Stroke

CLINICAL AND POPULATION SCIENCES

Quantitative Gait Impairments in Patients With Stroke or Transient Ischemic Attack

A Population-Based Approach

Alis Heshmatollah, MD; Sirwan K.L. Darweesh, MD, PhD; Lisanne J. Dommershuijsen, MSc; Peter J. Koudstaal, MD, PhD; Mohammad A. Ikram, MD, PhD; Mohammad K. Ikram, MD, PhD

BACKGROUND AND PURPOSE: Gait is a complex process involving various cortical and subcortical brain regions. An acute stroke or transient ischemic attack (TIA) may disrupt white and gray matter integrity and, therefore, affect gait in patients without evident neurological signs. We determined whether patients with stroke and TIA experience subtle changes in global gait and several independent gait domains.

METHODS: In the population-based Rotterdam Study, 4456 participants (median age, 65 years; 55% women) underwent detailed quantitative gait assessment (GAITRite) between 2009 and 2016. We summarized 30 gait parameters into a global gait score and 7 mutually independent gait domains. First, we assessed the association between prior stroke or TIA and global and domain-specific gait using linear regression models adjusted for age, sex, vascular risk factors, and cognition. Subsequently, we repeated the analysis stratified by the presence of different neurological symptoms in a subgroup of participants with ischemic stroke after study entry.

RESULTS: Compared with participants without prior stroke, patients with stroke had a worse global gait (SD, −0.49 [95% CI, −0.64 to −0.34]), especially in the gait domains Pace, Phases, and Turning. The detrimental effect of stroke on gait was amplified in participants with worse cognition. No gait differences were found between participants with and without prior TIA. Ischemic stroke patients without lower limb weakness, loss of coordination, or visuospatial problems still had a worse gait compared with participants without stroke. Stratification by different stroke symptoms showed that different gait domains were affected in each group.

CONCLUSIONS: Prior stroke without neurological signs that affect gait is still associated with gait difficulties compared with individuals without stroke. Our study suggests that stroke not only has a direct impact on gait through neurological impairments but also includes an indirect effect possibly through disruption of gray and white matter integrity and accelerated neurodegeneration.

Key Words: cognition ■ gait ■ ischemic attack, transient ■ linear models ■ stroke

Patients with stroke often experience difficulties with gait, which subsequently can lead to functional dependency, falls, and mortality.[1,2] Gait is a complex process involving an interplay of various cortical brain regions, white matter tracts, and the peripheral nervous system.[3] Apart from poststroke gait difficulties due to lower limb weakness, loss of coordination, or visuospatial problems, subtle changes in the brain including small vessel disease are also linked to walking problems, most likely through disruption of the intra- and interhemispheric integration of motor and sensory signals.[4–6] Moreover, because gait is also dependent on several cognitive abilities such as executive function and attention,[7] poststroke

Correspondence to: Mohammad K. Ikram, MD, PhD, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, the Netherlands. Email m.ikram@erasmusmc.nl

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Nonstandard Abbreviations and Acronyms

HDL	high-density lipoprotein
TIA	transient ischemic attack

cognitive impairment may further negatively impact gait in these patients.[8]

In view of these observations, we hypothesized that patients experiencing a stroke or transient ischemic attack (TIA), without neurological signs that affect gait, may also experience subtle changes in their gait patterns, in particular, those who are cognitively impaired. Thus far, only 1 study has investigated gait in 12 patients with minor stroke and TIA and found worse gait speed, step length, and double support.[9] This small study highlighted that problems with gait may be subtle and not easily assessable with standard neurological examination. Conversely, quantitative assessment can reveal different aspects of a person's gait pattern, including various domains such as Base of Support (stride width), Rhythm (stride time), and Tandem (heel-to-toe walking).

In the current study, we determined whether patients with a stroke or TIA experience subtle changes in global and domain-specific gait and whether cognition modifies this association. Specifically, we examined whether stroke patients without lower limb weakness, loss of coordination, or visual problems still experienced subtle gait problems compared with participants without stroke.

