Longitudinal Study of the Transition From Healthy Aging to Alzheimer Disease

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Background: Detection of the earliest cognitive changes signifying Alzheimer disease is difficult.

Objective: To model the cognitive decline in preclinical Alzheimer disease.

Design: Longitudinal archival study comparing individuals who became demented during follow-up and people who remained nondemented on each of 4 cognitive factors: global, verbal memory, visuospatial, and working memory.

Setting: Alzheimer Disease Research Center, Washington University School of Medicine, St Louis, Missouri.

Participants: One hundred thirty-four individuals who became demented during follow-up and 310 who remained nondemented.

Main Outcome Measures: Inflection point in longitudinal cognitive performance.

Results: The best-fitting model for each of the 4 factors in the stable group was linear, with a very slight downward trend on all but the Visuospatial factor. In contrast, a piecewise model with accelerated slope after a sharp inflection point provided the best fit for the group that progressed. The optimal inflection point for all 4 factors was prior to diagnosis of dementia: Global, 2 years; Verbal and Working Memory, 1 year; and Visuospatial, 3 years. These results were also obtained when data were limited to the subset (n=44) with autopsy-confirmed Alzheimer disease.

Conclusions: There is a sharp inflection point followed by accelerating decline in multiple domains of cognition, not just memory, in the preclinical period in Alzheimer disease when there is insufficient cognitive decline to warrant clinical diagnosis using conventional criteria. Early change was seen in tests of visuospatial ability, most of which were speeded. Research into early detection of cognitive disorders using only episodic memory tasks may not be sensitive to all of the early manifestations of disease.

Arch Neurol. 2009;66(10):1254-1259

Recent studies have focused on identifying the beginning of the transition from healthy aging to dementia. As new interventions become available, it will become important to identify the disease as early as possible. A piecewise regression analysis of a measure of episodic memory identified an inflection point 5 years before diagnosis in the Bronx Aging Study. A flat trajectory followed by decline beginning 7 years before diagnosis of dementia was reported for the same measure in the Baltimore Longitudinal Study of Aging, which also found decline in executive function that increased in rate 2 to 3 years before diagnosis. Episodic memory is not the only aspect of cognition that can be affected in preclinical Alzheimer disease (AD). Indeed, mild cognitive impairment, often thought to represent a transitional state between healthy cognitive aging and AD, is defined on the basis of deficits in cognitive domains in addition to memory.

In this article we examine cognitive domains beyond episodic memory and executive function to test hypotheses about the existence of inflection points before clinical diagnosis of dementia. Based on the identification of common factor structures in cognitively healthy individuals and those with AD, we examined global mental ability and 3 specific cognitive domains (verbal memory, working memory, and visuospatial ability) through a long preclinical period as people developed dementia and compared them with those who remained cognitively healthy. Results from longitudinal studies support an early observation that the overall course of healthy aging is relatively stable compared with the cognitive decline, often precipitous, experienced by those who develop dementia. We sought to model...
that change to determine when the inflection occurs before dementia detection and the rate of change afterward for different cognitive domains and to validate these clinical observations in an autopsy-confirmed sample.

## METHODS

### PARTICIPANTS

Longitudinal archival data were examined from 444 volunteers initially aged 60 to 101 years enrolled in the Alzheimer Disease Research Center, Washington University School of Medicine, St Louis, Missouri, between October 1, 1979, and December 31, 2006 (Table 1). All the participants were clinically evaluated to be cognitively healthy (Clinical Dementia Rating [CDR] = 0) at the time of their first psychometric assessment and had at least 1 additional annual clinical evaluation through November 30, 2006 (progressed group, n = 134; autopsied group, n = 44). The Washington University Human Studies Committee approved all the procedures. Data from these participants have been used in other publications.

### CLINICAL EVALUATION

Research-trained clinicians and nurses determined whether the participant was demented (CDR > 0) or not demented (CDR = 0) based on semistructured interviews with the participant and a knowledgeable collateral source (usually the spouse or an adult child), a health history, medication and depression inventories, an aphasia battery, and a neurologic examination of the participant. The diagnosis of dementia was based on a history of gradual onset and progressive cognitive decline that interfered with the person’s ability to perform accustomed activities. The CDR has high interrater reliability, is sensitive to clinical progression, and is highly predictive (93%) of autopsy-confirmed AD. Participants were seen by different physicians initially aged 60 to 101 years enrolled in the Alzheimer Disease Research Center, Washington University School of Medicine, St Louis, Missouri, between October 1, 1979, and December 31, 2006 (stable group, n = 310).

