THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Medical Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2020, Vol. 75, No. 6, 1184–1190
doi:10.1093/gerona/glz282
Advance Access publication December 6, 2019

OXFORD

Research Article

Unraveling the Association Between Gait and Mortality—One Step at a Time

Lisanne J. Dommershuijsen, MSc,[1] Berna M. Isik, MSc,[1] Sirwan K. L. Darweesh, MD, PhD,[1,2] Jos N. van der Geest, PhD,[3] M. Kamran Ikram, MD, PhD,[1,4] and M. Arfan Ikram, MD, PhD[1,*]

[1]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands. [2]Department of Neurology, Radboud University Medical Center, Nijmegen, the Netherlands. [3]Department of Neuroscience and [4]Department of Neurology, Erasmus University Medical Center, Rotterdam, the Netherlands.

*Address correspondence to: M. Arfan Ikram, MD, PhD, Department of Epidemiology, Erasmus University Medical Center, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands. E-mail m.a.ikram@erasmusmc.nl

Received: September 18, 2019; Editorial Decision Date: November 21, 2019

Decision Editor: Anne Newman, MD, MPH

Abstract

Background: Slowness of walking is one of the very first signs of aging and is considered a marker for overall health that is strongly associated with mortality risk. In this study, we sought to disentangle the clinical drivers of the association between gait and mortality.

Methods: We included 4,490 participants of the Rotterdam Study who underwent a gait assessment between 2009 and 2015 and were followed-up for mortality until 2018. Gait was assessed with an electronic walkway and summarized into the domains Rhythm, Phases, Variability, Pace, Tandem, Turning, and Base of Support. Cox models adjusted for age, sex, and height were built and consecutively adjusted for six categories of health indicators (lifestyle, musculoskeletal, cardiovascular, pulmonary, metabolic, and neurological). Analyses were repeated in comorbidity-free individuals.

Results: Multiple gait domains were associated with an increased risk of mortality, including Pace (hazard ratio (HR) per SD worse gait, adjusted for other domains: 1.34 [1.19–1.50]), Rhythm (HR: 1.12 [1.02–1.23]) and Phases (HR: 1.12 [1.03–1.21]). Similarly, a 0.1 m/s decrease in gait speed was associated with a 1.21 (1.15–1.27) times higher hazard of mortality (HR fully adjusted: 1.14 [1.08–1.20]). In a comorbidity-free subsample, the HR per 0.1 m/s decrease in gait speed was 1.25 (1.09–1.44). Cause-specific mortality analyses revealed an association between gait speed and multiple causes of death.

Conclusions: Several gait domains were associated with mortality risk, including Pace which primarily represents gait speed. The association between gait speed and mortality persisted after an extensive adjustment for covariates, suggesting that gait is a marker for overall health.

Keywords: Mobility, General population, Etiology

Difficulties in walking are a major hallmark of the aging process (1,2). In fact, walking problems often have a considerable impact on quality of life and may lead to loss of independence and institutionalization (3–5). Accordingly, walking speed has been used as a marker for overall health and has been associated with mortality risk (6,7).

Yet, speed is merely one temporal parameter of the complex walking motion, which consists of many more parameters that collectively are termed gait. Other parameters of gait include for example swing time and stride width. Several studies have shown that different gait parameters reflect various aspects of gait. These parameters can be summarized into mutually independent gait domains, including for example Pace, Rhythm, and Base of Support (Figure 1) (7,8).

Gait has been shown to be differentially influenced by several lifestyle factors, health indicators, and diseases (9–11). For instance, smoking behavior (11), kidney function (12), and dementia (13) are all associated with different aspects of gait. However, it remains unclear whether these factors also drive the association between gait and mortality.

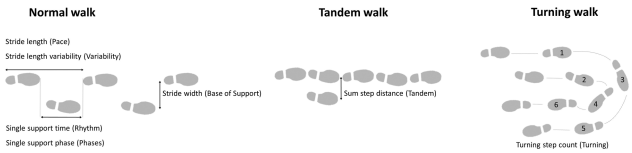

Figure 1. Gait parameters and the corresponding domains for all three walking conditions. The seven gait domains are shown between parentheses. Each gait domain is represented by one of the highest correlating variables with that domain.

In this study, we aimed to disentangle the clinical drivers of the association between gait and mortality risk. Hereto, we studied the association of different gait domains with mortality, we determined whether health indicators and prevalent diseases drive the association between gait speed and mortality, and we studied whether gait speed is related to specific causes of death.