METHODS

The Rotterdam Study data can be made available to interested researchers upon request. Requests can be directed to data manager Frank J.A. van Rooij (f.vanrooij@erasmusmc.nl). We are unable to place data in a public repository due to legal and ethical restraints. Sharing of individual participant data was not included in the informed consent of the study, and there is potential risk of revealing participants' identities as it is not possible to completely anonymize the data. This is of particular concern given the sensitive personal nature of much of the data collected as part of the Rotterdam Study.

Study Population

This study was embedded in the Rotterdam Study—a prospective population-based cohort based in the Netherlands investigating causes and consequences of diseases in people aged ≥45 years.[10] The study was initiated in 1990 and expanded in 2000 and 2005 and currently consists of 14 926 participants. At study entry and every 4 years, participants are interviewed at home and undergo extensive physical examination at the research center. Gait assessment has been implemented in the core protocol since March 2009. In total, 6405 participants were asked to participate of whom eventually 4525 underwent gait assessment between 2009 and 2016 (Table I in the Data Supplement). We used the first gait assessment of each participant. Participants who did not give informed consent to review their medical records (n=22) or who were lost to continuous follow-up before their gait assessment (n=47) were excluded, resulting in 4456 participants available for further analysis.

The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus Medical Center and by the Review Board of the Ministry of Health, Welfare, and Sports of the Netherlands according to the Population Study Act Rotterdam Study. All participants provided written informed consent to participate in the study.

Stroke and TIA Ascertainment

Stroke was defined according to the World Health Organization criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting ≥24 hours or leading to death, with no apparent cause other than of vascular origin.[11] TIA was defined as an attack of sudden focal neurological symptom(s) that completely resolved within 24 hours, with no clear evidence for the diagnosis of migraine, epilepsy, Ménière disease, hyperventilation, cardiac syncope, hypoglycemia, or orthostatic hypotension.[12] History of stroke or TIA at study entry was assessed during baseline interview and verified by medical records. After enrollment, participants were continuously monitored for stroke and TIA through automated linkage of the study database with files from general practitioners. Nursing home physician and general practitioner files of participants who moved out of the district were checked on a regular basis as well. Additional information was obtained from hospital records. In the Dutch healthcare system, the general practitioner and nursing home physician function as gatekeepers for referral to secondary and tertiary care providers. These providers then report back to the general practitioner or nursing home physician, including when patients visit without a referral. Therefore, the Rotterdam Study has data on all centers participants visited, without limiting it to specific centers. Potential strokes were reviewed by research physicians and verified by an experienced stroke neurologist. Final stroke diagnosis was adjudicated in accordance with the abovementioned standardized diagnostic World Health Organization criteria, which were held constant over the entire follow-up time. Stroke subtype (hemorrhagic or ischemic), location, cause, and other stroke-specific characteristics were based on neuroimaging reports or hospital discharge letters. If these were absent, then the stroke subtype was classified as unspecified. Follow-up until January 2016 was virtually complete (person-years/potential person-years, 96.5%). Participants were identified as prior stroke or TIA when they had a history of stroke or TIA before their gait assessment. For participants who had a history of stroke at study entry in the Rotterdam Study, complete information on the neurological signs during the event was not always available. Therefore, for the analysis stratified by neurological symptoms, we only included participants who had an ischemic stroke during follow-up in the Rotterdam Study but before gait assessment (n=76). For these participants, medical records including neurological signs during the event were available, and all neurological signs and localization mentioned by the physician were noted. For participants who had multiple strokes before gait assessment (n=8), we gathered all neurological signs of every event. The

medical records of 1 participant were not completely available, and this participant was excluded.

Gait Assessment

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)—a reliable and valid device for the evaluation of gait.[13,14] The standardized gait protocol consisted of 3 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 8×; the first recording was considered a practice walk. In the tandem walk, participants walked heel-to-toe on a line across the walkway. In turning walk, participants walked the walkway at their usual pace, turned halfway, and returned to the starting position. The tandem and turning walk were performed once. After visual inspection of the recordings, the walkway software calculated 30 parameters based on the recorded gait, including 25 parameters for the normal walk, 3 parameters for the tandem walk, and 2 parameters for the turning walk (Table II in the Data Supplement).[15] We performed a principal component analysis with Varimax rotation to summarize gait parameters into independent domains as previously described in detail.[15] This approach yielded 7 independent gait domains with an eigenvalue above 1, which we labeled in accordance with the gait parameters that were highly correlated with that domain: Base of Support, Pace, Phases, Rhythm, Tandem, Turning, and Variability (Figure 1).[15] Global gait—a reflection of the gait pattern in general—was calculated by averaging the 7 gait domains and standardizing them into a *Z* score.

