The Trajectory of Gait Speed Preceding Mild Cognitive Impairment

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Objectives: To compare the trajectory of motor decline, as measured by gait speed and finger-tapping speed, between elderly people who developed mild cognitive impairment (MCI) and those who remained cognitively intact. We also sought to determine the approximate time at which the decline in motor function accelerated in persons who developed MCI.

Design: Longitudinal cohort study.

Participants: Participants were 204 healthy seniors (57.8% women) from the Oregon Brain Aging Study evaluated for up to 20 years using annual neurologic, neuropsychological, and motor examinations.

Main Outcome Measures: The pattern of motor decline with aging was compared using a mixed-effects model with an interaction term for age and a clinical diagnosis of MCI. The time before diagnosis of MCI, when the change in gait or finger-tapping speed accelerates, was assessed using a mixed-effects model with a change point for men and women, separately and combined, who developed MCI.

Results: The rates of change, with aging, in gait speed ($P < .001$) and finger-tapping speed in the dominant hand ($P = .003$) and nondominant hand ($P < .001$) were significantly different between participants who developed MCI (converters) and those who did not (nonconverters). Using a change point analysis for MCI converters, the decrease in gait speed accelerated by 0.023 m/s/y ($P < .001$), occurring 12.1 years before the onset of MCI. An acceleration in gait speed decline occurred earlier in men than women. For tapping speed, the change point occurred after the onset of MCI for both dominant and nondominant hands when men and women were combined.

Conclusions: Motor decline as indexed by gait speed accelerates up to 12 years before MCI. Longitudinal changes in motor function may be useful in the early detection of dementia during preclinical stages, when the utility of disease-modifying therapies would be greatest.

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Mild Cognitive Impairment (MCI) represents an early clinical stage of cognitive impairment, considered distinct from normal aging, with the potential for further progression to Alzheimer disease or other dementias. Predicting the earliest stages of cognitive impairment has important implications for initiating treatment and monitoring the progression of disease. Slowing of motor function is commonly observed in older persons with cognitive impairment compared with those who are cognitively intact. Motor changes may precede the onset of MCI by years. In addition, slower gait speed in those who are cognitively intact at baseline may be predictive of the subsequent onset of cognitive impairment.

Motor changes with aging initially appear with the slowing of fine motor movements and mild parkinsonian signs. The causes are unclear but may include pathologic changes caused by neurologic illnesses, such as stroke or Parkinson disease, or by nonneurologic illnesses. These changes are not benign and may predict disability, institutionalization, and mortality in community-residing elderly people.

Several studies have shown that motor slowing precedes and may predict the onset of cognitive impairment; however, the time at which this slowing begins in relation to the onset of cognitive impairment is not clear. We used data from a longitudinal aging study to test the hypothesis that persons who develop MCI have a greater rate of decline in motor function, as measured by gait and finger-tapping speed, than those who remain cognitively intact. We also used a change point statistical model to determine the approximate time at which this change in the rate of decline occurs in relation to the onset of MCI.
Subjects were participants in the Oregon Brain Aging Study, a longitudinal study of healthy elderly people that began in 1989 at the National Institute on Aging's Layton Aging and Alzheimer's Disease Center at Oregon Health & Science University. Study procedures have been previously described. Inclusion criteria required that participants be community dwelling, functionally independent, and free of comorbid illnesses; have a baseline Mini-Mental State Examination score of 24 or higher; have a Clinical Dementia Rating (CDR) Scale score of 0; and exhibit no depression by screening with the Geriatric Depression Scale. Participants underwent annual medical histories, neurologic examinations, and neuropsychological testing. Assessments were performed until death. Between March 7, 1989, and May 27, 2005, 289 subjects were evaluated and 216 met inclusion criteria and were enrolled. Of those, 204 subjects were older than 65 years and were included in this analysis. Attrition rates caused by loss to follow-up other than death were less than 1% per year. The study and consent forms were approved by the Oregon Health & Science University Institutional Review Board; all subjects signed written informed consent.

**CLINICAL ASSESSMENTS**

Annual evaluations were performed by trained neurologists and geriatric nurse practitioners and included a medical history, mental status examination, and standardized neurologic examination. Neurologic examination results were quantified and coded. Interrater reliability has been previously reported. The Mini-Mental State Examination and the Cognistat were performed as brief cognitive evaluations. Health assessments consisted of review of medical histories, medication lists, and scores on the modified Cumulative Illness Rating Scale. Height and weight were assessed annually. Blood specimens were obtained for determination of APOE genotype by DNA extraction and analysis using standard methods.