Methods

This study was performed within the Rotterdam Study, an ongoing, population-based cohort study in the Netherlands. Details of the Rotterdam study have been described previously (14). The initial cohort started in 1990. All inhabitants of the district Ommoord in Rotterdam who were 55 years and over were invited to participate and 7,983 agreed. In 2000, the cohort was extended with 3,011 inhabitants who had become 55 years and over or who moved into Ommoord. The cohort was further expanded with 3,932 participants aged 45 years and over in 2006. The response rate over the three cohorts was 72%. At baseline and at the 4-year follow-up visits, participants underwent a home interview and examinations at the research center.

In March 2009, gait assessments were included into the core protocol of the Rotterdam Study as part of a research center visit. In the period until June 2015, 6,473 participants were invited to participate in this research center visit, of whom 5,261 participants agreed. Participants of 45 years and older who were willing to perform the walking protocol and could walk without use of a walking aid were eligible for gait assessment. In this study, we included 4,490 participants who underwent a gait assessment.

Gait Assessment

Gait was assessed using a 5.79 m long walkway (GAITRite Platinum; CIR systems, Sparta, NJ: 4.88-m active area; 120-Hz sampling rate), a reliable and valid device for the evaluation of gait (15,16). A standardized gait protocol was used consisting of three walking conditions: normal walk, tandem walk, and turning walk. In the normal walk, participants walked across the walkway at their usual pace. This walk was performed eight times; the first recording was considered a practice walk. In the tandem walk, participants walked heel-to-toe on a line across the walkway. The turning walk comprised a walk at the participant's own pace, turning halfway, and returning to the starting position. All recordings were visually inspected, after which the walkway software calculated 30 parameters based on the recorded gait: 25 parameters for the normal walk, 3 parameters for the tandem walk, and 2 parameters for the turning walk (8). The 30 gait parameters were summarized into seven independent domains (Figure 1). A description of all gait parameters and domains can be found in Supplementary Table S1 in the Supplementary Material.

Mortality Assessment

The records of the municipal administration of Rotterdam, general practitioner files, and nursing home files were checked continuously to obtain information on the participants' vital status. To determine the cause of death, participants' medical records were reviewed by trained research assistants. The cause of death was coded by two independent research physicians and reviewed by a medical expert in the field (14). Cause of death was coded according to the International Classification of Diseases, 10th edition (ICD-10) (17). In the current study, we classified causes of death into neurodegenerative diseases, cardiovascular diseases, neoplasms, and other diseases. Supplementary Table S2 in the Supplementary Material shows the coding of the causes of death in our study population. Follow-up for all-cause mortality was complete until May 2018 and follow-up for cause-specific mortality until January 2015.

Covariates

One of our aims was to study how health indicators influence the association between gait speed and mortality. Hereto, we categorized our covariates into lifestyle factors, musculoskeletal factors, cardiovascular factors, pulmonary factors, metabolic factors, and neurological factors.

Educational attainment, smoking status, alcohol consumption, and hip and knee pain were assessed with questionnaires during the home interview. The Longitudinal Aging Study Amsterdam Physical Activity Questionnaire was used to assess physical activity in metabolic equivalent of task hours per week (18). Depressive symptoms were evaluated using the Centre for Epidemiologic Studies Depression scale (CES-D) (19). Height and weight were obtained during a research center visit. In accordance with previous studies (20), a global cognition score was calculated using five cognitive tests: the Stroop Test (21), the Letter-Digit Substitution Test (22), the Word Fluency Test (23), the 15-Word Learning Test (24), and the Purdue Pegboard Test (25). Muscle strength was measured with a dynamometer and defined as the maximum value of three trials obtained from the nondominant hand. Blood pressure measurements were performed twice with the participant in sitting position. Carotid intima media thickness was determined with ultrasound of the distal common carotid artery. Serum glucose and creatinine were determined from fasting blood samples. Estimated glomerular filtration rate was calculated using the CKD-EPI formula (26). The Forced expiratory volume in 1 second (FEV1)/Forced vital capacity (FVC) ratio was obtained using spirometry. To evaluate vision, we used the mean best corrected visual acuity of both eyes.

Diagnoses of heart failure, coronary heart disease, asthma, dementia, parkinsonism, stroke, and cancer were based on repeated screening and review of medical records. In addition to the review of medical records, diagnoses of chronic obstructive pulmonary disease and diabetes involved spirometry and fasting glucose levels, respectively. Diagnoses of hip and knee osteoarthritis were based on radiological signs of arthritis and defined as a Kellgren and Lawrence grade of two or higher (27). Depression was defined as a CES-D score above 16 and kidney failure as a glomerular filtration rate below 60 mL/min/1.73m^2.

Statistical Analysis

All parameters of the normal walk were complete, the tandem walk was missing for 6% of the participants and the turning walk for 4% of the participants. Multiple imputations were performed for missing gait parameters and covariates. The missing gait parameters were imputed with an imputation model including all covariates and the outcome as predictors. The imputed datasets were used for all further analyses.