Covariates

Educational attainment, smoking status, and physical activity were assessed during the home interview. To quantify the intensity of activity, we assigned metabolic equivalent of task scores to all activities according to the Compendium of Physical Activities.[16] Metabolic equivalent of task hours per week was calculated by multiplying the metabolic equivalent of task scores with hours per week spent in each activity. Body mass index was calculated as weight (kg) divided by the square of height (m^2). Blood pressure was measured at the right upper arm using a sphygmomanometer during 2 consecutive readings, and the average of the 2 readings was used for further analysis. Blood samples were drawn to assess lipid and glucose levels. Diabetes mellitus type 2 was defined as a fasting glucose of ≥7.0 mmol/L, a nonfasting or post-load serum glucose of ≥11.1 mmol/L, or blood glucose–lowering medication use. Furthermore, diagnosis of diabetes mellitus type 2 and atrial fibrillation was based on repeated screening and review of medical records. Participants also underwent extensive cognitive assessment including verbal fluency test, 15-word learning test, letter-digit substitution test, Stroop test, and Purdue pegboard test.[17] We calculated global cognition (g factor) as the first component of a principal component analysis that incorporated tasks from all available cognitive function tests. For tests with multiple subtasks, only one subtask was included to prevent highly correlated tasks distorting the factor loadings (ie, the interference task for Stroop test and delayed recall task for 15-word learning test). The g factor explained 53.5% of the variance in cognitive test scores in our study population.

Statistical Analysis

All individuals who participated in gait assessment had complete data on the normal walk; data on tandem walk were missing in 6% of the participants and data on turning walk in 4% of the participants. The percentage of missing values in covariates ranged from 0.4% to 3.4%. We used multiple imputation for missing data on gait parameters and covariates based on all covariates and outcome. Gait parameters with a skewed distribution were log transformed.

We determined the association between prior stroke or TIA and global gait and gait domains using linear regression models. Model I was adjusted for age and sex; model II compromised additional adjustments for education, smoking, body mass index, cholesterol, HDL (high-density lipoprotein), systolic and diastolic blood pressure, blood pressure–lowering medication, lipid-lowering medication, diabetes mellitus type 2, atrial fibrillation, and smoking; and in model III, an additional adjustment for global cognition (g factor) was added. We tested for

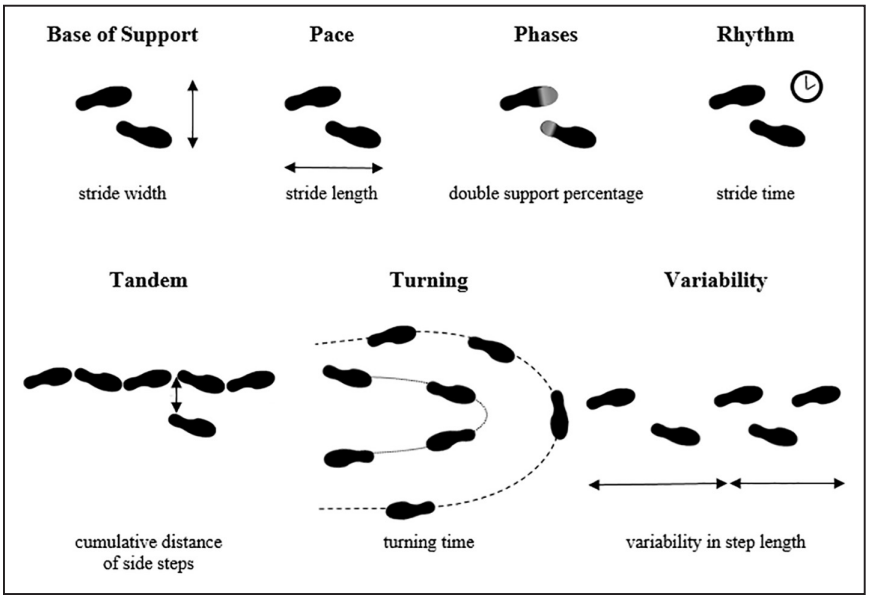

Figure 1. Independent gait domains. We performed a principal component analysis to summarize gait parameters into 7 independent domains: Base of support, pace, phases, rhythm, tandem, turning, and variability. For each gait domain, a single gait parameter that has high correlation with the domain is illustrated.

