

# Association of Dual-Task Gait With Incident Dementia in Mild Cognitive Impairment

## Results From the Gait and Brain Study

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 Supplemental content

**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 for 6 years, with biannual visits including neurologic, cognitive, and gait assessments. Data were collected from July 2007 to March 2016.

**MAIN OUTCOMES AND MEASURES** Incident all-cause dementia was the main outcome measure, and single- and dual-task gait velocity and dual-task gait costs were the independent variables. A neuropsychological test battery was used to assess cognition. Gait velocity was recorded under single-task and 3 separate dual-task conditions using an electronic walkway. Dual-task gait cost was defined as the percentage change between single- and dual-task gait velocities:  $([\text{single-task gait velocity} - \text{dual-task gait velocity}] / \text{single-task gait velocity}) \times 100$ . Cox proportional hazard models were used to estimate the association between risk of progression to dementia and the independent variables, adjusted for age, sex, education, comorbidities, and cognition.

**RESULTS** Among 112 study participants with MCI, mean (SD) age was 76.6 (6.9) years, 55 were women (49.1%), and 27 progressed to dementia (24.1%), with an incidence rate of 121 per 1000 person-years. Slow single-task gait velocity ( $<0.8$  m/second) was not associated with progression to dementia (hazard ratio [HR], 3.41; 95% CI, 0.99-11.71;  $P = .05$ ) while high dual-task gait cost while counting backward (HR, 3.79; 95% CI, 1.57-9.15;  $P = .003$ ) and naming animals (HR, 2.41; 95% CI, 1.04-5.59;  $P = .04$ ) were associated with dementia progression (incidence rate, 155 per 1000 person-years). The models remained robust after adjusting by baseline cognition except for dual-task gait cost when dichotomized.

**CONCLUSIONS AND RELEVANCE** Dual-task gait is associated with progression to dementia in patients with MCI. 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.

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Mild cognitive impairment (MCI) is considered a pre-dementia state associated with a 10-fold increased risk of progression to dementia.<sup>1</sup> However, almost one-third of individuals with MCI remain clinically stable after the initial diagnosis or even revert to normal cognitive functioning,<sup>2</sup> which highlights the hazard of considering patients with MCI as a homogeneous group.<sup>3</sup> This heterogeneity of outcomes challenges clinical treatment once MCI is identified because it is problematic to accurately predict progression to dementia including Alzheimer 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.<sup>4-7</sup>

During 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.<sup>8-10</sup> Although the main clinical hallmark of MCI is memory impairment,<sup>11</sup> motor dysfunction and gait impairment have been previously described.<sup>8,11,12</sup> 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 patients with MCI.<sup>13,14</sup> Dual-task gait testing challenges the cognitive component of locomotion and can provide insight into the mechanisms of brain motor control and cognitive performance.<sup>13</sup> 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.<sup>13,15-17</sup> 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 individuals with cognitive impairment who have less cognitive reserve.<sup>13,18</sup>

The dual-task gait test is unique in that it reflects the motor-cognitive interface.<sup>19-21</sup> There is a linear association between the magnitude of gait slowing while dual tasking and deficits in executive, attention, and memory processes in MCI.<sup>4,20,22-24</sup> The magnitude of changes in gait during dual-task performance owing to a concurrent cognitive challenge can be expressed as a dual-task gait cost, which adjusts for an individual's baseline gait characteristics.<sup>25</sup> To our knowledge, the capacity of dual-task gait testing to predict progression to dementia in patients 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 progressed 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 designed to determine whether quantitative gait deficits can predict incident cognitive and mobil-

### Key Points

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

**Findings** In this cohort study of 112 older adults with mild cognitive impairment with up to 6 years of follow-up, poor performance in dual-task gait testing was significantly associated with a 2- to 3-fold risk of dementia incidence independent of age, sex, education, comorbidities, and baseline cognition.

