Dual-Task Gait Predicts Incident Dementia in Mild Cognitive Impairment.

Results from the Gait and Brain Study

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Tweet: Dual-task gait test (walking while performing a cognitive challenge) can identify MCI patients at risk of progression to dementia

ABSTRACT

IMPORTANCE: Gait performance is affected by neurodegeneration in aging and has the potential to be used as a clinical marker for progression from mild cognitive impairment (MCI) to dementia. A dual-task gait test evaluating the cognitive-motor interface may predict dementia progression in older adults with MCI.

OBJECTIVE: To determine whether a dual-task gait test is associated with incident dementia in MCI.

DESIGN, SETTING, AND PARTICIPANTS: The Gait and Brain Study is an ongoing prospective cohort study of community-dwelling older adults that enrolled 112 older adults with MCI. Participants were followed-up to six years with bi-annual visits including neurologic, cognitive, and gait assessments. Data were collected from July 2007 to March 2016 and analyzed from June 2016 to December 2016.

MAIN OUTCOME AND MEASURES: Incident all-cause dementia was the main outcome measure and single and dual-task gait velocity and dual-task costs were the tested independent variables. A neuropsychological-test battery was used to assess cognition. Gait velocity was recorded under single and three separate dual-task conditions using an electronic walkway (GAITRite System). Dual-task gait cost was defined as the percent change between single (S) and dual-task (D) gait velocities: [(S-D)/S] x 100. Multivariable Cox proportional hazards modeling was used to estimate the association between risk of progression to dementia and the independent variables, adjusted for age, sex, education, comorbidities, and cardiovascular diseases, and baseline cognitive function.

RESULTS: Among 112 study participants with MCI, mean age (SD) was 76.6 (6.9) years, 55

(49.1%) were women, and 27 (24.1%) progressed to dementia with an incidence rate (IR) of 121 per 1000 person-years. Slow single-task gait velocity (<0.8 m/s) did not predict progression to dementia (*P*=.113); while high dual-task cost in gait velocity while counting backwards (Hazard ratio, HR, 3.84; 95% CI, 1.58-9.31, *P*= .003) and naming animals (HR, 2.51; 95% CI, 1.07-5.89; *P*= .034) were associated with dementia progression (IR=155 per 1000 person-years). The models remain robust after adjusting by baseline cognition expect for dual dual-task cost in gait velocity while naming animals.

CONCLUSION AND RELEVANCE: Dual-task gait is associated with progression to dementia in MCI patients. Dual-task gait testing is easy to administer and may be used by clinicians to decide further biomarker testing, preventive strategies, and follow-up planning in patients with MCI.

Key Points (75-100 words) – At 98 words

Question. Can dual-task gait testing (assessing gait while performing a challenging cognitive task) identify MCI patients at risk of progression to dementia?

Findings. In this cohort study of 112 elderly subjects with MCI with up to six years of follow-up, poor performance in dual-task gait testing was significantly associated with a two to three-fold risk of dementia incidence independent of age, sex, education, vascular factors, and comorbidities.

Meaning. Dual-task gait testing may serve clinicians to detect patients with MCI at higher risk of progression to dementia, allowing for optimization of further biomarker testing and initiation of early interventions.

INTRODUCTION

Mild cognitive impairment (MCI) is considered a pre-dementia state associated with a ten-fold increased risk of progression to dementia.[1] However, almost one third of individuals with MCI remain clinically stable after the initial diagnosis or even revert to normal cognitive functioning,[2] which highlights the potential hazard of considering MCI patients as a homogeneous group.[3] This heterogeneity of outcomes challenges clinical management once MCI is identified as it is problematic to accurately predict progression to dementia, including Alzheimer's disease (AD). To overcome this challenge, the identification of clinically useful and readily available biomarkers of progression to dementia, including motor markers, is highly needed in MCI.[4-7]

Over the past decade, large cohort studies have shown that motor impairment, in particular slowing of gait, is not only evident early in Alzheimer and non-Alzheimer dementias, but also predicts progression to dementia in the general population.[8-10] Although the main clinical hallmark of MCI is memory impairment,[11] motor dysfunction and gait impairment have been previously described.[8;11;12] Few studies have focused on dual-task gait testing (walking while simultaneously performing a cognitive challenge) as a means to determine the association between cognitive-motor interaction and risk of progression to dementia in subjects with MCI.[13;14] Dual-task gait testing challenges the cognitive component of locomotion and can provide insight into the mechanisms of brain motor control and cognitive performance.[13] Mechanistically, structural and functional brain imaging studies have shown that cognition and motor control share common brain networks, particularly in the prefrontal and temporal areas.[13;15-17] Based on the limited capacity model these networks can become overloaded when a

motor task is concurrently performed with a cognitive task, more so in cognitively-impaired individuals who have less cognitive reserve.[13;18]

As a test, the dual-task gait test is unique in that it reflects the motor-cognitive interface.[19-21]. There is a linear association between the magnitude of gait slowing while dual-tasking and deficits in executive, attention, and memory processes in MCI.[20;22-25] The magnitude of changes in gait during dual- task performance due to a concurrent cognitive challenge can be expressed as a dual-task cost, which adjusts for an individual's baseline gait characteristics.[26] To date, the capacity of dual-task gait testing to predict progression to dementia in subjects with MCI has not been investigated.

