-ethnicity. Residual confounding is likely in our study as NOMAS did not collect data on relevant covariates such as peripheral arterial disease, hearing, or language function. Lastly the gait and balance sub-study participants were healthy enough to return for a visit and this could represent a selection bias. On the other hand, in previous analyses we have not found significant differences between those who were enrolled in the gait and balance cohort in comparison to the rest of the MRI cohort (manuscript in press).

In summary, our study showed that WMHV, and in particular anterior WMHV, as well as cardiovascular disease risk factors are associated with a lower SPPB after 5 years. Therapeutic interventions aimed at improvement in motor control and treating cardiovascular disease have the potential to reduce the disability in aging associated with a decline in gait and balance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

All authors have contributed to the design of the study and have made meaningful contributions in the writing or editing of this manuscript. The authors report no conflicts of interest. The funding agency had no role in the design of the study or writing of this manuscript.

Funding for this study: NINDS K23 NS 073104; NINDS R01 NS 29993

Funding:

This work was supported by the National Institutes of Health (NINDS K23 073104, R01029993)

References

1. del Zoppo GJ. Aging and the neurovascular unit. *Ann N Y Acad Sci.* 2012; 1268:127–33. [published Online First: 2012/09/22]. DOI: 10.1111/j.1749-6632.2012.06686.x [PubMed: 22994231]
2. Holtzer R, Epstein N, Mahoney JR, et al. Neuroimaging of mobility in aging: a targeted review. *The journals of gerontology.* 2014; 69(11):1375–88. [pii] [published Online First: 2014/04/18]. DOI: 10.1093/gerona/glu052glu052 [PubMed: 24739495]
3. Hajjar I, Quach L, Yang F, et al. Hypertension, white matter hyperintensities, and concurrent impairments in mobility, cognition, and mood: the Cardiovascular Health Study. *Circulation.* 2011; 123(8):858–65. doi: CIRCULATIONAHA.110.978114 [pii] 10.1161/CIRCULATIONAHA.110.978114 [published Online First: 2011/02/16]. [PubMed: 21321150]
4. Zheng JJ, Delbaere K, Close JC, et al. Impact of white matter lesions on physical functioning and fall risk in older people: a systematic review. *Stroke; a journal of cerebral circulation.* 2011; 42(7):2086–90. doi: STROKEAHA.110.610360 [pii] 10.1161/STROKEAHA.110.610360 [published Online First: 2011/06/04].
5. 2001-2011: a decade of the LADIS (Leukoaraiosis And DISability) Study: what have we learned about white matter changes and small-vessel disease? *Cerebrovascular diseases (Basel, Switzerland).* 2011; 32(6):577–88. [published Online First: 2012/01/27].
6. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *Journal of the American Geriatrics Society.* 1986; 34(2):119–26. [PubMed: 3944402]
7. Baezner H, Blahak C, Poggesi A, 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]
8. Wolfson L, Wei X, Hall CB, et al. Accrual of MRI white matter abnormalities in elderly with normal and impaired mobility. *Journal of the neurological sciences.* 2005; 232(1-2):23–7. [PubMed: 15850578]
9. Blahak C, Baezner H, Pantoni L, et al. Deep frontal and periventricular age related white matter changes but not basal ganglia and infratentorial hyperintensities are associated with falls: cross sectional results from the LADIS study. *Journal of neurology, neurosurgery, and psychiatry.* 2009; 80(6):608–13.
10. Willey JZ, Moon YP, Paik MC, et al. Physical activity and risk of ischemic stroke in the Northern Manhattan Study. *Neurology.* 2009; 73(21):1774–9. [PubMed: 19933979]
11. Sacco RL, Elkind M, Boden-Albala B, et al. The protective effect of moderate alcohol consumption on ischemic stroke. *Journal of the American Medical Association.* 1999; 281(1):53–60. doi: joc81062 [pii] [published Online First: 1999/01/19]. [PubMed: 9892451]
12. Willey JZ, Paik MC, Sacco R, et al. Social Determinants of Physical Inactivity in the Northern Manhattan Study (NOMAS). *Journal of community health.* 2010
13. Willey JZ, Gardener H, Moon YP, et al. Lipid Profile Components and Subclinical Cerebrovascular Disease in the Northern Manhattan Study. *Cerebrovascular diseases (Basel Switzerland).* 2014; 37(6):423–30. doi: 000362920 [pii] 10.1159/000362920 [published Online First: 2014/07/19].
14. Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp.* 2002; 17(3):143–55. DOI: 10.1002/hbm.10062 [PubMed: 12391568]
15. Zhang Y, Brady M, Smith S. Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging.* 2001; 20(1):45–57. DOI: 10.1109/42.906424 [PubMed: 11293691]
16. DeCarli C, Fletcher E, Ramey V, et al. Anatomical mapping of white matter hyperintensities (WMH): exploring the relationships between periventricular WMH, deep WMH, and total WMH burden. *Stroke; a journal of cerebral circulation.* 2005; 36(1):50–5. DOI: 10.1161/01.STR.0000150668.58689.f2
17. Alperin N, Oliu CJ, Bagci AM, et al. Low-dose acetazolamide reverses periventricular white matter hyperintensities in iNPH. *Neurology.* 2014; 82(15):1347–51. DOI: 10.1212/WNL.0000000000000313 [PubMed: 24634454]
18. Willey JZ, Moon YP, Kulick ER, et al. Physical Inactivity Predicts Slow Gait Speed in an Elderly Multi-Ethnic Cohort Study: The Northern Manhattan Study. *Neuroepidemiology.* 2017; 49(1-2):24–30. DOI: 10.1159/000479695 [PubMed: 28810247]

