PAPER

Quantitative gait dysfunction and risk of cognitive decline and dementia

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J Neurol Neurosurg Psychiatry 2007;**78**:929–935. doi: 10.1136/jnnp.2006.106914

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Received 14 September 2006
Revised 26 December 2006
Accepted 9 January 2007
Published Online First 19 January 2007

Background: Identifying quantitative gait markers of preclinical dementia may lead to new insights into early disease stages, improve diagnostic assessments and identify new preventive strategies.
Objective: To examine the relationship of quantitative gait parameters to decline in specific cognitive domains as well as the risk of developing dementia in older adults.
Methods: We conducted a prospective cohort study nested within a community based ageing study. Of the 427 subjects aged 70 years and older with quantitative gait assessments, 399 were dementia-free at baseline.
Results: Over 5 years of follow-up (median 2 years), 33 subjects developed dementia. Factor analysis was used to reduce eight baseline quantitative gait parameters to three independent factors representing pace, rhythm and variability. In linear models, a 1 point increase on the rhythm factor was associated with further memory decline (by 107%), whereas the pace factor was associated with decline on executive function measured by the digit symbol substitution (by 29%) and letter fluency (by 92%) tests. In Cox models adjusted for age, sex and education, a 1 point increase on baseline rhythm (hazard ratio (HR) 1.48; 95% CI 1.03 to 2.14) and variability factor scores (HR 1.37; 95% CI 1.05 to 1.78) was associated with increased risk of dementia. The pace factor predicted the risk of developing vascular dementia (HR 1.60; 95% CI 1.06 to 2.41).
Conclusion: Our findings indicate that quantitative gait measures predict future risk of cognitive decline and dementia in initially non-demented older adults.

Dementia is widely recognised as a global public health problem. There is increasing evidence that subtle clinical and physiological abnormalities precede the diagnosis of dementia by many years.[1] Identifying early markers of dementia may help identify high risk elderly patients for further evaluation and interventions. We previously reported in another cohort (Bronx Ageing Study)[2] that clinical gait abnormalities predicted risk of non-Alzheimer's dementia in older adults. While an integral aspect of patient evaluation, clinical gait assessments have several limitations. Most assessment protocols are not standardised or validated. Most gait abnormalities are mild,[3] and detection is dependent on the examiner's expertise. Clinicians may use the presence of gait abnormalities to assign dementia subtypes raising issues of diagnostic circularity.[2 4] Quantitative gait assessments, independent of clinical diagnosis, may help avoid these shortcomings.

It has been reported that slowing of gait may precede development of cognitive impairment.[5–8] However, gait is a complex motor behaviour with many measurable facets besides velocity, and with an intricate relationship to different aspects of cognition.[9] Moreover, single gait variables are often highly correlated with one another so that their independent effects on risk of cognitive decline and dementia may be hard to observe while adjusting for other gait variables. To address this issue, we used factor analysis to identify independent gait domains derived from quantitative assessments.[9 10] Gait variability has been linked to multiple adverse outcomes in older adults, including Alzheimer's disease.[11 12] However, its role in predicting dementia is not established. Hence we included gait variability measures in our analyses.

Based on our and other studies[2 5–9] we hypothesised that quantitative gait assessments may help reveal subtle alterations in brain function early in the course of the dementia. Our aim was to examine the relationship of quantitative gait parameters with decline in general and specific cognitive domains in a population of non-demented older adults. We also studied whether quantitative gait parameters could predict risk of incident dementia. Identifying quantitative gait markers of preclinical dementia may provide new insights into early biological stages of dementia, improve diagnosis and risk assessment procedures, and facilitate development of novel preventive strategies.

METHODS

Study population

We undertook a prospective cohort study nested within the Einstein Ageing Study.[3 13 14] The primary aim of the Einstein Ageing Study was to identify risk factors for dementia. Study design and methods have been previously reported.[3 13 14] In brief, potential subjects (age 70 years and over) identified from population lists of Bronx County were contacted by letter explaining the purpose and nature of the study, and then by telephone. The telephone interview included verbal consent, medical history questionnaire and cognitive screening tests.[13] Following the interview, an age stratified sample of subjects who matched on a computerised randomisation procedure were invited for further evaluation at our research centre. Informed consent was obtained at enrolment according to protocols approved by the local institutional review board. Subjects returned at yearly intervals. Between 1993 and 2005, 1148 subjects were enrolled. Mean age at entry was 77.4 (5.2) years. The inception cohort was mostly women (59%) and 67% were white subjects (black 27%).

