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Assessing the Temporal Relationship Between Cognition and Gait: Slow Gait Predicts Cognitive Decline in the Mayo Clinic Study of Aging

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Background. The association between gait speed and cognition has been reported; however, there is limited knowledge about the temporal associations between gait slowing and cognitive decline among cognitively normal individuals.

Methods. The Mayo Clinic Study of Aging is a population-based study of Olmsted County, Minnesota, United States, residents aged 70–89 years. This analysis included 1,478 cognitively normal participants who were evaluated every 15 months with a nurse visit, neurologic evaluation, and neuropsychological testing. The neuropsychological battery used nine tests to compute domain-specific (memory, language, executive function, and visuospatial skills) and global cognitive z-scores. Timed gait speed (m/s) was assessed over 25 feet (7.6 meters) at a usual pace. Using mixed models, we examined baseline gait speed (continuous and in quartiles) as a predictor of cognitive decline and baseline cognition as a predictor of gait speed changes controlling for demographics and medical conditions.

Results. Cross-sectionally, faster gait speed was associated with better performance in memory, executive function, and global cognition. Both cognitive scores and gait speed declined over time. A faster gait speed at baseline was associated with less cognitive decline across all domain-specific and global scores. These results were slightly attenuated after excluding persons with incident mild cognitive impairment or dementia. By contrast, baseline cognition was not associated with changes in gait speed.

Conclusions. Our study suggests that slow gait precedes cognitive decline. Gait speed may be useful as a reliable, easily attainable, and noninvasive risk factor for cognitive decline.

Key Words: Gait speed—Cognition—Longitudinal—Cohort study.

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GAIT control is a complex brain process that involves the integration of motor, perceptual, and cognitive processes, including memory, attention, and executive functions (1). Although several gait parameters can be assessed with sophisticated equipment or neurologic examination, the time to walk a short distance (eg, 25 feet) at usual pace is an inexpensive, easy, noninvasive, and highly reliable measure that has been successfully utilized in many epidemiological studies (2,3). Given the complex cognitive processes involved in gait speed, it has been hypothesized that slowing could be a sensitive, early indicator of subclinical cognitive deficits among cognitively normal individuals. Indeed, several studies have shown that slow gait predicts cognitive decline (4–7) and incident dementia (8–11). Alternatively, it has also been hypothesized that cognitive changes precede or co-occur with slowing gait because gait requires intact complex integrated cognitive processes (12–17).

Notably, few investigators have assessed the temporal relationship between gait slowing and cognitive decline within the same study population. Identifying which is affected first will provide important insight into the underlying pathophysiological mechanisms and the opportunity to identify individuals at greatest risk of cognitive or physical decline. Therefore, the aims of this study were to assess (i) whether baseline gait speed was associated with changes in global and/or domain-specific cognitive decline and (ii) whether global and/or domain-specific cognitive decline was associated with changes in

gait speed among participants enrolled in the population-based Mayo Clinic Study of Aging.

Methods

Study Sample

The study design and methodology have been published in detail elsewhere (18,19). Briefly, we identified all Olmsted County, Minnesota, United States, residents aged 70–89 years on October 1, 2004, using the medical records-linkage system of the Rochester Epidemiology Project (20,21). From this sampling list, we randomly selected an age- and sex-stratified sample of 5,233 participants who were evaluated for eligibility to participate. Of the 4,398 participants considered eligible, 2,719 agreed to participate (61.8% response) in a face-to-face evaluation (n = 2,050) or via telephone (n = 669). Of the 2,050 with a face-to-face evaluation at baseline, 67 were diagnosed with dementia, 329 were diagnosed with mild cognitive impairment (MCI), and 14 had incomplete assessments (Figure 1). Thus, 1,640 cognitively normal participants were eligible for this analysis, of which 1,478 (90.1%) had complete data on both gait speed and a neuropsychological battery. Comparison of participants and nonparticipants using information obtained from the medical records-linkage system showed that nonparticipants were more likely to be older, men, and less educated; they also had greater medical comorbidity (18). Participants were re-evaluated every 15 months, blinded to previous diagnoses and data, using the same protocol until the time of death, drop out of study, or last study examination. The study was approved by the institutional review boards of the Mayo Clinic and Olmsted Medical Center. Written informed consent was obtained for all participants.

