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Featured Article

Quantitative gait, cognitive decline, and incident dementia: The Rotterdam Study

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Abstract

Introduction: Poor gait has recently emerged as a potential prodromal feature of cognitive decline and dementia. We assessed to what extent various aspects of poor gait are independently associated with cognitive decline and incident dementia.

Methods: We leveraged detailed quantitative gait (GAITRite™) and cognitive assessments in 4258 dementia-free participants (median age 67 years, 55% women) of the population-based Rotterdam Study (baseline 2009–2013). We summarized 30 gait parameters into seven mutually independent gait domains and a Global Gait score. Participants underwent follow-up cognitive assessments between 2014 and 2016 and were followed up for incident dementia until 2016 (median 4 years).

Results: Three independent gait domains (Base of Support, Pace, and Rhythm) and Global Gait were associated with cognitive decline. Two independent gait domains (Pace and Variability) and Global Gait were associated with incident dementia. Associations of gait with cognitive decline and incident dementia were only present in individuals who had been cognitively unimpaired at baseline.

Discussion: Poor performance on several independent gait domains precedes cognitive decline and incident dementia.

Keywords: Gait; Cognitive decline; Dementia; Population based; Cohort study

1. Introduction

Poor gait has recently emerged as a potential prodromal feature of cognitive decline and dementia [1–3]. However, it is unclear to what extent various aspects of poor gait independently associate with cognitive decline and incident dementia.

Gait encompasses a broad array of quantifiable parameters, such as speed, stride width, or stride time. Although these parameters are to a varying extent correlated, they reflect various aspects of gait that can be summarized into mutually independent gait domains, such as Pace (which includes several parameters, including gait speed), Base of Support (stride width), Rhythm (stride time), or Variability (variability in stride time and width) [4].

Interestingly, several independent gait domains have been cross-sectionally associated with cognitive performance [5]. Also, in the Mayo Clinic Study of Aging, several gait parameters were associated with decline in global and domain-specific cognitive performance [6]. However, only one relatively small (n = 427) population-based study has published data on associations of independent gait domains with cognitive decline and dementia. In that study, worse Pace was associated with a decline in Global Cognition over a median 2-year follow-up period, while worse Variability and Rhythm were associated with incident dementia [7]. The findings of that study warrant corroboration in a larger sample with longer follow-up. They also leave the important question unanswered whether associations of

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poor gait with cognitive decline and incident dementia vary by baseline cognitive performance. Of particular interest is whether poor gait may be a determinant of cognitive decline and incident dementia in cognitively unimpaired individuals.

We hypothesized that several gait domains are independently associated with cognitive decline and incident dementia. We also hypothesized that associations of poor gait with cognitive decline and incident dementia would remain present in individuals free of cognitive dysfunction at baseline. We tested these hypotheses by leveraging detailed quantitative gait assessments, serial cognitive assessments, and follow-up for incident dementia in a large, population-based cohort.

2. Methods

The study was embedded in the Rotterdam Study, a large, prospective, population-based study in the Netherlands [8,9]. In 1990, inhabitants of the well-defined Ommoord district in the city of Rotterdam who were aged 55 years and older were invited to participate, and 7983 individuals agreed (first subcohort). In 2000, all inhabitants who had become 55 years of age and older or who moved into the study district since the start of the study were invited to be included in the Rotterdam Study, and 3011 agreed (second subcohort). The cohort was further extended in 2006 (third subcohort; age range 45 years and older) to a total of 14,926 participants (overall response 72%). Participants were subsequently invited for follow-up examinations at the research center, with a mean interval between visits of 4 years. By 2016, the first subcohort had a total of up to six visits, whereas the second subcohort had four visits, and the third subcohort had two visits.

Gait assessments were implemented into the core protocol of the Rotterdam Study in 2009. Between 2009 and 2013, 4258 participants free of dementia across the three subcohorts underwent detailed gait and cognitive assessments. We will refer to this assessment as "baseline". Between 2014 and 2016, 3253 (76%) of these participants underwent follow-up cognitive assessments. Reasons for missing data on a follow-up cognitive assessment were death (n = 208), follow-up cognitive assessment planned after current study period (n = 167), or refusal or inability (n = 697). The follow-up period for dementia was defined as the interval between baseline dementia screening at the research center and the first of the following three scenarios: diagnosis of dementia, death, or January 1, 2016. Follow-up for dementia included in-person examinations as well as continuous surveillance through electronic linkage of the study database with medical records and was 99% complete [10].