19. Coppin AK, Ferrucci L, Lauretani F, et al. Low socioeconomic status and disability in old age: evidence from the InChianti study for the mediating role of physiological impairments. *The journals of gerontology*. 2006; 61(1):86–91. [PubMed: 16456198]
20. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and ageing*. 2010; 39(4):412–23. [PubMed: 20392703]
21. Prabhakaran S, Wright CB, Yoshita M, et al. Prevalence and determinants of subclinical brain infarction: the Northern Manhattan Study. *Neurology*. 2008; 70(6):425–30. [PubMed: 17898325]
22. Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *The New England journal of medicine*. 1988; 319(26):1701–7. [PubMed: 3205267]
23. Rantanen T, Guralnik JM, Foley D, et al. Midlife hand grip strength as a predictor of old age disability. *Journal of the American Medical Association*. 1999; 281(6):558–60. [PubMed: 10022113]
24. Gill TM, Gahbauer EA, Murphy TE, et al. Risk factors and precipitants of long-term disability in community mobility: a cohort study of older persons. *Annals of internal medicine*. 2012; 156(2): 131–40. 156/2/131[pii] 101059/00034819-156-2-201201170-00009[published Online First: 2012/01/18]. [PubMed: 22250144]
25. Guttmann CR, Benson R, Warfield SK, et al. White matter abnormalities in mobility-impaired older persons. *Neurology*. 2000; 54(6):1277–83. [PubMed: 10746598]
26. Srikanth V, Phan TG, Chen J, et al. The location of white matter lesions and gait—a voxel-based study. *Annals of neurology*. 2010; 67(2):265–9. [PubMed: 20225293]
27. Sudarsky L. Neurologic disorders of gait. *Current neurology and neuroscience reports*. 2001; 1(4): 350–6. [PubMed: 11898541]
28. Tinetti ME, Inouye SK, Gill TM, et al. Shared risk factors for falls, incontinence, and functional dependence. Unifying the approach to geriatric syndromes. *Journal of the American Medical Association*. 1995; 273(17):1348–53. [PubMed: 7715059]
29. Perkowski LC, Stroup-Benham CA, Markides KS, et al. Lower-extremity functioning in older Mexican Americans and its association with medical problems. *Journal of the American Geriatrics Society*. 1998; 46(4):411–8. [PubMed: 9560061]
30. Tinetti ME, Kumar C. The patient who falls: “t” always a trade-off”. *Journal of the American Medical Association*. 2010; 303(3):258–66. [PubMed: 20085954]
31. Kulick ER, Moon YP, Cheung K, et al. Racial-ethnic disparities in the association between risk factors and diabetes: The Northern Manhattan Study. *Prev Med*. 2016; 83:31–6. DOI: 10.1016/j.ypmed.2015.11.023 [PubMed: 26658025]
32. de Leeuw FE, de Groot JC, Oudkerk M, et al. Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain*. 2002; 125(Pt 4):765–72. [PubMed: 11912110]
33. Willey JZ, Xu Q, Boden-Albala B, et al. Lipid profile components and risk of ischemic stroke: the Northern Manhattan Study (NOMAS). *Archives of neurology*. 2009; 66(11):1400–6. [PubMed: 19901173]
34. de Laat KF, van Norden AG, Gons RA, et al. Diffusion tensor imaging and gait in elderly persons with cerebral small vessel disease. *Stroke; a journal of cerebral circulation*. 2011; 42(2):373–9. doi: STROKEAHA.110.596502 [pii] 10.1161/STROKEAHA.110.596502 [published Online First: 2011/01/05].
35. Kantarci K, Schwarz CG, Reid RI, et al. White matter integrity determined with diffusion tensor imaging in older adults without dementia: influence of amyloid load and neurodegeneration. *JAMA Neurol*. 2014; 71(12):1547–54. 1919069 [pii] [published Online First: 2014/10/28]. DOI: 10.1001/jamaneurol.2014.1482 [PubMed: 25347157]
36. Tian Q, Glynn NW, Erickson KI, et al. Objective measures of physical activity, white matter integrity and cognitive status in adults over age 80. *Behav Brain Res*. 2015; 284:51–7. S0166-4328(15)00062-5[pil] [published Online First: 2015/02/07]. DOI: 10.1016/j.bbr.2015.01.045 [PubMed: 25655514]