Gait parameters with a skewed distribution were log-transformed. A principal component analysis with Varimax rotation was performed to summarize the gait parameters into independent domains, as described previously in more detail (8). Seven independent gait Z-scores with an eigenvalue above one were found using this approach. These seven domains were labeled in accordance with previous work (8): Rhythm, Phases, Variability, Pace, Tandem, Turning, and Base of Support. Higher scores on each gait domain reflect a worse gait.

Cox proportional hazard models were built to analyze the associations between the gait domains, gait speed, and mortality. We used follow-up time in years as the time scale in all models. The basic model was adjusted for age, sex, and height. Additionally, we adjusted the gait domain models for all other gait domains. To facilitate comparison with other studies, we also repeated the analyses using the highest correlating variable with each domain as determinant. The proportional hazard assumption was examined by visual inspection of the Schoenfeld residuals (28). If the hazard was not constant over time, time-stratified analyses were performed.

To determine what drives the association between gait speed and mortality, we categorized our covariates into lifestyle factors, musculoskeletal factors, cardiovascular factors, pulmonary factors, metabolic factors, and neurological factors (see Supplementary Table S3 for an overview of all covariates included in these categories). The model for the association of gait speed with mortality was adjusted for each of these categories separately, and finally for all covariate categories together. To determine whether gait speed is a marker for overall health beyond known diseases, we repeated the analyses excluding all participants with prevalent diseases (hip and/or knee osteoarthritis, heart failure, coronary heart disease, asthma, chronic obstructive pulmonary disease, diabetes, kidney failure, dementia, parkinsonism, stroke, depression, and cancer). Subsequently, we adjusted the basic model in this subpopulation for the covariate categories to find out whether the association between gait speed and mortality persists after accounting for all diseases and health indicators. In addition, we estimated the association between gait speed and cause-specific mortality. We used cox proportional hazard models for these analyses and censored causes of death other than the event of interest. Mortality from neurodegenerative diseases, cardiovascular diseases, neoplasms, and other diseases was considered in these analyses.

We performed three sensitivity analyses on the association between gait and mortality risk. First, we tested what effect missing not at random of the tandem and turning walk could have on our results. For this purpose, we studied the implications of imputing a two standard deviation (SD) worse tandem and turning gait score than predicted in participants who did not perform these walks. Second, we tested the effect of an additional adjustment for the nonlinear effect of age in our models. Third, we studied whether gait speed explains the association between the gait domain Pace and mortality by adjusting the basic model of Pace additionally for gait speed. All analyses were performed in R version 3.5.2.

Results

At baseline, the mean age of our study population was 67.4 (*SD* 9.5) years and 55.1% were women (Table 1). The average gait speed was 120.2 (*SD* 19.9) cm/s. Characteristics of other gait parameters can be found in Supplementary Table S1 in the Supplementary Material. The mean follow-up duration between the gait assessment and the mortality or censor date was 4.5 years. During the entire follow-up, 469 participants died.

Table 1. Baseline Characteristics

Characteristics	Total (n = 4,490)
Demographics	
Women, *n* (%)	2,474 (55.1)
Age, years	67.4 (9.5)
Education[a], *n* (%)	
Primary	366 (8.1)
Lower	1,694 (37.7)
Intermediate	1,372 (30.5)
Higher	1,058 (23.6)
Covariates	
Height, cm	169.4 (9.5)
Weight, kg	78.5 (14.3)
Smoking, *n* (%)	
Current	572 (12.7)
Former	2,363 (52.6)
Never	1,555 (34.6)
Alcohol, g/d	6.4 [0.5–8.6]
Physical activity, MET-hours/week	41.5 [17.5–79.0]
Grip strength, kg	29.1 (10.3)
Knee pain, *n* (%)	
No pain	3,854 (85.8)
Some pain	551 (12.3)
A lot of pain	85 (1.9)
Hip pain, *n* (%)	
No pain	4,067 (90.6)
Some pain	351 (7.8)
A lot of pain	72 (1.6)
Systolic blood pressure, mmHg	141.5 (21.5)
Diastolic blood pressure, mmHg	83.0 (11.2)
Maximum carotid intima-media thickness, mm	1.0 (0.2)
FEV1/FVC ratio	0.8 (0.1)
Glomerular filtration rate, mL/min/1.73 m^2	110.5 (19.3)
Glucose, mmol/L	5.5 [5.1–6.0]
Cognition	
Stroop test, s	46.2 [38.8–56.9]
Letter-Digit Substitution Test, correct items	29.3 (7.0)
Word Fluency Test, correct items	22.8 (5.9)
15-Word Learning Test[b], correct items	7.8 (3.0)
Purdue Pegboard Test[c], correct items	34.8 (5.3)
Visual acuity	0.6 (0.1)
Comorbidities, *n* (%)	
Knee osteoarthritis	896 (20.0)
Hip osteoarthritis	628 (14.1)
Heart failure	91 (2.0)
Coronary heart disease	253 (5.6)
Asthma	343 (7.6)
Chronic obstructive pulmonary disease	463 (10.3)
Diabetes	749 (16.7)
Kidney failure	61 (1.4)
Dementia	33 (0.7)
Parkinsonism	14 (0.3)
Stroke	147 (3.3)
Depression	335 (7.5)
Cancer	435 (9.7)

