

Slowing gait and risk for cognitive impairment

The hippocampus as a shared neural substrate

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ABSTRACT

Objective: To identify the shared neuroimaging signature of gait slowing and cognitive impairment.

Methods: We assessed a cohort of older adults ($n = 175$, mean age 73 years, 57% female, 65% white) with repeated measures of gait speed over 14 years, MRI for gray matter volume (GMV) at year 10 or 11, and adjudicated cognitive status at year 14. Gait slowing was calculated by bayesian slopes corrected for intercepts, with higher values indicating faster decline. GMV was normalized to intracranial volume, with lower values indicating greater atrophy for 10 regions of interest (hippocampus, anterior and posterior cingulate, primary and supplementary motor cortices, posterior parietal lobe, middle frontal lobe, caudate, putamen, pallidum). Nonparametric correlations adjusted for demographics, comorbidities, muscle strength, and knee pain assessed associations of time to walk with GMV. Logistic regression models calculated odds ratios (ORs) of gait slowing with dementia or mild cognitive impairment with and without adjustment for GMV.

Results: Gait slowing was associated with cognitive impairment at year 14 (OR per 0.1 s/y slowing 1.47; 95% confidence interval 1.04–2.07). The right hippocampus was the only region that was related to both gait slowing ($\rho = -0.16$, $p = 0.03$) and cognitive impairment (OR 0.17, $p = 0.009$). Adjustment for right hippocampal volume attenuated the association of gait slowing with cognitive impairment by 23%.

Conclusions: The association between gait slowing and cognitive impairment is supported by a shared neural substrate that includes a smaller right hippocampus. This finding underscores the value of long-term gait slowing as an early indicator of dementia risk. **Neurology® 2017;89:336–342**

GLOSSARY

CI = confidence interval; **Health ABC** = Health Aging and Body Composition; **MCI** = mild cognitive impairment; **OR** = odds ratio; **ROI** = region of interest; **3 MS** = Modified Mini-Mental State; **WMH** = white matter hyperintensity.

Prevention and early treatment may hold the key to reducing the global burden of dementia.¹ Early detection of those most at risk will be necessary to appropriately target early treatments, but the current screening approaches are too invasive and costly to be used at a population level. Therefore, early clinical indicators of risk are needed.

Slow gait speed predicts future onset of dementia and mild cognitive impairment (MCI),^{2–6} and changes in gait may appear earlier than cognitive changes.^{7,8} Gait speed decline may occur as early as 12 years before the onset of MCI.⁹ Therefore, repeated measures of gait speed could provide an early screening tool for increased dementia risk. Gait speed declines are multifactorial in nature,¹⁰ and risk factors include age-related changes in cerebral integrity.¹¹ Slow gait speed is related to specific age-related MRI abnormalities in those without neurologic disease, including smaller volume of motor regions, prefrontal cortex, basal ganglia, and medial temporal lobe.^{11,12} Changes in gray matter regions, including the hippocampus, have been proposed as a shared underlying mechanism for declines in both cognitive and physical functioning with age.¹¹

Supplemental data
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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

We propose that gait slowing is indicative of dementia risk due to reduced cerebral integrity, possibly specific to hippocampal atrophy.

We used a well-characterized cohort of older adults with annual follow-up over 14 years to assess the associations of long-term changes in gait speed with later cognitive impairment. We then assessed how regional gray matter volumes (GMVs) were associated with both gait slowing and cognitive impairment and whether GMV attenuated the association between gait decline and cognitive impairment.

METHODS Study population. The Health Aging and Body Composition (Health ABC) study is a prospective cohort study of black and white older adults. At baseline in 1997, participants were 70 to 79 years of age and lived in Memphis, TN, or Pittsburgh, PA. Participants were recruited from designated ZIP codes by a random sample of Medicare-eligible adults. Eligibility was based on reporting no difficulties in performing activities of daily living, walking a quarter mile, or climbing 10 steps without resting. Men and black participants were oversampled.