Gait speed was assessed by asking participants to walk from a starting point to a marker 15 ft away, turn, and walk back at a normal casual gait for a total of 30 ft (9.14 m). Time (in seconds) was recorded with a stopwatch to the nearest second for 2 trials, and the mean was recorded. Finger tapping was measured by having the participants push a lever with an attached counter using the index finger of each hand for a 10-second period. Three trials were performed with each hand, and the mean value was recorded.

Health conditions or states with the potential to affect mobility were obtained from medical histories and examination results. These included heart disease, chronic pulmonary conditions, stroke, Parkinson disease, cancer, diabetes mellitus, major surgical procedures, musculoskeletal or head injuries, and depression. Presence of depression was based on a score higher than 4 on the Geriatric Depression Scale long form before November 4, 2003, and a score higher than 4 on the Geriatric Depression Scale short form after that time. These were coded as dichotomous variables, either present or absent. Body mass index was calculated from height and weight recorded at annual visits.

Cognitive impairment was considered present with a CDR score of 0.5 or higher. The CDR scores were determined by interviews with participants and collateral informants who provided information on cognitive and functional status. The Cognistat (but not the psychometric battery test) scores were included in the determination of the CDR score. The onset of MCI was defined by the first of 2 consecutive semiannual CDR scores of 0.5 or higher to minimize the possible inclusion of subjects with transient or reversible cognitive impairment. The term conversion is used to describe the development of incident MCI during the follow-up period.

**ANALYSIS**

Characteristics at baseline and presence of health conditions were compared between participants who developed MCI (converters) and those who did not (nonconverters) using the t test and Wilcoxon rank sum test for continuous variables and Pearson χ² test for categorical variables. Longitudinal mixed-effects models estimated the patterns of change across time in gait and tapping speeds. First, an interaction term between age and clinical diagnosis was used to test whether the aging pattern for MCI converters differed from nonconverters during follow-up. Analyses were adjusted for baseline speed (gait or tapping), years of education, sex (when combining both sexes), and APOE ε4 genotype. Analyses were also adjusted for the presence of depression and stroke during the entire follow-up in nonconverters and before conversion in MCI converters.

A second analysis investigated whether the annual rate of decline in gait or tapping speed changed at some point relative to clinical diagnosis using a longitudinal mixed-effects model with a change point. The inclusion of a change point in the mixed-effects model allowed the rates of change to differ before and after the change point. The change point in the coefficients is relative to the time of diagnosis of MCI, as opposed to age. The model assumes that the timing of the change point relative to the MCI diagnosis is common across all subjects. Normality of distribution of outcomes was confirmed by examining normal probability plots. As described previously, analyses were adjusted for age, years of education, sex, APOE ε4 genotype, baseline speed, stroke, and depression. The analyses were run for men and women separately and combined because of differences in baseline gait and tapping speeds (ie, men walked or tapped faster than women).

Change point models can be sensitive to a few influential observations. In the gait speed data, 6 outliers among women and 2 outliers among men, indicated by DFFITS statistics greater than 0.2, were excluded in the first mixed-effects models and change point models. Exclusion of these observations did not change the main results for gait speed but improved overall model fit. Therefore, we report the results of change point analysis excluding these influential observations. For tapping speed, DFFITS tests identified no outlying influential cases.

The location of the change point relative to the MCI diagnosis was estimated by maximum likelihood using the SAS procedure NL MIXED (SAS Institute, Cary, North Carolina). Separate mixed-effects models were fit with the change point at fixed 1-month intervals up to 15 years before and after diagnosis. The model with the highest likelihood was used to summarize the results. We tested whether there was a significant change in the rate of change in outcomes relative to the MCI diagnosis by calculating a 95% confidence interval around the measure on the change point term using a likelihood ratio approach. The significance of the other terms in the mixed-effects model was determined using a Wald test statistic. Standard errors for the measure estimates were calculated using the conditional variance, as proposed previously.