In this study, we examined the longitudinal association of dual-task gait performance and the incidence of dementia in a well characterized MCI cohort with 6 years of follow-up. We hypothesized that participants who progress to dementia would have a higher dual-task cost in gait velocity than participants who did not progress to dementia.

METHODS

Study participants

Participants were part of the "Gait and Brain Study", an ongoing prospective cohort study (clinicaltrial.gov identifier: NTC03020381) designed to determine whether quantitative gait deficits can predict incident cognitive and mobility decline, and progression to dementia among community-dwelling older adults. Design and logistics have been described in detail elsewhere.[27-29] After consent was obtained, participants underwent a comprehensive baseline evaluation as well as biannual assessments during 6 years of follow-up. For this analysis, participants were required to have at least two assessments including the baseline visit, and to

fulfill MCI diagnostic criteria.[3;30] All participants were community-living adults fulfilling the following inclusion criteria: age 65 years and older, able to walk 10 meters independently without a gait aid, having MCI as ascertained by scoring 0.5 on the global rating of the Clinical Dementia Rating (CDR) scale and satisfying the following four criteria:[1] i) subjective cognitive complaints; ii) objective cognitive impairment in at least one of the following cognitive domains: memory, executive function, attention, and language[3;30] ; iii) preserved activities of daily living[31] confirmed by clinician's interviews; iv) absence of dementia using criteria from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition revised (DSM IV-TR).[32] Exclusion criteria included lack of English proficiency, parkinsonism or any neurological disorder with residual motor deficits (e.g. stroke), musculoskeletal disorders of lower limbs (e.g. severe osteoarthritis or history of knee/hip replacement) affecting gait performance at clinical examination, use of neuroleptics or benzodiazepines, and major depression. Ethics approval was obtained from the University of Western Ontario Health Sciences Research Ethics Board and participants' signed informed consents were obtained at enrollment. Data collection occurred between July 2007 and March 2016.

Medical and cognitive assessments

Sociodemographic characteristics, comorbidities, chronic medications, physical activity level, history of falls, and basic and instrumental activities of daily living were collected using standardized questionnaires during face-to-face interviews (Table 1). Study clinicians performed a physical examination including a neurological exam on all participants.

Global cognition was assessed by using the Mini-Mental State Examination (MMSE)[33] and the Montreal Cognitive Assessment (MoCA),[34] with alternative test versions used in consecutive assessments to avoid potential learning effects. The CDR scale was also performed at all visits.[35] A neuropsychological test battery was administered to characterize MCI subtype and to help ascertain progression to dementia. Executive function was assessed using Trail Making Tests A and B;[36] verbal episodic memory using the Rey Auditory Verbal Learning Test;[37] naming using the Boston Naming Test; [38] attention using the Digit Span Test (forward and backward), and working memory using the Letter-Number Sequencing test.[39] Impaired cognitive domains were identified using a cut-off of 1.5 SD below the age-adjusted norms.[14;40] Participants were classified as pure amnestic MCI (a-MCI, impairment only in verbal episodic memory), as multidomain aMCI (ma-MCI, impairment in more than one domain including memory), and as as non-amnestic MCI (na-MCI, solely impairment in one or more non-memory tests).[14;41]

Gait assessments

Gait velocity under single and dual-tasks was assessed using an electronic walkway (GAITRite® System, 600 cm long and 64cm wide) which provides data to assess both spatial and temporal gait parameters.[27] Start and end points were marked on the floor one meter from either walkway end to avoid recording acceleration and deceleration phases. Each participant performed one practice trial walking on the mat. For the single-gait test, participants were asked to walk on the walkway at their usual pace in a quiet well-lit room wearing comfortable footwear, and without the use of any mobility aids For the dual-task tests, participants walked at their usual pace, while doing the following cognitive tasks aloud, i) counting backwards from one hundred by ones ii) subtracting serial sevens from one hundred and iii) naming animals. Rationale for dual-task

condition selection has been described elsewhere.[27] To balance and minimize the effects of learning and fatigue, only one trail was performed in each condition and the order of single and dual-tasks was randomized. Reliability has been previously established for this protocol in people with MCI.[27] The magnitude of the effect of the cognitive challenge on gait performance was assessed by calculating the dual-task gait cost (%), as ([single-task gait velocity – dual-task gait velocity]/ single-task gait velocity) x 100.[19]

Outcome variable

Incident dementia was the main endpoint, as determined by a clinician investigator during follow-up visits per DSM-IV-TR criteria[32] and when CDR increased to a score of one or higher. At the time of diagnosis, clinicians were blinded to baseline gait or baseline neuro-psychological test scores. The type of dementia was established using standardized clinical criteria for Alzheimer's disease (AD) dementia,[42] frontotemporal dementia,[43] Lewy body dementia,[44] and vascular dementia (VaD).[45] Participants were re-assessed after six months to confirm dementia status and subtype.