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

ity decline and progression to dementia among community-dwelling older adults. Design and logistics have been described in detail elsewhere.<sup>26-28</sup> After written 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 2 assessments, including the baseline visit, and to fulfill MCI diagnostic criteria.<sup>3,29</sup> All participants were community-living adults meeting the following inclusion criteria: age 65 years and older, able to walk 10 m independently without a gait aid, having MCI as ascertained by scoring 0.5 on the global rating of the Clinical Dementia Rating scale and satisfying the following 4 criteria<sup>1</sup>: (1) subjective cognitive challenges; (2) objective cognitive impairment in at least 1 of the following cognitive domains: memory, executive function, attention, and language<sup>3,29</sup>; (3) preserved activities of daily living<sup>30</sup> confirmed by a clinician's interviews; and (4) absence of dementia using criteria from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision).<sup>31</sup> Exclusion criteria included lack of English proficiency, parkinsonism or any neurologic disorder with residual motor deficits (eg, stroke), musculoskeletal disorders of lower limbs (eg, 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 written informed consent was obtained from participants 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 examination on all participants.

Global cognition was assessed by using the Mini-Mental State Examination<sup>32</sup> and the Montreal Cognitive Assessment,<sup>33</sup> with alternative test versions used in consecutive assessments to avoid potential learning effects. The Clinical Dementia Rating scale was also performed at all visits.<sup>34</sup> A neuropsychological test battery was administered to characterize MCI

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 <sup>a</sup>
Age, mean (SD), y	75.97 (6.88)	78.75 (6.35)	75.05 (6.84)	.01 <sup>b</sup>
Women, No. (%)	55 (49.1)	12 (42.9)	43 (51.2)	.45
No. of medications, mean (SD)	7.14 (3.98)	7.43 (4.17)	7.04 (3.94)	.66
No. of comorbidities, mean (SD)	5.56 (3.06)	4.57 (2.85)	5.90 (3.08)	.05 <sup>b</sup>
BP systolic, mean (SD), mm Hg	128.66 (10.13)	129.78 (12.40)	128.48 (9.84)	.72
BP diastolic, mean (SD), mm Hg	71.52 (8.04)	71.78 (7.34)	71.48 (8.20)	.92
Comorbidities, No. (%)				
Hypertension	67 (60.4)	19 (70.4)	48 (57.1)	.23
Diabetes	22 (19.8)	4 (14.8)	18 (21.4)	.46
Atrial fibrillation	9 (8.0)	2 (7.4)	7 (8.2)	.89
CHF	2 (1.8)	1 (3.7)	1 (1.2)	.40
Myocardial infarction	11 (10.0)	4 (14.8)	7 (8.4)	.34
Stroke/TIA	13 (11.7)	1 (3.7)	12 (14.3)	.14
Smoking	37 (56.1)	3 (37.5)	34 (58.6)	.27
Osteoarthritis	37 (33)	6 (5)	31 (28)	.17
MMSE score, mean (SD)	27.46 (2.45)	25.71 (3.15)	28.05 (1.86)	<.001 <sup>b</sup>
MMSE score, median (range)	28 (18-30)	26 (18-30)	28 (20-30)	.002 <sup>b</sup>
MoCA, mean (SD)	23.14 (3.39)	21.25 (3.05)	23.77 (3.28)	.001 <sup>b</sup>
APOE ε4 carrier, No. (%) <sup>c</sup>	23 (39.0)	5 (55.6)	18 (36)	.28
a-MCI, No. (%)	77 (86.2)	15 (57.4)	62 (73.0)	<.001 <sup>b</sup>
Multiple domain MCI, No. (%)	30 (33)	12 (43.4)	18 (22.6)	.02 <sup>b</sup>
Non a-MCI, No. (%)	3 (3.336)	0	3 (73.6)	NA
Cognitive tests, mean (SD)				
RAVLT, delayed recall	4.54 (3.04)	2.50 (1.52)	4.77 (3.09)	.08
Digit span forward	10.97 (2.083)	11.38 (2.72)	10.91 (2.00)	.56
Digit span backward	6.82 (2.35)	5.25 (1.98)	7.03 (2.32)	.04 <sup>b</sup>
TMT A, s	48.74 (17.35)	57.54 (25.08)	47.53 (15.93)	.30
TMT B, s	151.63 (136.06)	320.65 (294.80)	128.31 (76.65)	.11
BNT	13.27 (1.57)	12.13 (1.36)	13.45 (1.54)	.03 <sup>b</sup>
LNS	7.62 (2.58)	6.14 (4.14)	7.79 (2.32)	.34
Gait velocity, mean (SD), cm/s				
Single-task	107.43(21.26)	105.21 (21.91)	108.13 (21.13)	.54
Counting	98.49 (26.38)	88.42 (25.62)	101.84 (25.92)	.03 <sup>b</sup>
Serial sevens	80.59 (29.21)	70.02 (24.26)	83.86 (29.96)	.03 <sup>b</sup>
Naming animals	87.46 (27.48)	78.04 (26.90)	90.45 (27.13)	.04 <sup>b</sup>
Gait cost, mean (SD), No. (%)				
DTC counting	8.82 (14.09)	15.95 (16.01)	6.56 (12.70)	.002 <sup>b</sup>
DTC serials sevens	24.54 (19.49)	33.69 (18.67)	21.67 (18.95)	.006 <sup>b</sup>
DTC naming animals	19.18 (17.27)	26.57 (16.52)	16.84 (16.83)	.01 <sup>b</sup>