**RESULTS**

Participant characteristics are summarized in Table 1. Among 204 participants with a mean of 9 years of follow-
up, 95 (46.6%) converted to MCI. The MCI converters were a mean of 4.5 years older (\(P = .001\)), scored 0.2 points lower on the Mini-Mental State Examination at baseline (\(P = .03\)), had a longer mean follow-up time (\(P = .001\)), and were more likely to have the \(APOE \varepsilon 4\) genotype (\(P = .001\)) than nonconverters (Table 1). There was a significant difference in baseline gait speed between the 2 groups for women only. Among all health factors assessed (see the “Clinical Assessments” subsection in the “Methods” section), only stroke was significantly more frequent in the MCI group before the onset of cognitive impairment (\(P = .001\)) and was thus taken into account in subsequent models. Although depression was not significantly more frequent in the MCI group, it was included in the analyses because of its reported association with motor slowing.27

Table 1. Participant Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls (at Baseline)</th>
<th>Converters to MCI (at Baseline)</th>
<th>(P) Value(^b)</th>
<th>Converters to MCI (at Time of Conversion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size, No.</td>
<td>Combined 109</td>
<td>95</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 60</td>
<td>58</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 49</td>
<td>37</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Age, y [range]</td>
<td>Combined 79.0 (8.8) [65.2-100.5]</td>
<td>83.5 (7.0) [65.1-98.5]</td>
<td>&lt;.001</td>
<td>89.8 (5.4) [73.1-99.7]</td>
</tr>
<tr>
<td></td>
<td>Women 78.7 (8.7) [65.2-97.4]</td>
<td>84.7 (6.2) [68.6-98.5]</td>
<td>&lt;.001</td>
<td>90.5 (4.9) [76.1-99.7]</td>
</tr>
<tr>
<td></td>
<td>Men 79.3 (9.2) [65.2-100.5]</td>
<td>81.6 (7.8) [65.1-91.8]</td>
<td>.21</td>
<td>88.8 (6.1) [73.1-99.4]</td>
</tr>
<tr>
<td>Education, y</td>
<td>Combined 14.5 (2.7)</td>
<td>14.7 (2.6)</td>
<td>.57</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 14.1 (2.3)</td>
<td>14.1 (2.7)</td>
<td>.99</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 15.0 (3.1)</td>
<td>15.6 (2.3)</td>
<td>.26</td>
<td>...</td>
</tr>
<tr>
<td>MMSE score</td>
<td>Combined 28.3 (1.5)</td>
<td>28.1 (1.6)</td>
<td>.03</td>
<td>26.2 (2.9)</td>
</tr>
<tr>
<td></td>
<td>Women 28.7 (1.2)</td>
<td>28.0 (1.8)</td>
<td>.01</td>
<td>26.3 (2.5)</td>
</tr>
<tr>
<td></td>
<td>Men 28.3 (1.2)</td>
<td>28.2 (1.4)</td>
<td>.77</td>
<td>26.0 (3.5)</td>
</tr>
<tr>
<td>(APOE \varepsilon 4) genotype, %</td>
<td>Combined 12.6</td>
<td>27.7</td>
<td>.001</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 12.7</td>
<td>25.9</td>
<td>.08</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 12.5</td>
<td>30.6</td>
<td>.04</td>
<td>...</td>
</tr>
<tr>
<td>Stroke, %(^c)</td>
<td>Combined 1.8</td>
<td>13.7</td>
<td>.001</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 0</td>
<td>15.5</td>
<td>&lt;.001</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 4.1</td>
<td>10.8</td>
<td>.23</td>
<td>...</td>
</tr>
<tr>
<td>Depression, %(^c)</td>
<td>Combined 6.4</td>
<td>13.7</td>
<td>.08</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 5.0</td>
<td>15.5</td>
<td>.06</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 8.2</td>
<td>10.8</td>
<td>.68</td>
<td>...</td>
</tr>
<tr>
<td>Follow-up, y [range]</td>
<td>Combined 8.4 (5.0) [0.1-19.2]</td>
<td>10.5 (4.0) [2.5-19.3]</td>
<td>.001</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women 8.4 (5.2)</td>
<td>10.2 (3.7)</td>
<td>.04</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men 8.3 (4.8)</td>
<td>11.9 (4.5)</td>
<td>.01</td>
<td>...</td>
</tr>
<tr>
<td>Time to conversion, y</td>
<td>Combined ...</td>
<td>6.37 (4.04)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Women ...</td>
<td>5.78 (3.95)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>Men ...</td>
<td>7.32 (4.06)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Gait speed, m/s</td>
<td>Combined 0.96 (0.23)</td>
<td>0.91 (0.24)</td>
<td>.10</td>
<td>0.78 (0.23)</td>
</tr>
<tr>
<td></td>
<td>Women 0.94 (0.24)</td>
<td>0.84 (0.03)</td>
<td>.03</td>
<td>0.78 (0.25)</td>
</tr>
<tr>
<td></td>
<td>Men 1.00 (0.21)</td>
<td>1.01 (0.04)</td>
<td>.79</td>
<td>0.78 (0.20)</td>
</tr>
<tr>
<td>Finger-tapping speed, dominant hand, taps per second</td>
<td>Combined 3.87 (0.80)</td>
<td>3.77 (0.85)</td>
<td>.40</td>
<td>3.86 (0.95)</td>
</tr>
<tr>
<td></td>
<td>Women 3.53 (0.71)</td>
<td>3.49 (0.80)</td>
<td>.72</td>
<td>3.64 (0.97)</td>
</tr>
<tr>
<td></td>
<td>Men 4.29 (0.77)</td>
<td>4.21 (0.73)</td>
<td>.60</td>
<td>4.23 (0.79)</td>
</tr>
<tr>
<td>Finger-tapping speed, nondominant hand, taps per second</td>
<td>Combined 3.83 (0.65)</td>
<td>3.62 (0.71)</td>
<td>.89</td>
<td>3.64 (0.79)</td>
</tr>
<tr>
<td></td>
<td>Women 3.41 (0.57)</td>
<td>3.38 (0.65)</td>
<td>.76</td>
<td>3.48 (0.73)</td>
</tr>
<tr>
<td></td>
<td>Men 3.91 (0.65)</td>
<td>3.99 (0.64)</td>
<td>.59</td>
<td>3.90 (0.83)</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses not calculated; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination.