Participants at the Pittsburgh study site were asked to participate in a neuroimaging substudy between 2006 and 2008 (year 10 or 11 of the study; figure 1). Cognitive adjudication occurred at the Pittsburgh site during the 2011 to 2012 visit (year 14 of the study). Because we wanted to look at preclinical neuroimaging markers, participants were excluded if they had a Modified Mini-Mental State (3 MS) score <85 at the time of MRI, indicating likely major cognitive impairment. The mean time between MRI and cognitive adjudication was 3.3 years (SD 0.5 years).

Of the 1,527 participants enrolled in the study in 1997 to 1998 at the Pittsburgh site, 819 were alive and were contacted to participate in the neuroimaging substudy; 315 completed it. Participants with cognitive adjudication ($n = 246$) were excluded from our analytic sample if they did not have at least 2 gait measures ($n = 1$), had no MRI data ($n = 5$), were missing ≥ 1 covariates ($n = 22$), or had a 3 MS score <85 at the time of MRI ($n = 27$). Our final analytic sample included 193 participants. There were no differences between included and excluded participants in age, sex, heart disease, diabetes mellitus, hypertension, knee pain, muscle strength, baseline gait speed, gait slope, or total GMV (all $p > 0.1$). The included individuals were more likely to be white ($p = 0.01$) and to have at least a high school education ($p = 0.0006$) compared to the excluded individuals.

Standard protocol approvals, registrations, and patient consents. This study was approved by institutional review boards of all participating institutions. All participants signed written informed consent.

Gait speed. Repeated measures of time to walk 6 m at the usual pace were collected between 2 and 9 times between 1997 to 1998 and 2011 to 2012. Changes in time to walk 6 m were computed with bayesian slopes from longitudinal mixed models with random slopes and intercepts corrected for intercepts and are reported as increases in seconds to walk per year. Slopes were calculated separately by sex. Higher values indicate a greater increase in time to walk (i.e., faster slowing of gait speed).

Cognitive impairment. Cognitive status was clinically adjudicated on Health ABC participants who were seen at the year 14 site visit in 2011 to 2012 from data collected at the year 14 and prior visits, as described elsewhere.¹³ Because of the restricted sample size, participants were categorized as cognitively normal or cognitively impaired (MCI or dementia) for these analyses.

Neuroimaging. A 3T Siemens Tim Trio magnetic resonance scanner with a Siemens 12-channel head coil was used (Siemens, Munich, Germany). Image acquisition and analysis for this study have been previously described.¹⁴ Magnetization-prepared rapid gradient echo images were acquired to obtain GMV of regions of interest (ROIs).

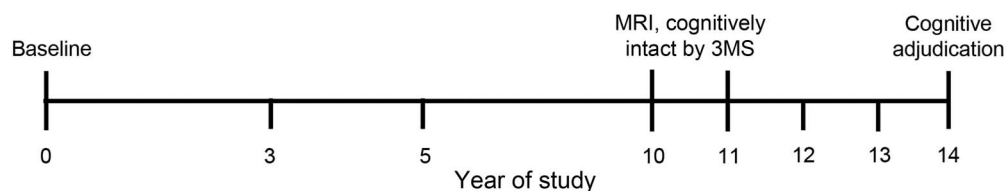
GMV was normalized to intracranial volume, with lower values indicating greater atrophy, and was assessed bilaterally for 10 prespecified ROIs on the basis of previous literature^{11,12,15} (hippocampus, anterior and posterior cingulate, primary and supplementary motor cortices, posterior parietal lobe, middle frontal lobe, caudate, putamen, and pallidum).

White matter hyperintensity (WMH) volumes were obtained from T2-weighted fluid-attenuated inversion recovery images with a semiautomated method.¹⁶ Total brain WMH volume was normalized to brain volume.

APOE genotype. APOE genotype was quantified by standard single-nucleotide polymorphism genotyping techniques and categorized as having any APOE $\epsilon 4$ alleles or no allele.