Abbreviation: HR, hazard ratios

Table 1 Definition of quantitative gait parameters. All quantitative parameters described below are automatically calculated as the mean of two trials by the gait software

Variable	Unit	Definition
Velocity	cm/s	Distance covered on two trials by the ambulation time
Stride length	cm	Distance between heel points of two consecutive footfalls of the same foot. Variability in length between strides is reported as standard deviation.
Cadence	steps/min	No of steps taken in a minute
Double support	s	Time elapsed between first contact of current footfall and the last contact of previous footfall, added to the time elapsed between the last contact of current footfall and the first contact of next footfall
Swing time	s	Duration when the foot is in the air and is the time taken from toe off to heel strike of the same foot. Variability in swing time is reported as standard deviation.
Stance time	s	Duration when the foot is on the ground and is the time taken from heel strike to toe off of the same foot

Quantitative gait

Quantitative gait evaluations were introduced in 2001. Of the 510 subjects seen between 2001 and 2005, 427 (84%) had quantitative assessments. Reasons for not obtaining assessments included tester unavailability (n = 53), subject illness (n = 10) or refusal (n = 20). Subjects who did and did not receive quantitative assessments were similar in terms of age, sex, education and cognitive status at enrolment. We report follow-up until March 2006.

Research assistants conducted quantitative studies, independent of clinician's evaluations, using a computerised walkway (180×35.5×0.25 inches) with embedded pressure sensors (GAITRite; CIR systems, Havertown, PA, USA).[14] Subjects were asked to walk on the mat at their ''normal pace'' for two trials in a quiet well-lit hallway wearing comfortable footwear and without any attached monitoring devices. Start and stop points were marked by white lines on the floor, and included three feet from the walkway edge for initial acceleration and terminal deceleration. Based on footfalls recorded on the walkway, the software automatically computes gait parameters (see table 1) as the mean of two trials. The GAITRite system is widely used in clinical and research settings, and excellent reliability has been reported in our and other centres.[14 15]

Cognitive assessment

An extensive neuropsychological test battery validated in our and other ageing populations was administered at all visits to all subjects to assess cognition and assign dementia diagnosis.[2 13] We examined performance on the following tests based on associations between gait and cognition noted in our and other studies[5–9]: general cognition (Blessed Information–Memory–Concentration Test[16]), memory (Free and Cued Selective Reminding Test[17]), executive function (Digit Symbol Substitution[18] and Letter Fluency Tests),[19] and attention (Digit Span[18]).

Covariates

Data collected at each visit from subjects and caregivers included sociodemographic variables (age, sex and education), medications and depressive symptoms.[3 13 20] Research assistants administered the Lawton–Brody scale[21] to assess limitations on activities of daily living. Study clinicians also obtained a history of functional decline during the clinical evaluation.[2 9 13] The presence of diabetes, heart failure, hypertension, angina, myocardial infarction, depression, stroke, Parkinson disease, chronic obstructive lung disease and arthritis was used to calculate a summary comorbidity index, as previously described.[9] Additional sources consulted included medical records and primary care providers. Study neurologists conducted gait evaluations at each visit using previously described methods.[2 3 14] Abnormal gaits were classified as non-neurological (eg, arthritis) or neurological (hemiparetic, unsteady, ataxic, spastic, neuropathic, parkinsonian and frontal).[2 3] Gait abnormalities were clinically graded as mild (walks without assistance), moderate (uses walking aids) or severe (wheelchair bound or stands with assistance).[2 3] Clinicians computed the Hachinski ischaemic score as a cerebrovascular disease risk score based on medical history and examination.[22]

Dementia diagnosis

During follow-up, subjects with suspected dementia received a diagnostic workup, including imaging studies and blood tests.[2 13] Triggers included new cognitive complaints by subjects or caregivers, study staffs' observations and a pattern of worsening neuropsychological test scores.[2 13] All available clinical and neuropsychological information on all subjects was reviewed at consensus case conferences attended by study neurologists, neuropsychologist and a social worker, irrespective of whether subjects had triggers or whether or not they were evaluated for dementia. Dementia diagnosis was assigned using the Diagnostic and Statistical Manual, fourth edition,[23] and subtyped using established criteria for Alzheimer's disease,[24] vascular dementia[4] and other dementias. In subjects diagnosed with dementia, neuroimaging was used to help allocate the diagnosis of ''probable'' Alzheimer's disease or ''probable'' vascular dementia. We have reported good agreement between clinical diagnoses of Alzheimer's disease,[25] vascular dementia[2] and dementia with Lewy bodies,[26] and pathological findings in our study. Study clinicians did not have access to quantitative gait parameters during evaluations or at the diagnostic conferences.