Measurements of Cognitive Function

At all visits, participants had a nurse interview, neurologic evaluation, and neuropsychological testing (18). The interview included questions about memory administered to the participant; the Clinical Dementia Rating scale (22) and the Functional Activities Questionnaire (23) were administered to an informant. The neurologic evaluation, performed by a physician, included the short test of mental status (24), a medical history review, the Unified Parkinson's Disease Rating scale (25), and a complete neurologic examination.

A psychometrist administered a neuropsychological battery that used nine tests to assess function in four domains: (i) *memory* (delayed free recall percent retention scores for Wechsler Memory Scale-Revised Logical Memory and Visual Reproduction tasks [26], and the Auditory Verbal Learning test [27]); (ii) *language* (Boston Naming test [28] and category fluency [29]); (iii) *executive function* (Trail Making test B [30] and Digit Symbol Substitution subtest from the Wechsler Adult Intelligence Scale-Revised [31]); and (iv) *visuospatial skills* (picture completion and block design [26]). The raw scores on each test were adjusted for age using normative data from the Mayo's Older American Normative Studies (27). The adjusted test scores within each domain were summed and scaled to obtain domain-specific and global z-scores (18).

Diagnostic Categories

Impairment in a cognitive domain was assessed by comparing the person's domain score with the score in normal participants from the same population. A score of ≤ 1.0 *SD* below the age-specific mean in the general population was considered possible cognitive impairment. However, a decision about impairment in a cognitive domain was not based merely on a computer algorithm but on a consensus agreement among the examining physician, nurse, and neuropsychologist, taking into account years of education, prior occupation, and visual or hearing deficits (18,19).

Participants were characterized as cognitively normal according to published criteria from normative data developed on the community (18,19). MCI was diagnosed according to the following published criteria: (i) cognitive concern by participant, informant (from Clinical Dementia Rating scale), nurse, or physician; (ii) impairment in one or more of the four cognitive domains; (iii) essentially normal functional activities (from Clinical Dementia Rating scale and Functional Activities Questionnaire); and (iv) absence of dementia (32). Dementia was diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition (33).

Measurement of Gait Speed

Gait speed was assessed over a marked distance of 25 feet (7.62 m) at a self-selected pace. The time taken to walk this distance was recorded from the first footfall at the starting point, from a standing position, to the last footfall at the finish line. Participants are instructed to walk past the finish line. The use of a cane or walker was allowed if this was normally used. Gait speed was computed as distance/time (m/s). Usual gait speed has previously been shown to be a valid and reliable indicator and predictor of physical performance and decline (2,3,34).

Covariates

Demographics (age, sex, and years of education) were assessed by interview. A medication inventory was taken at each examination and cross-checked with the medical record. Medical comorbidities (eg, diabetes, hypertension, history of stroke) and the Charlson comorbidity index were ascertained by medical record abstraction using the medical records-linkage system of the Rochester Epidemiology Project (18,19). Depressive symptoms were assessed using the Neuropsychiatric Inventory Questionnaire (35). Apolipoprotein E (APOE) E4 genotype and body mass index were determined at baseline.