### NEUROPATHOLOGIC ASSESSMENT

All the brains were examined according to a standard protocol. After fixation in neutral-buffered 10% formalin, tissue blocks were obtained from 30 brain regions. Sections (6 µm) from paraffin-embedded tissue blocks were stained with hematoxylin-eosin, Gallyas and modified Bielschowsky silver stains, and immunohistochemical methods. Histologic criteria for AD were based on the quantification of diffuse and neuritic amyloid deposition in 5 cortical regions with 10-mm² microscias from year to year, and physicians did not have access to previous clinical evaluations or to previous or current psychometric test results.

### PSYCHOMETRIC ASSESSMENT

The psychometric battery was administered to all the participants by trained psychometricians usually 1 to 2 weeks after the annual clinical assessment. The tests assessed a broad spectrum of abilities across multiple cognitive domains, including Logical Memory, Associate Learning, Mental Control, and Digit Span from the Wechsler Memory Scale (WMS); Information, Block Design, and Digit Symbol from the Wechsler Adult Intelligence Scale; the Boston Naming Test; Letter Fluency for S and P; Trailmaking Test Part A; and Form D (copy) of the Benton Visual Retention Test (Table 2). The raw scores from each test were converted to standard scores using the means and standard deviations from the initial assessment of the stable group (Table 2). Initial values for the group that progressed are included solely for descriptive purposes; recall that they were initially older, on average, than the stable group.

Based on confirmatory factor analyses of these measures cross-validated across demented and nondemented samples, we formed 4 factor scores for each person at each assessment. The Global factor included all 12 measures; it was uncorrelated with the 3 specific factors, which each included 4 measures. The measures on the Verbal Memory factor were Logical Memory, Associate Learning, Information, and Boston Naming. The 4 measures on the Working Memory and Executive Function factor were Mental Control, Digit Span Forward and Backward, and Letter Fluency. The Visuospatial factor included Block Design, Digit Symbol, Trailmaking A, and Benton (copy). A prorated factor score was computed if 1 or 2 values were missing for the Global factor and if 1 value was missing for the specific factors; otherwise, the factor value for that assessment for that person was excluded from the analyses.

### Initial Neuropsychological Performance for the Stable and Progressed Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Stable Group</th>
<th>Progressed Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical Memory</td>
<td>8.87 (2.91)</td>
<td>7.39 (2.93)</td>
</tr>
<tr>
<td>Associate Learning</td>
<td>13.42 (2.53)</td>
<td>11.90 (3.30)</td>
</tr>
<tr>
<td>Information</td>
<td>20.60 (4.43)</td>
<td>18.94 (5.04)</td>
</tr>
<tr>
<td>Boston Naming</td>
<td>54.55 (5.69)</td>
<td>51.00 (7.02)</td>
</tr>
<tr>
<td>Mental Control</td>
<td>7.21 (1.78)</td>
<td>7.07 (1.97)</td>
</tr>
<tr>
<td>Digit Span Forward</td>
<td>6.55 (1.25)</td>
<td>6.40 (1.15)</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>4.75 (1.28)</td>
<td>4.62 (1.18)</td>
</tr>
<tr>
<td>Letter Fluency</td>
<td>29.41 (9.73)</td>
<td>27.21 (9.79)</td>
</tr>
<tr>
<td>Block Design</td>
<td>30.05 (8.63)</td>
<td>26.86 (7.02)</td>
</tr>
<tr>
<td>Digit Symbol</td>
<td>45.67 (15.53)</td>
<td>26.86 (7.02)</td>
</tr>
<tr>
<td>Trailmaking A</td>
<td>40.94 (19.86)</td>
<td>51.21 (21.82)</td>
</tr>
<tr>
<td>Benton, copy</td>
<td>9.59 (0.88)</td>
<td>9.78 (0.47)</td>
</tr>
</tbody>
</table>