Abbreviations: APOE, apolipoprotein E; BNT, Boston Naming Test; CHF, congestive heart failure; DTC, dual-task gait cost, calculated as [(single-task gait value - dual-task gait value) / single-task gait value] × 100; LNS, Letter-Number Sequencing; MCI, mild cognitive impairment; NA, not applicable; RAVLT, Rey Auditory Verbal Learning Test; TIA, transient ischemic attack; TMT A, Trail Making Test A; TMT B, Trail Making Test B.

<sup>a</sup> P value determined using  $\chi^2$  or t tests, as deemed appropriate.

<sup>b</sup> Statistically significant value.

<sup>c</sup> Data available for 59 participants.

subtype and to help ascertain progression to dementia. Executive function was assessed using Trail Making Tests A and B<sup>35</sup>; verbal episodic memory using the Rey Auditory Verbal Learning Test<sup>36</sup>; naming using the Boston Naming Test<sup>37</sup>; attention using the Digit Span Test (forward and backward), and working memory using the Letter-Number Sequencing test.<sup>38</sup> Impaired cognitive domains were identified using a cutoff of 1.5 SD below the age-adjusted norms.<sup>14,39</sup> Participants were classified as pure amnesic MCI (impairment only in verbal episodic memory), multidomain amnesic MCI (impairment in more than 1 domain including memory), and nonamnesic MCI (solely impairment in 1 or more nonmemory domain).<sup>14,40</sup>

### Gait Assessments

Gait velocity within single and dual tasks was assessed using an electronic walkway (GAITRite System, 600 cm long and 64 cm wide; CIR Systems Inc) that provides data to assess both spatial and temporal gait parameters.<sup>26</sup> Start and end points were marked on the floor 1 meter from either walkway end to avoid recording acceleration and deceleration phases. Each participant performed 1 practice trial walking on the walkway. For the single-gait test, participants were asked to walk 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: (1) counting backward from 100 by ones, (2) subtracting serial sevens from 100, and (3) naming animals. Rationale for dual-task condition selection has been described elsewhere.<sup>26</sup> To balance and minimize the effects of learning and fatigue, only 1 trial was performed in each condition, and the order of single and dual tasks was randomized. Reliability has been previously established for this protocol in participants with MCI.<sup>26</sup> The magnitude of the effect of the cognitive challenge on gait performance was assessed by calculating the dual-task gait cost (percent) as<sup>19</sup>:

$$\left( \frac{\text{[single-task gait velocity - dual-task gait velocity]}}{\text{single-task gait velocity}} \right) \times 100$$

### Outcome Variable

Incident dementia was the main end point as determined by a clinician investigator during follow-up visits per *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) criteria<sup>31</sup> and when Clinical Dementia Rating increased to a score of 1 or higher. At the time of diagnosis, clinicians were blinded to baseline gait or baseline neuropsychological test scores. The type of dementia was established using standardized clinical criteria for AD dementia,<sup>41</sup> frontotemporal dementia,<sup>42</sup> Lewy body dementia,<sup>43</sup> and vascular dementia.<sup>44</sup> Participants were reassessed after 6 months to confirm dementia status and subtype.