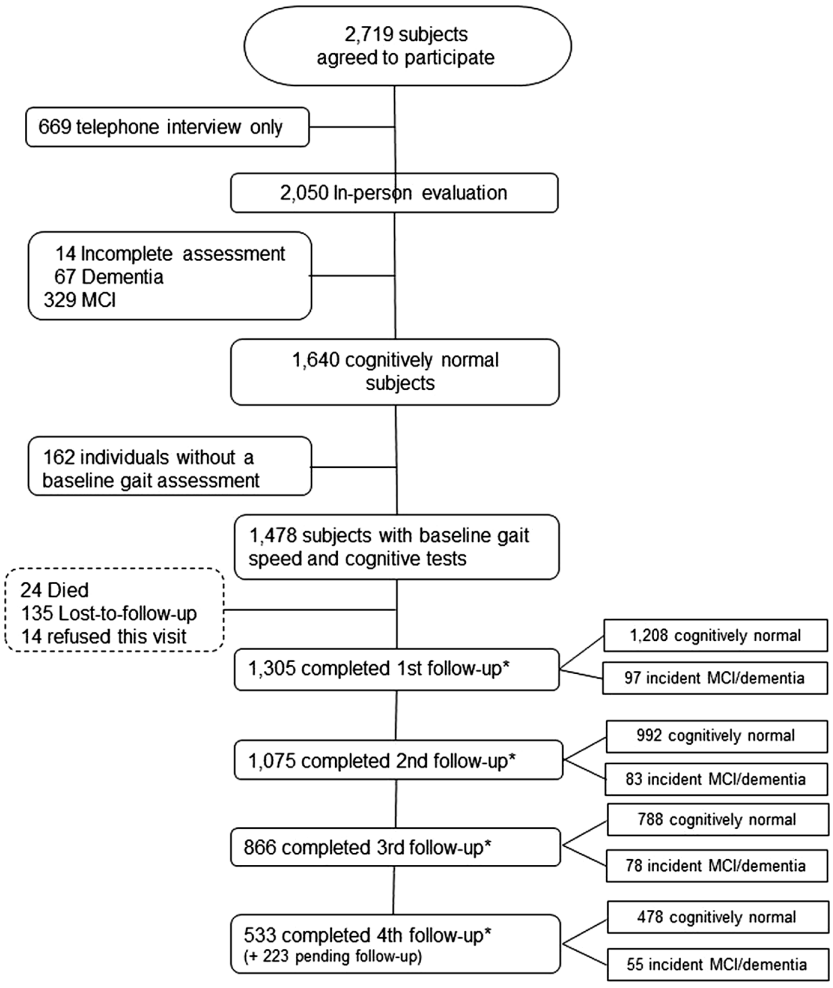

Figure 1. Flow chart of participation in the Mayo Clinic Study of Aging.

Statistical Analyses

Differences in baseline demographic and health-related characteristics between participants who did and did not have available gait speed data at baseline were examined using chi-square tests for categorical variables and Wilcoxon Rank Sum tests for continuous variables.

To determine whether gait speed predicted cognitive decline, we examined the association between baseline gait (both as a continuous variable and in quartiles) and average annual change in each domain-specific and global z-score from baseline using mixed effects models and treating participant-specific intercepts and linear change with time as random effects. This approach permitted assessment of baseline gait, a key fixed effect, on average rate of change in the global and domain-specific z-scores while accounting for the dependence of within-participant repeated measures over time. Model 1 included baseline gait (indicating the relationship between baseline gait and baseline cognitive z-score), time (indicating annual change in the cognitive z-score over the follow-up), and the interaction between gait and time (indicating whether baseline gait speed predicted change in cognition). Model 2 included variables in Model 1 plus age, sex, education, APOE E4 genotype, and the following variables measured at baseline: body mass index, depression, number of medications, and the Charlson comorbidity index. In order to understand the temporal relationship between cognition and gait, we then assessed whether baseline domain-specific and global z-scores (continuous variables and in quartiles) predicted change in gait speed using the same methods and models. As gait changes among incident MCI/dementia cases may be driving associations between gait and cognition, we repeated the previously mentioned analyses excluding participants with incident MCI/dementia.

We also conducted several sensitivity analyses. First, we controlled for specific conditions instead of the Charlson

comorbidity index including diabetes, hypertension, history of stroke, and parkinsonism. However, controlling for these individual conditions did not change the results, so we have presented the most parsimonious model, only including the Charlson comorbidity index. Second, we excluded participants with one or more of the following diagnoses: stroke, alcoholism, Parkinson's disease, subdural hemorrhage, head injury, and normal pressure hydrocephalus. However, the results of these models also did not differ from Model 2, so these results are not presented. Lastly, compared with participants with gait speed data, participants without such data had more medical comorbidities and performed worse on cognitive testing at baseline (Table 1). Therefore, in additional analyses, we also calculated imputed values for the missing gait speed data (10 times) to assess the effect of missingness on the assessed relationships. As there was little difference between the nonimputed and imputed results, only the nonimputed results are presented.

Results

The characteristics of the 1,478 cognitively normal participants with baseline gait speed and the 162 without baseline gait speed are shown in Table 1. Compared with those with baseline gait speed, those without were older and performed worse in all cognitive domains; they were also more likely to be women, hypertensive, diabetic, to have a history of a stroke and parkinsonian symptoms, have a higher Charlson comorbidity index, take more medications, and to develop incident MCI/dementia over the follow-up. Of those with gait speed, the median follow-up time was 4.1 years (interquartile range = 2.6–5.2).

Baseline Gait Is Cross-sectionally and Longitudinally Associated with Cognitive Decline

In separate linear mixed models examining gait speed as a continuous variable and each cognitive z-score, there were sizeable cross-sectional associations between faster gait speed and better domain-specific and global cognitive performance (Table 2; Model 1). Controlling for potential confounders in Model 2 slightly attenuated the cross-sectional associations but all remained significant. For example, each m/s increase in gait speed (Model 2) was cross-sectionally associated with a .467 z-score increase ($p < .0001$) in executive functioning.