2.1. Assessment of gait

Gait was evaluated using a 5.79-m long walkway (GAITRite™ Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate). The reliability and validity of this device have been previously established [5,11–13]. The standardized gait protocol comprises three walking conditions: normal, turning, and tandem walk (Fig. 1). In the normal walk, which was repeated up to eight times, participants walked at their usual pace across the walkway. We calculated mean values across these walks, apart from the first walk, which we considered a practice walk. In turning, participants walked at

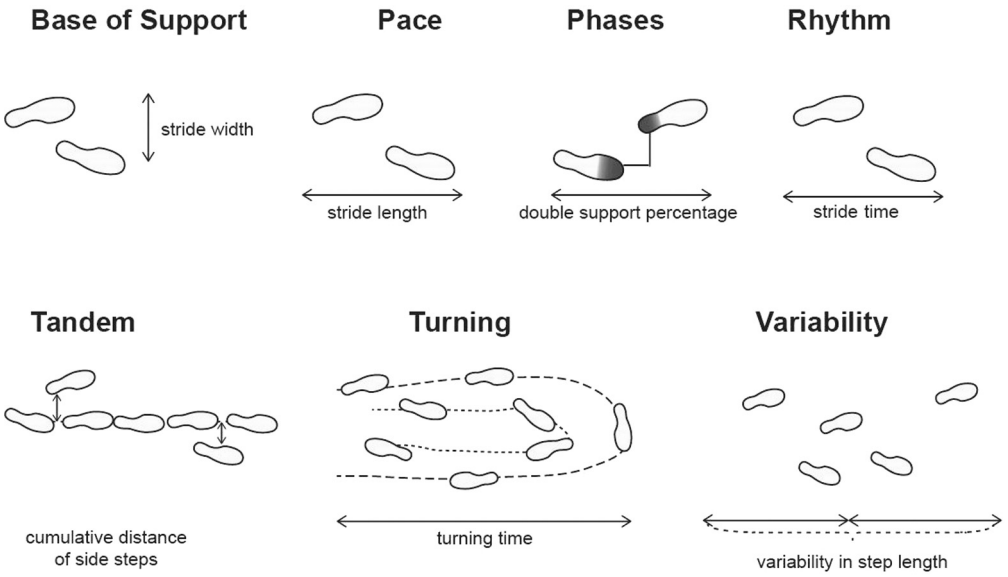

Fig. 1. Independent gait domains. To summarize gait parameters into independent domains, we performed a principal component analysis. This yielded 7 independent gait domains: Base of Support, Pace, Phases, Rhythm, Tandem, Turning, and Variability. For each gait domain, a single gait parameter that has high correlation with the domain is illustrated.

Table 1
Original gait parameters and correlating domains

Parameter	Description	Indication of "worse" gait	Correlating domain
Single support time	The time elapsed between the last contact of the opposite foot and the first contact of the next footfall of the opposite foot when a foot touches the ground	Higher	Rhythm
Swing time	The time elapsed between the last contact of the current footfall to the first contact of the next footfall on the same foot in seconds	Higher	Rhythm
Step time	The time elapsed between the first contact of one foot and the first contact of the opposite foot	Higher	Rhythm
Stride time	The elapsed time between the first contacts of two consecutive footfalls of the same foot in seconds	Higher	Rhythm
Cadence	The number of steps/minute	Lower	Rhythm
Stance time	The time elapsed between the first contact and the last contact of two consecutive footfalls on the same foot in seconds. It is initiated by heel contact and ends with the toe off of the same foot	Higher	Rhythm
Stride length SD	The standard deviation in the stride length in centimeters	Higher	Variability
Step length SD	The standard deviation in the step length in centimeters	Higher	Variability
Stride velocity SD	The standard deviation in the stride velocity (stride length/stride time) in centimeters/second	Higher	Variability
Stride time SD	The standard deviation in the stride time in seconds	Higher	Variability
Step time SD	The standard deviation in the step time in seconds	Higher	Variability
Stance time SD	The standard deviation in the stance time in seconds	Higher	Variability
Swing time SD	The standard deviation in the swing time in seconds	Higher	Variability
Single support time SD	The standard deviation in the single support time in seconds	Higher	Variability
Double support time SD	The standard deviation in the double support time in seconds	Higher	Variability
Single support (%GC)	The single support time as a percentage of the stride time	Lower	Phases
Swing (%GC)	The swing time as a percentage of the stride time	Lower	Phases
Stance (%GC)	The stance time as a percentage of the stride time	Higher	Phases
Double support (%GC)	The double support time as a percentage of the stride time	Higher	Phases
Double support time	The amount of time that two feet are on the ground at the same time within one footfall in seconds	Higher	Phases
Stride length	The distance between the heel points of two consecutive footprints of the same foot on the line of progression in centimeters	Lower	Pace
Step length	The distance between the heel points of two consecutive opposite footprints on the line of progression in centimeters	Lower	Pace
Velocity	The velocity in centimeters/second	Lower	Pace
Sum of feet surface	The sum of the surfaces of the side steps* as a percentage of the surface of a normal step	Higher	Tandem
Sum of step distance	The sum of the distances of the side steps* from the line on the walkway in centimeters	Higher	Tandem
Double step	A double step was a step with one foot, followed by a step with the same foot, where both feet were on the line of the walkway	Higher	Tandem
Turning step count	The number of steps used within the turning time	Higher	Turning
Turning time	The turning time was defined as the time between the last contact of the second foot before the first turn foot and the first contact of the second foot with a normal angle coming out of the turn. In which the first turn foot is defined as the first foot deviating from the normal angle of the feet (subject dependent)	Higher	Turning
Stride width SD	The standard deviation in the stride width in centimeters	Higher	Base of support
Stride width	The distance from heel center of one footprint to the line of progression formed by two footprints of the opposite foot in centimeters	Lower	Base of support