Data analysis

Baseline characteristics were compared with descriptive statistics, applying non-parametric tests as appropriate. Factor analysis using the principal component method was performed on baseline scores on eight individual gait variables in 399 non-demented subjects.[10] The initial factors were then subjected to an orthogonal varimax rotation to reduce the larger number of highly correlated variables to a smaller number of uncorrelated independent predictors to be used in the final analysis. To identify clinical correlates of quantitative gait dysfunction, the prevalence of neurological gait abnormalities[2] among subjects in the lowest tertile of each factor was examined.

Firstly, to determine whether gait was related to decline on specific cognitive domains, regardless of development of dementia, linear mixed effects models controlled for age, sex and education were applied to the 399 initially non-demented subjects.[27] A random intercept was included in the model to allow the entry point to vary across individuals. The ''factor'' term in the model (see table 5) represents the association between gait factors and selected tests at baseline. ''Time''

Table 2 Baseline characteristics by final cognitive status

Variable	No dementia (n = 366)	Developed dementia (n = 33)	p Value
Age (y)	78.9 (4.7)	82.6 (5.7)	0.003
Women (%)	56.3	57.6	0.89
Education (y)	13.4 (3.5)	14.0 (3.6)	0.36
Clinical gait abnormalities (%)			
Neurological	19.0	27.0	0.11
Non-neurological	16.5	9.2	0.20
Mixed	5.2	3.1	0.81
Falls (%)	22	24	0.89
ADL scale limitations* (%)			
Physical self maintenance	1	3	0.33
Instrumental	5	17	0.03
Illness index (0–10)	2.4 (1.7)	2.5 (1.7)	0.90
Hachinski ischaemic score (0–15)	2.5 (1.7)	3.2 (2.7)	0.34
Blessed Test score (0–32)	2.4 (2.2)	5.8 (3.7)	<0.001
FCSRT, total recall (0–48)	47.7 (1.1)	47.1 (1.2)	0.03
Digit Symbol Substitution Test, total	37.9 (12.6)	28.3 (10.3)	<0.001
Letter Fluency Test, total	35.2 (13.1)	28.2 (12.9)	0.005
Digit Span Test, total	13.4 (3.6)	11.5 (4.0)	0.01
Geriatric Depression Scale (0–15)	1.9 (2.0)	2.2 (2.4)	0.21

ADL, activities of daily living; FCSRT, Free and Cued Selective Reminding Test.
Values are mean (SD) unless otherwise stated.
*Subjects with impairment in one or more physical self maintenance or instrumental activities on the Lawton–Brody scale.[21]

represents average rate of change in test performance over time. An interaction between ''factor'' and ''time'' was included to model the effect of baseline gait factors on rate of change in cognitive function. We analysed performance at baseline and yearly follow-up visits on the Blessed Test[16] and specific cognitive domains, including memory,[17] executive function[18 19] and attention.[18] Model assumptions were examined graphically and analytically, and were adequately met.

Cox proportional hazards models[28] were used to compute hazard ratios (HR) with 95% confidence intervals (CI) for developing dementia[19] based on baseline gait factors in 399 non-demented subjects.[3] We also studied Alzheimer's disease[24] and vascular dementia[4] as outcomes.[28] Given the low number of incident Alzheimer's disease and vascular dementia cases, these secondary analyses are intended to support and complement the linear models examining decline in individual cognitive domains implicated in the early stages of these dementia subtypes.

All analyses reported are adjusted for age, sex and education. We conducted analyses using both follow-up time and age as the time scale, and the results were not materially different. Using age as the time scale in Cox models is considered more appropriate than follow-up time in cohort studies.[29] When age is the time scale, the hazard function can be directly interpreted as the age specific incidence function and age is accounted for in the non-parametric term of the hazard function providing a more flexible and effective control of age.[29] Time to event was from age at assessment, which accounts for the left truncation occurring at study inclusion, to age at dementia or to final study contact, whichever came first. Proportional hazards assumptions of the models were examined analytically and graphically and were adequately met.