Covariates. At baseline, demographic data, including age, race, sex, and education, were self-reported. Prevalent and incident disease algorithms based both on self-report and on physician diagnoses, recorded medications, and laboratory data were used to create time-dependent comorbidity variables indicating the development of diabetes mellitus, coronary heart disease, and hypertension during the entire study period. Fall history was assessed for the past year at each annual visit. History of recurrent falls over the entire study was defined as reporting multiple falls at

Figure 1 Timeline of measures from the Health ABC



Participants in Health ABC were seen annually with gait speed measured at study years 0, 3, and 5 and annually after year 10. MRI was conducted in year 10 or 11, and participants were included in these analyses if they had a 3 MS score ≥ 85 at time of MRI. Cognitive adjudication for dementia or mild cognitive impairment occurred in year 14. Health ABC = Health Aging and Body Composition; 3 MS = Modified Mini Mental State.

least once or reporting a single fall at multiple visits. Muscle strength, measured as peak torque of quadriceps strength measured on a dynamometer (125 AP, Kin-Com, Chattanooga, TN), and self-reported joint pain at the knee were collected at the time of MRI.

Statistical analysis. Descriptive statistics comparing those who were cognitively normal and those who were cognitively impaired at the end of the study were calculated by *t* tests for continuous variables and by χ^2 statistics for categorical variables.

Associations of 5 different gait speed measures (3 single time points and 2 slopes) with cognitive impairment were assessed by logistic regression to determine which had the strongest association using odds ratios (ORs) and 95% confidence intervals (CIs). The measures included time to walk 6 m at study baseline, at the time of MRI, and at the time of cognitive adjudication, as well as the slope of time to walk during the full 14-year study period and during the last 4 years of the study between the MRI and cognitive adjudication. Of those gait measures, the one most strongly associated with cognitive impairment was then assessed in relation to GMV of the prespecified ROIs, with an emphasis on hippocampal volume. Left and right ROIs were assessed separately. Because of nonnormal distributions of some ROI GMVs, partial Spearman correlations were used to obtain

correlation coefficients (ρ) and *p* values. Associations of total GMV and ROI GMV with cognitive impairment were assessed by logistic regression. Sensitivity analyses assessed the associations separately for MCI and dementia. Analyses were repeated stratified by *APOE* $\epsilon 4$ allele status.

To determine whether differences in ROI GMV might explain the association between gait slope and cognitive impairment, GMV variables from regions associated with both gait slowing and cognitive impairment were included in logistic regression models to assess how much each GMV variable attenuated the association between gait slope and cognitive impairment. All analyses were adjusted for age, sex, race, education, coronary heart disease, diabetes mellitus, hypertension, falls, knee pain, muscle strength, and WMH. All analyses used SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS At baseline, the sample was on average 73 years old. A slight majority (57.5%) were female, and 34.2% were black (table 1). At adjudication, 104 (53.9%) had cognitive impairment. Of these, 69 (35.8%) had MCI and 35 (18.1%) had dementia. Participants with cognitive impairment were more likely to be black (41.4% vs 25.8%, *p* = 0.02) and

Table 1 Characteristics of the analytic sample by cognitive status for adults 70 to 79 years of age at baseline (n = 193)