Table 1

Baseline demographics of the NOMAS gait-balance cohort and association with the total short physical performance battery

		Mean(Standard deviation) or n (proportion)	Parameter estimate (standard error)	p-value
Age		74.3 (8.6)	−0.9 (0.1)	<0.0001
Women		419 (62.7)	−0.2 (0.3)	0.4
Race-ethnicity	Hispanic	470 (70.4)	0.1 (0.3)	0.8
	Non-Hispanic black	100 (14.9)	−0.4 (0.3)	0.3
	Non-Hispanic white	85 (12.7)	Reference	Reference
Medicaid or no insurance		342 (51.2)	−0.3 (0.2)	0.2
Did not complete high school		359 (54.3)	0.2 (0.2)	0.5
Moderate alcohol use		284 (42.5)	0.3 (0.2)	0.1
Former tobacco user		242 (36.2)	−0.2 (0.2)	0.4
Cardiac disease		79 (11.8)	0.02 (0.3)	0.9
Diabetes		130 (19.5)	−0.5 (0.2)	0.04
Hypertension		447 (66.9)	0.5 (0.2)	0.02
Waist size (inches) (parameter estimate per standard deviation)		37.7 (4.7)	−0.6 (0.1)	<0.0001
Low-density lipoprotein cholesterol (mg/dl) (parameter estimate per standard deviation)		116 (36)	0.06 (0.1)	0.5
High-density lipoprotein cholesterol (mg/dl) (parameter estimate per standard deviation)		53 (16)	0.05 (0.1)	0.6
White matter hyperintensity volume (parameter estimate per standard deviation)		0.55 (0.72)	−0.3 (0.1)	0.004
Silent brain infarcts, number of participants (proportion) (parameter estimate per standard deviation)		78 (12.3)	−0.1 (0.3)	0.7
Mean grip strength (Newtons) (parameter estimate per standard deviation)		44.9 (19.9)	1.0 (0.1)	<0.0001
Arthritis		366 (54.8)	−0.4 (0.2)	0.03

Table 2

Association of regional white matter hyper-intensity volumes^{*} with the Short Physical Performance Battery total score and individual components

	Total SPPB. Parameter estimate (standard error, p-value)	Chair stands (per seconds). Parameter estimate (standard error p-value)	Gait speed (meters/second). Parameter estimate (standard error, p-value)	Balance score category (0 to 4). Parameter estimate (standard error, p-value)
Frontal	-0.3 (0.1, 0.002)	0.5 (0.2, 0.02)	-0.001 (0.008, 0.9)	-0.1 (0.05, 0.03)
Parietal	-0.2 (0.1, 0.02)	0.6 (0.2, 0.01)	-0.01 (0.008, 0.2)	-0.04 (0.05, 0.5)
Occipital	-0.003 (0.1, 0.9)	-0.1 (0.2, 0.6)	-0.001 (0.008, 0.9)	0.02 (0.05, 0.7)
Temporal	-0.1 (0.1, 0.3)	0.4 (0.2, 0.08)	-0.03 (0.009, 0.002)	-0.03 (0.05, 0.5)
Anterior white matter	-0.3 (0.1, 0.001)	0.2 (0.3, 0.5)	-0.02 (0.009, 0.03)	-0.15 (0.05, 0.005)
Posterior white matter	-0.1 (0.1, 0.2)	0.2 (0.3, 0.4)	-0.01 (0.01, 0.2)	-0.05 (0.06, 0.4)
Cerebellum	-0.7 (0.1, 0.4)	0.4 (0.2, 0.08)	-0.006 (0.008, 0.5)	-0.01 (0.05, 0.8)

^{*} log transformed, bilateral, per standard deviation