

# Motor and Cognitive Trajectories Before Dementia: Results from Gait and Brain Study

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**OBJECTIVES:** To compare the trajectories of motor and cognitive decline in older adults who progress to dementia with the trajectories of those who do not. To evaluate the added value of measuring motor and cognitive decline longitudinally versus cross-sectionally for predicting dementia.

**DESIGN:** Prospective cohort study with 5 years of follow-up.

**SETTING:** Clinic based at a university hospital in London, Ontario, Canada.

**PARTICIPANTS:** Community-dwelling participants aged 65 and older free of dementia at baseline (N=154).

**MEASUREMENTS:** We evaluated trajectories in participants' motor performance using gait velocity and cognitive performance using the MoCA test twice a year for 5 years. We ascertained incident dementia risk using Cox regression models and attributable risk analyses. Analyses were adjusted using a time-dependent covariate.

**RESULTS:** Overall, 14.3% progressed to dementia. The risk of dementia was almost 7 times as great for those whose gait velocity declined (hazard ratio (HR)=6.89, 95% confidence interval (CI)=2.18–21.75,  $p=.001$ ), more than 3 times as great for those with cognitive decline (HR=3.61, 95% CI=1.28–10.13,  $p=.01$ ), and almost 8

times as great in those with combined gait velocity and cognitive decline (HR=7.83, 95% CI=2.10–29.24,  $p=.002$ ), with an attributable risk of 105 per 1,000 person years. Slow gait at baseline alone failed to predict dementia (HR=1.16, 95% CI=0.39–3.46,  $p=.79$ ).

**CONCLUSION:** Motor decline, assessed according to serial measures of gait velocity, had a higher attributable risk for incident dementia than did cognitive decline. A decline over time of both gait velocity and cognition had the highest attributable risk. A single time-point assessment was not sufficient to detect individuals at high risk of dementia. *J Am Geriatr Soc* 66:1676–1683, 2018.

**Key words:** cognition; gait velocity; cohort study; dementia; trajectories

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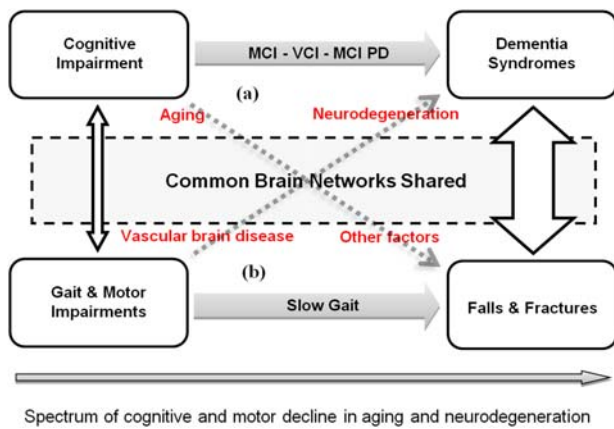
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Motor and cognitive decline frequently occur as we age, and can lead to disability.<sup>1–3</sup> Studies have shown that the coexistence of motor and cognitive impairment are prevalent in older adults at risk of dementia<sup>4,5</sup>, but little is known about their natural trajectories before dementia. Cognitive decline precedes progression to dementia by several years, and emerging evidence shows that motor decline, particularly in gait velocity, can precede cognitive decline by more than a decade.<sup>4,6–9</sup> This evidence guides our conceptual framework (Figure 1) for untangling the unknown behavior of independent and combined trajectories of motor and cognitive decline in those who progress to dementia and those who do not.

The added value of serial over single assessments of motor and cognitive performance and whether serial assessments would improve prediction of conversion to dementia has not been previously evaluated. With limited exceptions, previous studies assessing both types of decline



**Figure 1.** Conceptual framework for association between motor and cognitive decline in aging and neurodegeneration. Cognitive function and gait performance decline with aging, leading to dementia and falls. Emerging research supports the view that cognition predicts not only dementia incidence, but also mobility decline and falls, whereas mobility decline and slow gait predict cognitive deterioration and progression to dementia. These simultaneous declines may occur because of burden in shared common brain networks. Grey arrows: cognitive impairment predicts dementia, with mild cognitive impairment (MCI), vascular cognitive impairment (VCI) and MCI in Parkinson's disease (MCI-PD) as intermediate states. Gait impairments increase fall risk, and slow gait mediates this association. White arrows show associations between cognitive and gait impairment, and dementia and falls, respectively (arrow thickness represents strength of association). Red: factors and diseases damaging brain areas and brain network integrity. Dotted lines: (a) cognitive impairment can predict falls and fractures, (b) motor impairment can predict dementias. From Montero-Odasso et al.<sup>2,34,46</sup> [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

were in population-based cohorts involving infrequent assessment or had intervals ranging from 12 to 24 months, making the resulting trajectories difficult to assess.<sup>6–8,10–12</sup>