	Total (n = 193)	Remained cognitively normal (n = 89)	Cognitively impaired (n = 104)	<i>p</i> Value
Demographics				
Baseline age, y	72.7 (2.6)	72.4 (2.4)	72.9 (2.7)	0.2
Female, n (%)	111 (57.5)	48 (53.9)	63 (60.6)	0.4
Black, n (%)	66 (34.2)	23 (25.8)	43 (41.4)	0.02
Less than high school education, n (%)	82 (42.5)	33 (37.1)	49 (47.1)	0.2
Health characteristics				
Prevalent or incident CHD, ^a n (%)	46 (23.8)	21 (23.6)	25 (24.0)	0.9
Prevalent or incident diabetes mellitus, ^a n (%)	49 (25.4)	22 (24.7)	27 (26.0)	0.8
Prevalent or incident hypertension, ^a n (%)	164 (85.0)	70 (78.7)	94 (90.4)	0.02
Knee pain at time of MRI, n (%)	92 (47.7)	41 (46.1)	51 (49.0)	0.7
Quadriceps strength at time of MRI, N·m	84.0 (31.4)	87.9 (33.3)	80.7 (29.3)	0.1
Recurrent faller, n (%)	89 (46.1)	41 (46.1)	48 (46.2)	0.9
Markers of dementia risk				
Total GMV/ICV	0.28 (0.02)	0.28 (0.02)	0.28 (0.02)	0.5
Total WMH	0.005 (0.007)	0.004 (0.006)	0.006 (0.007)	0.05
<i>APOE</i> $\epsilon 4$ carrier, n (%)	46 (25)	15 (17.7)	31 (31.3)	0.03
Gait speed measures				
Time to walk at baseline, s	4.69 (0.88)	4.59 (0.81)	4.77 (0.94)	0.2
Time to walk at MRI, s	5.87 (1.31)	5.81 (1.29)	5.91 (1.33)	0.6
Time to walk at cognitive adjudication, s	6.56 (1.61)	6.36 (1.55)	6.78 (1.67)	0.2
Last 4 y slope of walk time, s/y	0.27 (0.61)	0.11 (0.54)	0.41 (0.64)	0.001
14 y slope of walk time, s/y	0.15 (0.11)	0.13 (0.09)	0.17 (0.12)	0.004

Abbreviations: CHD = coronary heart disease; GMV = gray matter volume; ICV = intracranial volume; WMH = white matter hyperintensity.

Values are mean \pm SD when appropriate.

^aPrevalent at study baseline or incident at any time during follow-up.

to be hypertensive (90.4% vs 78.7%, $p = 0.02$) than those who were cognitively normal (table 1). Those with cognitive impairment also had higher WMH volumes than those who remained cognitively normal ($p = 0.05$; table 1). Faster gait slowing was associated with older age, presence of knee pain, lower muscle strength, lower total GMV, greater WMH volume, and being an *APOE* $\epsilon 4$ carrier (table e-1 at Neurology.org).

The mean time to walk 6 m was consistently longer (i.e., slower gait) for the cognitively impaired group during all 14 years of follow-up (figure 2), but no single time point gait measure was significantly associated with later cognitive impairment (table 1). The greatest mean differences between the 2 groups appeared during the last 4 years before cognitive adjudication (figure 2). However, the slope of gait change during the last 4 years was only weakly associated with cognitive impairment in unadjusted models (OR per 0.1-s/y slowing 1.10, 95% CI 1.04–1.17) and after adjustment for demographic and health variables (OR per 0.1-s/y slowing 1.13, 95% CI 1.05–1.22). In contrast, the slope of gait change over the full 14 years before cognitive adjudication was more strongly associated with later cognitive impairment before (OR per 0.1-s/y slowing 1.52, 95% CI 1.13–2.04) and after adjustment for demographic and health variables (OR per 0.1-s/y slowing 1.47, 95% CI 1.04–2.07). Sensitivity analyses assessed the association of gait slowing with MCI and dementia separately and found similar results for each (MCI: OR 1.45, 95% CI 0.99–2.15; dementia: OR 1.69, 95% CI 1.05–2.71).