Predictor variables

Gait velocity and dual-task gait cost were our main predictor variables as they have been previously associated with cognitive performance in MCI studies.[14;28] These variables were modelled as continuous variables to ascertain the strength of associations, and as dichotomous variables to identify potential thresholds to be used in clinics. Slow gait velocity in the single-task condition was defined as <0.8 m/s, a threshold previously established for predicting adverse events, including cognitive decline, in ambulatory patients.[46-48] Since there is not an established

cut-off for dual-task gait testing, ROC curves were produced to determine the optimal threshold value for high dual-task gait cost as a predictor of dementia, for the three dual-tasks conditions.

Covariates

Analyses were adjusted for covariates that included demographics (age, sex, and educational level), number of comorbidities, a cardiovascular index [49](including hypertension, coronary heart disease heart failure, atrial fibrillation, and stroke/TIA) and baseline cognition..

Statistical Analysis

Demographics and clinical characteristics were summarized using either means and standard deviations, or frequencies and percentages, as appropriate. Comparisons of baseline characteristics between MCI who progressed (Progressed-MCI) to dementia and those who did not (Stable-MCI) were made using Chi square (X^2) or Student *t*-tests, as deemed appropriate. Multivariable Cox proportional hazards regression analyses were completed to assess the risk, measured as hazard ratios (HRs), for progression to dementia for gait velocity as continuous (single and dual-task gait velocity, and dual-task cost) and as dichotomous (slow gait velocity, and high dual-task gait cost in each condition) variables, unadjusted and adjusted for the above covariates. Dual-task cost cut-offs were determined using ROC analysis. Time to event was calculated from enrollment to the assessment visit at which dementia was diagnosed. Proportional hazards assumption was tested using methods based on scaled Schoenfeld residuals. To account for different follow-up times, incident dementia is also presented as incident rate (IR) expressed as "total person-years at risk" for all the models. Associations were also explored by stratifying dual-task gait velocities into quartiles. Statistical significance was set at $p < 0.05$ (two-

sided). Statistical analyses were conducted using SPSS (v21.0, IBM Corporation, Chicago) and occurred from June 2016 to December 2016.

RESULTS

Participant characteristics

One hundred and twelve participants aged 65 and older (mean age 76 ± 6.88; 49% women) were assessed with a mean follow-up of 24 months (range, 12 to 76 months). Characteristics of the study sample, stratified by progression to dementia (Progressed-MCI versus Stable-MCI) are presented in Table 1. Ninety two of our MCI participants fulfilled criteria for a-MCI while thirty for na-MCI. A total of 24% of the sample (n=27, 43% women) progressed to dementia, with an overall incidence rate (IR) of 121 per 1,000 person-years. From the 27 participants who progressed to dementia, 23 (85%) progressed to AD, 2 (7%) to Lewy body dementia, 1 (4%) to fronto-temporal dementia, and 1 (4%) to vascular dementia.

Table 1 shows that MCI participants who progressed to dementia were older and had fewer comorbidities. They had higher hypertension prevalence (70.4% vs 57.1%) and were more likely to carry at least one APOE ε4 allele, although these differences were not significant. Both groups had a mean baseline single-gait velocity above the normality cut-off of 0.8 m/s, however participants who progressed to dementia had a significantly lower dual-task gait velocity and higher dual-task gait cost in the three test conditions.

Associations between gait performance and incident dementia

Table 2 reports the Cox proportional hazard models for our main outcome, incident dementia, for our two predictor variables: gait velocity and dual-task gait cost. When modeling our predictors as a continuous variable (model 1, 2 and 3), single-gait velocity test failed to predict dementia, *P*=.098; while all dual-task gait velocity tests (velocities and costs) predicted progression to dementia, except for dual-task gait cost in serial sevens subtractions when adjusted by cogntion.

Modeling gait velocity as a dichotomous variables (model 4, 5 and 6) showed that slow single-task gait velocity (<0.8 m/s) failed to predict progression to dementia (*P*=.113). Alternative slow single-task gait velocity cut-offs, determined by ROC analysis (<1.08 m/s) or using 1.5 SD below the cohort mean gait velocity (<0.76m/s), were also not associated with incident dementia (eTable 1 in the Supplement). However, high dual-task cost in gait velocity while counting backwards (HR, 3.84; 95% CI, 1.58-9.31, *P*= .003) and naming animals (HR, 2.51; 95% CI, 1.07-5.89; *P*= .034) were both associated with dementia progression (Table 2, and Figures 1a and 1c). After adjusting for baseline cognition (MMSE scores, Model 3) the associations with progression to dementia still hold true but they are attenuated for dual-task gait as a dichotomous variable.