Abbreviations: SD, standard deviation; %GC, as a percentage of the stride time.
*A sidestep was defined as a step next to the line on the walkway, which was followed by a step with the same foot or a step with the other foot.

their usual pace, turned halfway, and returned to the starting position. In the tandem walk, participants walked heel-to-toe on a line across the walkway. Based on the recorded footfalls, the walkway software calculated 30 parameters, including 25 from the normal walk, 2 from turning, and 3 from the tandem walk. In Table 1, we provide a description of these parameters. All recordings were visually inspected.

From a clinical point of view, an individual with "poor" gait (i.e., z-score = 2 or ≥1 double step during tandem walk) may have a combination of some of the following gait characteristics: low cadence (<91 steps/min), highly variable step length (average standard deviation in step length>5 cm), high double support time (>0.4 s), low gait speed (<81 cm/s), difficulty maintaining balance while tandem walking (≥1 double step), slow turning (>4 s), or wide base (>18 cm).

2.2. Assessment of cognitive function and manual dexterity

We previously published a detailed description of our assessment methods of cognitive performance and manual dexterity [14]. We used the Stroop color word test [15], Letter Digit Substitution Test [16], Word Fluency Test [17], 15-Word List Learning Test [18], and the Purdue Pegboard

Table 2
Population characteristics

Characteristic	Population	
	Population for the dementia analysis* (N = 4258)	Population for the cognitive decline analysis† (N = 3253)
Age, years, mean (SD)	67 (9)	66 (9)
Women, N (%)	2395 (55)	1820 (56)
Higher vocational or university education, N (%)	2358 (54)	1837 (56)
Baseline Global Cognition, mean (SD)	0.0 (1.0)	+0.2 (0.9)
Baseline Global Gait, mean (SD)	0.0 (1.0)	+0.1 (0.9)

NOTE. For Global Cognition and Global Gait, higher values represent better performance.

Abbreviations: N, number; SD, standard deviation.

*Dementia follow-up comprised both in-person examinations at the research center as well as continuous surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care.

†The subgroup with serial cognitive assessments at the research center. Reasons for missing data on a follow-up cognitive assessment were death (n = 208), follow-up cognitive assessment planned after current study period (n = 167), or refusal or inability (n = 697).

Test [19]. In Supplementary Material 1, we provide a description of each test.

2.3. Assessment of dementia

A detailed description of assessment methods has previously been published [20]. In short, participants were screened for dementia at baseline and subsequent center visits with the Mini-Mental State Examination and the Geriatric Mental Schedule organic level. Those with a Mini-Mental State Examination score <26 or Geriatric Mental Schedule score >0 underwent further investigation and informant interview, including the Cambridge Examination for Mental Disorders of the Elderly. In addition, the entire cohort was continuously under surveillance for dementia through electronic linkage of the study database with medical records from general practitioners and the regional institute for outpatient mental health care. This provided detailed information and was used for diagnosis of dementia and for accurately determining time of diagnosis. Available information on clinical neuroimaging was used if required for diagnosis of dementia subtype.

A consensus panel led by a consultant neurologist established the final diagnosis according to standard criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, Third Edition–Revised) and Alzheimer's disease (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association).

2.4. Statistical analysis

A detailed description is available in Supplementary Material 2.

3. Results

The average age in the study population at baseline was 67 years, 55% of study participants were women, and just over half of the study population attained a higher vocational or university education (Table 2). The average age was somewhat lower in the subgroup with two cognitive assessments, whereas the proportion with higher vocational or university education and baseline Global Cognition and Global Gait scores were somewhat higher than in the total study population (Table 2). Compared to individuals with complete data on all walks, individuals who did not complete baseline tandem walk, turning walk, or one or two cognitive tasks were generally older (mean age 75.7 vs. 66.3 years), more commonly female (60.5% vs. 54.7%), and less commonly highly educated (44.1% vs. 55.6%).

3.1. Baseline gait and cognitive decline

A total of 3253 participants underwent follow-up cognitive assessments after a median interval (between cognitive assessments) of 5 years. Of all 30 measured original gait parameters, 20 were nominally associated with decline in Global Cognition, including 13 that survived multiple hypothesis testing (Supplementary Material 3).