### Characteristics of the Samples at Entry, Time of Dementia Diagnosis, and Last Assessment

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stable Group</th>
<th>Progressed Group</th>
<th>Autopsied Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assessments, No.</td>
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<td>957</td>
<td>330</td>
</tr>
<tr>
<td>Age at entry, mean (SD), y</td>
<td>74.4 (8.6)</td>
<td>80.4 (8.9)</td>
<td>83.6 (9.2)</td>
</tr>
<tr>
<td>Age at diagnosis, mean (SD), y</td>
<td>NA</td>
<td>84.1</td>
<td>90.2 (7.2)</td>
</tr>
<tr>
<td>Age at last assessment, mean (SD), y</td>
<td>79.6 (8.5)</td>
<td>88.2 (8.2)</td>
<td>92.2 (6.3)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>37</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>APOE4 carrier, %</td>
<td>28</td>
<td>27</td>
<td>18</td>
</tr>
<tr>
<td>Education, mean, y</td>
<td>14.8</td>
<td>14.1</td>
<td>13.8</td>
</tr>
<tr>
<td>SBT score at entry, mean (SD)</td>
<td>1.4 (2.1)</td>
<td>1.6 (2.1)</td>
<td>1.5 (2.1)</td>
</tr>
<tr>
<td>SBT score at diagnosis, mean (SD)</td>
<td>NA</td>
<td>4.6 (4.8)</td>
<td>5.5 (6.1)</td>
</tr>
<tr>
<td>SBT score at last assessment, mean (SD)</td>
<td>1.2 (1.9)</td>
<td>7.1 (7.0)</td>
<td>9.9 (8.7)</td>
</tr>
<tr>
<td>CDR-SB at entry, mean (SD)</td>
<td>0.05 (0.2)</td>
<td>0.17 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>CDR-SB at diagnosis, mean (SD)</td>
<td>NA</td>
<td>1.5 (1.8)</td>
<td>1.7 (2.4)</td>
</tr>
<tr>
<td>CDR-SB at last assessment, mean (SD)</td>
<td>0.03 (0.1)</td>
<td>3.3 (3.7)</td>
<td>4.5 (5.1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** APOE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating sum of boxes; NA, not applicable; SBT, Short Blessed Test.
inflection point (ŶT1) and the next assessment thereafter (ŶT2).
ning with the difference of the predicted value at the optimized
the difference between the −2LL of a simpler model and a more
beginning with the simple linear model. Deviance scores equal
consistent with simultaneous models.25 A simultaneous model
motion is robust, is straightforward, and can be estimated with-
linear unbiased predictor). Using these latent values from each
factor scores at each time of assessment for each person (best
model. First, we used the optimal piecewise model to predict the
slopes across time). Technically, this was not a test of a nested
inflection and tested whether rates of cognitive decline differed
before and after that point.22 To determine the optimum place-
ment of the change point in the piecewise model, we tested in-
flection points from 1 to 6 years before the last assessment for
the stable group. For those who progressed, we tested for an
inflection point at the time of diagnosis of dementia and from
4 years before diagnosis to 2 years after diagnosis (>50 obser-
vations at each selected time point). The quadratic piecewise
model added a quadratic term for the postinflection time vari-
able using the optimal inflection point.
We conducted additional analyses to determine whether in-
stead of a quadratic function after inflection there was accelera-
tion in the rate of progression (ie, a change in the slope of the
slopes across time). Technically, this was not a test of a nested
model. First, we used the optimal piecewise model to predict the
factor scores at each time of assessment for each person (best
linear unbiased predictor). Using these latent values from each
time of assessment rather than observed values, we calculated
latent difference scores (LDSs) for each person. The LDS equals
the difference between the predicted values at 2 adjacent times
of assessment (ŶT1−ŶT2, ŶT2−ŶT3, ŶT3−ŶT4, and so forth) begin-
nings with the simple linear model. Deviance scores equal
the difference between the −2LL of a simpler model and a more
complex one (Δχ²).
The linear piecewise change model specified a point of in-
flection and tested whether rates of cognitive decline differed
before and after that point.22 To determine the optimum place-
ment of the change point in the piecewise model, we tested in-
flection points from 1 to 6 years before the last assessment for
the stable group. For those who progressed, we tested for an
inflection point at the time of diagnosis of dementia and from
4 years before diagnosis to 2 years after diagnosis (>50 obser-
vations at each selected time point). The quadratic piecewise
model added a quadratic term for the postinflection time vari-
ble using the optimal inflection point.
We conducted additional analyses to determine whether in-
stead of a quadratic function after inflection there was accelera-
tion in the rate of progression (ie, a change in the slope of the
slopes across time). Technically, this was not a test of a nested
model. First, we used the optimal piecewise model to predict the
factor scores at each time of assessment for each person (best
linear unbiased predictor). Using these latent values from each
time of assessment rather than observed values, we calculated
latent difference scores (LDSs) for each person. The LDS equals
the difference between the predicted values at 2 adjacent times
of assessment (ŶT1−ŶT2, ŶT2−ŶT3, ŶT3−ŶT4, and so forth) begin-
ning with the difference of the predicted value at the optimized
inflection point (ŶT1) and the next assessment thereafter (ŶT2).
Then we tested a linear mixed model using the LDS as the
dependent variable to determine whether the slope of the LDS
values (ie, the slope of the slopes) changed across time. The
acceleration coefficient tested herein is a 2-stage regression ana-
logue to other acceleration models derived from structural equa-
tion modeling22 and the functional equivalent of acceleration
in kinematics (ie, the second derivative of position/intercept).
Although this method of measurement may slightly attenuate
ture acceleration values because of the tendency for latent val-
tes to “shrink” in the presence of missing data,24 its computa-
tion is robust, is straightforward, and can be estimated with-
out multiple imputation of missing data. It yields results
consistent with simultaneous models.22 A simultaneous model
that approximates slopes and acceleration was not attempted
because we did not know the functional form of the data (the
primary aim of this investigation).
After determining the optimal models within each group,
slope estimates were based on a mixed model for each factor
that included covariates, effects for group (stable vs pro-
gressed), time (before and after inflection), and group × time
interactions. Acceleration coefficients for the group that pro-
gressed were estimated from the second stage of the LDS model
and were added to slope coefficients after the point of inflec-
tion. All analyses were repeated for the subset of the group that
progressed that had autopsy confirmation of AD.