Associations were also analyzed by stratifying the sample into quartiles of dual-task gait velocity (eTable 2 in the Supplement). Participants in the lowest dual-task gait velocity quartile had the highest risk of progression to dementia while counting backwards (HR, 13.39; 95%CI, 3.76-47.75, *P*<.001, Figure 2a) and while naming animals (HR=9.89; 95%CI, 2.91-33.62; *P*<.001, Figure 2c).

Sensitive Analyses

Associations with APOE 4 carrier status and gait performance, single and dual-tasking, were explored and no significant differences were found. Baseline global cognition (MMSE and MoCA) was associated with incident dementia with similar ratios than dual- task gait (eTable X in the Supplement). Associations were attenuated after adjustments by baseline gait performance.

DISCUSSION

Our results suggest that dual-task gait testing can predict the progression to dementia in a well characterized cohort of older adults with MCI. Specifically, a high dual-task gait cost while counting backwards and naming animals was associated with an increased risk of progression to dementia by 2.4 and 3.8 times, respectively. The predictive ability of single-task gait performance appeared high though not statistically significant revealing that the unique utility of dual-task gait testing in the clinical encounter when assessing patients with normal gait velocity. To the best of our knowledge, this is the first study establishing the ability of dual-task gait testing to detect incident dementia in patients with MCI. [4;14;19;27;50-52] [4;14;19;27;50-54]

Assessing gait velocity is easy to perform and provides an excellent general measure of overall function. However, dual-task gait testing can uncover valuable subtleties regarding the role of cognitive control on a participant's gait.[46;55-58] It is also important to note that the single-task gait velocity in our MCI sample was above 0.8 m/s, the threshold recommended to identify slow gait indicative of adverse events, and consistent with the high functional abilities seen in the early stages of cognitive decline, and with previous studies assessing gait in MCI. [14;26;28] Thus, among our participants, using solely a slow

velocity threshold would have been insufficient to identify individuals at a high risk of progression to dementia.

Our results complement the recently described Motoric Cognitive Risk syndrome, where subjects with cognitive complaints and slower gait had a higher risk of developing dementia[7] by showing that dual-task gait may predict dementia in MCI subjects while single-task gait velocity does not. Whether dual-task changes in gait in MCI patients is associated with progression to vascular dementia or AD is unknown. Previous studies in general populations have suggested that gait slowing during dual-tasking is most likely associated with incident vascular dementia.[7;9] In the current study, dual-task gait change was mostly associated with AD, which can be explained by the fact that our study focused only in MCI individuals. Interestingly, emerging evidence is linking gait performance with AD neurodegenerative changes, as in a recent study that showed, in older adults free of dementia, that gait performance, including dual-task gait, was cross-sectionally associated with amyloid beta brain deposition[59;60], independent of the burden of vascular changes. Taken together, these data suggest that both vascular and neurodegenerative changes may contribute to dementia progression in MCI patients with impaired dual-task gait.[61]

The underlying mechanisms affecting dual-task gait performance remain not completely understood. What does seem clear is that executive demands used for gait and for the selected cognitive tasks may share a similar pathogenic mechanism at the brain level.[28;62;63] Episodic memory, a cognitive domain that was affected in all of our participants who progressed to dementia, relies on frontal-hippocampal circuits that are also central for gait control. In addition, gait control also relies on the prefrontal-striatal networks that are involved in executive function, which was, similarly, impaired in all of our participants who progressed to dementia.[64] Prior imaging brain studies in MCI revealed that higher dual-task gait cost is associated with altered neurochemistry and low volume of the primary motor cortex, which is part of the executive network circuit of normal locomotion.[17;65;66] In the same manner, stride time correlated

negatively with hippocampal neurochemistry in MCI [67], which could reflect the role of the hippocampus in the retrieval of complex foot movement sequences necessary for regular gait patterns.[68] Ultimately, these brain circuits shared by both cognition and motor-gait performance can be affected by aging, neurodegenerative, and microvascular mechanisms, providing a rationale to propose that dual-task gait testing may serve as a "brain stress test" to detect impending cognitive decline in subjects with subclinical damage (Figure 3).[69]

Current candidate dementia biomarkers, including amyloid beta and tau protein related markers, are promising; however, thecorrelation between pathologic biomarker load and actual dementia status lessen with age.[21;70] In other words, MCI patients with similar degrees of neuropathology burden may present very different functional and clinical states, as they aged. This warrants the need to expand the prediction of dementia progression by adding "functional markers", such as the motor-cognitive interface assessed by dual-task gait.[21]