Of the seven independent gait domains, Pace ([regression coefficient standardized by baseline gait and cognitive scores] $\beta = 0.06$; 95% confidence interval [0.04; 0.09]; $P < .001$), Base of Support ($\beta = 0.03$ [0.01; 0.05]; $P = .003$), and Rhythm ($\beta = 0.02$ [0.00; 0.04]; $P = .02$) were associated with decline in Global Cognition (Fig. 2). Pace was associated with a decline in each cognitive test except the Word Learning Test recognition task, and Pace was most distinctly associated with decline in the Word Fluency Test ($\beta = 0.09$ [0.06; 0.11]; $P < .001$) and Word Learning Test immediate recall task ($\beta = 0.09$ [0.06; 0.11]; $P < .001$). Base of Support was associated with decline in the Stroop interference ($\beta = 0.05$ [0.02; 0.07]; $P < .001$) and naming task ($\beta = 0.03$; [0.00; 0.05]; $P = .03$). Rhythm was associated with decline in the Stroop interference task ($\beta = 0.03$; [0.00; 0.05]; $P = .04$) and Word Fluency Test ($\beta = 0.03$; [0.01; 0.06]; $P = .01$). Variability was

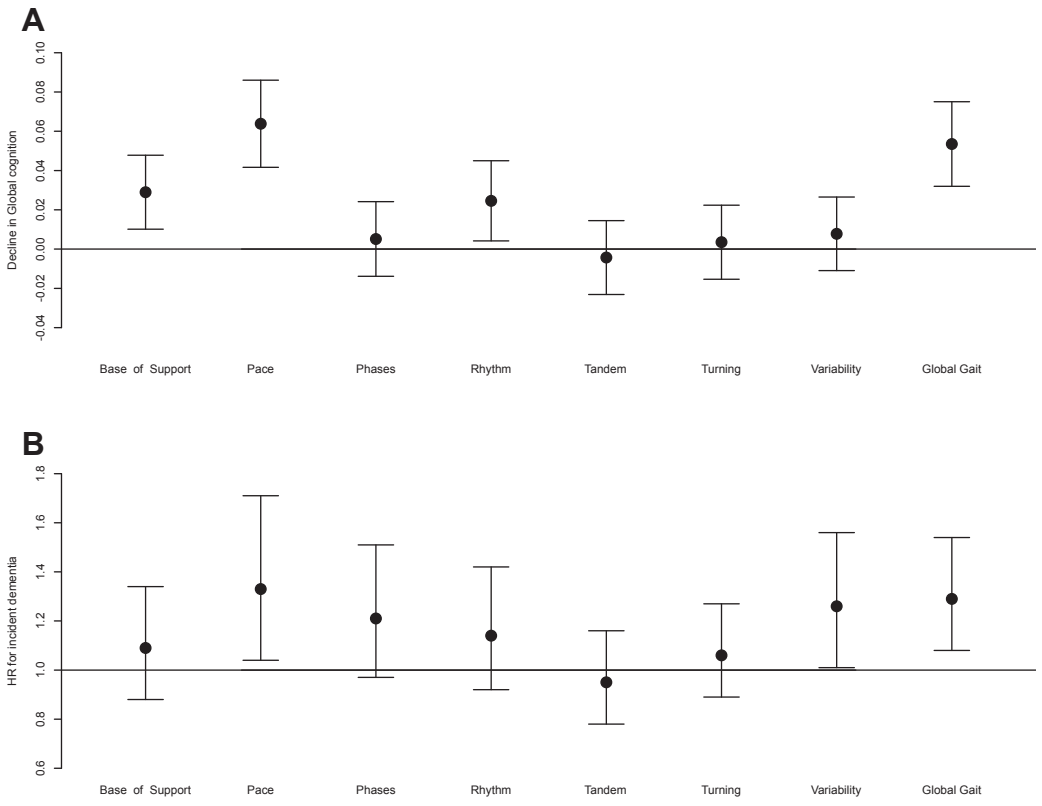

Fig. 2. Baseline gait domains: associations with subsequent decline in Global Cognition and incident dementia. (A) Association of baseline independent gait domains with subsequent decline in Global Cognition. For all gait domains, higher scores correspond with worse gait. Dots represent regression coefficients standardized by baseline gait and cognitive scores, bars indicate 95% confidence intervals. Regression coefficients were standardized by baseline gait and cognitive scores. Analyses were adjusted for age, sex, and education. The illustrated regression coefficients, 95% confidence intervals, and *P* values for Global Cognition are Base of Support (β = 0.03 [0.01; 0.05]; *P* = .003), Pace (β = 0.06; [0.04; 0.09]; *P* < .001), Phases (β = 0.01 [−0.01; 0.02]; *P* = .595), Rhythm (β = 0.02 [0.00; 0.04]; *P* = .02), Tandem (β = 0.00 [−0.02; 0.01]; *P* = .654), Turning (β = 0.00 [−0.02; 0.02]; *P* = .716), Variability (β = 0.01 [−0.01; 0.03]; *P* = .415), Global Gait (β = 0.05 [0.03; 0.08]; *P* < .001). (B) Association of independent gait domains with incident dementia. For all gait domains, higher scores correspond with worse gait. HR, hazard ratio per standard deviation "worse" gait. Dots represent hazard ratio, bars represent 95% confidence interval. Analyses were adjusted for age, sex, and education. The illustrated hazard ratios, 95% confidence intervals and *P* values for dementia are Base of Support (HR = 1.09 [0.88; 1.34]; *P* = .44), Pace (HR = 1.33 [1.04; 1.71]; *P* = .02), Phases (HR = 1.21 [0.97; 1.51]; *P* = .09), Rhythm (HR = 1.14 [0.92; 1.42]; *P* = .22), Tandem (HR = 0.95 [0.78; 1.16]; *P* = .60), Turning (HR = 1.06 [0.89; 1.27]; *P* = .50), Variability (HR = 1.26 [1.01; 1.56]; *P* = .04), Global Gait (HR = 1.29 [1.08; 1.54]; *P* = .006).