Longitudinally, domain-specific and global z-scores declined over time. In mixed models examining baseline gait as a predictor of cognitive decline, a faster baseline gait speed was associated with less cognitive decline in all domains after controlling for covariates (Table 2). For example, each 1 m/s increase in gait speed at baseline was associated with a .112 higher annual executive functioning z-score ($p < .0001$).

The inclusion of 320 incident MCI/dementia cases with baseline gait speed in the previous analyses may have driven the association between gait and cognitive decline. Therefore, we repeated the previous analyses excluding these incident cases (Table 2). The cross-sectional

Table 1. Baseline Characteristics of the Cognitively Normal MCSA Participants by Presence of Gait Speed Data

Characteristics	All (n = 1,640)	With Baseline Gait Speed (n = 1,478)	Without Baseline Gait Speed (n = 162)	p
Men	810 (49.4)	762 (51.6)	48 (29.6)	<.0001
Age (y)	79.63 (75.07, 83.63)	78.81 (74.66, 82.93)	84.20 (81.92, 87.23)	<.0001
Education (y)	13 (12,16)	13 (12,16)	12 (12,16)	<.001
APOE E4 allele	346 (21.9)	320 (22.4)	26 (17.3)	.153
Hypertension	1243 (75.8)	1106 (74.8)	137 (84.6)	.006
Diabetes	284 (17.3)	245 (16.6)	39 (24.1)	.017
Stroke	160 (9.8)	133 (9.0)	27 (16.7)	.002
BMI	27.21 (24.40, 30.35)	27.22 (24.52, 30.34)	26.63 (23.24, 30.55)	.273
NPI depression	182 (11.5)	154 (10.8)	28 (18.1)	.007
Parkinsonian symptoms	373 (22.8)	295 (20.0)	78 (48.8)	<.0001
Charlson comorbidity index	3 (1,5)	3 (1,5)	4 (2,6)	<.0001
Charlson index ≥2	1147 (70.0)	1018 (68.9)	129 (79.6)	.005
Total number of medications	6 (4,9)	6 (4,9)	8 (6,11)	<.0001
Incident MCI/dementia	366 (25.2)	320 (24.2)	46 (35.7)	.004
Gait speed, m/s	1.09 (.95, 1.27)	1.09 (.95, 1.27)		
Number of visits	4 (3,5)	4 (3,5)	3 (2,4)	<.0001
Years of follow-up	4.04 (2.50, 5.14)	4.11 (2.58, 5.16)	2.63 (1.39, 4.02)	<.0001
Cognitive z-scores				
Memory	.21 (−.42,.84)	.21 (−.39,.86)	.07 (−.70,.71)	.008
Executive function	.27 (−.33,.79)	.34 (−.26,.83)	−.53 (−1.09,.07)	<.0001
Language	.22 (−.36,.77)	.26 (−.30,.82)	−.22 (−.86,.32)	<.0001
Visuospatial skills	.22 (−.46,.77)	.26 (−.38,.80)	−.35 (−1.03,.26)	<.0001
Global score	.25 (−.33,.84)	.30 (−.25,.90)	−.42 (−.98,.16)	<.0001

Notes: BMI = body mass index; IQR = interquartile ratio; MCI = mild cognitive impairment; MCSA = Mayo Clinic Study of Aging; NPI = Neuropsychiatric Inventory. Data are n (%) or median (IQR).

Table 2. Associations Between Baseline Gait Speed (m/s) and Cognitive Z-Scores Cross-sectionally and Longitudinally