### Predictor Variables

Gait velocity and dual-task gait cost were our main predictor variables because they have been previously associated with cognitive performance in MCI studies.<sup>14,27</sup> These variables were modeled 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 less than 0.8 m/second, a threshold previously established for predicting adverse events, including cognitive decline, in ambulatory patients.<sup>45-47</sup> Because there is not an established cutoff for dual-task gait testing, receiver operating characteristic curves were produced to determine the optimal threshold value for high dual-task gait cost as a predictor of dementia for the 3 dual-task conditions.

### Covariates

Analyses were adjusted for covariates that included demographics (age, sex, and educational level), number of comorbidities, 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 patients with MCI who progressed to dementia and those who did not were made using  $\chi^2$  or *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 variables (single- and dual-task gait

velocity and dual-task gait cost) and as dichotomous variables (slow gait velocity and high dual-task gait cost in each condition), unadjusted and adjusted for the previously mentioned covariates. Dual-task gait cost cutoffs were determined using receiver operating characteristic 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 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  $P < .05$  (2-sided). Statistical analyses were conducted using SPSS, version 23 (IBM Corporation) and occurred from June 2016 to March 2017.

## Results

### Participant Characteristics

One hundred twelve participants (mean [SD] age, 76 [6.88] years; 55 women) were assessed with a mean follow-up of 24 months (range, 12-76 months). Characteristics of the study sample, stratified by progression to dementia (patients with MCI who progressed to dementia vs those who did not) are presented in Table 1. Ninety-two participants with MCI fulfilled criteria for pure amnesic MCI while 30 fulfilled criteria for non-amnesic MCI. A total of 24% of the sample ( $n = 27$ ; 11 women [43%]) progressed to dementia, with an overall incidence rate of 121 per 1000 person-years. From the 27 participants who progressed to dementia, 23 progressed to AD (85%), 2 to Lewy body dementia (7%), 1 to frontotemporal dementia (4%), and 1 to vascular dementia (4%).

Table 1 shows that participants with MCI 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 1 apolipoprotein E  $\epsilon 4$  allele, although these differences were not significant. Both groups had a mean baseline single-gait velocity greater than the normality cutoff of 0.8 m/second; however, participants who progressed to dementia had a significantly lower dual-task gait velocity and higher dual-task gait cost in the 3 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 2 predictor variables, gait velocity and dual-task gait cost, in 1 unadjusted and 2 adjusted models. When modeling our predictors as a continuous variable, single-gait velocity test failed to predict dementia (HR, 1.02; 95% CI, 0.99-1.04;  $P = .10$ ), 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 for covariates.

Modeling gait velocity as dichotomous variables showed that slow single-task velocity ( $<0.8$  m/second) was not associated with dementia progression (HR, 3.41; 95% CI, 0.99-11.71;  $P = .05$ ). Alternative slow single-task gait velocity cut-

**Table 2. Cox Proportional Hazard Regression of the Association of Gait Velocity and Dual-Task Gait Cost With Incident Dementia Modeled as Continuous and Dichotomous Variables<sup>a</sup>**