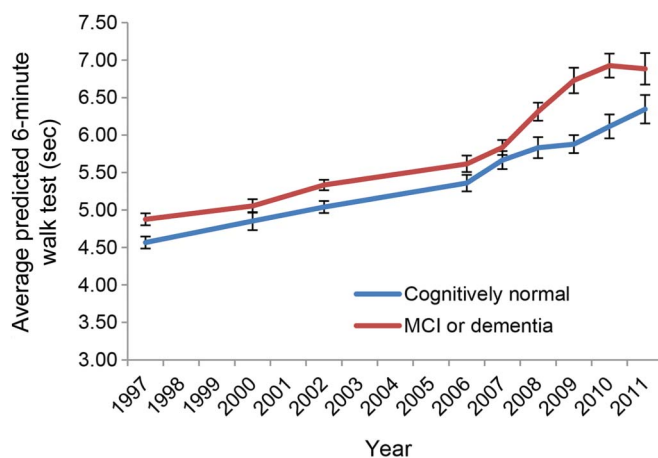
Lower total GMV was significantly associated with greater gait slowing over 14 years ($\rho = -0.18$, $p = 0.02$). Smaller right hippocampus ($\rho = -0.16$, $p = 0.03$), but not left hippocampus ($\rho = -0.03$, $p = 0.6$), was associated with faster gait slowing (table 2). A number of additional ROIs were associated with faster gait slowing in fully adjusted models (table 2), including the right anterior cingulate gyrus, bilateral caudate, and bilateral putamen (ρ range -0.17 to -0.25 , p range 0.001–0.02). Of the ROIs associated with gait slowing, only smaller volume of the right hippocampus was significantly associated with greater odds of being cognitively impaired (OR = 0.17, 95% CI 0.05–0.55; table 3) and attenuated the association between gait slowing and cognitive impairment (23% attenuation; table 3). In contrast, left hippocampal volume was also associated with cognitive impairment (OR = 0.30, 95% CI 0.11–0.83) but was not associated with gait slowing (table 2) and did not appreciably attenuate the association between gait slowing and cognitive impairment (table 3).

To assess the possible modifying role of *APOE* $\epsilon 4$ allele status, we reran analyses stratified by *APOE*. Associations between right hippocampal volume and both gait slowing and cognitive impairment were stronger in *APOE* $\epsilon 4$ allele carriers (data not shown). In models testing the association of gait slowing with cognitive impairment, there was no significant interaction between gait slowing and *APOE* status (p for interaction = 0.8).

DISCUSSION We found that a longitudinal measure of gait speed decline over 14 years predicted later cognitive impairment (adjudicated MCI or dementia) in an initially healthy sample of older adults. This association was independent of a number of demographic and health characteristics, including WMH volume. Gait speed change predicted cognitive impairment in the absence of associations for single time point gait speed measures. This association was attributable, at least in part, to differences in right hippocampal volume.

These findings support the theory that the relation between gait speed and cognitive impairment is due to a shared underlying neuropathology.¹¹ While multiple brain regions are likely implicated in both gait slowing and cognitive decline, smaller right hippocampal volume appears to be shared by both. This provides a mechanistic link between gait slowing and cognitive decline, indicating that the observed association is not just due to parallel, independent declines in the 2 domains during aging. Loss of hippocampal integrity is a well-recognized contributor to cognitive impairment. Volume of the hippocampus is implicated in cognitive decline and dementia onset,¹⁷ and hippocampal atrophy is observed in both Alzheimer

Figure 2 Mean gait speed by cognitive status over 14 years



Predicted mean time and standard errors in seconds to walk 6 m over the full 14-year follow-up of the Health ABC study for those who were cognitively normal or cognitively impaired (MCI or dementia) at adjudication in year 14. Predicted estimates come from longitudinal mixed models. Health ABC = Health Aging and Body Composition; MCI = mild cognitive impairment.

Table 2 Spearman correlations of GMV^a with gait slowing^b among adults 70 to 79 years of age at baseline (n = 193)