Note: Presented are the mean values of the five imputations. Values are numbers (percentage), mean (*SD*), or median (interquartile range). FEV1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity; MET = Metabolic equivalent of task.

[a]Education was categorized as follows: Primary, primary education; Lower, lower or intermediate general education or lower vocational education; Intermediate, intermediate vocational education or higher general education; Higher, higher vocational education or university. [b]The delayed 15-Word Learning Test results are shown. [c]The sum score of left, right and both hands is shown.

Table 2 shows the associations between the gait domains and mortality. Of the gait domains, worse Pace was most strongly associated with mortality risk (hazard ratio [HR] per one SD worse gait for basic model: 1.42; 95% confidence interval [1.28–1.57]). Furthermore, worse Rhythm (HR basic model: 1.20 [1.09–1.31]), Phases (HR basic model: 1.15 [1.05–1.25]), and Base of Support (HR basic model: 1.13 [1.04–1.22]) were associated with an increased mortality risk. After adjusting the basic model additionally for all other gait domains, Pace still showed the strongest association with mortality risk (HR: 1.34 [1.19–1.50]) followed by Rhythm (HR: 1.12 [1.02–1.23]), Phases (HR: 1.12 [1.03–1.21]), and Tandem (HR: 1.10 [1.03–1.18]). Supplementary Table S4 in the Supplementary Material shows the association between the highest correlating gait parameters with each domain and mortality. Time-stratified analyses for Phases, Pace, Tandem, and Turning are presented in Supplementary Table S5 in the Supplementary Material.

Table 2. The Association of the Seven Gait Domains with Mortality

	Basic Model	Adjusted for Other Gait Domains
Domain	HR [95% CI]	HR [95% CI]
Rhythm	1.20 [1.09–1.31]	1.12 [1.02–1.23]
Phases	1.15 [1.05–1.25]	1.12 [1.03–1.21]
Variability	0.97 [0.88–1.07]	0.98 [0.89–1.08]
Pace	1.42 [1.28–1.57]	1.34 [1.19–1.50]
Tandem	1.08 [1.01–1.16]	1.10 [1.03–1.18]
Turning	1.08 [1.00–1.16]	1.07 [1.00–1.15]
Base of Support	1.13 [1.04–1.22]	1.05 [0.96–1.15]

Note: Shown are the hazard ratios [95% confidence intervals] for mortality per SD increase in gait. A higher score on any of the seven gait domains indicates a worse gait. The model was adjusted for age, sex, and height and subsequently also for all other gait domains. The domains are ordered according to the percentage explained variability of all the gait parameters, from highest (Rhythm) to lowest (Base of Support). CI = Confidence interval; OR = Odds ratio.

Figure 2 shows the association between gait speed and mortality, adjusted consecutively for the six covariate categories (see Supplementary Table S5 in the Supplementary Material for the time-stratified analysis of gait speed). A 0.1 m/s decrease in gait speed was associated with a 21% increase in mortality risk (HR basic model: 1.21 [1.15–1.27]). Adjustment for neurological factors (HR: 1.16 [1.10–1.22]) resulted in a decrease of the effect estimate. Cognition was the main cause of the effect attenuation by neurological factors. After adjustment for all considered covariates, the relation between gait speed and mortality persisted (HR: 1.14 [1.08–1.20]).

We repeated the analyses after excluding participants with prevalent comorbidities, resulting in the inclusion of 1,231 participants, of which 73 died during follow-up. The basic model in this subpopulation showed an association between gait speed and mortality (HR: 1.25 [1.09–1.44]), which attenuated, but was still observable after adjusting for all covariates (HR: 1.18 [1.01–1.37]).