The goal of this study was to elucidate and compare the trajectories of motor and cognitive decline in older adults who progress to dementia and those who do not and to assess whether longitudinal measurement of motor and cognitive decline will improve prediction of incident dementia over that of cross-sectional assessment in community-dwelling older adults. We hypothesized that cognitive and motor trajectories would decline steadily before the onset of dementia and that those experiencing both types of decline would be associated with the highest risk of progression to dementia. We also hypothesized that decline over time would better estimate dementia risk than a single time-point measure.

Elucidation of the natural history of motor and cognitive function decline before dementia, controlling for important covariates such as age, sex, and incident comorbidities, will contribute to a better understanding of prodementia states, which in turn would enhance early identification of individuals at higher risk of progression.

## METHODS

### Design and Participants

The Gait and Brain Study is an ongoing longitudinal prospective cohort study (NTC03020381) aimed at elucidating cognitive and motor predictors of dementia, and its design and logistics have been described elsewhere.<sup>13–15</sup> Participants underwent a comprehensive baseline assessment followed by biannual assessments during 5 years of follow-up. All assessments included medical questionnaires, cognitive tests, and quantitative gait assessments.

Participants were eligible to participate if they were aged 65 and older, English speaking, and able to walk 10 m without a mobility aid. Exclusion criteria included any neurological disorder with residual motor deficits (e.g., stroke), musculoskeletal disorders of lower limbs (e.g., severe osteoarthritis, history of knee or hip replacement) affecting gait performance at clinical examination, use of neuroleptics or benzodiazepines, major depression, or diagnosis of dementia as ascertained by a clinician using criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised* (DSM-IV TR).<sup>16</sup>

Ethical approval was obtained from the University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects and participants' signed informed consent was obtained at enrollment. Data collection occurred between September 2008 and August 2015.

### Medical, Cognitive, and Motor Assessments

Information on sociodemographic characteristics, chronic medications, history of falls, and comorbidities was collected using standardized questionnaires in face-to-face interviews at each biannual visit (Table 1). Cognition was assessed using the Mini-Mental State Examination<sup>17</sup> and the Montreal Cognitive Assessment (MoCA).<sup>18</sup> Alternate versions of the MoCA were used in consecutive assessments to minimize learning effects.<sup>19</sup> The Clinical Dementia Rating Scale (CDR)<sup>20</sup> was also administered at all visits.

Motor performance was evaluated at all visits by quantifying gait velocity (cm/s) using an electronic walkway (GAITRite System, 600 cm long, 64 cm wide, CIR Systems, Inc. NJ, USA) following a validated gait protocol.<sup>13</sup> Start and end points were marked on the floor 1 m from each end of the mat to avoid recording acceleration and deceleration phases. Participants were asked to walk on the walkway at their usual pace.

### Ascertainment of Cognitive and Motor Trajectories and Declines

Cognitive and motor trajectories were described by plotting cognitive (MoCA) and motor (gait velocity) test results at baseline and each succeeding follow-up. The threshold used to define cognitive decline during follow-up was operationalized as a decrease of at least 2 points in MoCA score between baseline and the final assessment, as previously validated.<sup>21</sup>

For example, data from the Dallas Heart Study showed that a change of 1.73 points in MoCA score during 3 years of follow-up represented a clinically