Finally, to corroborate our findings and facilitate comparisons with other studies, we derived a reduced set of predictors selected from the highest loading variable on each factor (see table 4). We also included velocity, which has been reported to predict dementia.[5–8] The association of these single variables with incident dementia were examined individually as well as entered together in Cox models, adjusted for age, sex and education.

RESULTS

Of the 427 subjects, 28 with dementia diagnosed at or before the visit they received the quantitative assessments were excluded. In the remaining 399 subjects over 798 person years (median 2 years), 33 developed dementia.[23] Of these, 12 were subtyped as Alzheimer's disease,[24] 17 vascular dementia[4] and 4 other dementias. Of the 399 subjects (median 3 visits), 384 had one or more yearly follow-ups, 16 were active but had not had their first follow-up visit and 6 died.

Table 2 shows the characteristics of the participants at enrolment. Subjects with incident dementia were older at entry. There were no significant group differences in abnormal gait subtypes.[2 3] Most gait abnormalities were of mild severity (61.9%). Moderate (35.4%) and severe (2.7%) gait abnormalities were less common in this community based sample as

Table 3 Quantitative gait parameters at baseline by final cognitive status.

Parameter	No dementia (n = 366)	Developed dementia (n = 33)	p Value
Velocity (cm/s)	94.1 (23.6)	79.5 (23.0)	0.002
Cadence (steps/min)	101.5 (12.1)	95.3 (11.8)	0.007
Stride length (cm)	110.6 (21.1)	99.3 (23.1)	0.004
Stride length variability (SD)	4.55 (2.82)	5.56 (2.42)	0.01
Swing time (s)	0.43 (0.04)	0.45 (0.05)	0.02
Swing time variability (SD)	0.03 (0.02)	0.04 (0.02)	0.001
Stance time (s)	0.77 (0.13)	0.84 (0.18)	0.01
Double support time (s)	0.34 (0.11)	0.37 (0.11)	0.13

Values are mean (SD).

Table 4 Factor loading of eight quantitative variables on the three independent gait factors rotated and extracted by factor analysis

Gait variable	Pace factor	Rhythm factor	Variability factor
Velocity (cm/s)	–0.891	–0.322	–0.140
Stride length (cm)	–0.948	0.064	–0.146
Double support time (s)	0.773	0.468	0.028
Cadence (steps/min)	–0.463	–0.863	–0.096
Swing time (s)	–0.027	0.927	0.149
Stance time (s)	0.631	0.714	0.077
Stride length variability (SD)	0.047	0.058	0.944
Swing time variability (SD)	0.487	0.319	0.538
Variance explained (%)	39.3	31.8	15.7

Higher factor scores denote worse performance.

previously reported.[3] A higher proportion of subjects who developed dementia reported limitations on instrumental but not basic activities of daily living. While the mean scores on the cognitive test scores were in the normal range, subjects who developed dementia had worse scores compared with controls at enrolment.

Table 3 shows impairment in multiple baseline gait variables compared with controls in initially non-demented subjects who went on to develop dementia.

Factor analysis with varimax rotation yielded exactly three orthogonal factors that accounted for 87% of the variance in baseline quantitative gait performance (table 4).[10] The factor with the highest variance had strong loadings by velocity and length measures, and was termed ''pace'' factor. The second loaded on variables reflecting gait rhythm such as cadence and timing, and was termed ''rhythm'' factor. The final factor loaded heavily on gait ''variability'' measures.[11 12] Mean factor score was 0 (SD 1). The factors can be conceptualised as summary risk scores with higher scores denoting worse performance.

Cognition

Table 5 summarises the results of our primary analyses using linear models.[27] Only the pace factor was associated with global cognitive decline measured using the Blessed Test. At the average level of the pace factor, Blessed scores worsened by 0.23 points per year. This rate increased annually by 0.15 points (by 65%) for every additional point on the baseline pace score.

To determine whether quantitative gait dysfunction was related to decline in some cognitive domains but not others, we examined selected tests (table 5). Episodic memory declined by 0.15 units (by 107%) for each 1 point increase in rhythm factor scores. Each 1 point increase in the pace factor was associated with an increased annual rate of decline in executive function measured on the Digit Symbol Substitution Test by 0.73 points (by 29%) and on the Letter Fluency Test by 0.46 points (by 92%). Variability was not associated with decline on general or specific cognitive measures.