STATISTICAL ANALYSES
Cross-sectional comparisons of quantitative demographic vari-
ables (age and education) in the 2 groups (stable vs progressed)
were made using t tests for independent groups; the χ² test was
used for categorical variables. A multistep longitudinal
modeling procedure was used for each of the 4 factors. All longitudi-
nal analyses were conducted using random coefficient models
(SAS v9.1.3, PROC MIXED; SAS Institute Inc, Cary, North Caro-
olina) and included the covariates of age and education.
To determine the best form of a factor score’s trajectory
through time for each group (stable and progressed), we used
χ² tests for −2 log likelihood ratios (−2LLs) for nested models
of increasing complexity of the slope across time (linear, qua-
Dratic, linear piecewise, linear piecewise optimized, and qua-
Dratic piecewise); simpler models are nested in more complex
models. Model comparisons used χ² tests of deviance scores
beginning with the simple linear model. Deviance scores equal
the difference between the −2LL of a simpler model and a more
complex one (Δχ²).

RESULTS

SAMPLE CHARACTERISTICS
All the participants were not demented (CDR=0) at entry
and either remained CDR=0 (stable) throughout follow-
up (n=310, 37% men) or progressed to CDR>0
(n=134, 34% men) with a clinical diagnosis of uncer-
tain dementia (CDR=0.5) or dementia of the Alzheimer
type (CDR≥0.5) by the time of their last evaluation
(Table 1). Participants who progressed and whose clin-
cal diagnosis was non-AD dementia (eg, vascular demen-
tia associated with Parkinson disease) were excluded. In-
dividuals who came to autopsy with a clinical diagnosis
of dementia of the Alzheimer type but who had another
dementia abnormality were also excluded (n=14). Maxi-

mum follow-up was 25.7 years (mean [SD], 5.9 [3.3]
years). The stable group was slightly more educated
(mean, 14.8 years) than the group that progressed (mean,
14.1 years). As might be expected given that AD is age
associated, those who progressed were older at entry
(mean [SD], 80.4 [8.9] years) than those whose perfor-
ance remained stable (mean [SD], 74.4 [8.6] years).
Apolipoprotein E4 status did not differ between the stable
(28% carriers) and progressed (27% carriers) groups. Au-
opsy confirmation of a diagnosis of AD was available for
a subset (n=44, 36% men) of the group that progressed.
At the time of progression, they were older (mean age,
90.2 years) than the rest of the group (mean age, 84.1
years), although their mean educational level (13.8 years)
was comparable with that of those without autopsy (14.1
years).