Variable	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
<b>Gait variable (continuous)</b>						
<b>Gait velocity</b>						
Single-task	1.01 (0.99-1.03)	.26	1.02 (0.99-1.04)	.10	1.02 (0.99-1.04)	.20
Counting	1.02 (1.00-1.03)	.01 <sup>b</sup>	1.03 (1.01-1.04)	.001 <sup>b</sup>	1.03 (1.01-1.04)	.01 <sup>b</sup>
Serial sevens	1.01 (1.00-1.02)	.04 <sup>b</sup>	1.01 (1.00-1.03)	.05 <sup>b</sup>	1.02 (0.99-1.03)	.11
Naming animals	1.02 (1.00-1.03)	.01 <sup>b</sup>	1.03 (1.01-1.04)	.002 <sup>b</sup>	1.02 (1.01-1.04)	.02 <sup>b</sup>
<b>Gait cost</b>						
DTC counting	1.04 (1.01-1.06)	.003 <sup>b</sup>	1.06 (1.03-1.09)	<.001 <sup>b</sup>	1.04 (1.00-1.07)	.01 <sup>b</sup>
DTC serial sevens	1.03 (1.01-1.05)	.008 <sup>b</sup>	1.02 (0.99-1.04)	.08	1.01 (0.99-1.03)	.20
DTC naming animals	1.03 (1.01-1.06)	.004 <sup>b</sup>	1.04 (1.02-1.07)	.001 <sup>b</sup>	1.03 (1.00-1.05)	.04 <sup>b</sup>
<b>Gait variable (dichotomous)</b>						
<b>Gait velocity</b>						
Slow single-task (<0.8m/s)	2.31 (0.80-6.69)	.12	3.41 (0.99-11.71)	.05	3.17 (0.92-10.88)	.07
<b>Gait cost</b>						
DTC counting	2.27 (1.04-4.97)	.04 <sup>b</sup>	3.79 (1.57-9.15)	.003 <sup>b</sup>	2.39 (0.91-6.27)	.08
DTC serial sevens	2.50 (1.00-6.24)	.05 <sup>b</sup>	1.89 (0.73-4.93)	.19	1.30 (0.48-3.54)	.61
DTC naming animals	2.25 (1.01-5.01)	.05 <sup>b</sup>	2.41 (1.04-5.59)	.04 <sup>b</sup>	1.96 (0.81-4.72)	.13

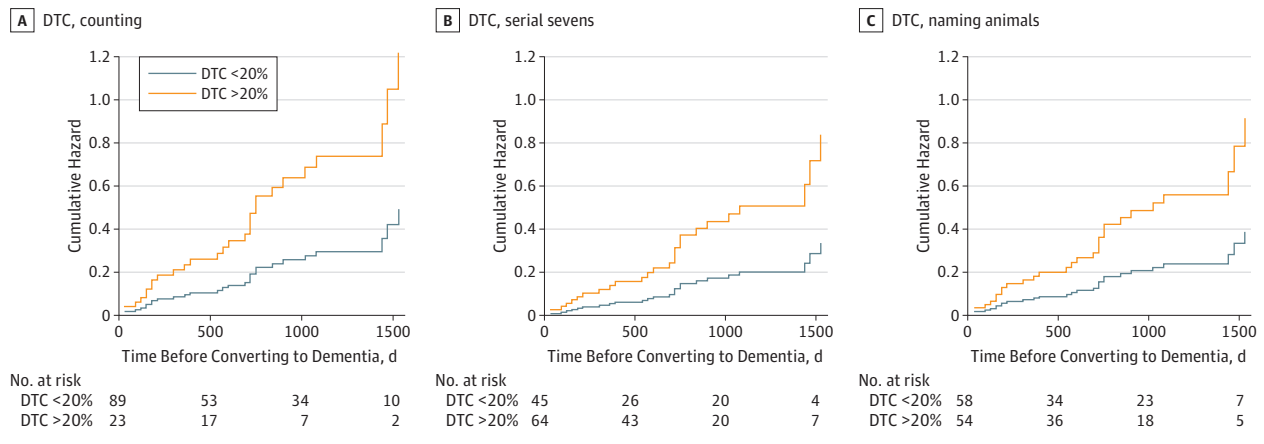
Abbreviations: DTC, dual-task gait cost, calculated as ([single-task gait velocity - dual-task gait velocity]/ single-task gait velocity) × 100; MMSE, Mini-Mental State Examination.

number of comorbidities Model 3: adjusted for age, sex, years of education, number of comorbidities and MMSE.

<sup>b</sup> Statistically significant values.