Dementia

Modelled as a continuous variable (table 6), baseline rhythm (HR 1.48; 95% CI 1.03 to 2.14; $p = 0.03$) and variability factors (HR 1.37, 95% CI 1.05 to 1.78; $p = 0.02$) predicted future risk of dementia. The incident dementias were diagnosed early and at mild severity; mean Blessed score was 10.5 (3.9) (worst score 32, >7 abnormal)[16] at diagnosis.

When we excluded nine subjects who developed dementia in the first year following quantitative assessment from the analysis to account for any diagnostic misclassification and the possibility that quantitative abnormalities may occur only close to the time of dementia diagnosis, the significant associations noted between gait factors and dementia were unchanged. Both slow and fast gait velocity may be associated with increased gait variability. When the analyses were repeated using coefficient of variation (SD/mean ×100) instead of SD to define variability, the rhythm (HR 1.53; 95% CI 1.01 to 2.21) and variability factors (HR 1.46, 1.14 to 1.86) still predicted incident dementia.

Baseline neuropsychological test performance was worse in subjects who went on to develop dementia, although most

Table 5 Summary of association of the three gait factors with baseline and rate of change on general and specific cognitive domains assessed by linear mixed models, controlled for age, sex and education

Cognitive domain	General	Memory	Executive function		Attention
Cognitive test	**Blessed**	**FCSRT**	**Digit Symbol**	**Letter Fluency**	**Digit Span**
Pace factor					
Factor	0.40 (0.14, 0.66)	–0.0002 (–0.15, 0.15)	–3.57 (–4.86, –2.29)	–3.02 (–4.28, –1.77)	–0.53 (–0.89, –0.16)
Time	0.23 (0.11, 0.34)	–0.14 (–0.27, –0.02)	2.48 (2.08, 2.88)	0.50 (0.16, 0.84)	0.71 (0.58, 0.83)
Factor×time	**0.15 (0.03, 0.27)****	–0.09 (–0.22, 0.04)	**–0.73 (–1.15, –0.31)*****	**–0.46 (–0.82, –0.11)*****	–0.09 (–0.23, 0.04)
Rhythm factor					
Factor	0.34 (0.08, 0.59)	–0.05 (–0.19, 0.08)	–1.05 (–2.30, 0.19)	–0.92 (–2.14, 0.29)	–0.18 (–0.53, 0.18)
Time	0.23 (0.11, 0.34)	–0.14 (–0.27, –0.02)	2.48 (2.08, 2.88)	0.50 (0.16, 0.84)	0.71 (0.58, 0.83)
Factor×time	0.05 (–0.07, 0.17)	**–0.15 (–0.28, –0.02)***	–0.09 (–0.51, 0.33)	–0.01 (–0.37, 0.34)	–0.09 (–0.22, 0.04)
Variability factor					
Factor	0.16 (–0.08, 0.41)	–0.11 (–0.24, 0.02)	–0.61 (–1.81, 0.58)	–0.20 (–1.36, 0.96)	–0.14 (–0.48, 0.20)
Time	0.23 (0.11, 0.34)	–0.14 (–0.27, –0.02)	2.48 (2.08, 2.88)	0.50 (0.16, 0.84)	0.71 (0.58, 0.83)
Factor×time	0.08 (–0.04, 0.20)	0.04 (–0.09, 0.16)	–0.11 (–0.53, 0.32)	–0.21 (–0.57, 0.15)	0.07 (–0.05, 0.20)

FCSRT, Free and Cued Selective Reminding Test.
See methods for explanation of model terms.
Values are estimates with 95% CI.
Significant interactions are in bold.
*p=0.02, **p=0.01, ***p<0.001.

Table 6 Hazard ratios with 95% CI for developing any dementia, Alzheimer's disease and vascular dementia as a function of baseline quantitative gait factors adjusted for age, sex and years of education

	Hazard ratio (95% CI)		
	Dementia (n = 33)	Alzheimer's disease (n = 12)	Vascular dementia (n = 17)
Pace	1.30 (0.95 to 1.78)	0.95 (0.48 to 1.88)	1.60 (1.06 to 2.41)
Rhythm	1.48 (1.03 to 2.14)	1.55 (0.81 to 2.99)	1.59 (0.95 to 2.67)
Variability	1.37 (1.05 to 1.78)	1.18 (0.67 to 2.00)	1.22 (0.78 to 1.9)

Higher factor scores denote worse performance.

scores were within the normal range (table 1). To examine whether quantitative gait abnormalities predicted dementia independent of baseline cognitive test performance, we repeated the full models with additional adjustments for memory and executive function. Adjusting for baseline memory scores[17] in the full model made the association of the rhythm factor with incident dementia non-significant (HR 1.36, 95% CI 0.86 to 2.13), but not the variability factor (HR 1.56, 95% CI 1.10 to 2.23). Adjusting for digit symbol scores[18] made the association of the variability factor with dementia non-significant (HR 1.29, 95% CI 0.99 to 1.67), but not the rhythm factor (HR 1.48, 95% CI 1.01 to 2.15).