NONDEMENTED AGING
The linear regression model provided the best fit for each
factor in the stable group. The −2LL values were as fol-
ows: Global, 4255.5; Verbal Memory, 3045.3; Visuo-
spatial, 2796.7; and Working Memory, 5912.5. More com-
plex models did not improve fit (Δχ²>14.4 for all,
P>.05).

CHARACTERIZING PRECLINICAL AD:
INFLECTION POINTS
In the progressed group, the linear model provided ade-
quate fit for all 4 factors (−2LL values) (Table 3). Fit
was not improved using a quadratic model for any fac-
tor (P>.05 for all), although it was improved using a
piecewise model with an inflection point at the time of
diagnosis. The piecewise model fit was improved by mov-
ing the inflection point before diagnosis (P<.001)
(Table 3). The optimal inflection point varied for the 4
factors: 2 years before clinical diagnosis for the Global

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factor, 1 year before diagnosis for the Verbal and Working Memory factors, and 3 years before diagnosis for the Visuospatial factor (Figure).

The Verbal Memory factor included episodic and semantic memory measures. An inflection point for a single measure of episodic memory occurred substantially longer than 1 year before diagnosis in previous studies.1,2 Therefore, we also examined each of the 2 measures of episodic memory independently. The inflection point occurred 4 years before diagnosis for WMS Associate Learning and 2 years before diagnosis for WMS Logical Memory.

The fit of the piecewise model did not improve with the addition of a quadratic term after the optimal inflection point ($P > .05$ for all) (Table 3). There was, however, a significant increase in the rate of decline after the inflection point for all 4 factors using the LDS models of acceleration ($t > 12.10$ for all, $P < .001$). Thus, the optimal model in the group that progressed was piecewise, with linear slope before inflection and accelerated slope

<table>
<thead>
<tr>
<th>Model</th>
<th>df</th>
<th>$-2LL$</th>
<th>$\Delta \chi^2$</th>
<th>df</th>
<th>$-2LL$</th>
<th>$\Delta \chi^2$</th>
<th>df</th>
<th>$-2LL$</th>
<th>$\Delta \chi^2$</th>
<th>df</th>
<th>$-2LL$</th>
<th>$\Delta \chi^2$</th>
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<td>Simple linear</td>
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<td>NA</td>
<td>9</td>
<td>2277.7</td>
<td>NA</td>
<td>9</td>
<td>1938.8</td>
<td>NA</td>
<td>9</td>
<td>3737.8</td>
<td>NA</td>
</tr>
<tr>
<td>Quadratic</td>
<td>9</td>
<td>3019.5</td>
<td>268.7</td>
<td>2277.7</td>
<td>0</td>
<td>1938.8</td>
<td>0</td>
<td>3737.8</td>
<td>0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Piecewise linear</td>
<td>At diagnosis</td>
<td>9</td>
<td>2705.1</td>
<td>−45.7</td>
<td>2255.9</td>
<td>−21.8</td>
<td>1939.6</td>
<td>−44.2</td>
<td>3690.1</td>
<td>−47.7</td>
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<tr>
<td>Optimizedb</td>
<td>9</td>
<td>2690.3</td>
<td>−14.8</td>
<td>2243.5</td>
<td>−12.4</td>
<td>1910.3</td>
<td>−29.3</td>
<td>3676.0</td>
<td>−20.1</td>
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<td>Piecewise quadraticc</td>
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<td>2243.9</td>
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<td>0</td>
<td>3675.6</td>
<td>−0.4</td>
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</table>

Abbreviations: $-2LL$, −2 log likelihood ratio (smaller values indicate better fit); NA, not applicable.

a 1 df for deviance tests.
b The optimal inflection point was 2 years before diagnosis for the Global factor, 3 years before diagnosis for the Visuospatial factor, and 1 year before diagnosis for the Verbal and Working Memory factors.
c Quadratic term after the inflection point.