We included 4,440 participants in the cause-specific mortality analyses. The mean follow-up duration for cause-specific mortality was 3.4 years. Out of a total of 192 deaths during follow-up for cause-specific mortality, 20 participants died from neurodegenerative diseases, 45 from cardiovascular diseases, 81 from neoplasms, and 46 from other diseases (see Supplementary Table S2 in the Supplementary Material for the numbers per ICD-10 code). In the basic model, gait speed was most strongly associated with death from neurodegenerative diseases (Figure 3, HR: 1.44 [1.16–1.78]) and other causes (HR: 1.42 [1.24–1.63]), but was also associated with death from neoplasms (HR: 1.18 [1.05–1.32]), and cardiovascular death (HR: 1.17 [1.01–1.35]).

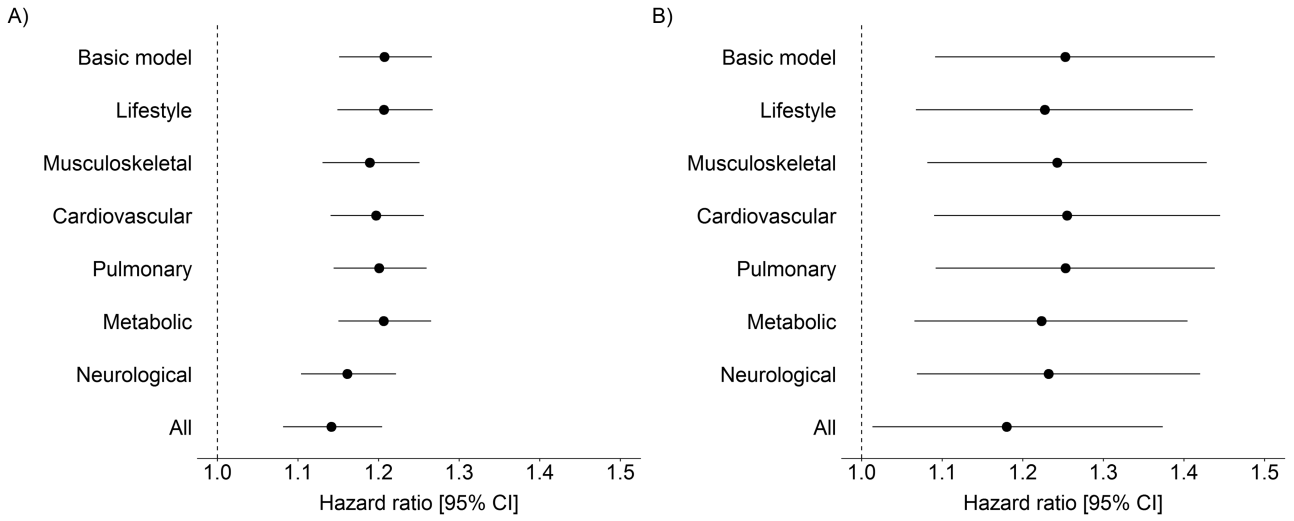

Figure 2. The association between gait speed and mortality adjusted for different covariate categories. Shown are the hazard ratios for mortality per 0.1 m/s decrease in gait speed with the 95% confidence intervals. (**A**) The basic model was adjusted for age, sex, and height. Further adjustments included the following factors: Lifestyle factors (education, smoking, alcohol, physical activity, and weight); Musculoskeletal factors (grip strength and hip and knee pain); Cardiovascular factors (blood pressure and carotid intima-media thickness); Pulmonary factors (FEV1/FVC ratio); Metabolic factors (GFR and glucose); and Neurological factors (cognition, CES-D, and visual acuity). The last model was adjusted for all these covariates. (**B**) Restricted to comorbidity-free participants (n = 1,231). Participants were excluded if they had prevalent hip and/or knee osteoarthritis, heart failure, CHD, asthma, COPD, diabetes, kidney failure, dementia, parkinsonism, stroke, depression, or cancer. CES-D = Centre for Epidemiologic Studies Depression scale; CHD = Coronary heart disease; COPD = Chronic obstructive pulmonary disease; FEV1 = Forced expiratory volume in 1 s; FVC = Forced vital capacity; GFR = Glomerular filtration rate.