Neurological gaits, which we reported to predict risk of vascular dementia in another cohort,[2] were diagnosed in 94 subjects at baseline. Prevalence of neurological gaits among subjects with scores in the worst tertile on the rhythm factor was 27%, variability 31% and pace 41%. The association of the rhythm (HR 1.55; 95% CI 1.06 to 2.27) and variability factors (HR 1.35; 95% CI 1.03 to 1.76) and dementia remained significant, even after adjustments for neurological gaits,[2] chronic illnesses[9] and the Hachinski ischaemic score.[22] Exclusion of subjects with Parkinson disease and strokes did not materially change the results.

Dementia subtypes

None of the factors predicted Alzheimer's disease (table 6). Only the pace factor (HR 1.60; 95% CI 1.06 to 2.41; $p = 0.02$) predicted the risk of vascular dementia.

Single gait variables

Swing time (1/10 s), stride length (cm) and stride length variability (SD) were the highest loading individual variables on the three factors. Swing time (HR 3.11, 95% CI 1.43 to 6.78), stride length (cm) (HR 0.98, 95% CI 0.96 to 1.00), stride length variability (SD) (HR 1.71, 95% CI 1.19 to 2.45) and velocity (cm/s) (HR 0.98, 95% CI 0.96 to 0.99) predicted dementia when each variable was individually fitted into the Cox model adjusted for age, sex and education. However, these individual variables were highly correlated, and did not show independent associations when entered together in the same model.

DISCUSSION

Our findings show that quantitative gait dysfunction predicts risk of cognitive decline in initially non-demented older adults. The pace factor predicted decline in executive function, the cognitive domain primarily involved in vascular dementia.[30] A 1 point increase in the pace factor predicted decline on executive function measured by the Digit Symbol Substitution[18] (by 29%) and the Letter Fluency tests[19] (by 92%). A 1 point increase in the rhythm factor was associated with episodic memory[17] decline (by 107%). Quantitative gait dysfunction also predicted risk of dementia. A 1 point increase in both the rhythm (by 48%) and variability factors (by 37%) predicted risk of developing dementia, adjusted for age, sex and education. The associations remained robust after additional adjustments for other potential confounders, such as medical illnesses, cerebrovascular disease, baseline cognitive status, preclinical dementia and neurological gaits.

This study has a number of limitations that need to be considered. While our gait variables were selected based on our and prior studies,[5–9] all possible aspects of gait were not measured or analysed. However, most other gait variables (such as step length) either can be derived or are highly correlated with our selected variables. Subjects walked at their normal pace. In future studies, walking at different speeds, or using stressors such as the walking while talking test[31] could be studied as predictors of cognitive decline. This nested cohort study was necessarily restricted to subjects who received quantitative assessments since 2001 in our study, but subjects seen previously in our cohort were not differentially excluded and our analyses accounted for staggered entry.[29] Our small sample size, short follow-up and multiple analyses necessitate caution. However, to our knowledge, this is among the first and largest study to report longitudinal associations between multivariate quantitative gait measures and cognition.[5–9] The confidence intervals for significant associations in our analyses were narrow, but we may have seen stronger associations with additional follow-up. While some diagnostic misclassification is inevitable, we have reported good reliability for our dementia diagnostic procedures using pathology as the gold standard.[2 25 26]

The upper brainstem contains neurons that control musculature for gait through their projections to the lower brainstem and spinal cord.[32] These brainstem nuclei are, in turn, under the influence of descending inputs from the basal ganglia, cerebellum and cortical motor areas.[32 33] It is assumed that stride length and velocity (pace) are controlled supraspinally by phasic output from the basal ganglia to the supplementary motor area, whereas spinal and brainstem mechanisms may determine cadence (rhythm).[32 33] Neural substrates of gait variability are less understood.[11] It has been suggested that regulation of gait variability is automated and requires minimal cognitive input in healthy adults, but may be perturbed in the presence of disease.[11 12]