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effect modification of cognition between the association of prior stroke/TIA and global gait by adding an interaction term between global cognition and stroke/TIA to model III and by repeating the analysis for stroke after stratification by mean global cognition.

Furthermore, we repeated the analysis and determined the association between prior stroke and gait after stratification by the presence of neurological signs that may affect gait (weakness, sensory symptoms, disturbed coordination or reduced skillfulness in the lower limbs, reported walking difficulty, neglect, visual deficit, or diplopia), presence of isolated aphasia (as a reliable symptom indicating cortical involvement), and clinical localization of stroke.

Data analysis was performed using IBM SPSS, version 25, and R, version 3.6.2, software.

RESULTS

In total, 4456 participants completed gait assessment and were included in the analysis. Mean age (SD) of these participants was 67.4 years (9.5), and 55.1% were women (Table 1). Of these participants, 147 (3.3%) experienced a stroke and 202 (4.5%) a TIA before their gait assessment.

Participants with prior stroke had a −0.49-SD (95% CI, −0.64 to −0.34) worse global gait compared with those without a history of stroke (Table 2). The association attenuated slightly after adjusting for vascular risk factors and additionally for global cognition. Of the 7 independent gait domains, participants with prior stroke had in particular worse scores on Pace, Phases, and Turning compared with those without stroke (Figure 2A). In contrast, patients with a TIA did not have worse global or domain-specific gait compared with those free of stroke and TIA. We found a significant interaction between stroke and global cognition (SD, −0.19 [95% CI, −0.31 to −0.07]; *P* for interaction, <0.005) but not between TIA and global cognition. The effect of prior stroke on gait was even more detrimental in participants with worse global cognition compared with those with cognition scores above the mean (Figure 2B), especially on global gait and the Phases domain.

In total, 76 participants were stroke free at study entry in the Rotterdam Study but had an ischemic stroke during study follow-up and before gait assessment. The first stroke event of these patients occurred with a median (SD) of 4.3 years (4.5) before gait assessment. Most frequently reported neurological signs were weakness of the upper limb (46.7%), weakness of the lower limb (38.7%), and aphasia (33.3%; Table 3). The participants with prior stroke had a −0.51-SD (95% CI, −0.70 to −0.31) worse global gait compared with stroke-free participants in the fully adjusted model. Stratification by neurological symptoms showed that stroke patients without lower limb paresis or visuospatial symptoms during the event still had a worse global gait compared with participants without stroke (SD, −0.57 [95% CI, −0.91 to −0.24]; Table III in the Data Supplement). Regarding gait domains, patients with lower limb paresis or visuospatial symptoms were the most affected in the Phases domain, whereas stroke patients without these symptoms had in particular a worse Rhythm (Figure 3A). Stroke patients with aphasia as their only symptom still had a worse gait than participants without stroke (SD, −0.95 [95% CI, −1.51 to −0.40]; Table II Data Supplement), they were in particular affected in the Tandem and Turning domains. Finally, a stroke in the left or right hemisphere was associated with a worse global gait, whereas stroke in the cerebellum/brain stem was not significantly associated with a worse gait (Table III Data Supplement; Figure 3C). Left hemispheric stroke was most strongly associated with a worse Tandem, and right hemispheric stroke was in particular associated with impairments in the Phases domain.