**Table 1. Participant Baseline Characteristics Stratified According to Progression to Dementia**

Characteristic	Full Sample, N = 154	Progressed to Dementia, n = 22	Did Not Progress to Dementia, n = 132	P-Value
Age, mean ± SD	74.1 ± 6.7	78.6 ± 6.8	73.1 ± 6.3	<.001
Female, n (%)	84 (54.5)	10 (45.4)	74 (56.0)	.19
Education years, mean ± SD	13.4 ± 3.3	13.7 ± 2.8	13.4 ± 3.4	.66
Mini-Mental State Examination score, mean ± SD	28.0 ± 2.2	26.2 ± 3.0	28.4 ± 1.8	<.001
Montreal Cognitive Assessment score, mean ± SD	24.8 ± 3.5	21.6 ± 3.0	25.5 ± 3.2	<.001
Number of medications, mean ± SD	6.5 ± 3.8	7.4 ± 4.3	6.3 ± 3.6	.18
Comorbidities, mean ± SD	5.0 ± 2.8	4.5 ± 3.1	5.1 ± 2.7	.29
Fall in past 12 month, n (%)	44 (29.1)	4 (18.2)	40 (31.0)	.31
Gait speed, cm/s, mean ± SD	113.3 ± 22.0	108.3 ± 20.5	114.4 ± 22.3	.22
Follow-up, months, mean ± SD	24.7 ± 18.8	22.5 ± 13.8	25.1 ± 19.6	.43
Number of assessments, mean ± SD	5.1 ± 3.1	4.7 ± 2.3	5.2 ± 3.3	.44
Comorbidities, n (%)				
Hypertension	72 (53.3)	17 (70.8)	55 (49.5)	.08
Diabetes mellitus	20 (14.8)	4 (16.7)	16 (14.4)	.78
Osteoporosis	15 (11.1)	0 (0)	15 (13.5)	.06
Lung disease	10 (7.4)	2 (8.3)	8 (7.2)	.81
Osteoarthritis	47 (34.8)	6 (25.0)	41 (36.9)	.27
Cancer	44 (32.6)	6 (25.0)	38 (34.2)	.38
Hearing problems	47 (34.8)	10 (41.7)	37 (33.3)	.45
Depression	24 (17.8)	4 (16.7)	20 (18.0)	.87
Stroke	2 (1.5)	0 (0)	2 (1.8)	.51
Congestive heart failure, myocardial infarction, angina pectoris	16 (11.9)	4 (16.7)	12 (10.8)	.42
Atrial fibrillation	6 (4.4)	2 (8.3)	4 (3.6)	.41

Baseline characteristics of patients who progressed to dementia and those who did not progress to dementia were compared using chi-square tests for categorical variables and Student t-tests for continuous variables. SD = standard deviation.

meaningful difference based on its association with higher risk of progression to mild cognitive impairment or mild dementia in community-dwelling older adults.<sup>22</sup> Motor decline was operationalized as a reduction of 10 cm/s or more in gait velocity between baseline and the final assessment. A change of 10 cm/s in gait velocity is considered a clinically meaningful change in motor performance.<sup>23</sup> This threshold has been previously established and validated as a substantial meaningful change that occurs after interventions, including physical exercise and stroke rehabilitation strategies, and it is associated with improvement in activities of daily living.<sup>23</sup> An association between a 10-cm/s change in gait velocity and better self-reported physical performance in activities of daily living has also been found in the Lifestyle Interventions and Independence for Elders Pilot Study.<sup>24</sup> In participants experiencing decline in the current study, we described the decline as “intermittent” when a transient improvement greater than the used thresholds (>10 cm/s for gait velocity, >2 points for MoCA) was seen on two consecutive assessments. Conversely, if a transient improvement between consecutive assessments was never greater than the established thresholds, decline in the trajectories were described as “sustained.” This approach has been previously used in a cohort of older adults to describe disability trajectories over time.<sup>25</sup>

### Independent Variables

Motor and cognitive trajectories were the independent variables selected and were modeled as having no decline,

intermittent decline, or sustained decline, as described above. In our sensitivity analysis, slow gait velocity at baseline was used as a predictor variable, modeled as continuous and dichotomous (<0.8 m/s and <1.0 m/s) variables.<sup>26–28</sup>

### Outcome Measure

Incident dementia was the main outcome, determined by a clinician investigator during follow-up visits using DSM-IV TR criteria and when global CDR score increased to 1 or higher. Different raters assessed the DSM-IV TR and CDR independently. A geriatrician blinded to motor assessment and to CDR, but not to MoCA results, administered the DSM-IV TR because having objective cognitive impairments is required for dementia diagnosis according to the DSM-IV TR. Trained certified research assistants performed cognitive testing and administered the CDR. Type of dementia was established using standardized criteria for Alzheimer’s disease (AD),<sup>29</sup> frontotemporal dementia,<sup>30</sup> Lewy body dementia,<sup>31</sup> and vascular dementia.<sup>32</sup> All types of dementia were grouped together as a general outcome of conversion to dementia.