<sup>a</sup> Model 1: unadjusted. Model 2: adjusted for age, sex, years of education, and

**Figure 1. Cumulative Hazard Ratio for Progression to Dementia for Low and High Dual-Task Cost in Gait Velocity (n = 112)**



A, Dual-task gait cost (DTC) while counting backward. B, While performing serial sevens subtractions. C, While naming animals.

offs, determined by receiver operating characteristic analysis (<1.08 m/second) or using 1.5 SD below the cohort mean gait velocity (<0.76 m/second) were also not associated with dementia progression (eTable 1 in the Supplement). However, high dual-task cost in gait velocity while counting backward (HR, 3.79; 95% CI, 1.57-9.15; *P* = .003) and naming animals (HR, 2.41; 95% CI, 1.04-5.59; *P* = .04) were both associated with dementia progression (Table 2 and Figure 1A and C). After adjusting for baseline cognition (Mini-Mental State Examination scores, model 3) the associations with progression to dementia were only attenuated for dual-task gait as a dichotomous variable.

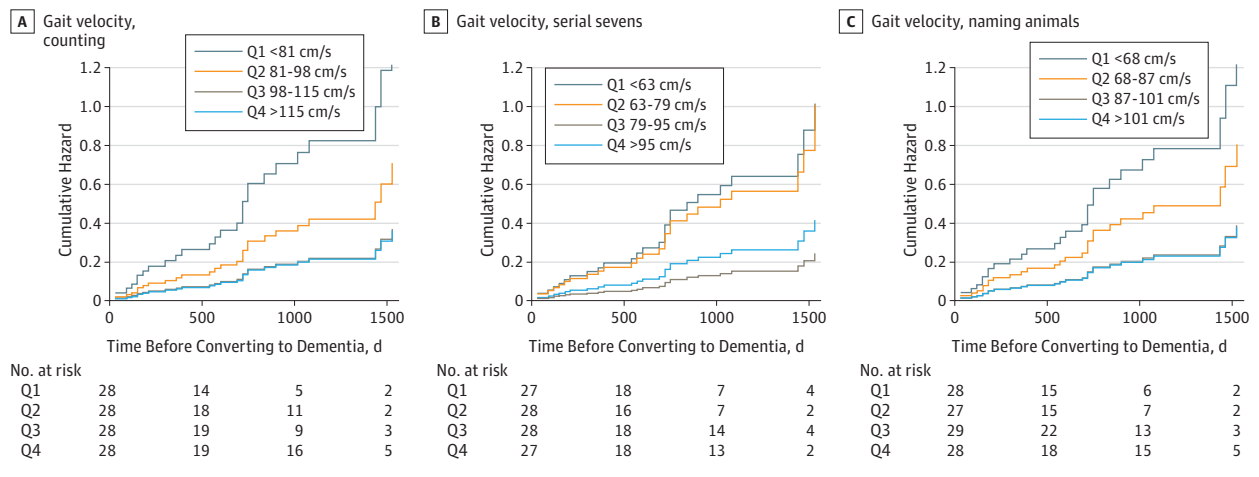
Stratification of the sample into quartiles of dual-task gait velocity (eTable 2 in the Supplement) showed that participants in the lowest quartile had the highest risk of progression to dementia while counting backward (HR, 13.39; 95% CI, 3.76-47.75; *P* < .001; Figure 2A) and while naming animals (HR, 9.89; 95% CI, 2.91-33.62; *P* < .001; Figure 2C).

**Sensitivity Analyses**

Associations with apolipoprotein E ε4 carrier status and single- and dual-tasking gait performance were explored, and differences were small and in both directions (eTable 3 in the Supplement). Baseline global cognition (Mini-Mental State



Figure 2. Risk of Dementia Stratified by Gait Velocity (Centimeters per Second) Quartiles in 3 Dual-Tasks Conditions



The 3 dual-tasks conditions are counting backward (A), serial sevens subtractions (B), and naming animals (C).

Examination and Montreal Cognitive Assessment) was associated with incident dementia, with comparable HRs to dual-task gait (eTable 4 in the Supplement).