Table 1. Baseline Characteristics of Study Population (n=4456)

Characteristic	
Age at gait assessment, y	67.4 (9.5)
Women	2453 (55.1)
Educational attainment	
Primary	359 (8.1)
Low/intermediate	1687 (37.9)
Intermediate	1372 (30.8)
Higher	1038 (23.3)
Systolic blood pressure, mm Hg	141 (21)
Diastolic blood pressure, mm Hg	83 (11)
Blood pressure–lowering medication use	1903 (42.7)
Body mass index, kg/m^2	27.3 (4.2)
Total serum cholesterol, mmol/L	5.5 (1.1)
Serum high-density lipoprotein, mmol/L	1.5 (0.4)
Lipid-lowering medication use	1326 (29.8)
Smoking status	
Current	581 (13.0)
Former	2406 (54.0)
Never	1469 (33.0)
Prior stroke	147 (3.3)
Prior transient ischemic attack	276 (6.2)
Diabetes mellitus type 2	648 (14.5)
Atrial fibrillation	236 (5.3)
Physical activity, MET-hours per week*; median (interquartile range)	42.0 (17.7–79.7)

Data presented as frequency (percentage) for categorical values and mean±SD for continuous variables, unless stated otherwise. MET indicates metabolic equivalent of task.

*Data on physical activity were missing in n=716 participants.

DISCUSSION

In this study, we found that prior stroke without lower limb weakness, loss of coordination or visuospatial problems

Table 2. Association of Global Gait and Different Gait Categories With Prior Stroke

	Global Gait (SD)		
	Model I	Model II	Model III
Prior stroke			
No. of participants with stroke/no stroke	147/4301		
β (95% CI)	−0.49 (−0.64 to −0.34)*	−0.44 (−0.58 to −0.29)*	−0.34 (−0.48 to −0.19)*
Prior TIA			
No. of participants with TIA/no TIA or stroke	202/4107		
β (95% CI)	−0.07 (−0.20 to 0.05)	−0.06 (−0.18 to 0.06)	−0.03 (−0.15 to 0.09)

Model I: adjusted for age and sex. Model II: additional adjustments for education, smoking, BMI, cholesterol, HDL, systolic and diastolic blood pressure, blood pressure–lowering medication, lipid-lowering medication, diabetes mellitus type 2, atrial fibrillation, and smoking. Model III: additional adjustment for global cognition. BMI indicates body mass index; HDL, high-density lipoprotein; and TIA, transient ischemic attack.

*Significant ($P<0.05$) association.

at the time of the event was associated with a worse gait compared with stroke-free participants, especially in participants with cognitive impairment. Furthermore, impairments in different gait domains were associated with stroke patients with different neurological symptoms. These results suggest that a stroke not only affects gait in patients in a direct way due to obvious physical impairment but has an additional detrimental impact on gait through other pathways.

One previous study also reported several gait parameters in 12 minor stroke and TIA patients.[9] These patients had a worse gait speed, step length, and double support compared with healthy controls. These gait parameters could be compared with the Pace and Phases domains of our study. However, this study included 4 patients (25%) who did report gait disturbances at the time of the event, and no adjustments for vascular risk factors or cognition were made. Moreover, an additional difference with the study was that gait was assessed on average 20 weeks after the event, whereas our study assessed gait in participants with various time after stroke and TIA. Although this can highlight the more long-term consequences of stroke and TIA, it does provide a more heterogeneous group.

We found that prior stroke without gait-affecting neurological signs was associated with a worse global gait compared with participants without a history of stroke. However, different gait domains were impaired in different