### Covariates

Analyses were adjusted for age, sex, number of comorbidities at baseline, and development of new comorbidities. New comorbidities acquired during follow-up were treated as a time-dependent covariate to control for their potential competitive risk of incident dementia. Baseline MoCA score

and gait velocity were also included in the models, allowing each participant to serve as her or his own control.

## Data Analysis

Demographic and clinical characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Baseline between-group comparisons of characteristics were performed using chi-square tests for dichotomous variables and Student t-tests for continuous variables. Trajectories were visualized using spaghetti plots for motor (gait velocity) and cognitive (MoCA scores) performance for the complete cohort and separately for those who did and did not progress to dementia. To describe overall trends, lines of best fit were calculated for each motor and cognitive performance type (no decline, intermittent decline, sustained decline). Cox models were used to estimate the risk of progressing to dementia for participants with motor and cognitive decline (intermittent and sustained), unadjusted and adjusted for covariates.

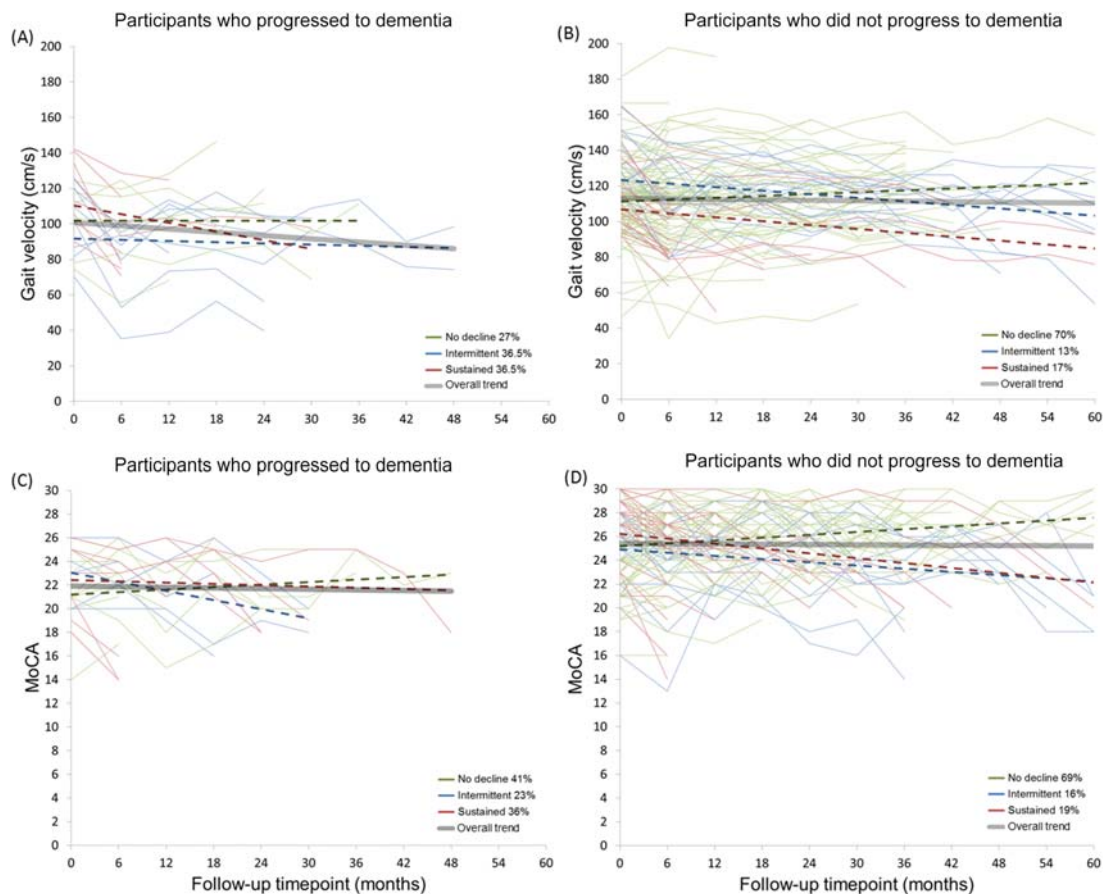
We also grouped participants with pure cognitive decline (intermittent or sustained but no mobility decline), pure mobility decline (intermittent or sustained but no cognitive decline), and with both, cognitive and mobility

decline (intermittent or sustained). Cox regression was used to model progression to dementia in each group. To account for different follow-up times, incident dementia is also presented as incident rate (IR) expressed as total person-years at risk. Attributable risks were explored comparing IRs across the four categories of interest: no decline, pure motor decline, pure cognitive decline, motor and cognitive decline combined. Statistical significance was set at  $P < .05$  (two-sided), and analyses were conducted using SPSS version 23.0 (IBM Corp., Armonk, NY).