Our findings could be easily translated to the clinical setting due to the simplicity, non-invasive nature, and low cost of dual-task gait assessment. Our sensitive analysis showed that dual-task gait was comparable with cognitive testing to predict incident dementia and adjustments for baseline cognition only partially attenuated the associations, suggesting that dual-task gait test is providing extra information not captured by cognitive testing. Performances in the three dual-tasks used were all associated with a high risk of progression to dementia, providing flexibility to clinicians to choose the most appropriate dual-task test to cognitively stress a given patient. Clinicians may utilize dual-task gait testing in screening patients with MCI who could benefit the most from additional testing, optimizing recommendations for imaging, spinal fluid exams, and genetic testing. Similarly, our findings can assist to identify high-risk individuals with MCI to

plan the frequency of follow-up visits to monitor function. Finally, dual-task gait testing could help researchers plan primary prevention or intervention studies in MCI through the selection of subjects at higher and faster risk of decline and progression to dementia.

Limitations

Our sample was limited to 112 individuals with MCI which may have led to a relative low rate of events (27 progressed to dementia); however, the events per independent variable ratio (EPV) for our Cox regression model (27/5=5.4) is considered robust for models with binary endpoint outcomes.[71] Our annual conversion rate to AD was 7% which is in line with clinic-based studies including amnestic MCI but higher than populational studies, and thus our results are generalizable to clinic-based settings only. Quantitative techniques were used to measure velocity, which can be a limitation to wide clinical applicability. However, dual-task gait velocity can be simply measured using a stopwatch and dual-task cost easily calculated. Although predictive validity might be improved by considering cognitive errors on dual-tasking, that would make it more difficult to apply in clinics.Finally, our results need cross-validation in other MCI cohorts. The strengths of our study include a well-characterized MCI cohort with a long period of follow-up, and with bi-annual assessments to adequately monitor time to progression to dementia. We used a validated dual-task protocol on quantitative gait analysis and standardized assignment of dementia diagnoses blinded to gait categories, and with robust analyses adjusting for a number of important covariates.

CONCLUSION

Dual-task gait testing can detect individuals with MCI at increased risk of progression to dementia. Our results support the hypothesis that cognitive and motor dysfunction in MCI may reflect a shared pathogenic mechanism at the brain level and that gait is a candidate motor biomarker of progression to dementia.[13;16;28;72;73] Future studies should confirm if adding dual-

task gait testing to the clinical and cognitive evaluation of patients with MCI can improve dementia prediction. Cross-validation of this approach in other MCI cohorts would further support the clinical applicability.

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Table 1. Baseline characteristics of participants stratified by progression to dementia (n=112)

Characteristics	**Full Sample** (n=112)	**Progressed-MCI** (n=27)	**Stable-MCI** (n=85)	***P* value***
Age (mean, SD)	75.97 (6.88)	78.75 (6.35)	75.05 (6.84)	**.013**
Female (n, %)	55 (49.1%)	12 (42.9%)	43 (51.2%)	.449
# of medications (mean, SD)	7.14 (3.98)	7.43 (4.17)	7.04 (3.94)	.655
# of comorbidities (mean, SD)	5.56 (3.06)	4.57 (2.85)	5.90 (3.08)	**.047**
MMSE (mean, SD)	27.46 (2.45)	25.71 (3.15)	28.05 (1.86)	**<.001**
MMSE (median, range)	28 (18-30)	26 (18-30)	28 (20-30)	**.002**
MoCA (mean, SD)	23.14 (3.39)	21.25 (3.05)	23.77 (3.28)	**.001**
APOE ε4 carrier (n, %)	23 (39.0%)	5 (55.6%)	18 (36%)	.276
a-MCI (n,%)	77 (86.2%)	15 (57.4%)	62 (73.0%)	**<.001**
ultiple domain MCI (n,%)	30 (33%)	12 (43.4%)	18(22.6%)	**.020**
Non a-MCI	3 (3.336%)	0 (0.0%)	3 (73.6%)	n/a
Cognitive tests (mean, SD)				
RAVLT (delay recall)	4.54 (3.04)	2.50 (1.52)	4.77 (3.09)	.083
Digit Span Fwd	10.97 (2.083)	11.38 (2.72)	10.91 (2.00)	.561
Digit Span Bckwd	6.82 (2.35)	5.25 (1.98)	7.03 (2.32)	.043
TMT A, sec.	48.74 (17.35)	57.54 (25.08)	47.53 (15.93)	.304