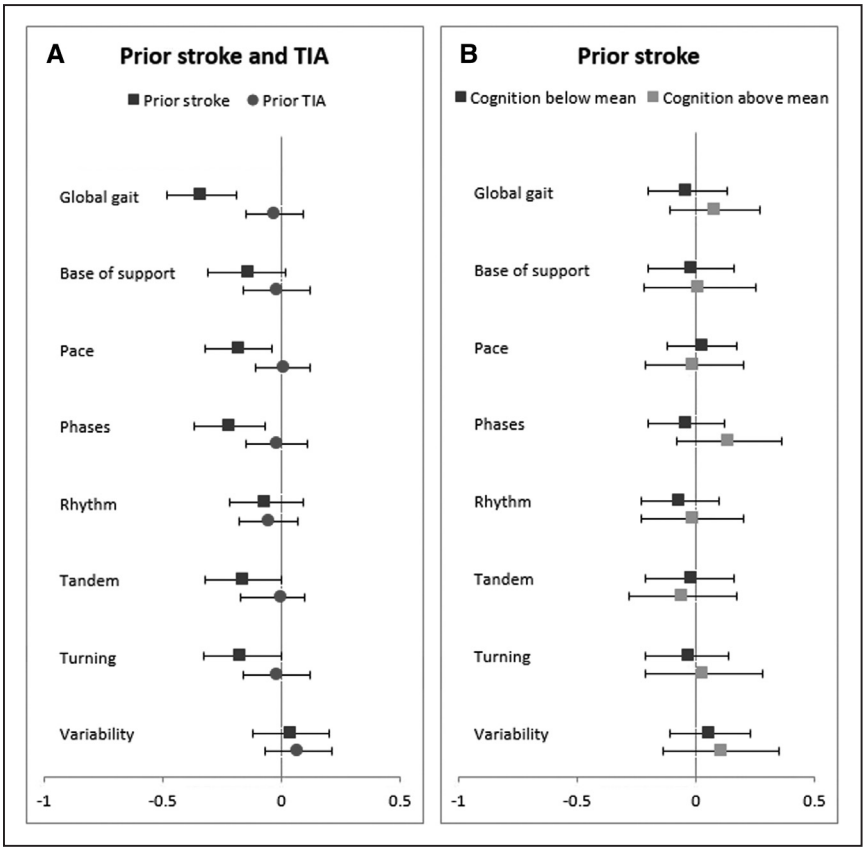

Figure 2. Association of prior stroke and transient ischemic attack (TIA) with gait.
A, Association of prior stroke and TIA with global gait and independent gait domains. Data points represent SD change of global gait or gait domain in participants with prior stroke (gray marker) or prior TIA (gray circle) compared with participants without stroke or TIA; bars indicate 95% CIs. Analyses were adjusted for age, sex, education, smoking, body mass index (BMI), cholesterol, HDL (high-density lipoprotein), systolic and diastolic blood pressure, blood pressure–lowering medication, lipid-lowering medication, diabetes mellitus type 2, atrial fibrillation, smoking, and global cognition. **B**, Association of prior stroke with global gait and independent gait domains after stratification by mean global cognition. Data points represent SD change of global gait or gait domain in participants with prior stroke compared with participants without stroke; bars indicate 95% CIs. Analyses were adjusted for age, sex, education, smoking, BMI, cholesterol, HDL, systolic and diastolic blood pressure, blood pressure–lowering medication, lipid-lowering medication, diabetes mellitus type 2, atrial fibrillation, and smoking.

Table 3. Neurological Signs During Stroke Events Before Gait Assessment of 75 Participants

Neurological Signs at Stroke Event	
Weakness, upper limb	35 (46.7%)
Weakness, lower limb	29 (38.7%)
Aphasia	25 (33.3%)
Sensory symptom, upper limb	23 (30.7%)
Weakness, face	20 (26.7%)
Dysdiadochokinesia or reduced skillfulness, upper limb	19 (25.3%)
Sensory symptom, lower limb	14 (18.7%)
Walking difficulty	14 (18.7%)
Disturbed coordination, upper limb	13 (17.3%)
Vertigo	10 (13.3%)
Dysarthria	10 (13.3%)
Visual deficit	10 (13.3%)
Sensory symptoms, face	9 (12.0%)
Disturbed coordination, lower limb	9 (12.0%)
Reduced skillfulness, lower limb	8 (10.7%)
Neglect	3 (4.0%)
Diplopia	2 (2.7%)
Dysphagia	2 (2.7%)
Nystagmus	2 (2.7%)
Memory deficit	2 (2.7%)
Apraxia	0

Data presented as frequency (percentage).

patient groups. Lower limb paresis or visuospatial symptoms were most strongly associated with difficulties in the Base of Support, Phases, and Turning gait domain, which correlate with the classic hemiparetic gait characterized by poor disrupted equilibrium reactions and reduced weight bearing on the paretic limb.[8,18] Prior stroke without these symptoms was associated with difficulties in the Pace, Phases, Tandem, Turning, and Rhythm gait domains. Furthermore, both right and left hemisphere strokes were associated with a poor global gait compared with stroke-free participants. Left hemispheric strokes were in particular associated with impairments in the Tandem domain, whereas right hemispheric strokes were mostly associated with worse scores on the Phases domain. In contrast, prior strokes in the cerebellum/brain stem were not significantly associated with poor gait. This last finding is based on a small number of stroke patients (n=13), and replication in different studies is needed.