## RESULTS

### Participant Characteristics and Progression to Dementia

One hundred thirty-five participants aged 65 and older (mean  $74 \pm 6.7$ ; 54.8% female) were assessed over a mean follow-up of 24 months (range 6–60 months). Table 1 presents baseline characteristics of the study sample, stratified according to progression to dementia. During follow-up, 22 participants (14.3%) progressed to dementia, for an overall IR of 69 per 1,000 person-years. Of these 22 participants, 19 (86.4%) progressed to AD, 1 (4.5%) to vascular dementia, and 2 (9.1%) to Lewy body dementia.



**Figure 2.** Motor (gait velocity) and cognitive (Montreal Cognitive Assessment score) trajectories divided by dementia progression. Figure 2A and C show motor and cognitive trajectories in participants who progressed ( $n=22$ ), and Figure 2B and D show trajectories in those who did not progress to dementia ( $n=132$ ). No decline is shown in green, intermittent decline is shown in blue, and sustained decline is shown in red. Dashed lines indicate trend lines for each performance. Thick grey lines indicate overall trend.

**Table 2. Risk of Progression to Dementia According to Motor Decline, Cognitive Decline, and Motor and Cognitive Decline**

Decline Pattern	Unadjusted	Model 1	Model 2	Model 3	Model 4
Hazard Ratio (95% Confidence Interval) P-Value					
<b>Motor<sup>a</sup></b>					
Intermittent	2.60 (0.89–7.60) .08	3.52 (1.14–10.84) .03	2.72 (0.80–9.24) .11	2.54 (0.72–8.97) .15	2.29 (0.60–8.75) .22
Sustained	7.02 (2.42–20.35) <.001	6.21 (2.08–18.61) .001	5.70 (1.91–17.01) .002	5.53 (1.84–16.62) .002	6.89 (2.18–21.75) .001
<b>Cognitive<sup>b</sup></b>					
Intermittent	1.30 (0.44–3.82) .63	1.20 (0.40–3.56) .75	1.31 (0.44–3.87) .63	1.60 (0.53–4.81) .41	1.58 (0.53–4.76) .41
Sustained	3.03 (1.23–7.48) .02	2.78 (1.11–6.95) .03	2.32 (0.88–6.07) .09	3.18 (1.16–8.67) .02	3.61 (1.28–10.13) .01
<b>Combined<sup>c</sup></b>					
Pure motor	2.25 (0.60–8.46) .23	3.77 (0.96–14.91) .06	5.41 (0.98–29.91) .05	5.50 (0.98–30.89) .05	6.31 (1.08–36.87) .04
Pure cognitive	0.97 (0.18–5.30) .97	0.79 (0.14–4.53) .79	1.35 (0.21–8.47) .75	1.59 (0.25–10.13) .62	2.18 (0.33–14.39) .42
Motor and cognitive	5.33 (1.69–16.88) .004	5.41 (1.69–17.30) .004	6.26 (1.76–22.23) .005	6.57 (1.85–23.38) .004	7.83 (2.10–29.24) .002

No decline is the reference category.

<sup>a</sup>Model 1 adjusted for baseline Montreal Cognitive Assessment (MoCA) score; Model 2 adjusted for age, sex, baseline MoCA score; Model 3 adjusted for age, sex, baseline comorbidities, baseline MoCA score; Model 4: adjusted for age, sex, baseline comorbidities, baseline MoCA score, time-dependent covariate (comorbidities developed during follow-up).

<sup>b</sup>Model 1 adjusted for baseline gait velocity; Model 2 adjusted for age, sex, baseline gait velocity; Model 3 adjusted for age, sex, comorbidities, baseline gait velocity; Model 4 adjusted for age, sex, baseline comorbidities, baseline gait velocity, time-dependent covariate.