\(^a\) Data are presented as mean (SD) unless otherwise indicated.

\(^b\) Comparison between control group and converters at baseline.

\(^c\) Frequency during entire follow-up period for nonconverters and until conversion in converters.
There was a significant decline in gait speed across time in the mixed-effects model of 0.013 m/s/y \((P < .001)\) for all participants, demonstrating the effect of age on gait speed. The MCI converters had a further decline of 0.01 m/s/y compared with nonconverters \((P < .001)\).

In the change point model, profile likelihood values showed a clear peak 12.1 years (145 months) before the MCI diagnosis. On average, the MCI converters’ rate of decrease in gait speed accelerated by 0.023 m/s/y \((P < .017)\) approximately 12 years before diagnosis. The upper limit of the confidence interval could not be observed in our current data because the maximum follow-up duration observed before the MCI conversion was 16.3 years, too short to observe the upper limit in the change point (ie, left censoring).

When the model was run separately for men and women (Table 2), we found that for men, the MCI converters’ rate of decrease in gait speed accelerated by 0.023 m/s/y \((P < .017)\) at 14.2 years (95% confidence interval, 8.7 years to unknown) before the MCI diagnosis. For women, the MCI converters’ rate of decrease in gait speed accelerated by 0.025 m/s/y \((P < .012)\) at 6.0 years (95% confidence interval, 4.6 to 9.5 years) before the MCI diagnosis. Figure 1 shows an example of gait speed trajectory relative to the time of MCI conversion if the participant converted to MCI at age 89.9 years, the mean age of conversion among this cohort.

Although the change point analysis is modeled relative to MCI diagnosis, we wanted to further test whether the change point was also present in nonconverters as a result of a specific age. Therefore, we examined the change point among nonconverters relative to the age of 89.9 years, the mean age of conversion in MCI converters. No change point for nonconverters was found.

### FINGER TAPPING

There was a significant decline in finger-tapping speed across time in the mixed-effects model of 0.02 taps per second per year \((P < .001)\) and 0.01 taps per second per year \((P = .002)\) for the dominant and nondominant hands, respectively, for all participants. This shows the effect of age on tapping speed. The MCI converters had a further decline of 0.02 taps per second per year \((P = .003)\) for the dominant hand and 0.03 taps per second per year \((P < .001)\) for the nondominant hand compared with nonconverters. Change point analysis of tapping speed showed that change points occurred after MCI onset (indicated by nega-
ferences. One possible explanation is that there is a difference in baseline gait speed in women between converters and nonconverters, suggesting that the change point may have occurred in women before the start of this study. We might have found an earlier change point for women if we had a larger sample with a longer duration of follow-up. Another possibility is that the different change points may be attributed to underlying sex-specific physiological differences.