	Memory Z-Score		Language Z-Score		Executive Z-Score		Visuospatial Z-Score		Global Z-Score	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
All participants (*n* = 1,478)										
Model 1†										
Baseline gait (m/s)	.462 (.088)	<.0001	.571 (.088)	<.0001	.836 (.082)	<.0001	.700 (.092)	<.0001	.787 (.085)	<.0001
Time	−.071 (.021)	.001	−.122 (.018)	<.0001	−.183 (.019)	<.0001	−.089 (.018)	<.0001	−.146 (.017)	<.0001
Baseline gait*time	.069 (.019)	<.001	.060 (.016)	<.001	.110 (.017)	<.0001	.062 (.016)	<.0001	.095 (.015)	<.0001
Model 2‡										
Baseline gait (m/s)	.255 (.094)	.007	.270 (.093)	.004	.467 (.084)	<.0001	.218 (.097)	.025	.377 (.086)	<.0001
Time	−.075 (.022)	<.001	−.123 (.019)	<.0001	−.185 (.019)	<.0001	−.090 (.018)	<.0001	−.146 (.017)	<.0001
Baseline gait*time	.074 (.020)	<.001	.062 (.017)	<.001	.112 (.017)	<.0001	.063 (.016)	<.0001	.097 (.016)	<.0001
Excluding incidence cases of MCI/dementia (*n* = 1,158)										
Model 1†										
Baseline gait (m/s)	.431 (.095)	<.0001	.464 (.096)	<.0001	.665 (.087)	<.0001	.571 (.102)	<.0001	.651 (.089)	<.0001
Time	.025 (.020)	.214	−.050 (.017)	.005	−.088 (.017)	<.0001	−.048 (.019)	.011	−.054 (.015)	<.001
Baseline gait*time	.019 (.018)	.296	.021 (.015)	.179	.058 (.015)	<.001	.040 (.016)	.015	.045 (.013)	<.001
Model 2‡										
Baseline gait (m/s)	.237 (.103)	.021	.223 (.102)	.029	.352 (.090)	<.001	.119 (.109)	.275	.266 (.092)	.004
Time	.019 (.021)	.379	−.052 (.018)	.003	−.089 (.018)	<.0001	−.050 (.019)	.009	−.059 (.015)	<.001
Baseline gait*time	.026 (.019)	.160	.023 (.016)	.136	.060 (.016)	<.001	.042 (.017)	.013	.049 (.013)	<.001

Notes: MCI, mild cognitive impairment

Baseline gait refers to the cross-sectional association between baseline gait speed and baseline cognitive performance. Time refers to the annual change in z-score for the cognitive z-score-dependent variable. The baseline gait*time variable refers to annual rate of change in the dependent cognitive variable for each m/s increase in baseline gait speed.

†Model 1 includes gait, time, and gait*time interaction.

‡Model 2 includes the same variables as Model 1 and controls for age, sex, education, APOE E4 genotype, baseline depression, baseline Charlson index, baseline number of medications, and BMI.

associations between faster gait speed and better cognitive performance remained significant after controlling for variables in Model 2, with the exception of the visuospatial z-score. Longitudinally, although there was a trend for an association between a faster baseline gait and better performance in memory (b = .026, p = .160) and language (b = .023, p = .136) z-scores over time, the results were no longer significant. However, the memory z-score did not decline over time after the exclusion of incident cases, which may have influenced the lack of association. In contrast, a faster baseline gait speed was still significantly associated with better performance over time in executive functioning (b = .060, p < .001), visuospatial (b = .042, p = .013), and global z-scores (b = .049, p < .001).

In additional analyses, we examined whether there was a dose-response association across baseline gait speed quartiles: Quartile 1 (slowest, <.85 m/s); Quartile 2 (.85–.96 m/s); Quartile 3 (.97–1.09 m/s); and Quartile 4 (fastest, >1.09 m/s). Both cross-sectional and longitudinal results suggested a dose-response relationship such that the slowest quartile was associated with the greatest reduction in each cognitive z-score (Table 3; Figure 2). However, similar to the continuous analyses, the results were attenuated after excluding the 320 incident MCI/dementia cases. Compared with the fastest quartile, the lowest quartile had annual faster z-score declines in memory (b = −.020, p = .151), language (b = −.019, p = .115), executive function (b = −.036, p = .002), visuospatial (b = −.023, p = .070), and global cognition (b = −.033, p = .001).

Baseline Cognition Does Not Predict Changes in Gait Speed

We next examined whether baseline cognition predicted change in gait speed using separate models for each cognitive z-score (Table 4). There were sizeable cross-sectional associations between gait speed and domain-specific and global z-scores. Gait speed significantly declined over time in all models. However, baseline domain-specific and global z-scores did not predict changes in gait speed in any of the models (Table 3), and there was no dose-response effect across quartiles of baseline cognitive domain scores (data not shown). Excluding individuals with incident MCI/dementia did not change the results (data not shown).