associated with decline in the Stroop naming (β = 0.03; [0.00; 0.05]; *P* = .02), color (β = 0.04 [0.02; 0.06]; *P* < .001), and interference (β = 0.03; [0.00; 0.05]; *P* = .03) tasks.

Global Gait was also associated with subsequent decline in Global Cognition (β = 0.06 [0.03; 0.08]; *P* < .001). Baseline Global Gait was statistically significantly associated with decline in each cognitive test apart from the Word Learning Test delayed recall task, and the most distinct effect estimate was for the association with decline in Stroop interference task score (β = 0.09; [0.06; 0.12]; *P* < .001, Table 3). After additional adjustment of the association between Global Gait and longitudinal change in the Stroop interference task for Stroop naming and color task test scores, the association only marginally attenuated (β = 0.08 [0.05; 0.10]; *P* < .001).

3.2. Baseline gait and incident dementia

During follow-up (median 4 years; range 1-6 years), 78 individuals were diagnosed with incident dementia, including 64 (82%) with Alzheimer's disease. Twenty-three original gait parameters were nominally associated with incident dementia; of these, 4 associations survived the multiple hypothesis-adjusted statistical significance threshold (Supplementary Material 3), including gait speed (hazard ratio [HR] = 1.49 [1.19; 1.86]; [*P* = .001]). Of the independent gait domains, Pace (HR = 1.33 [1.04; 1.71]; *P* = .02) and Variability (HR = 1.26 [1.01; 1.56]; *P* = .04) were associated with incident dementia. We also observed a suggestive, albeit not statistically significant association of Phases with incident dementia (HR = 1.21 [0.97; 1.51]; *P* = .09) (Fig. 2). One standard deviation decrease in Global

Table 3
Baseline gait domains: associations with subsequent decline in cognitive test score

Decline in cognitive test score	Baseline gait domain: Base of Support	Pace	Phases	Rhythm	Tandem	Turning	Variability	Global Gait
Letter-Digit Substitution Test	0.02 [0.00; 0.04]	0.04 [0.02; 0.06]	0.01 [-0.01; 0.03]	0.02 [-0.01; 0.04]	0.01 [-0.01; 0.03]	0.00 [-0.02; 0.02]	0.02 [0.00; 0.03]	0.05 [0.03; 0.07]
Stroop naming task	0.03 [0.00; 0.05]	0.08 [0.05; 0.11]	-0.01 [-0.04; 0.01]	0.02 [-0.01; 0.05]	0.01 [-0.02; 0.03]	0.01 [-0.01; 0.04]	0.03 [0.00; 0.05]	0.07 [0.04; 0.10]
Stroop color task	0.01 [-0.01; 0.03]	0.06 [0.03; 0.08]	0.00 [-0.02; 0.02]	0.01 [-0.02; 0.03]	-0.01 [-0.03; 0.01]	-0.02 [-0.04; 0.01]	0.04 [0.02; 0.06]	0.04 [0.01; 0.06]
Stroop interference task	0.05 [0.02; 0.07]	0.08 [0.06; 0.11]	0.00 [-0.02; 0.03]	0.03 [0.00; 0.05]	0.01 [-0.02; 0.03]	0.02 [0.00; 0.05]	0.03 [0.00; 0.05]	0.09 [0.06; 0.12]
Word Fluency Task	0.02 [0.00; 0.05]	0.09 [0.06; 0.11]	0.00 [-0.02; 0.02]	0.03 [0.01; 0.06]	0.00 [-0.03; 0.02]	-0.01 [-0.03; 0.02]	0.01 [-0.02; 0.03]	0.05 [0.02; 0.08]
Word Learning Test -delayed recall task	0.01 [-0.02; 0.04]	0.05 [0.02; 0.08]	-0.02 [-0.04; 0.01]	0.02 [-0.01; 0.05]	0.00 [-0.03; 0.02]	-0.01 [-0.03; 0.02]	0.01 [-0.02; 0.04]	0.03 [-0.01; 0.06]
Word Learning Test -immediate recall task	0.03 [0.00; 0.05]	0.09 [0.06; 0.13]	0.00 [-0.03; 0.03]	0.03 [0.00; 0.06]	0.00 [-0.03; 0.03]	0.01 [-0.02; 0.04]	-0.01 [-0.03; 0.02]	0.06 [0.03; 0.09]
Word Learning Test -recognition task	0.02 [-0.01; 0.05]	0.03 [-0.01; 0.06]	0.00 [-0.03; 0.03]	0.03 [0.00; 0.06]	0.00 [-0.03; 0.03]	0.00 [-0.03; 0.03]	0.02 [-0.01; 0.05]	0.04 [0.01; 0.07]
Global Cognition	0.02 [0.00; 0.04]	0.04 [0.02; 0.06]	0.01 [-0.01; 0.03]	0.02 [-0.01; 0.04]	0.01 [-0.01; 0.03]	0.00 [-0.02; 0.02]	0.02 [0.00; 0.03]	0.05 [0.03; 0.07]