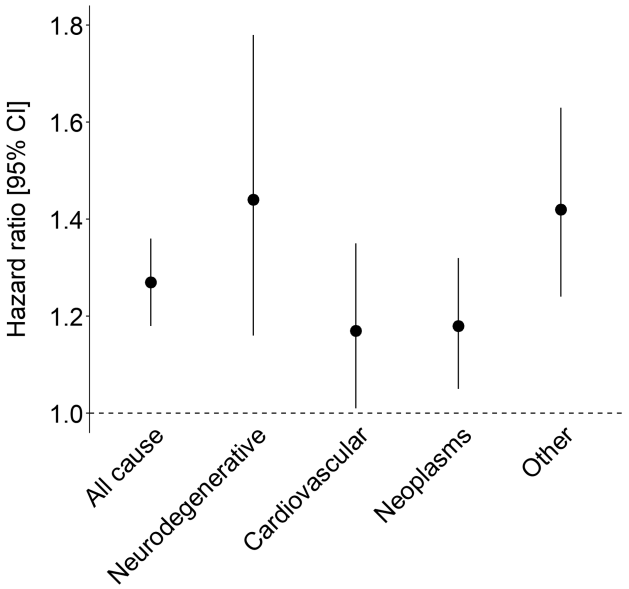

Figure 3. The association between gait speed and cause-specific mortality. Shown are the hazard ratios for mortality per 0.1 m/s decrease in gait speed with the 95% confidence intervals, $n = 4,440$. The hazard ratios were adjusted for age, sex, and height. During follow-up, 192 participants died due to the following causes: 20 participants died from neurodegenerative diseases, 45 from cardiovascular diseases, 81 from neoplasms, and 46 from other diseases.

Sensitivity Analysis

Assuming a 2 *SD* worse Tandem and Turning gait in participants with missing values for these domains resulted in slightly different effect estimates for these domains. Under this assumption, the HR increased for the Tandem domain (HR basic model: 1.16 [1.08–1.23]) and decreased for the Turning domain (HR: 1.04 [0.98–1.11]).

Correction for age squared did not substantially alter our results. Instead of a 21% increase in mortality per 0.1 m/s decrease in gait speed, we found a 20% increase in mortality risk after adjusting the basic model additionally for age squared (HR: 1.20 [1.15–1.26]). When we additionally adjusted for the nonlinear effect of age in the model adjusted for all our covariate categories, the HR remained equal (HR: 1.14 [1.08–1.20]).

We studied the effect of adjusting the analysis of the association between Pace and mortality for gait speed. As expected, the HR for mortality largely disappears after adjusting the basic model of Pace additionally for gait speed (HR: 1.08 [0.92–1.28]).

Discussion

In this cohort study among community-dwelling participants, we demonstrated that gait was associated with mortality risk in a complex, yet consistent pattern. In particular, the domain Pace, which represents mainly gait speed, was associated with mortality, followed by the domains Rhythm and Phases. The relation between gait speed and mortality could not be fully explained by a broad set of health indicators and diseases, however, the effect attenuated most after adjustment for cognitive function. Furthermore, gait speed was associated with multiple causes of death, most notably with death from neurodegenerative diseases.

Strengths of our study include the objective and comprehensive measurement of gait. Our gait protocol allowed the identification of an elaborate set of gait measures, which made it possible to study subtle gait differences between individuals. In addition, we studied gait in a large number of individuals. Finally, attrition in our study was low because we continuously checked for mortality in our participants; we observed 95% of the potential follow-up time (29).

Some aspects of our study warrant further consideration. First, gait was assessed during an extra research center visit in which a subsample of the study population participated. The participants of the Rotterdam Study who did not take part in the gait assessment were at baseline on average 2 years older and had a 1-year shorter survival than those who participated in the gait assessment. Second, a few relevant covariates, such as falling history and polyneuropathy, were not included in the analyses because they were only available for a small subset of the study population. Adjustment for these covariates could have further attenuated the effect of gait speed on mortality. Third, the available number of events for the cause-specific mortality analyses was small.

Previous studies have established a relation between gait speed and mortality (6,7). Veronese et al. reported in their meta-analysis an adjusted HR of 1.12 (1.09–1.14) per 0.1 m/s decrease in gait speed (7), which corresponds well to our adjusted HR of 1.14 (1.08–1.20) per 0.1 m/s decrease in gait speed. However, it remained unclear which aspects of gait were associated with mortality, which health indicators explained the association of gait speed with mortality, whether the association persisted in comorbidity-free individuals, and which causes of death associated most with gait speed. Our study addressed each of these key gaps in knowledge.

A unique feature of our study is the measurement of gait domains beyond simple gait speed. We showed that Pace had the strongest association with mortality, which was primarily driven by gait speed. Importantly, we also showed associations of Rhythm and Phases with mortality, independent from other gait domains. These gait domains include many parameters that cannot be assessed visually, such as single support phase, which indicates that even subtle gait differences between individuals can expose mortality risk. We might speculate on the different processes that underlie the relation between worse performance on each of the gait domains and mortality. The gait domain Pace might reflect decreased cognition (30), as well as many other health-related factors such as locomotor problems, peripheral vascular disease, and polyneuropathy. The domains Rhythm and Phases more selectively seem to point towards a role of neurodegeneration, they both might reflect parkinsonism (31).