ROI GMV ^a	ρ (p Value)	
	Unadjusted	Adjusted ^c
Whole brain	-0.18 (0.01)	-0.18 (0.02)
Hippocampus left	-0.08 (0.3)	-0.03 (0.6)
Hippocampus right	-0.18 (0.01)	-0.16 (0.03)
Anterior cingulate left	-0.10 (0.2)	-0.11 (0.2)
Anterior cingulate right	-0.14 (0.05)	-0.17 (0.02)
Middle cingulate left	-0.07 (0.3)	-0.08 (0.3)
Middle cingulate right	-0.06 (0.4)	-0.10 (0.2)
Posterior cingulate left	0.008 (0.9)	0.09 (0.2)
Posterior cingulate right	0.01 (0.8)	0.08 (0.3)
Primary motor cortex left	-0.11 (0.1)	-0.07 (0.3)
Primary motor cortex right	-0.18 (0.01)	-0.13 (0.08)
Supplementary motor cortex left	-0.07 (0.4)	-0.06 (0.5)
Supplementary motor cortex right	-0.07 (0.3)	-0.04 (0.6)
Posterior parietal lobe left	0.04 (0.6)	0.01 (0.9)
Posterior parietal lobe right	-0.03 (0.7)	0.02 (0.8)
Middle frontal lobe left	-0.05 (0.5)	-0.07 (0.3)
Middle frontal lobe right	-0.11 (0.1)	-0.14 (0.07)
Caudate left	-0.12 (0.09)	-0.25 (0.001)
Caudate right	-0.10 (0.2)	-0.24 (0.001)
Putamen left	-0.15 (0.03)	-0.21 (0.006)
Putamen right	-0.10 (0.2)	-0.18 (0.01)
Pallidum left	-0.08 (0.3)	-0.14 (0.06)
Pallidum right	-0.006 (0.9)	-0.10 (0.2)

Abbreviations: GMV = gray matter volume; ROI = region of interest.

^aPer 0.001 mm³.

^bPer 0.1 s/y.

^cAdjusted for age, sex, race, education, coronary heart disease, diabetes mellitus, hypertension, recurrent falls, knee pain, quadriceps strength, and white matter hyperintensities; models for gait slope additionally adjusted for gait intercept.

disease¹⁷ and vascular dementia.¹⁸ Of the gray matter regions assessed previously, the hippocampus has been most consistently associated with measures indicating

Table 3 Associations of gait slowing with cognitive impairment before and after adjustment for GMVs of specified regions among adults 70 to 79 years of age at baseline (n = 193)

	Cognitive impairment, OR ^a (95% CI)	Attenuation, %
Gait slowing	1.47 (1.04-2.07)	
Gait slowing, adjusted for whole GMV	1.47 (1.03-2.08)	0
Gait slowing, adjusted for left hippocampus	1.44 (1.02-2.03)	6
Gait slowing, adjusted for right hippocampus	1.36 (0.96-1.92)	23

Abbreviations: CI = confidence interval; GMV = gray matter volume; OR = odds ratio.

^aPer 0.1-s/y change in time to walk 6 m; all models adjusted for gait intercept, age, sex, race, education, coronary heart disease, diabetes mellitus, hypertension, recurrent falls, knee pain, quadriceps strength, and white matter hyperintensities.

slower and less stable gait patterns.¹⁹⁻²⁷ Cross-sectional studies have found positive associations between gait measures and hippocampal integrity,¹⁹⁻²⁵ but 2 other studies found no association.^{15,28} The only study to assess longitudinal, concurrent changes in gait and regional GMV found that only hippocampal atrophy was associated with declines in gait speed over a mean of 30 months.²⁶ Studies that have assessed associations of gait and hippocampal integrity cross-sectionally in cognitively healthy individuals and those with MCI found more consistent associations in the healthy individuals,^{22,23} indicating that the association may be present only before the onset of cognitive impairment.

In our analyses, hypertension was significantly associated with cognitive impairment and marginally significantly associated with gait slowing. Hypertension is a known risk factor for both gait slowing and cognitive impairment and has been shown to be related to smaller hippocampal volumes.²⁹ It is possible that hypertension is a key risk factor for hippocampal volume loss leading to both gait and cognitive declines.

The majority of studies have not assessed laterality of the hippocampal association with gait. One study using an ROI approach and assessing right and left hippocampal volume separately found that only right hippocampal volume was associated with the Timed Up and Go Test in cognitively healthy individuals.²² A second study found that smaller volumes of the right, but not left, medial temporal lobe were associated with worse Timed Up and Go Test performance.²⁷ The hippocampus is involved in sensorimotor integration,³⁰ and the right side, in particular, is involved in spatial memory.^{31,32} Patients with multiple cognitive domain MCI have greater atrophy of the temporal gyrus on the right side compared to greater atrophy on the left in those with amnesic MCI.³³ This is consistent with gait speed having stronger associations with nonamnesic MCI³⁴ and vascular dementia³⁵ as opposed to amnesic MCI and Alzheimer disease. It should be noted, however, that atrophy of the right hippocampus has also been associated with Alzheimer disease.^{36,37}