NOTE. The presented values are regression coefficients of the association between gait domains and change in cognitive performance, standardized by baseline gait and cognitive scores. We modeled change by using the follow-up value of the cognitive outcome as dependent variable while adjusting for its baseline value. Positive correlation coefficients indicate that poor baseline gait correlated with decline in cognitive performance. We inverted Stroop test scores to facilitate a consistent interpretation of scores across cognitive tests, that is, that a higher score indicates better cognitive performance. Multiple hypothesis-adjusted statistical significance threshold was set to $P = .004$.

Color indicates P value of the association:

Statistical significance of the association				
Multiple hypothesis-adjusted		*Nominal*		*None*
<0.001	<0.004	<0.01	<0.05	≥0.05

Gait was associated with a 29% increased hazard of developing dementia (HR = 1.29 [1.08; 1.54]; $P = .006$).

3.3. Effect modification by baseline cognitive performance

The association between Global Gait and decline in Global Cognition varied substantially by baseline cognitive performance (p for interaction = 0.04). In analyses stratified by baseline cognitive dysfunction, the association of Global Gait with decline in Global Cognition was apparent in individuals without baseline cognitive dysfunction ($\beta = 0.05$ [0.02; 0.07]; $P < .001$) but not in individuals with baseline cognitive dysfunction ($\beta = 0.03$ [−0.03; 0.09]; $P = .38$). We observed suggestive, yet not statistically significant effect modification by sex regarding the association between Global Gait and decline in Global Cognition ($P = .06$), with a higher effect estimate in men ($\beta = 0.10$ [0.07; 0.13]; $P < .001$) compared to women ($\beta = 0.03$ [0.01; 0.06]; $P = .02$). We did not observe evidence for effect modification of the association between Global Gait and decline in Global Cognition by age ($P = .37$).

In line with the present effect modification on the association between Global Gait and Global Cognition, the association between Global Gait and incident dementia also varied substantially by baseline cognitive performance (p for interaction = 0.008). In analyses stratified by baseline cognitive dysfunction, we only observed an association of Global Gait with incident dementia in individuals without baseline cognitive dysfunction (HR = 1.28 [0.96; 1.69]; $P = .09$), which was not apparent in individuals with baseline cognitive dysfunction (HR = 1.03 [0.80; 1.33]; $P = .82$). We observed no statistically significant effect modification of the association between Global Gait and incident dementia by age ($P = .44$) or sex ($P = .46$).

3.4. Sensitivity analyses and post hoc analyses

The association between Global Gait and incident dementia remained robust after exclusion of the first year of follow-up (HR = 1.28 [1.06; 1.54]; $P = .01$), among individuals without a history of stroke (HR = 1.31 [1.10; 1.57]; $P = .002$), in those without prevalent parkinsonism (HR = 1.33 [1.10; 1.62]; $P = .004$), or after additional adjustment for Purdue Pegboard score (HR = 1.26 [1.05; 1.51]; $P = .02$). The hazard ratio of Global Gait for incident non–Alzheimer's disease dementia (HR = 1.66 [1.13; 2.45]; $P = .01$) was higher than for incident Alzheimer's disease dementia (HR = 1.22 [0.99; 1.49]; $P = .06$). The association between Global Gait and incident dementia attenuated and was no longer statistically

significant after additional adjustment for baseline Global Cognition (HR = 1.16 [0.96; 1.40]; $P = .12$). Compared to individuals who completed all walks, individuals who did not complete the baseline tandem walk, turning walk, or one or two cognitive tasks generally had more distinct cognitive decline at the follow-up assessment ($\beta = 0.03$ [0.01; 0.05]; $P = .006$) and an increased risk of incident dementia (HR = 2.98 [1.82; 4.85]; $P < .001$).

We had follow-up gait assessment data on 1701 of 4258 participants (39.9%). In this subgroup, baseline Global Cognition was associated with longitudinal decline in Global Gait ($\beta = 0.09$ [0.04; 0.14]; $P = .001$). Baseline Stroop (each task), Word Fluency Test, and Letter Digit Substitution Test scores were also associated with longitudinal decline in Global Gait (Supplementary Material 4).

4. Discussion

In this large, population-based study, worse quantitative gait was strongly associated with subsequent decline in cognitive performance and the risk of dementia. After stratifying by baseline cognitive performance, these associations were only present in cognitively unimpaired individuals. We identified independent associations of several gait domains with cognitive decline and the risk of dementia, suggesting that a detailed assessment of gait can potentially provide novel insight into the etiology of cognitive decline and dementia. From a clinical perspective, associations of poor gait with decline in specific cognitive functions may also have predictive utility.