<sup>c</sup>Model 1 adjusted for baseline MoCA score, baseline gait velocity; Model 2 adjusted for age, sex, baseline MoCA score, baseline gait velocity; Model 3 adjusted for age, sex, baseline comorbidities, baseline MoCA score, baseline gait velocity; Model 4 adjusted for age, sex, baseline comorbidities, baseline MoCA score, baseline gait velocity, time-dependent covariate.

Baseline cognitive impairment, defined as a MoCA score less than 26, was more prevalent in the group that progressed to dementia (P=.03).

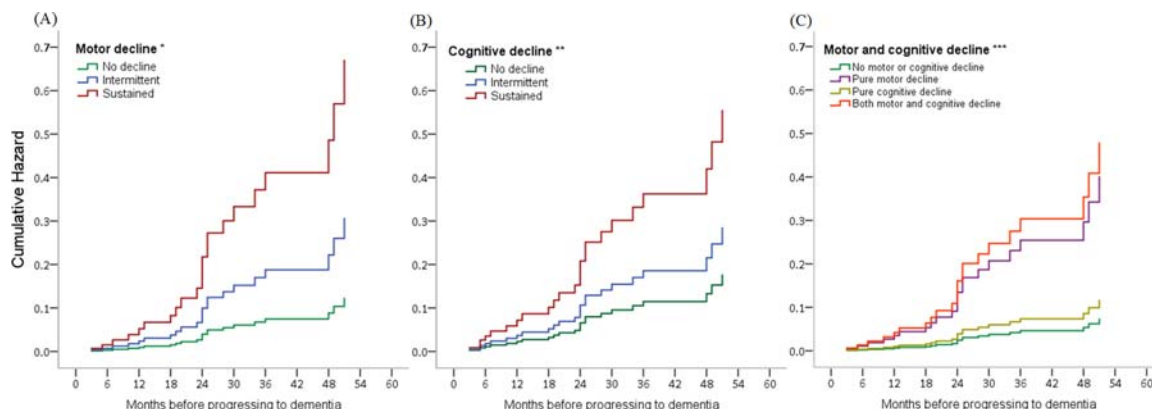
**Motor and Cognitive Trajectories and Associations with Incident Dementia**

Trajectories from the complete cohort revealed that 64% did not experience motor decline during follow-up, 16% had intermittent decline, and 20% sustained decline. Similarly, 65% of participants had no cognitive decline, 14% had intermittent decline, and 21% had sustained decline (Supplementary Figure S1).

Trajectories of participants who progressed to dementia showed that 73% experienced motor decline (Figure 2A, 36.5% intermittent, 36.5% sustained) before progression to

dementia, whereas only 30% of participants who did not progress to dementia experienced motor decline (Figure 2B, 13% intermittent, 17% sustained). Cognitive trajectories for participants who progressed to dementia (Figure 2C) showed that 41% had no decline, 23% had intermittent decline, and 36% had sustained decline. Cognitive trajectories for those who did not progress to dementia (Figure 2D) showed that 69% had no decline, 16% had intermittent decline, and 19% had sustained decline. Motor decline (trendline slope=-0.81) had a steeper slope than cognitive decline (trendline slope=-0.02) in those who progressed to dementia.

Sustained motor decline was associated with progression to dementia for all 5 models (unadjusted and Models 1 to 4), increasing the risk 5 to 6 times (Table 2, Figure 3A). Similarly, sustained cognitive decline predicted



**Figure 3.** Cox proportional hazards for incident dementia according to (A) motor decline, (B) cognitive decline, and (C) both motor and cognitive decline. Risk of progressing to dementia stratified according to no decline, intermittent decline, and sustained decline. \*Adjusted for age, sex, comorbidities, and baseline Montreal Cognitive Assessment (MoCA) score. \*\*Adjusted for age, sex, comorbidities, and baseline gait velocity. \*\*\*Adjusted for age, sex, comorbidities, baseline MoCA score, and baseline gait velocity.

progression to dementia in the unadjusted model, Model 1, Model 3, and Model 4, increasing the risk 3 times, but not in Model 2 (Table 2, Figure 3B). Participants having combined motor and cognitive decline had the highest risk of progression to dementia in all 5 models (unadjusted, Models 1, 2, 3, 4), increasing the risk 7 times (Table 2, Figure 3C), yielding an IR of 179 per 1,000 person-years. Our results hold true when using a time-dependent covariate adjustment (Model 4, Table 2). Supplementary Table S1 shows that baseline slow gait failed to predict dementia ( $P \geq .10$ ).