TMT B, sec.	151.63 (136.06)	320.65 (294.80)	128.31 (76.65)	.108
BNT	13.27 (1.57)	12.13 (1.36)	13.45 (1.54)	**.025**
LNS	7.62 (2.58)	6.14 (4.14)	7.79 (2.32)	.338
Gait Velocity, (mean, SD), cm/sec.				
Single-task	107.43(21.26)	105.21 (21.91)	108.13 (21.13)	.536
Counting	98.49 (26.38)	88.42 (25.62)	101.84 (25.92)	**.027**
Serial Sevens	80.59 (29.21)	70.02 (24.26)	83.86 (29.96)	**.034**
Naming Animals	87.46 (27.48)	78.04 (26.90)	90.45 (27.13)	**.040**
Gait cost, (mean, SD), %				
DTC Counting	8.82 (14.09)	15.95 (16.01)	6.56 (12.70)	**.002**
DTC Serials Sevens	24.54 (19.49)	33.69 (18.67)	21.67 (18.95)	**.006**
DTC Naming Animals	19.18 (17.27)	26.57 (16.52)	16.84 (16.83)	**.010**

.

Abbreviations: RAVLT: Rey Auditory Verbal Learning Test; TMT A&B: Trail Making Tests A and B; BNT: Boston Naming Test; LNS: Letter-Number Sequencing; sec: seconds; DTC: Dual-task cost, calculated as ([single-task gait value – dual-task gait value]/ single-task gait value) x 100. **P*-value determined using Chi square (X^2) or Student *t*-tests, as deemed appropriate

Table 2. Cox proportional hazard regression of the association of gait velocity and dual-task gait cost (gait cost) with incident dementia modeled as continuous and dichotomous variables.

Gait Variable (continuous)	**Model 1 (unadjusted)**		**Model 2 (adjusted)**		**Model 3 (adjusted + MMSE)**	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Gait Velocity						
Single-task	1.01 (0.99-1.03)	.256	1.02 (0.99-1.04)	.098	1.02 (0.99-1.04)	0.204
Counting	1.02 (1.00-1.03)	**.012**	1.03 (1.01-1.04)	**.001**	1.03 (1.01-1.04)	**0.010**
Serial Sevens	1.01 (1.00-1.02)	**.042**	1.01 (1.00-1.03)	**.045**	1.02 (0.99-1.03)	0.112
Naming Animals	1.02 (1.00-1.03)	**.011**	1.03 (1.01-1.04)	**.002**	1.02 (1.01-1.04)	**0.024**
Gait Cost						
DTC Counting	1.04 (1.01-1.06)	**.003**	1.06 (1.03-1.09)	**<0.001**	1.04 (1.00-1.07)	**0.014**
DTC Serial Sevens	1.03 (1.01-1.05)	**.008**	1.02 (0.99-1.04)	.081	1.01 (0.99-1.03)	0.204
DTC Naming Animals	1.03 (1.01-1.06)	**.004**	1.04 (1.02-1.07)	**0.001**	1.03 (1.00-1.05)	**0.036**
Gait Variable (dichotomous)	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Gait Velocity						
Slow Single-task (<0.8m/s)	2.31 (0.80-6.69)	.123	3.41 (0.99-11.71)	.051	3.17 (0.92-10.88)	0.067
Gait Cost						
DTC Counting	2.27 (1.04-4.97)	**.040**	3.79 (1.57-9.15)	**.003**	2.39 (0.91-6.27)	0.076
DTC Serial Sevens	2.50 (1.00-6.24)	**.050**	1.89 (0.73-4.93)	.193	1.30 (0.48-3.54)	0.605
DTC Naming animals	2.25 (1.01-5.01)	**.047**	2.41 (1.04-5.59)	**.040**	1.96 (0.81-4.72)	0.133

Abbreviations: DTC: dual-task cost, calculated as ([single-task gait velocity – dual-task gait velocity]/ single-task gait velocity) x 100.
Model 1: unadjusted
Model 2: adjusted for age, sex, years of education, and number of comorbidities
Model 3: adjusted for age, sex, years of education, number of comorbidities and MMSE