Discussion

In this population-based study of cognitively normal elderly, we observed sizeable cross-sectional associations between gait speed and cognitive performance. Longitudinally, a faster gait speed at baseline was associated with less cognitive decline across all domains, including memory, and in global cognition. After excluding incident cases of MCI/dementia, a faster gait remained

Table 3. Associations Between Baseline Gait Speed (m/s), in Quartiles, and Cognitive Z-Scores Cross-sectionally and Longitudinally (n = 1,478)

	Memory Z-Score		Language Z-Score		Executive Z-Score		Visuospatial Z-Score		Global Z-Score	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Model 1[†]										
Quartile 4 (highest)	Reference		Reference		Reference		Reference		Reference	
Quartile 3	−.203 (.061)	<.001	−.206 (.061)	<.001	−.170 (.056)	.003	−.264 (.063)	<.0001	−.263 (.058)	<.0001
Quartile 2	−.277 (.070)	<.0001	−.302 (.069)	<.0001	−.384 (.064)	<.0001	−.265 (.072)	.0002	−.397 (.066)	<.0001
Quartile 1 (slowest)	−.347 (.064)	<.0001	−.396 (.064)	<.0001	−.582 (.059)	<.0001	−.555 (.066)	<.0001	−.573 (.061)	<.0001
Time	.021 (.009)	.016	−.038 (.007)	<.0001	−.029 (.007)	.0001	−.007 (.007)	.312	−.018 (.007)	.009
Quartile 4*time	Reference		Reference		Reference		Reference		Reference	
Quartile 3*time	−.005 (.013)	.687	−.018 (.011)	.101	−.040 (.011)	<.001	−.012 (.011)	.272	−.019 (.010)	.058
Quartile 2*time	−.026 (.015)	.079	−.027 (.012)	.029	−.042 (.013)	<.001	−.026 (.012)	.029	−.035 (.012)	.003
Quartile 1*time	−.056 (.014)	<.0001	−.048 (.012)	<.0001	−.081 (.012)	<.0001	−.037 (.012)	.002	−.070 (.011)	<.0001
Model 2[‡]										
Quartile 4 (highest)	Reference		Reference		Reference		Reference		Reference	
Quartile 3	−.122 (.060)	.041	−.071 (.059)	.223	−.035 (.053)	.502	−.095 (.061)	.121	−.106 (.054)	.049
Quartile 2	−.133 (.069)	.054	−.127 (.068)	.062	−.169 (.061)	.006	−.058 (.071)	.418	−.168 (.062)	.007
Quartile 1 (slowest)	−.221 (.069)	.001	−.169 (.068)	.013	−.328 (.062)	<.0001	−.204 (.071)	.004	−.291 (.063)	<.0001
Time	.026 (.009)	.004	−.036 (.007)	<.0001	−.027 (.008)	.0003	−.006 (.007)	.379	−.015 (.007)	.032
Quartile 4*time	Reference		Reference		Reference		Reference		Reference	
Quartile 3*time	−.009 (.013)	.483	−.019 (.011)	.095	−.041 (.011)	.0003	−.013 (.011)	.225	−.021 (.010)	.048
Quartile 2*time	−.033 (.015)	.028	−.028 (.013)	.025	−.054 (.013)	<.0001	−.022 (.012)	.070	−.038 (.012)	.002
Quartile 1*time	−.059 (.014)	<.0001	−.051 (.012)	<.0001	−.082 (.012)	<.0001	−.040 (.012)	<.001	−.071 (.011)	<.0001

Notes: Quartile ranges of gait speed (m/s): Quartile 1: <.85; Quartile 2: .85–.96; Quartile 3: .97–1.09; Quartile 4: >1.09.

[†]Model 1 includes gait, time, and gait*time interaction.

[‡]Model 2 includes the same variables as Model 1 and controls for age, sex, education, APOE E4 genotype, baseline depression, baseline Charlson index, baseline number of medications, and BMI.