Figure. Longitudinal course of the stable, progressed, and autopsy-confirmed Alzheimer disease (AD) groups before and after diagnosis of AD (DX) on Global factor (A), the Verbal Memory factor (B), the Visuospatial factor (C), and the Working Memory factor (D). All available data were used for the analysis, but the plotted values for the stable and progressed groups include at least 50 observations per time point per group.
CHARACTERIZING PRECLINICAL AD: SLOPE AND ACCELERATION ESTIMATES

Estimates and their standard errors are given in Table 4. Change in performance in all 4 factors is demonstrated in the Figure. The stable and progressed groups shared similar preinflection trajectories; the group \times time (before inflection) interactions were not significant for any of the 4 factors ($P > .19$ for all). There was a significant downward linear trend in global cognitive abilities and in verbal and working memory ($P < .01$); however, no longitudinal decline was detected in the Visuospatial factor ($P = .29$) (Figure). Results were similar when data from the group that progressed were limited to individuals with autopsy-confirmed AD.

A different pattern of longitudinal cognitive performance was seen in the group that progressed to dementia. Compared with preinflection slopes, they had steeper downward slopes after inflection ($P < .001$), and the rate of decline accelerated with time (Table 4 and Figure). The greatest preclinical slope change was in the Working Memory factor (slope $= -0.66$, acceleration $= -0.17$) beginning 1 year before dementia diagnosis followed by the Global factor (slope $= -0.32$, acceleration $= -0.06$). Postinflection slopes and accelerations were similar for the Verbal Memory and Visuospatial factors. Slopes were steeper when the sample that progressed was restricted to those with autopsy-confirmed AD, but rates of acceleration were comparable with those for the total group that progressed.

We demonstrate models of preclinical decline in a well-characterized longitudinal sample with inflection points in cognitive performance occurring several years before clinical diagnosis of dementia. It is apparent from these models that there is a clear turning point in the transition from normal aging to preclinical AD. A novel finding was that visuospatial abilities demonstrated an inflection point 3 years before clinical diagnosis. This decline on tests that were primarily speeded represented a sharp departure from the previous longitudinal pattern of these initially nondemented individuals, which was similar to that of those who did not become demented. Global cognitive abilities followed decline in visuospatial ability during the next year. Inflection points in the Verbal and Working Memory factors were not seen until 1 year before clinical diagnosis. The delayed inflection point for Verbal Memory probably results from the combination of episodic and semantic memory measures on one factor. If sufficient measures of each type of memory were available to form separate factors, an earlier inflection point for episodic memory would probably emerge based on the results obtained for the 2 individual measures of episodic memory.

The rate of decline accelerated after the downward course began. This was true for all 4 factors but was most apparent for Working Memory. Of course, the estimated rates of decline and acceleration depend on the tests administered, their level of difficulty, and floor and ceiling effects. For example, 3 tests in the battery (the Boston Naming Test, the copy version of the Benton Visual Retention Test, and the WMS Mental Control) have ceiling effects in the preinflection period in nondemented older adults. We were limited to these archival data from a battery that was originally constructed in 1979 for a study of mild dementia, and it does not contain more modern measurements of working memory.

The number of years before diagnosis of dementia that the inflection point occurs in the longitudinal course depends on the method of diagnosis and on the characteristics of the cognitive tests. The period will be longer if one relies on test norms, particularly if the sample is at a high level of function initially, than if one relies on collateral source reports of change from previous levels of function, captured by the CDR. Furthermore, inclusion of people in the preclinical stage in nondemented samples overestimates decline in cognitive ability traditionally attributed solely to age. This makes it more difficult to detect beginning dementia using conventional norms based on these contaminated samples.