### Attributable Risk for Incident Dementia

Participants with neither cognitive nor motor decline had an IR of 32 per 1,000 person-years for dementia, whereas for those with pure cognitive decline, it was only 33 per 1,000 person-years, yielding an attributable risk for pure cognitive decline of just 1 per 1,000 person-years. Conversely, the IR for pure motor decline was 73 per 1,000 person-years, and thus the attributable risk for pure motor decline was 41 (73/1,000–32/1,000 person-years). The expected IR for combined motor and cognitive decline is 74 (IR = 33/1,000 + 41/1,000 person-years), although our data show the IR of conversion to dementia in those with both factors to be 179 per 1,000 person-years, indicating that 105 (IR = 179/1,000–74/1,000 person-years) additional conversions to dementia could be attributable to the synergistic effects of both factors co-occurring.

### DISCUSSION

Motor and cognitive trajectories in our cohort of older adults free of dementia at baseline were dynamic and fluctuated among assessments within the same individuals. Clinically significant motor and cognitive decline occurred in two-thirds of participants who progressed to dementia and one-third of those who did not. Overall, participants with motor decline, assessed according to serial measures of gait velocity, had 2 to 6 times the risk of progressing to dementia and a higher attributable risk than those with cognitive decline, who had 1 to 3 times the risk of progressing. A decline over time of gait velocity and cognition combined had the highest risk of progression.

Current evidence suggests that trajectories of motor components of activities of daily living have a dynamic nature. For example, results from the Precipitating Events Project study showed that trajectories for motor disability fluctuated between assessments, changing frequently between disability and independent states in community older adults.<sup>25</sup> Previous population-based cohort studies have shown decline in motor and cognitive function with aging, and in few of them, decline in gait performance preceded cognitive decline.<sup>6–8,10</sup> Recent meta-analyses have also confirmed a longitudinal relationship between physical and motor function and cognition in aging independent of important comorbidities.<sup>12,33</sup>

Our study provides new evidence that motor and cognitive declines are common in individuals who progress to dementia, who have twice the prevalence of those who do not progress. This common occurrence is not merely due

to a high prevalence of these impairments in aging but to common mechanisms probably at the brain level.<sup>1</sup> Gait regulation shares common brain regions and networks with cognitive processes<sup>3,14,34</sup> that are essential for planning and monitoring goal-directed behavior.<sup>1,35</sup> Understanding gait and cognitive impairments as a result of underlying processes affecting function in these shared brain regions and networks may point to modifiable factors including vascular damage, chronic inflammation, neurodegeneration, and micronutrient deficiencies.<sup>1,36–41</sup>

We demonstrated that motor and cognitive declines before progression to dementia are not uniform or linear but present a fluctuating trajectory over time. These fluctuating trajectories, in some cases, even reached normality thresholds for gait velocity or cognitive performance. These findings suggest that single or isolated measures can be misleading, particularly when assessed in early stages of decline. Using solely a slow gait velocity threshold at a single assessment was not sufficient to identify individuals at high risk of progression to dementia, in our cohort. These findings may provide an explanation for the mixed results found in studies that predicted cognitive decline based solely on one, typically baseline, gait assessment.<sup>7,8,10,12,43,44</sup> Serial assessments of motor performance seem to be critical for early detection of risk of dementia, particularly in older adults with initial normal gait velocity.<sup>14,42</sup> Despite early studies showing that motor decline trajectories were more likely to be associated with non-Alzheimer's dementias,<sup>5,45</sup> mounting evidence suggests that motor impairment and declines are also associated with AD, which is aligned with our finding that 86% of participants who progressed to dementia progressed to AD.<sup>2,5,9,28,33,44,46,47</sup>