Our findings underscore the importance of assessing gait speed decline over a number of years as opposed to at a single time point, consistent with previous findings.⁵ While single time point measures of gait speed can be informative,³⁸ we found that only the slope of gait speed change was associated with later cognitive impairment. We also found that gait slowing measured over 14 years was more strongly associated with cognitive impairment than gait slowing over the last 4 years of follow-up. This was despite the fact that the largest differences in gait speed seemed to appear during the last 4 years. The variability in gait speed change was also much larger during this time period, which may have reduced the strength of the association. This larger variability between individuals

may be due to the onset of declines in multiple other systems that contribute to declines in gait speed¹⁰ as participants entered their 80s.

Our study has several important limitations. Our sample was likely healthier than the average population of older adults. They had to be free of mobility disability at baseline when they were on average 73 years of age. In addition, we excluded those individuals with likely cognitive impairment based on 3 MS scores at the time of MRI when participants were in their early 80s, and they had to survive until cognitive adjudication when they were in their mid-80s. We did not distinguish between types of cognitive impairment. By mixing amnesic/Alzheimer-type impairments and nonamnesic/vascular-type impairments, we could have underestimated associations if they were specific to a particular type of cognitive impairment.³⁹ However, we did not have power to assess subtypes of cognitive impairment. Finally, we did not assess nonspeed aspects of gait. Aspects of rhythm and variability of gait may also be predictive of dementia onset² and should be further explored as early markers of dementia risk. Together, these limitations likely led to a conservative estimate of the true association between gait changes and cognitive outcomes.

The association between gait slowing and cognitive impairment is supported by a shared neural substrate that includes a smaller right hippocampus. This finding underscores the value of long-term gait slowing as an early indicator of dementia risk. Gait speed has several advantages over other early indicators of risk for cognitive impairment. It is easily measured in clinical settings and may precede detectable changes on many cognitive tests. Assessment of gait speed should be included in regular geriatric evaluations⁴⁰ to flag those to be further evaluated for dementia risk, possibly with MRI to determine hippocampal integrity. Gait speed declines could be a key component of early detection for cognitive impairment and dementia that will allow better planning, prevention, and early treatment options.

AUTHOR CONTRIBUTIONS

Andrea L. Rosso: study concept and design, analysis and interpretation of data, statistical analysis, critical revision of manuscript for intellectual content. Joe Verghese: study concept and design, interpretation of data, critical revision of manuscript for intellectual content. Andrea L. Mettì and Robert M. Boudreau: analysis and interpretation of data, statistical analysis, critical revision of manuscript for intellectual content. Howard J. Aizenstein: critical revision of manuscript for intellectual content. Stephen B. Kritchevsky, Tamara B. Harris, Kristine Yaffe, and Suzanne Satterfield: study supervision, critical revision of manuscript for intellectual content. Stephanie A. Studenski: study concept and design, interpretation of data, critical revision of manuscript for intellectual content. Caterina Rosano: study concept and design, interpretation of data, critical revision of manuscript for intellectual content, study supervision.

ACKNOWLEDGMENT

The authors acknowledge coauthor Dr. Suzanne Satterfield, who passed away before the publication of this article.

STUDY FUNDING

Health ABC was supported by National Institute on Aging contracts (N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106; National Institute on Aging grant R01-AG-028050; and National Institute of Nursing Research grant R01-NR-012459). Healthy Brain Project was supported by the National Institute on Aging (K23-AG-028966, R01-AG-029232). This research was supported in part by the Intramural Research Program of the NIH, National Institute on Aging; the University of Pittsburgh Claude D. Pepper Older Americans Independence Center P30-AG-024827-07; the NIH through grant KL2-TR000146; and the National Institute on Aging through grant K01-AG053431.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received December 6, 2016. Accepted in final form April 24, 2017.

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