After adjustment for multiple testing, 13 gait parameters were associated with cognitive decline and 4 gait parameters with incident dementia. Since some of these parameters are strongly correlated (e.g., step time and stride time), we aimed to unravel associations of underlying, independent gait domains with cognitive decline and incident dementia. This approach is similar to the approach used in a British population-based study and the Einstein Ageing Study [7,21]. In both studies as well the Rotterdam Study, the following independent domains were identified: Pace, Rhythm, and Variability. The Base of Support domain in the Rotterdam Study and the Postural Control domain in the British study both included step width but had a different contributing parameter (step width variability vs. step length asymmetry). Furthermore, we identified Phases as an independent domain, and our assessment of gait under tandem and turning conditions facilitated the identification of additional parameters that contributed to two more domains (which we named Tandem and Turning). We note that the British study also systematically collected data on left-right differences, which facilitated the identification of the Asymmetry domain. The Einstein Ageing Study is the only previous study that we are aware of to have also reported associations of independent, quantitative gait domains with cognitive decline as well as incident dementia. That study had a 10-fold smaller sample size than this study (in the dementia analysis: 4258 vs. 399 individuals) and only half the follow-up duration (5 vs. 2 years). These differences likely contributed to the identification of a larger number of independent gait domains in the Rotterdam Study (7 vs. 3 domains), additional associations of gait domains with decline in global and domain-specific cognitive performance as well as incident dementia, and subgroup differences by baseline cognitive performance. In both the Einstein Ageing Study and the Rotterdam Study, worse Pace was associated with decline in Global Cognition, and the domains Base of Support and Rhythm each were also independently associated with decline in Global Cognition in the Rotterdam Study. Furthermore, several of these gait domains were associated with decline in specific cognitive functions in the Rotterdam Study, including executive functioning, memory, semantic fluency, and information processing on an interference task. These observations may have predictive utility, for instance, individuals with poor Pace and Base of Support may be at increased risk of impairment in the ability to process interfering information. Worse Variability was associated with incident dementia in both the Einstein Ageing Study and the Rotterdam Study. In the Einstein Ageing Study, the association of Rhythm with incident dementia was statistically significant, whereas the association of Pace was not, while the association with incident dementia of Pace but not of Rhythm was statistically significant in the Rotterdam Study. We note that HRs for both domains were direction-consistent across both studies.

Importantly, after stratification by baseline cognitive performance, the associations of poor gait with cognitive decline and incident dementia in the Rotterdam Study were only present in individuals who did not have objective cognitive dysfunction at the time of gait assessment. This observation suggests that cognitively unimpaired individuals with poor performance on specific gait domains (Variability and Pace) may constitute a currently underrecognized group at higher risk of dementia. It also suggests that decline in independent aspects of gait may precede decline in cognitive abilities and functional independence in some of these individuals. Previous studies have shown that longitudinal decline of gait speed is associated with incident dementia, even after accounting for low baseline gait speed [22,23]. Traditionally, damage to specific brain regions in specific subtypes of dementia diseases was believed to be associated with poor performance on particular gait domains, for instance, basal ganglia pathology with tendency to shuffle [Phases] in Parkinson's disease dementia, or cerebellar pathology for poor heel-to-toe balance [Tandem] in multiple-system atrophy C. However, there is now a growing understanding that

widespread pathology to the cerebral cortex may contribute to gait decline among patients with Alzheimer's disease or vascular dementia [7,24]. Furthermore, several cross-sectional studies in individuals (still) free of dementia suggest that the regional distribution of amyloid-β (Aβ) deposition is associated with specific gait parameters [25,26]. Furthermore, higher cerebral Aβ deposition is associated with subsequent decline in several gait parameters [27]. Also, the association between cerebral Aβ deposition with slow gait speed may be more distinct in individuals with mild cognitive impairment than in individuals who are cognitively unimpaired [28]. Furthermore, widespread disruption of microstructural white matter integrity may contribute to poor gait [29,30]. Interestingly, microstructural integrity and comorbidities may moderate effects of white matter hyperintensities on gait, as previous studies showed that white matter hyperintensities were more distinctly associated with gait speed in individuals with impaired microstructural integrity or with other conditions that affect gait (e.g., poor vision, low forced vital capacity) [31,32]. In the coming years, prospective cohort studies will accrue sufficient follow-up for dementia to robustly quantify how much damage in each of these (micro-)structures explains the association between gait and incident dementia. It is also noteworthy that previous studies have shown that the relationship between longitudinal decline in gait and cognition in the ageing population might be bidirectional [33–36]. In the Mayo Clinic Study of Aging, baseline gait speed was inversely associated with subsequent cognitive decline, while baseline cognition was not associated with subsequent decline in gait speed, yet, we note that no other aspects of gait were examined [33]. In this study, we observed in post hoc analyses that performance on several cognitive domains was associated with longitudinal decline in global gait performance. However, the proportion of participants without follow-up gait assessments was high (60.1%). Future studies specifically designed to examine the association between performance on several cognitive domains and longitudinal decline in gait are warranted to rule out that the observations in our exploratory analyses were affected by selective attrition. In addition to etiologic research, studies aiming to develop a population-feasible screening algorithm for individuals at high risk of dementia may primarily complement this with gait speed, which can easily be assessed on a wide scale and is associated with both cognitive decline and dementia [3]. Gait speed is commonly used to determine current functional health status and predict a broad spectrum of health outcomes, such as functional decline, potential for rehabilitation, and mortality [37]. In the coming years, prospective cohort studies with quantitative gait assessments may also accrue sufficient follow-up to examine the association between gait and other common disorders neurodegenerative syndromes in the elderly population, such as parkinsonism (including Parkinson's disease) and normal pressure hydrocephalus.