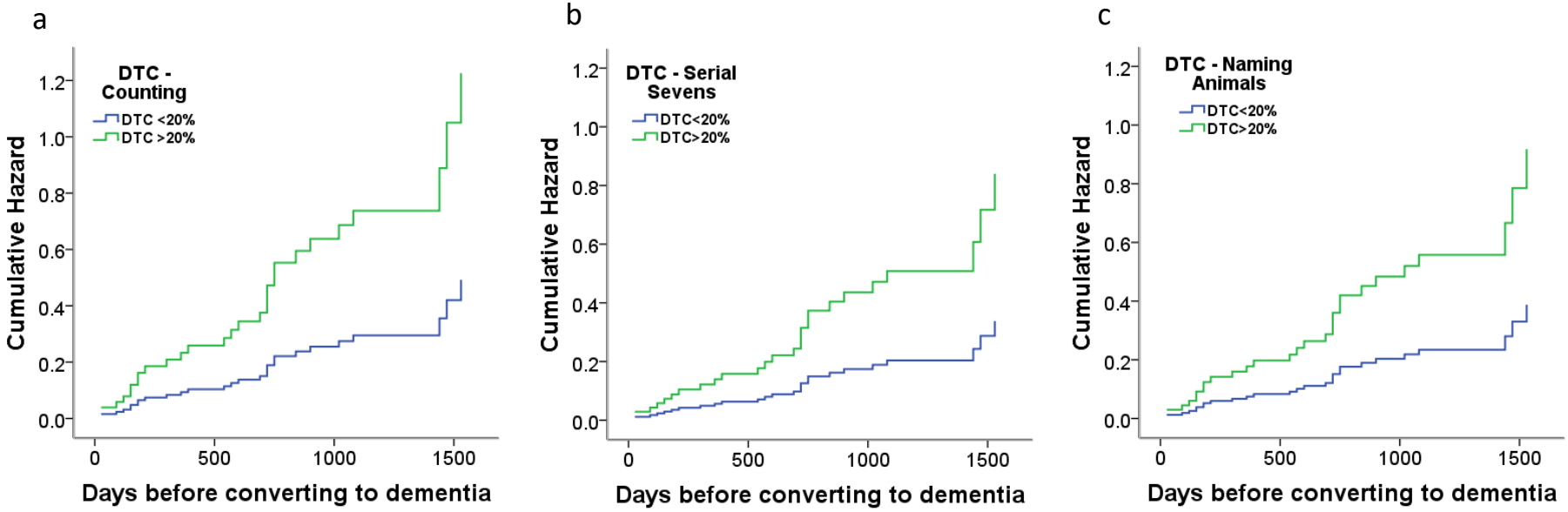

Figure 1. Cumulative hazard ratio for progression to dementia for low and high dual-task cost in gait velocity (n=112). Figure (a) shows dual-task cost (DTC) while counting backwards, (b) while performing serial sevens subtractions, and (c) while naming animals.

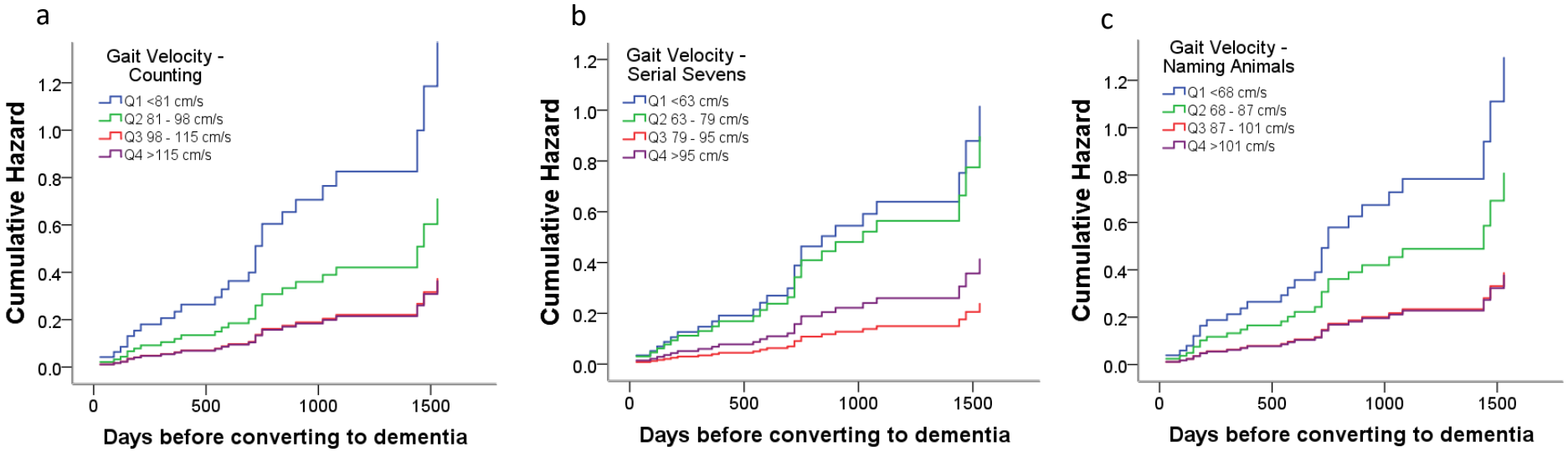

Figure 2. Risk of dementia, stratified by gait velocity (cm/s) quartiles in three dual-tasks conditions: counting backwards (2a), serial sevens subtractions (2b), and naming animals (2c).