A great strength of this study is the replication of the pattern of the longitudinal results observed in the larger sample that progressed in the subset with autopsy-confirmed AD. Although the rates of decline were somewhat steeper in the autopsied subset, the rates of acceleration were the same. The rate of progression in AD is

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**Table 4. Estimated Slopes and Rates of Acceleration for the 4 Cognitive Factors**

<table>
<thead>
<tr>
<th>Factor and Group</th>
<th>Before Inflection</th>
<th>After Inflection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>Slope</td>
</tr>
<tr>
<td>Global factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>-0.05 (0.01)</td>
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</tr>
<tr>
<td>Progressed</td>
<td>-0.07 (0.02)</td>
<td>-0.32 (0.02)</td>
</tr>
<tr>
<td>AD confirmed</td>
<td>-0.10 (0.03)</td>
<td>-0.40 (0.04)</td>
</tr>
<tr>
<td>Verbal Memory factor</td>
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</tr>
<tr>
<td>Stable</td>
<td>-0.02 (0.01)</td>
<td>NA</td>
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<tr>
<td>Progressed</td>
<td>-0.02 (0.01)</td>
<td>-0.15 (0.02)</td>
</tr>
<tr>
<td>AD confirmed</td>
<td>-0.03 (0.02)</td>
<td>-0.19 (0.03)</td>
</tr>
<tr>
<td>Visuospatial factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>0.00 (0.01)</td>
<td>NA</td>
</tr>
<tr>
<td>Progressed</td>
<td>-0.02 (0.01)</td>
<td>-0.13 (0.01)</td>
</tr>
<tr>
<td>AD confirmed</td>
<td>-0.02 (0.02)</td>
<td>-0.17 (0.02)</td>
</tr>
<tr>
<td>Working Memory factor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable</td>
<td>-0.08 (0.02)</td>
<td>NA</td>
</tr>
<tr>
<td>Progressed</td>
<td>-0.10 (0.03)</td>
<td>-0.66 (0.04)</td>
</tr>
<tr>
<td>AD confirmed</td>
<td>-0.12 (0.04)</td>
<td>-0.89 (0.06)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; NA, not applicable.

*a* Data are given as estimate (SE). Slope coefficients were estimated using the piecewise change model of raw data. Acceleration coefficients were estimated using latent difference score regression, in which intercepts were equivalent to piecewise change slope estimates ($±0.02$ U).

The optimal inflection point was 2 years before diagnosis for the Global factor, 1 year before diagnosis for the Verbal and Working Memory factors, and 3 years before diagnosis for the Visuospatial factor.
highly variable, perhaps those with autopsy-confirmed AD were individuals who progressed more rapidly. Another possibility is that the progressed group may contain individuals who do not have AD and, therefore, do not follow the same pattern of decline.

There are several implications of this study. Some of the earliest signs of preclinical disease may occur on tests of visuospatial and speeded psychomotor skills. Furthermore, the greatest rate of preclinical decline may occur on executive and attention tasks. These findings suggest that research into early detection of cognitive disorders using only episodic memory tasks, such as word lists or paragraph recall, may not be sensitive to either all of the earliest manifestations of disease or the most rapidly changing domain. Furthermore, the preclinical downward course comes after an inflection point. Before that point, the longitudinal course of those who did and did not develop AD was the same. In summary, converging longitudinal evidence suggests that after a sharp departure from the relatively flat course of normal aging there is a preclinical period in AD with insufficient cognitive decline to warrant clinical diagnosis using conventional criteria but that can be seen with longitudinal data from multiple domains of cognition and not just memory.

Accepted for Publication: February 25, 2009.
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Author Contributions: All authors had full access to all the data used in this study. Drs Johnson and Galvin take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Johnson, Storandt, and Galvin. Acquisition of data: Storandt, Morris, and Galvin. Analysis and interpretation of data: Johnson, Storandt, and Galvin. Drafting of the manuscript: Johnson, Storandt, and Galvin. Critical revision of the manuscript for important intellectual content: Johnson, Storandt, Morris, and Galvin. Statistical analysis: Johnson and Storandt. Obtained funding: Storandt and Morris. Administrative, technical, and material support: Galvin. Study supervision: Morris and Galvin.
Financial Disclosure: None reported.
Funding/Support: This study was supported by grants P01 AG03991, P50 AG05681, P01 AG026276 (Dr Morris), and K08 AG20764 (Dr Galvin) from the National Institute on Aging, National Institutes of Health.
Additional Contributions: We thank the Clinical and Neuropathology Cores of the Washington University Alzheimer Disease Research Center for the clinical, cognitive, and postmortem assessments and the Genetics Core for the apolipoprotein E genotype data.

REFERENCES