Our results indicate that to a large extent the relation between gait speed and mortality cannot be explained by health indicators or known diseases, since an association remained visible after adjusting for many health indicators and in comorbidity-free individuals. This observation corroborates the findings of a study of Elbaz et al. (32). who also found that an association between gait speed and mortality remained after adjusting their models for different health-related factors. Gait speed thus seems to be able to determine subclinical deterioration in overall health.

Yet, in three ways, our results also point towards a role of neurodegeneration in the relation between gait and mortality. First, we found that the association between gait speed and mortality could be partially explained by cognition, which might be considered a proxy for neurodegenerative brain damage. Second, in our cause-specific mortality analyses, gait speed was most strongly associated with death from neurodegenerative diseases. However, we must note that the numbers in this group were small and the effect size was only slightly greater than for other causes of death. Third, our domain-specific results further strengthen the notion that neurodegeneration may drive the association between gait and mortality. Future studies are warranted to further explore the effect of neurodegeneration on the relation between gait and mortality; imaging or cerebrospinal fluid markers of neurodegeneration might be a promising start.

Conclusion

We have shown that different aspects of gait are related to mortality risk in the general population. The domain Pace, particularly representing gait speed, showed the highest association with mortality risk. Our results further support the concept that gait is a marker for overall health, but also indicate a potential role of neurodegeneration in this association. Further research is warranted to elucidate the effect of neurodegeneration on the relation between gait and mortality risk.

Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

Funding

The Rotterdam Study is supported by the Erasmus University Medical Center and Erasmus University Rotterdam, the Netherlands Organization for Scientific Research, the Netherlands Organization for Health Research and Development, the Research Institute for Diseases in the Elderly, the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sport, The European Commission, and the Netherlands Genomics Initiative and the Municipality of Rotterdam. This study received further support from Stichting ParkinsonFonds. The funding sources had no role in the design or execution of the study; collection, analysis, or interpretation of the data; writing or review of the manuscript; and the decision to submit the article for publication.

Ethics Approval and Consent to Participate

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalogue number NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Acknowledgments

The authors are grateful to the study participants, the staff from the Rotterdam Study, and the participating general practitioners and pharmacists.

Author Contributions

L.J.D. and B.M.I. contributed to the design and conceptualization of the study, the data analysis and interpretation, and drafting the manuscript. S.K.L.D. contributed to the conceptualization of the study, data acquisition and processing, and revising the manuscript critically for important intellectual content. J.N.G. contributed to the implementation of the research, processing of data, and revising the manuscript critically for important intellectual content. M.K.I. and M.A.I. contributed to the design and conceptualization of the study, interpretation, and revising the manuscript critically for important intellectual content. M.A.I. is the guarantor and corresponding author and attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflict of Interest

None reported.