It is conceivable that the association of prior stroke without lower limb paresis or visuospatial symptoms with gait impairments can be explained by so called higher level gait disorders: walking difficulties that are due to disturbance of the highest sensorimotor systems that cannot be accounted for by obvious neurological signs.[19] Indeed, small vessel disease including white matter hyperintensities and lacunar infarcts, especially in the frontal and periventricular regions, is associated with gait difficulties.[4–6] In particular, loss of white matter microstructure integrity in interconnecting cortical and thalamic regions is linked to worse global gait and several gait domains including Phases, Variability, Pace, Base of Support, and Turning.[20,21] However, adjustment of vascular risk factors attenuated but did not eliminate the association between prior stroke and gait disorders. This suggests that stroke had an independent impact on gait, possibly by interrupting the white integrity further and acceleration of cerebral small vessel disease. Similarly, gray matter, through cortical infarcts, seems to be involved in this process since we also found that stroke with isolated aphasia was still associated with gait impairments. We did not find worse gait in participants with prior TIA compared with those without TIA, suggesting that these events did not result in permanent cerebrovascular damage.

Furthermore, we found that in participants with worse global cognition, the association of prior stroke and gait impairments was amplified, suggesting that cognition is an effect modifier in this association. Gait is indeed dependent on several cognitive abilities including executive function, attention, and judgement of external and internal cues[7] and has previously been linked to cognitive decline and dementia.[22–24] Cognitive impairment in patients with stroke is associated with concurrent gait difficulties that are amplified during cognitive challenging dual-task assessments of gait.[8,25–27] Different pathways are hypothesized: besides the detrimental impact of small vessel disease on both cognition and gait,[7,22,27] evidence is also emerging that neurodegeneration, possibly though amyloid-β depositions, has a more direct impact on gait domains such as cadence and increased double support time.[28]

Several limitations of this study need to be discussed. We obtained information about neurological signs during the stroke event from medical records, and thus it is possible that the treating physician may not have reported all signs of these patients. In particular, subtle neurological symptoms may have been missed. We also did not systematically assess stroke severity. Furthermore, gait difficulties in patients with lower limb difficulties or visuospatial symptoms are possibly underestimated due to nonparticipation of participants who had a severely disabling stroke. However, this has likely not occurred in stroke patients without these neurological signs, and, therefore, we have no indication that the gait assessment in these patients is not reliable. Conversely, we cannot rule out that we overestimated some of the associations due to nonparticipation of individuals with poor gait due to reasons other than stroke (eg, hip osteoarthritis).

CONCLUSIONS

Our study showed that prior stroke without lower limb difficulties, loss of coordination, or visuospatial problems