Five methodological issues of this study warrant consideration. First, we only had two cognitive assessment points, and the second cognitive assessment took place near the end of dementia follow-up. As a consequence, we could not investigate nonlinear change over time of gait and cognitive performance in individuals who were later diagnosed with dementia. Second, 24% of participants did not participate in the follow-up cognitive assessment. Participants in the subgroup with two cognitive assessments were on average slightly younger, more highly educated, and had slightly better baseline gait and cognitive performance than the total at-risk population. We cannot rule out that we overestimated some of the hazard ratios due to nonparticipation at the baseline or follow-up cognitive assessments of individuals with poor gait who were not at increased risk of cognitive decline or dementia (e.g., hip osteoarthritis). Conversely, nonparticipation of individuals with poor gait and an increased risk of cognitive decline or dementia (e.g., individuals with mild cognitive impairment) would have yielded underestimates of HRs. Third, our study was underpowered to compare effect estimates of gait domains for subtypes of dementia. Specific quantitative gait domains may be associated with different subtypes of dementia [38] and may similarly have distinct associations with specific subtypes of dementia. The majority of patients with dementia in the community have mixed pathology, often including Alzheimer's disease pathology as well as coexisting pathologies such as cerebrovascular lesions [39–44]. Clinically distinguishing dementia subtypes has proven challenging if not impossible in the light of the multitude of pathologies that co-occur in the elderly population. This is particularly troubling in a population-based setting as 90% of dementia patients in the population are diagnosed after the age of 70 years. As a consequence, the outcome of most population-based longitudinal studies of the preclinical phase of dementia (including this study) is the dementia syndrome. We note that our diagnostic approach of both dementia and subtypes of dementia is similar to other large, population-based studies [45]. Fourth, we only assessed gait under single-task conditions, and the battery of cognitive tests we used was not comprehensive. In individuals with mild cognitive impairment, associations of gait with incident dementia are amplified if gait is assessed under dual-task conditions [46], and a similar pattern may apply to cognitively unimpaired individuals. Fifth, we used multiple imputation to avoid loss of data on baseline gait performance, as 10% of participants did not complete the baseline tandem walk, turning walk, or one or two cognitive tasks. We did not systematically record the reason for these missing data. The subgroup of individuals with incomplete data was older, more commonly female, and less commonly highly educated. We are not

sure whether these subgroup differences explain any possible systematic difference between the missing values and the observed values. Therefore, we are unsure whether data were missing at random or missing not at random [47].

In conclusion, our findings suggest that poor performance on several independent gait domains precedes cognitive decline and incident dementia.

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Sirwan K.L. Darweesh, MD, MSc (Department of Epidemiology, Erasmus Medical Center) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Sirwan K.L. Darweesh, MD, MSc also conducted the data analysis.

Standard Protocol Approvals, Registrations, and Patient Consents: The Rotterdam Study has been approved by the medical ethics committee according to the Population Study Act Rotterdam Study, executed by the Ministry of Health, Welfare and Sports of the Netherlands. All participants provided written informed consent to participate in the study.

Data Availability Statement: Study protocol, statistical analysis, and key individual deidentified participant data restricted to this specific project will be shared on request from qualified investigators. An overview on the design and updates of the Rotterdam Study have previously been published elsewhere [8,9].

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2019.03.013.

RESEARCH IN CONTEXT

1. Systematic review: We searched PubMed, Embase, and Cochrane library for prospective cohort studies reporting associations of independent, quantitative gait domains with cognitive decline or incident dementia. We identified only one relatively small (n = 427) study with a 2-year follow-up for incident dementia that published data on these associations. We identified no studies that investigated whether such associations would apply in cognitively unimpaired individuals.
2. Interpretation: This large, population-based study with quantitative gait assessments and serial cognitive assessments shows that poor performance on several independent gait domains is associated with subsequent cognitive decline and incident dementia. In stratified analyses by baseline cognitive performance, these associations only held in individuals who had been cognitively unimpaired at baseline. These findings suggest that poor gait precedes cognitive decline and incident dementia.
3. Future directions: The findings in this study will guide future etiologic and prediction studies on the role of gait in cognitive decline and dementia.

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