## Discussion

Our results suggest that dual-task gait testing is associated with the progression to dementia in a well-characterized cohort of older adults with MCI. Specifically, a high dual-task gait cost while counting backward and naming animals was associated with an increased risk of progression to dementia by 3.8 and 2.4 times, respectively. The predictive ability of single-task gait performance appeared high although not statistically significant, revealing 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.<sup>4,14,19,26,48-52</sup>

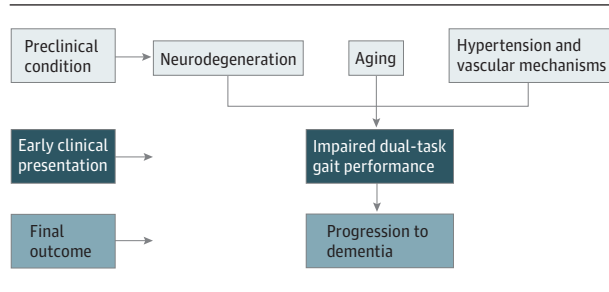
Assessing gait velocity is easy to perform and provides an excellent general measure of overall function. However, dual-task gait testing can uncover valuable subtleties regarding the role of cognitive control on a participant's gait.<sup>45,53-56</sup> It is also important to note that the single-task gait velocity in our MCI sample was greater than 0.8 m/second, 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.<sup>14,25,27</sup> Thus, among these 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 Motoric Cognitive Risk syndrome, where participants with cognitive challenges and slower gait had a higher risk of developing dementia,<sup>7</sup> by showing that dual-task gait may predict dementia in participants with MCI while single-task gait velocity does not. Whether dual-task changes in gait in patients with MCI is associated with progression to vascular dementia or AD is unknown. Previous stud-

ies in general populations have suggested that gait slowing during dual tasking is most likely associated with incident vascular dementia.<sup>7,9</sup> In this study, dual-task gait change was mostly associated with AD, which can be explained by the fact that our study focused only in individuals with MCI. Interestingly, emerging evidence is linking gait performance with AD neurodegenerative changes, as in a 2017 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,<sup>57,58</sup> independent of the burden of vascular changes. Taken together, these data suggest that both vascular and neurodegenerative changes may contribute to dementia progression in patients with MCI with impaired dual-task gait.<sup>59</sup>

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.<sup>27,60,61</sup> 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.<sup>62</sup> 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.<sup>17,63,64</sup> In the same manner, stride time correlated negatively with hippocampal neurochemistry in MCI,<sup>65</sup> which could reflect the role of the hippocampus in the retrieval of complex foot movement sequences necessary for regular gait patterns.<sup>66</sup> 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 patients with subclinical damage (Figure 3).<sup>67</sup>

**Figure 3. Proposal That Dual-Task Gait Could Be an Early Clinical Marker of Progression to Dementia Syndromes**



Dementia biomarkers, including amyloid  $\beta$  and tau protein-related markers, are promising; however, the correlation between pathologic biomarker load and actual dementia status lessens with age.<sup>21,68</sup> In other words, older patients with MCI with similar degrees of neuropathology burden may present different functional and clinical states as they age. This warrants expanding the prediction of dementia progression by adding “functional markers” such as the motor-cognitive interface.<sup>21</sup>

Our findings could be easily translated to the clinical setting owing to the simplicity, noninvasive nature, and low cost of dual-task gait assessment. Our sensitivity 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 when modeled as a dichotomous variable, suggesting that dual-task gait test is providing extra information not captured by cognitive testing. Performances in the 3 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 use dual-task gait testing in screening patients with MCI who could benefit the most from additional testing, optimizing recommendations for imaging, spinal fluid examinations, and genetic testing. Similarly, our findings can assist in identifying 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 inter-

vention studies in MCI through the selection of participants at greater risk of decline and progression to dementia.

### Limitations

Our sample was limited to 112 individuals with MCI and with a relatively low frequency of outcome events (27 progressed to dementia); however, the event per independent variable ratio for our Cox regression model ( $27/5 = 5.4$ ) is considered robust for models with binary end point outcomes.<sup>69</sup> Our annual conversion rate to AD was 7%, which is in line with clinic-based studies, including amnesic MCI, but higher than population studies; 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 gait cost can be 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 biannual 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, with robust analyses adjusting for a number of important covariates.

### Conclusions

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.<sup>13,16,27,70-72</sup> Future studies should confirm whether 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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