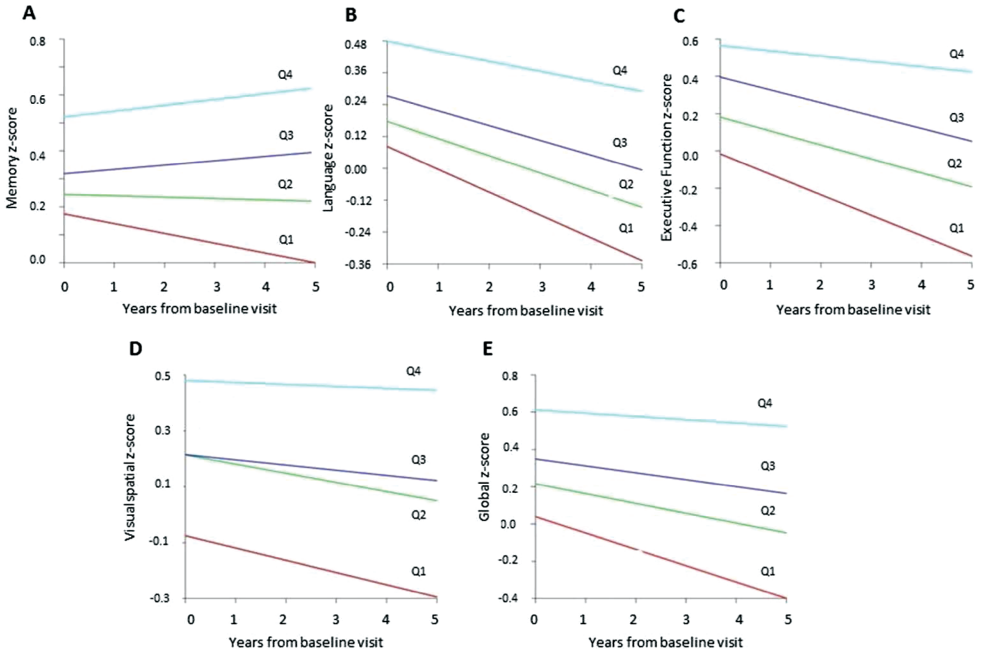

Figure 2. Slow gait speed, in quartiles, is cross-sectionally associated with worse cognitive score (see intercepts with y-axis) and longitudinally predict worse cognitive performance (see slow of trajectories over time) on composite z-scores of (**A**) memory, (**B**) language, (**C**) executive function, (**D**) visuospatial, and (**E**) global cognition. Quartile ranges of gait speed (m/s): Quartile 1 = <.85; Quartile 2 =.85–.96; Quartile 3 =.97–1.09; Quartile 4 = >1.09.

Table 4. Associations Between Baseline Cognitive Z-Score and Change in Gait Speed (m/s)

	All Participants (n = 1,478)				Excluding Incident MCI/Dementia (n = 1,158)			
	Model 1†		Model 2‡		Model 1†		Model 2‡	
	b (SE)	*p*	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Baseline memory z-score	.045 (.008)	<.0001	.026 (.007)	<.001	.045 (.009)	<.0001	.025 (.009)	.004
Time	−.029 (.002)	<.0001	−.030 (.002)	<.0001	−.026 (.002)	<.0001	−.027 (.002)	<.0001
Baseline memory*time	−.001 (.002)	.493	−.0003 (.002)	.865	−.003 (.002)	.135	−.003 (.002)	.243
Baseline language z-score	.055 (.008)	<.0001	.027 (.008)	<.001	.051 (.009)	<.0001	.026 (.009)	.003
Time	−.030 (.002)	<.0001	−.031 (.002)	<.0001	−.028 (.002)	<.0001	−.029 (.002)	<.0001
Baseline language*time	.0001 (.002)	.958	.001 (.002)	.662	−.001 (.002)	.767	−.0001 (.002)	.974
Baseline executive z-score	.085 (.008)	<.0001	.052 (.008)	<.0001	.078 (.010)	<.0001	.050 (.010)	<.0001
Time	−.031 (.002)	<.0001	−.031 (.002)	<.0001	−.029 (.002)	<.0001	−.029 (.002)	<.0001
Baseline executive*time	.002 (.002)	.417	.002 (.002)	.255	.001 (.002)	.686	.001 (.002)	.663
Baseline visuospatial z-score	.062 (.007)	<.0001	.023 (.007)	.001	.057 (.008)	<.0001	.020 (.008)	.016
Time	−.030 (.002)	<.0001	−.031 (.002)	<.0001	−.029 (.002)	<.0001	−.029 (.002)	<.0001
Baseline visuospatial*time	.001 (.002)	.448	.001 (.002)	.570	.002 (.002)	.436	.001 (.002)	.708
Baseline global z-score	.082 (.008)	<.0001	.045 (.008)	<.0001	.082 (.010)	<.0001	.045 (.010)	<.0001
Time	−.031 (.002)	<.0001	−.031 (.002)	<.0001	−.029 (.002)	<.0001	−.029 (.002)	<.0001
Baseline global z-score*time	.0004 (.002)	.835	.001 (.002)	.589	−.0004 (.002)	.869	−.0002 (.002)	.923

Notes: MCI, mild cognitive impairment.