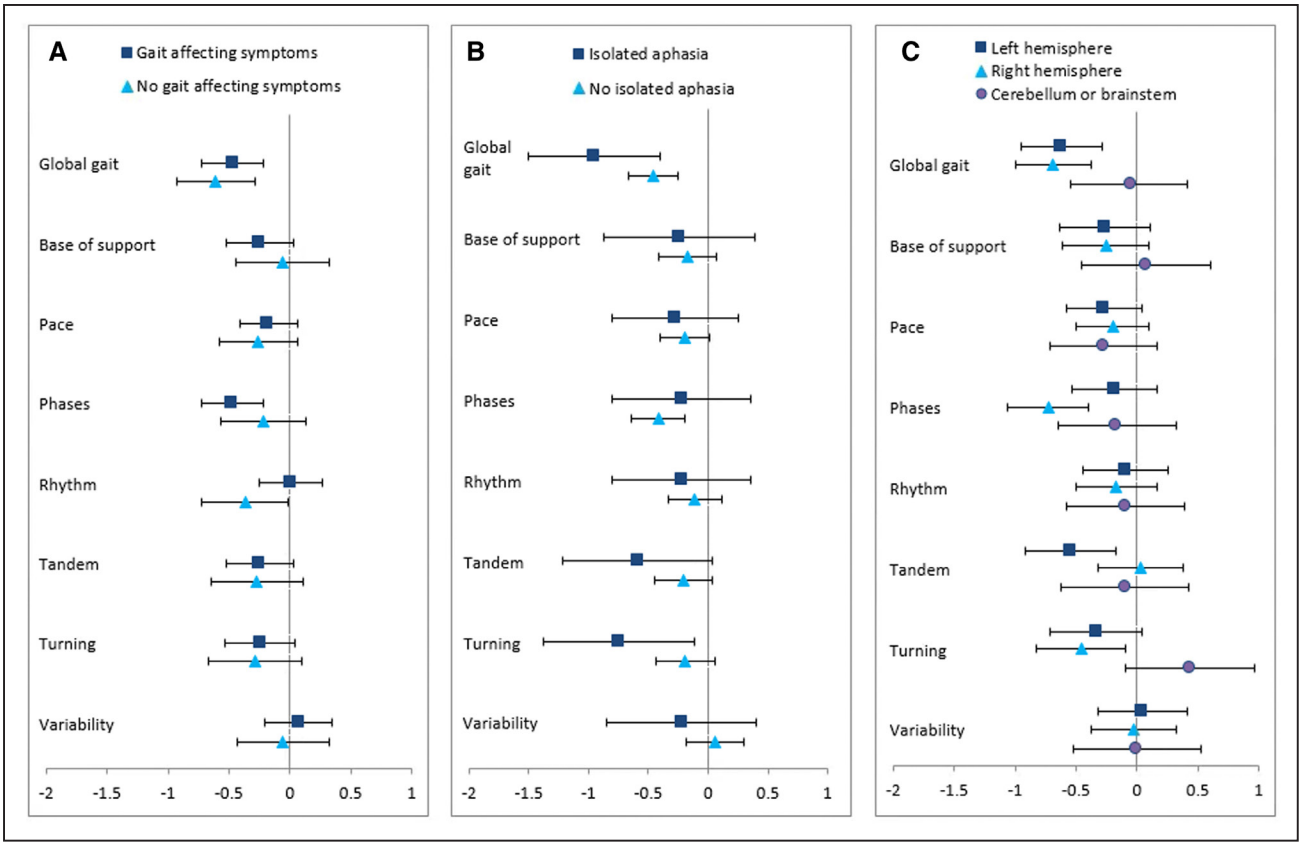

Figure 3. Association of prior ischemic stroke with global gait and independent gait domains.
Ischemic stroke patients were stratified by the presence of symptoms that may affect gait (weakness, lower limb; sensory symptom, lower limb; disturbed coordination, lower limb; reduced skillfulness, lower limb; walking difficulty; neglect; visual deficit; or diplopia; **A**), by aphasia as only presenting symptom (**B**), and by clinical localization of stroke (**C**). Data points represent SD change of global gait or gait domain in participants with prior stroke compared with participants without stroke; bars indicate 95% CIs. Analyses were adjusted for age, sex, education, smoking, body mass index, cholesterol, HDL (high-density lipoprotein), systolic and diastolic blood pressure, blood pressure–lowering medication, lipid-lowering medication, diabetes mellitus type 2, atrial fibrillation, smoking, and global cognition.

is still associated with a worse gait compared with stroke-free participants. Furthermore, we found that this association is amplified in participants with cognitive impairment. Our study suggests that stroke not only has a direct impact on gait through neurological impairment but also has an indirect effect possibly through accelerated gray and white matter disruption and neurodegeneration. Longitudinal research including dual-task and side-specific gait assessment and neuroimaging is needed to further elucidate the underlying pathways.

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Affiliation

Departments of Epidemiology (A.H., S.K.L.D., L.J.D., M.A.I., M.K.I.) and Neurology (A.H., P.J.K., M.K.I.), Erasmus MC University Medical Center, Rotterdam, the Netherlands.

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Disclosures

None.

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