References

1. Ferrucci L, Cooper R, Shardell M, Simonsick EM, Schrack JA, Kuh D. Age-related change in mobility: perspectives from life course epidemiology and geroscience. *J Gerontol A Biol Sci Med Sci*. 2016;71:1184–1194. doi: 10.1093/gerona/glw043
2. Ayis S, Gooberman-Hill R, Bowling A, Ebrahim S. Predicting catastrophic decline in mobility among older people. *Age Ageing*. 2006;35:382–387. doi: 10.1093/ageing/afl004
3. Shafrin J, Sullivan J, Goldman DP, Gill TM. The association between observed mobility and quality of life in the near elderly. *PLoS One*. 2017;12:e0182920. doi: 10.1371/journal.pone.0182920
4. Karakaya MG, Bilgin SC, Ekici G, Köse N, Otman AS. Functional mobility, depressive symptoms, level of independence, and quality of life of the elderly living at home and in the nursing home. *J Am Med Dir Assoc*. 2009;10:662–666. doi: 10.1016/j.jamda.2009.06.002
5. Fagerström C, Borglin G. Mobility, functional ability and health-related quality of life among people of 60 years or older. *Aging Clin Exp Res*. 2010;22:387–394. doi: 10.1007/bf03324941
6. Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. *JAMA*. 2011;305:50–58. doi: 10.1001/jama.2010.1923
7. Veronese N, Stubbs B, Volpato S, et al. Association between gait speed with mortality, cardiovascular disease and cancer: a systematic review and meta-analysis of prospective cohort studies. *J Am Med Dir Assoc*. 2018;19:981–988.e7. doi: 10.1016/j.jamda.2018.06.007
8. Verlinden VJ, van der Geest JN, Hoogendam YY, Hofman A, Breteler MM, Ikram MA. Gait patterns in a community-dwelling population aged 50 years and older. *Gait Posture*. 2013;37:500–505. doi: 10.1016/j.gaitpost.2012.09.005
9. Callisaya ML, Blizzard L, McGinley JL, Schmidt MD, Srikanth VK. Sensorimotor factors affecting gait variability in older people–a population-based study. *J Gerontol A Biol Sci Med Sci*. 2010;65:386–392. doi: 10.1093/gerona/glp184
10. Rosso AL, Sanders JL, Arnold AM, et al. Multisystem physiologic impairments and changes in gait speed of older adults. *J Gerontol A Biol Sci Med Sci*. 2015;70:319–324. doi: 10.1093/gerona/glu176
11. Verlinden VJ, Maksimovic A, Mirza SS, et al. The associations of alcohol, coffee and tobacco consumption with gait in a community-dwelling population. *Eur J Clin Nutr*. 2016;70:116–122. doi: 10.1038/ejcn.2015.120
12. Sedaghat S, Darweesh SKL, Verlinden VJA, van der Geest JN, Dehghan A, Franco OH, et al. Kidney function, gait pattern and fall in the general population: a cohort study. *Nephrol Dial Transplant*. 2018:2165–2172. doi: 10.1093/ndt/gfy043.
13. Beauchet O, Allali G, Berrut G, Hommet C, Dubost V, Assal F. Gait analysis in demented subjects: interests and perspectives. *Neuropsychiatr Dis Treat*. 2008;4:155–160. doi: 10.2147/ndt.s2070
14. Ikram MA, Brusselle GGO, Murad SD, et al. The Rotterdam study: 2018 update on objectives, design and main results. *Eur J Epidemiol*. 2017;32:807–850. doi: 10.1007/s10654-017-0321-4.
15. Menz HB, Latt MD, Tiedemann A, Mun San Kwan M, Lord SR. Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. *Gait Posture*. 2004;20:20–25. doi: 10.1016/S0966-6362(03)00068-7
16. Webster KE, Wittwer JE, Feller JA. Validity of the GAITRite walkway system for the measurement of averaged and individual step parameters of gait. *Gait Posture*. 2005;22:317–321. doi: 10.1016/j.gaitpost.2004.10.005
17. WHO. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. 2016. https://icd.who.int/browse10/2016/en
18. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P. Comparison of the LASA physical activity questionnaire with a 7-day diary and pedometer. *J Clin Epidemiol*. 2004;57:252–258. doi: 10.1016/j.jclinepi.2003.07.008
19. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1:385–401. doi: 10.1177/014662167700100306.
20. Hoogendam YY, Hofman A, van der Geest JN, van der Lugt A, Ikram MA. Patterns of cognitive function in aging: the Rotterdam Study. *Eur J Epidemiol*. 2014;29:133–140. doi: 10.1007/s10654-014-9885-4
21. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643–662. doi: 10.1037/h0054651.
22. van der Elst W, van Boxtel MP, van Breukelen GJ, Jolles J. The letter digit substitution test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age,

education, and sex. *J Clin Exp Neuropsychol*. 2006;28:998–1009. doi: 10.1080/13803390591004428

23. Welsh KA, Butters N, Mohs RC, et al. The consortium to establish a registry for alzheimer's disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology*. 1994;44:609–614. doi: 10.1212/wnl.44.4.609
24. Brand N, Jolles J. Learning and retrieval rate of words presented auditorily and visually. *J. Gen Psychol*. 1985;112:201–210. doi: 10.1080/00221309.1985.9711004.
25. Tiffin J, Asher EJ. The Purdue pegboard; norms and studies of reliability and validity. *J Appl Psychol*. 1948;32:234–247. doi: 10.1037/h0061266
26. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612. doi: 10.7326/0003-4819-150-9-200905050-00006
27. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16:494–502. doi: 10.1136/ard.16.4.494
28. Schoenfeld D. Partial residuals for the proportional hazards regression model. *Biometrika*. 1982;69:239–241. doi: 10.1093/biomet/69.1.239.
29. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359:1309–1310. doi: 10.1016/s0140-6736(02)08272-7
30. Hayat SA, Luben R, Dalzell N, et al. Understanding the relationship between cognition and death: a within cohort examination of cognitive measures and mortality. *Eur J Epidemiol*. 2018;33:1049–1062. doi: 10.1007/s10654-018-0439-z
31. Pistacchi M, Gioulis M, Sanson F, et al. Gait analysis and clinical correlations in early Parkinson's disease. *Funct Neurol*. 2017;32:28–34. doi: 10.11138/fneur/2017.32.1.028
32. Elbaz A, Sabia S, Brunner E, et al. Association of walking speed in late midlife with mortality: results from the Whitehall II cohort study. *Age (Dordr)*. 2013;35:943–952. doi: 10.1007/s11357-012-9387-9