Baseline cognitive z-score (for each domain, as listed) refers to the cross-sectional association between baseline cognitive z-score and baseline gait speed (m/s). Time refers to the annual change in gait speed (m/s). The baseline cognition*time variable refers to annual rate of change in the dependent gait speed variable for each z-score increase in the cognitive domain (or global) z-score.

†Model 1 includes baseline cognition, time, and baseline cognition*time interaction.

‡Model 2 includes the same variables as Model 1 and controls for age, sex, education, APOE E4 genotype, baseline depression, baseline Charlson index, baseline number of medications, and BMI.

significantly associated with less decline in executive function, visuospatial skills, and global cognition. However, baseline cognition did not predict changes in gait speed. These findings suggest that slow gait is a risk factor for cognitive decline.

The present results are in line with previous cross-sectional and longitudinal studies, which have reported that slow gait speed is associated with cognitive decline (4–7,14,15,36,37) and incident cognitive impairment and dementia (8–11,38). Although many of these studies

focused on change in a single test measuring global cognition (ie, Modified Mini-Mental State Examination or 3MS) (4,6,17) or executive function (ie, Digit Symbol Substitution) (37), our study utilized a comprehensive neuropsychological battery covering nine tests across four domains. We found that a slow gait was not only associated with decline in executive functioning but also in other cognitive domains.

Unlike other studies showing that cognition predicts changes in physical performance (14–17), including gait speed, we did not find such an association. One possible explanation for the discrepancy is that we only included participants who were considered cognitively normal at baseline, whereas other studies included persons who were already cognitively impaired (15). Additionally, gait speed was measured at usual pace in our study. Some studies assessing both usual and maximum pace have reported that baseline cognition is a stronger predictor of gait speed at maximum pace (15,16).

Our findings are also contrary to those reported in the only previous study that examined the temporality between gait speed and cognition in the Women's Health Initiative Memory Study clinical trial (17). The authors reported that baseline cognition predicted slowing in gait speed, but that baseline gait speed did not predict cognitive decline. However, the cognitive assessment (3MS) used in that study, on average, did not change over time and limited the ability to observe an association between baseline physical measures and cognitive decline. The association between baseline cognition and change in gait speed was borderline significant ($b = .037$, $p = .050$), and the study population was a highly educated and selected group of women enrolled in a clinical trial. Further research is needed to understand the temporal relationships between changes in gait speed and cognition at the population level.

Although we have focused on gait control as a complex brain process and its relation to cognition, gait speed may be a useful proxy for overall health and physical functioning as it places demands on several organ systems (39). Indeed, recent studies show strong associations between slow gait and mortality (40,41). Thus, it is possible that slow gait is not the sole factor predicting cognitive decline, but that other factors have an underlying role. Although we adjusted for several comorbidities at baseline, there may have been important unmeasured confounders. Moreover, this analysis focused on whether baseline gait speed could be a useful indicator of subsequent cognitive decline and thus adjusted for baseline health status. Future analyses will include time-dependent changes in health in order to better understand the temporal mechanisms involved and potential mediators and moderators of the complex relationship between gait and cognition.

Important strengths of this study include the population-based, prospective design, the comprehensive cognitive assessments, a median follow-up of 4 years, and the large sample size. These were important methodological improvements from previous studies that used only global cognitive measures, had limited assessment of cognition, or used a cross-sectional design. Measurement of gait was performed using an established, reproducible, and valid process. In addition, the medical records-linkage system of the Rochester Epidemiology Project provided a unique resource with which to assess and validate covariates and comorbidities including stroke, thereby reducing potential confounding by this and other variables (20,21).

Our study also had limitations. We assessed gait speed but not other gait parameters (eg, rhythm, stride length, and double limb support) that have been shown to predict memory decline (4). Factors which could affect gait speed, such as arthritis and limb and hip problems, were not assessed. Lastly, a single gait speed assessment may not simulate typical daily variations or effects of potential environmental factors.

In conclusion, slow gait is a risk factor for cognitive decline in this population-based study of cognitively normal elderly individuals. These results are consistent with the hypothesis that proper gait requires highly complex processes that share circuitry with cognition. Thus, slow gait could be considered a sensitive measure indicative of subclinical cognitive decline. Gait speed assessment takes little time, is inexpensive, and can be easily incorporated into the routine examination of elderly persons (42).

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Conflict of Interest

The authors declare no conflict of interest.

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