The specificity of the association of pace with executive function and vascular dementia (and not incident dementia overall) favours a vascular aetiology. We have reported a higher prevalence of mixed vascular pathology with advancing age in subjects with dementia in this cohort.[25] It is possible that some of our associations reflect mixed pathology although neuroimaging was used to assign dementia subtypes. Decreased velocity and stride length (which load on the pace factor) in older adults were associated with white matter disease and strokes on neuroimaging in a prior study.[34] Then again, the association of gait rhythm and variability with dementia in our study was significant even when controlled for cerebrovascular disease or excluding subjects with strokes. The presence of temporal lobe atrophy on imaging studies has been previously

correlated with poor mobility, independent of cerebrovascular disease.[35]

Gait rhythm predicted memory decline, which can start many years before Alzheimer's disease is diagnosed.[1] Increased gait variability has been reported in individuals with Alzheimer's disease.[11 12] However, Alzheimer involvement of the motor cortex is said to occur only late in the disease process and gait disturbances early in the disease is considered an exclusion criterion.[2 36–38] The low prevalence of neurological gaits among subjects in the worst factor score tertiles suggests that quantitative gait abnormalities may not have clinical correlates. Alternatively, non-specific gait patterns associated with quantitative gait abnormalities may be under-recognised by clinicians. Our study protocol[2 3] required clinicians to judge whether gait is normal or abnormal (including non-specific unsteady gaits) before assigning subtypes, minimising this possibility. A recent clinicopathological study reported that Parkinsonian gait in the absence of idiopathic Parkinson disease was correlated with substantia nigra neurofibrillary tangles, even in cases without clinical Alzheimer's disease or with minimal Alzheimer pathology.[39] These findings raise the possibility that Alzheimer pathology may involve brain regions regulating gait early but the subtle quantitative gait abnormalities may be overshadowed by behavioural symptoms. The unique relationships of individual gait factors with specific cognitive domains suggest aetiological roles for both vascular and neurodegenerative mechanisms. These findings also identify potential gait pathways, which may be amenable to intervention if our results are validated.

The strengths of this study include our validated diagnostic procedures,[2 13 25 26] systematic quantitative assessments[2 3 9] and minimal attrition. We conducted a number of sensitivity analyses to account for potential confounders such as preclinical dementia and neurological gaits. Given the limitations of categorical clinical gait classifications, the continuous quantitative gait measures may better help characterise motoric manifestations of the preclinical stages of dementia. Clinicians were blinded to quantitative gait data before and at the diagnostic conferences, minimising bias and diagnostic circularity. The quantitative measures are easily collected, do not require attached monitoring devices and do not require extensive training or specialised personnel.

Gait factors may be conceptualised as summary risk scores that can be easily derived for use in clinical or research settings. A 1 point (1 SD) increase in the factor score is associated with SD unit changes in all component variables with a larger contribution from higher loading variables. Factor analysis has been used to explain other complex physiological phenomenon,[40] and appears to be well suited for studying gait, as suggested by our findings and others.[41] This approach enabled us to identify empirically defined and statistically independent factors representing distinct gait domains. The single gait variables identified from the three factors support our main findings, and will facilitate comparisons with other studies.[5–8] We also identified single variables other than velocity,[5–8] such as swing time, that predicted dementia.

In conclusion, quantitative gait dysfunction is a marker for preclinical stages of dementia. The quantitative gait abnormalities and neuropsychological impairments at study onset can be interpreted as the consequence of accumulating dementia pathology. Quantitative gait performance predicts dementia even after accounting for baseline cognitive performance. However, our intent is not to replace neuropsychological tests in dementia assessment but to understand motoric manifestations of early dementia stages.[2 5–9] Vascular and non-vascular substrates, neuroanatomical pathways and physiological processes underlying quantitative gait dysfunctions should be further explored to develop effective preventive interventions to reduce the burden of dementia.

ACKNOWLEDGEMENTS

This paper was orally presented in part at the Fourth International Congress on Vascular Dementia, Porto, Portugal, in October 2005, and at the First International Congress on Gait and Mental Function, Madrid, Spain, in February 2006.

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Funding support: The Einstein Ageing Study is funded by the National Institute on Ageing (grant AG03949). Dr Verghese is funded by the National Institute on Ageing (grants K23 AG024848 and RO1 AG025119).

Competing interests: None.

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