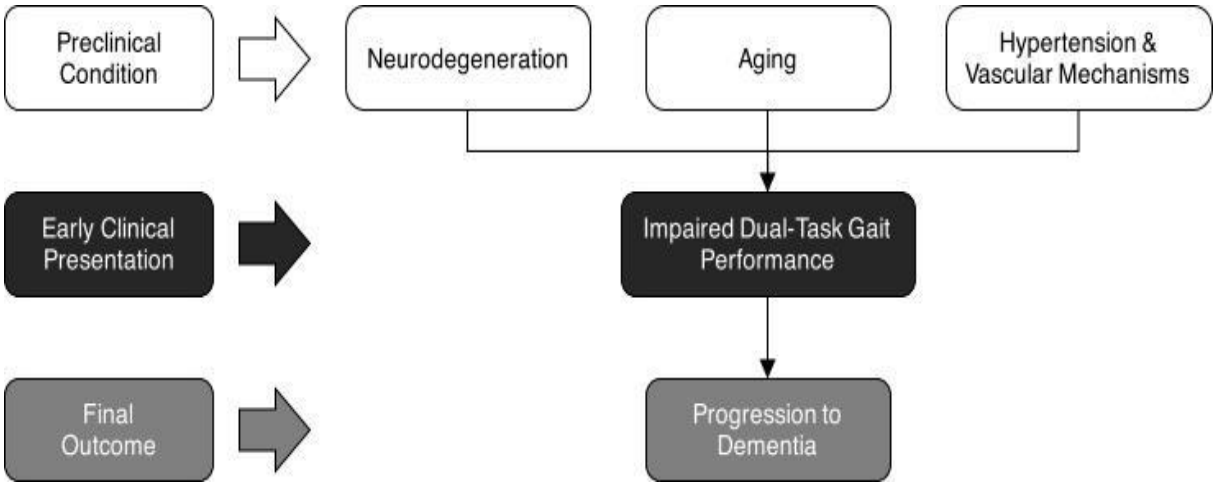

Figure 3: Proposal that dual-task gait could be an early clinical marker of progression to dementia syndromes.

Supplementary material

eTable 1. Cox proportional hazard regression of the association of gait velocity and incident dementia modeled as a dichotomous variable, using cut-offs based on 1.5SD below cohort mean and ROC analysis.

	unadjusted		adjusted†	
	HR, 95% CI	***p* value**	**HR**, 95% CI	***p* value**
Gait Velocity (single-task)				
Slow Gait (below 1.5SD)*	1.99 (0.60-6.64)	0.260	2.69 (0.70-10.29)	0.149
Slow Gait (below ROC)**	1.16 (0.54-2.47)	0.704	1.34 (0.57-3.15)	0.499

†Adjusted for age, gender, years of education, number of comorbidities, atrial fibrillation, myocardial infarct, stroke or TIA, and hypertension. *<0.76m/s; **<1.08 m/s.

eTable 2. Cox proportional hazard regression of the association of gait velocity stratified by quartiles, under single and dual-task conditions.

	unadjusted		adjusted†	
	HR, (95% CI)	*p* value	HR, (95% CI)	*p* value
Single Gait Velocity				
Quartile 1 (<94 cm/s)	1.60 (0.58-4.44)	.367	2.12 (0.63-7.17)	.227
Quartile 2 (94-107 cm/s)	0.91 (0.30-2.71)	.864	0.76 (0.24-2.39)	.643
Quartile 3 (107-121 cm/s)	0.74 (0.25-2.20)	.584	0.38 (0.098-1.50)	.167
Counting Gait Velocity				
Quartile 1 (<81cm/s)	3.84 (1.33-11.14)	**.013**	13.39 (3.76-47.75)	**<.001**
Quartile 2 (81-98 cm/s)	1.96 (0.62-6.18)	.252	2.53 (0.75-8.51)	.132
Quartile 3 (98-115 cm/s)	1.03 (0.27-3.83)	.969	0.55 (0.13-2.41)	.430
Serial Sevens Gait Velocity				
Quartile 1 (<63 cm/s)	2.46 (0.83-7.26)	.103	2.40 (0.77-7.45)	.130
Quartile 2 (63-79 cm/s)	2.17 (0.70-6.68)	.177	2.33 (0.68-7.98)	.177
Quartile 3 (79-95 cm/s)	0.57 (0.14-2.41)	.450	0.451 (0.09-2.15)	.318
Naming Animals Gait Velocity				
Quartile 1 (<68 cm/s)	3.47 (1.20-10.04)	**.022**	9.89 (2.91-33.62)	**<.001**
Quartile 2 (68-87 cm/s)	1.86 (0.56-6.11)	.309	1.16 (0.30-4.53)	.827
Quartile 3 (87-101 cm/s)	1.03 (0.30-3.57)	.961	0.96 (0.26-3.51)	.947

Note: Quartile 4 is the reference quartile

†Adjusted for age, gender, years of education, number of comorbidities, atrial fibrillation, myocardial infarct, stroke or TIA, and hypertension.