Several studies have examined baseline gait speed and other motor signs as predictors of the future development of cognitive impairment or dementia using survival analysis or linear regression analysis. To our knowledge, no other studies have prospectively examined the rates of change in gait speed or other motor signs and their relationship to incident MCI. We used up to 20 years of data to determine rates of motor changes and to identify the earliest time at which these changes occurred in relation to clinical findings of cognitive impairment.

The sensitivity of gait changes to early cognitive changes may be best understood if gait is viewed as a complex cognitive task. Gait requires an interplay of attention, executive function, and visuospatial function, as well as the motor processing functions of the motor cortex, basal ganglia, and cerebellum. Therefore, the same mechanisms that underlie decline in cognitive functioning may be associated with decline in gait. Gait speed change may be a bellwether of the efficiency of the central integration of multiple cognitive domains needed for this complex task. Decline in gait speed may also be viewed as part of a larger construct of physical frailty in elderly people. Physical frailty is common in this group; it is measured by gait speed, strength, body composition, and fatigue and is associated with incident dementia and pathologic characteristics of Alzheimer disease.

The underlying pathophysiologic mechanism behind motor decline is not clear. Motor slowing and parkinsonism were shown to be related to periventricular white matter changes. There may also be a relationship between gait dysfunction and the presence of neurofibrillary tangles in the substantia nigra and markers of Alzheimer disease in the frontal lobes and basal ganglia.

Our study has several limitations. First, the change point model requires large sample sizes and long-term follow-up and may be difficult to generalize to individuals owing to interindividual variability. This model does not allow for time-varying covariates, which limits the ability to assess the contributions of health conditions that develop during follow-up. Second, we were unable to determine the upper confidence limits of the change point in gait speed for men and in the combined analysis because of left censoring. This may be a result of the need for a larger sample size or longer follow-up. In addition, the change point is calculated relative to the age at MCI onset, and the use of alternate criteria to define the age at onset could move the change point either earlier or later than the values reported in this article.

Despite these limitations, there are several strengths to our study. We used longitudinal data with up to 20 years of follow-up for some participants. Standardized, validated testing measures were used in the evaluations. Our participants were generally healthy with no major comorbid illnesses at baseline and a low rate of intercurrence.

Our participants were generally healthy with no major comorbid illnesses at baseline and a low rate of intercurrence.
rent illnesses, which were accounted for in subsequent analyses.

Our study complements findings from other studies of this cohort showing accelerated cognitive decline on neuropsychological tests 3 to 4 years before MCI and accelerated expansion of ventricular volumes 2 years before the onset of MCI. Future studies may compare these different methods for assessing disease progression to determine which is the more sensitive measure predicting the onset of cognitive impairment. The use of annual data may be supplemented by the use of more continuous, home-based gait monitoring. This allows for a more frequent and ecologically representative assessment of gait speeds, which suggests differences in the variance of daily acquired gait speeds between participants with MCI and healthy control participants. These findings have important implications for identifying cognitive impairment at the earliest preclinical stages, when initiation of disease-modifying therapies may be most beneficial.

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Author Contributions: Drs Buracchio, Dodge, and Kaye had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Buracchio, Dodge, Howieson, and Kaye. Acquisition of data: Buracchio, Howieson, Wasserman, and Kaye. Analysis and interpretation of data: Buracchio, Dodge, and Kaye. Drafting of the manuscript: Buracchio and Kaye. Critical revision of the manuscript for important intellectual content: Buracchio, Dodge, Howieson, Wasserman, and Kaye. Statistical analysis: Dodge and Howieson. Obtained funding: Kaye. Administrative, technical, and material support: Buracchio, Wasserman, and Kaye. Study supervision: Kaye.

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REFERENCES


New Initiatives: Clinical Trials and Videos. We have embarked on 2 new initiatives: Clinical Trials and video presentations. We welcome manuscripts that describe double-blind, randomized, placebo-controlled clinical trials as our primary area of interest. We plan on expediting the review process and time to publication and to include them online ahead of print as these studies are time sensitive and of direct benefit to our patients. We hope you will take advantage of this new initiative. Please refer to the Instructions for Authors when submitting a Clinical Trials paper, including the requirement to register the trial with an accepted clinical trials site.

We plan to utilize videos as part of published papers that highlight and provide convincing information about the observational and visual features of a patient’s neurologic findings. Please refer to Instructions for Authors for instructions on submitting video presentations.