We have identified 2 patterns of declining trajectories, both associated with progression to dementia. In our cohort, the risk of progression to dementia was higher for motor than cognitive decline. One explanation may be that, despite the MoCA being a very sensitive measure of several cognitive domains, as a global score, it may not capture subtle variations in cognition that gait velocity as a motor-function test can capture. This observation may have interesting clinical implications for primary care, where global cognitive tests are routinely used to screen cognition in older adults for risk of dementia. Thus, testing gait velocity in general assessments can reveal important information along with cognitive functioning.<sup>5,14,28,34,48</sup> Further studies are needed to demonstrate the efficacy and feasibility of routine gait assessments in the primary care setting. Finally, the combination of cognitive and motor decline conferred the highest risk of progression to dementia, showing an incremental predictive ability for incident dementia over the two individual components and the highest attributable risk, indicating that 105 additional conversions to dementia for every 1,000 person-years evaluated (IR = 179/1,000–74/1,000 person-years) could be attributable to the synergistic effects of both factors co-occurring. Our results are in agreement with the proposed “motor signature” of cognitive decline, which shows that slow gait is associated with pre-dementia syndromes,<sup>6,14,49</sup> and with the recently described Motoric Cognitive Risk syndrome,<sup>28</sup> defined as slow gait and cognitive complaints, which has been associated with greater risk of progression to dementia.

Some limitations of our study need to be outlined. As with any observational study, risk of unmeasured or residual confounding is possible. Participants were mainly recruited from geriatric clinics to include subjects at high risk of dementia, and consequently, they already had some degree of cognitive impairment, although none of them met the criteria for dementia. Thus, our results may be generalizable only to clinic-based populations, and replication of our findings in a general population may be required. The small number of participants who progressed to dementia, as well as the hypothesis-generating nature of this study, may also affect the generalizability and precision of our estimates. Finally, it is possible that a neuropsychological battery for testing cognition would increase detection of cognitive decline. We chose MoCA because of its simplicity and clinical availability. The strengths of our study include a well-characterized cohort with long follow-up that was purposely designed to assess cognitive and motor changes over time with close follow-up intervals to capture their trajectories and to monitor time to progression to dementia and standardized assignment of dementia diagnoses. Our multivariable longitudinal modeling used robust analyses adjusted for known baseline covariates, as well as for time-dependent covariates, allowing adjustments for development of new comorbidities over time.

In conclusion, motor decline is a common and fluctuating phenomenon in older adults who convert to dementia and increases the risk of progression to dementia 6 times. If combined with global cognitive decline, it increases the risk 7 times. Our results support the hypothesis that motor and cognitive dysfunction may reflect shared pathogenic processes at the brain level and that gait is a candidate biomarker of progression to dementia.<sup>3,14,34,48,50</sup> Routine repeated measurement of gait velocity appears to be an important, simple, economical clinical tool to be used along with measures of cognition to identify heightened risk for future dementia in older adults.

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**Conflict of Interest:** MMO is member of the Board of the Canadian Geriatrics Society, Associate Editor of the *Journal of Alzheimer's Disease*, and Editorial Board Member of the *Journal of Gerontology Medical Sciences and Geriatrics*. JW was a part-time employee of Pfizer Pharmaceuticals and owns stock employee options.

**Author Contributions:** MMO: study concept and design; obtaining funding; recruiting and assessing study participants; acquisition, analysis, and interpretation of data;

drafting first version of manuscript and revising it for critically important intellectual content; approving final version to be published. MS, YSA: analysis and interpretation of data, drafting manuscript and revising it critically for important intellectual content, approving final version to be published. SMH: recruiting and assessing study participants, acquisition and interpretation of data, drafting manuscript and revising it critically for important intellectual content, approving final version to be published. LS: recruiting study participants, acquisition and interpretation of data, revising manuscript critically for important intellectual content, approving final version to be published. VH: interpretation of data, drafting manuscript and revising it critically for important intellectual content, approving final version to be published. MB: recruiting and assessing study participants, acquisition and interpretation of data, revising manuscript critically for important intellectual content, approving final version to be published. JW: recruiting and assessing study participants, interpretation of data, revising manuscript critically for important intellectual content, approving final version to be published. AB: recruiting study participants, interpreting data, revising manuscript critically for important intellectual content, approving final version to be published. ES, LB, HC: interpretation of data, revising manuscript critically for important intellectual content, approving final version to be published.

**Sponsor's Role:** None.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

**Figure S1.** Trajectories of (a) gait velocity and (b) Montreal Cognitive Assessment (MoCA) score for the complete cohort (n=154). No trajectory decline is shown in green, intermittent decline is shown in blue, and sustained decline is shown in red. Dash lines display the trend lines for each performance.

**Table S1.** Hazard ratios for progression to dementia determined by gait velocity (m/s) as a continuous variable and using two established thresholds.

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