Biracial Population Study of Mortality in Mild Cognitive Impairment and Alzheimer Disease

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Objective: To assess mortality associated with mild cognitive impairment (MCI) and Alzheimer disease (AD) among older African Americans and whites from an urban community.

Design: Longitudinal population-based observational study.

Setting: Four adjacent neighborhoods in Chicago, Illinois.

Participants: Persons deemed free of dementia in a previous wave of data collection (n=1715) underwent detailed clinical evaluation: 802 had no cognitive impairment (46.8%), 597 had MCI (34.8%), 296 had AD (17.3%), and 20 had other forms of dementia (1.2%).

Main Outcome Measure: All-cause mortality.

Results: During as many as 10 years of observation (mean [SD], 4.7 [3.0] years), 634 individuals died (37.0%). Compared with people without cognitive impairment, risk of death was increased by about 50% among those with MCI (hazard ratio [95% confidence interval], 1.48 [1.22-1.80]) and was nearly 3-fold greater among those with AD (2.84 [2.29-3.52]). These effects were seen among African Americans and whites and did not differ by race. Among participants with MCI, risk of death increased with more severe cognitive impairment, and this effect did not vary by race. A similar effect was seen among participants with AD, but it was slightly stronger for African Americans vs whites. In the MCI and AD groups, the association of cognitive impairment with survival was stronger for perceptual speed than for other cognitive functions.

Conclusion: The presence and severity of MCI and AD are associated with reduced survival among African Americans, and these effects are comparable to those seen among whites.

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viewed was selected for a detailed clinical evaluation. Approximately 3 years later, the population interview was repeated, and a stratified random sample of those determined to be without dementia in the previous wave of data collection underwent clinical evaluation. These 2 steps (population interview and clinical evaluation of a new sample of persons previously deemed to be free of dementia) have been repeated at intervals of approximately 3 years, with the fifth wave of data collection now in progress. For these analyses, we included all persons who completed a clinical evaluation during the second wave of data collection or a subsequent wave (ie, third, fourth, or fifth) and monitored their vital status after the date of the clinical evaluation. If a person was sampled for more than 1 clinical evaluation, we used the earliest date to maximize the length of the monitoring period. Those selected had a mean (SD) age of 80.1 (5.9) years and had completed 12.7 (3.6) years of education; 61.3% were women, and 52.5% were African American.

CLINICAL EVALUATION

Each participant had a structured, uniform clinical evaluation that included a medical history, complete neurological examination, and cognitive function testing, as previously described.22,23 On the basis of this evaluation and an in-person examination, an experienced physician classified individuals with respect to dementia and AD using the guidelines of the joint working group of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association.21 The criteria require a history of cognitive decline and impairment in at least 2 cognitive domains. For the diagnosis of AD, one of the impaired domains must be memory.

As previously described,22,23 MCI was diagnosed in a 2-step process. First, after review of all cognitive data, a neuropsychologist (R.S.W.) rated impairment in 5 cognitive domains. To maintain consistency in ratings, cutoff scores adjusted for educational level on 11 tests and algorithmic ratings of each domain were provided.22 Second, the physician determined whether dementia criteria were met. Those with cognitive impairment but without dementia were deemed to have MCI. In other cohorts, persons meeting these criteria have shown intermediate levels of dementia and related disorders association.21

ASSESSMENT OF COGNITIVE FUNCTION

In an approximately 1-hour session, cognitive function was assessed with a battery of 18 tests. The Mini-Mental State Examination was used to describe the level of global cognition but was not used in analyses. Episodic memory was assessed with 7 measures: immediate and delayed recall of the East Boston Story and story A from the Wechsler Memory Scale–Revised and Word List Memory. Recall, and Recognition. Semantic memory was assessed with a 15-item version of the Boston Naming Test, Verbal Fluency, and a 15-item version of the National Adult Reading Test. Digit Span Forward, Digit Span Backward, and Digit Ordering were used to measure working memory. Perceptual speed was measured with the oral version of the Symbol Digit Modalities Test and Number Comprehension, and visuospatial ability was assessed with a 15-item version of Judgment of Line Orientation and a 12-item version of Standard Progressive Matrices.

To minimize floor and ceiling artifacts and other sources of measurement error, we used composite measures of 2 or more tests in analyses. A composite measure of global cognition was constructed using all 17 tests. To develop measures of specific cognitive functions, we hypothesized that the tests could be grouped into 5 domains: episodic memory, semantic memory, working memory, perceptual speed, and visuospatial ability. In participants without dementia, we performed a factor analysis of the 17 tests with varimax rotation. The factor analytic grouping showed good agreement with the hypothesized grouping (Rand statistic,24 a measure of goodness of fit ranging from −1 to 1, was 0.62; P < .001). Therefore, we used the hypothesized groupings to make summary measures of episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (2 tests), and visuospatial ability (2 tests). For all composite scores, raw scores were converted to z scores, using the mean and standard deviation of the full group, and z scores on component tests were averaged to yield the composite, as previously described for other cohorts.25,26

DETERMINATION OF VITAL STATUS

Information about death was obtained through multiple sources, as previously reported.27 Study personnel often learned of the death of a participant when attempting to schedule follow-up interviews. In addition, we regularly scanned local newspapers for obituaries and searched Web sites such as http://www.ancestry.com. We also attempted to verify all deaths by acquiring a death record from the National Death Index.

DATA ANALYSIS

We analyzed the relation of diagnosis to risk of death in a series of proportional hazards models. In these analyses, persons without cognitive impairment were used as a reference group that was contrasted with each diagnostic group. Terms were also included to control for age, sex, educational level, and race. In subsequent analyses, we added terms for comorbid medical conditions, possession of a copy of the apolipoprotein E ε4 allele, or socioeconomic status. We also conducted separate analyses of whites and African Americans and repeated the original analysis with terms for the interaction of race with MCI and with AD.

In separate analyses within the MCI and AD groups, we examined the relation of severity of cognitive impairment to risk of death. The initial analyses included a term for level of global cognition at baseline. We then conducted separate analyses in African Americans and whites and repeated the initial analysis of the AD group with a term for the interaction of race with global cognitive score. In subsequent analyses, we substituted measures of specific cognitive functions for the global measure, first in separate models and then together in a single model.

Models were graphically and analytically validated. Programming was done with SAS statistical software.31

RESULTS

A total of 802 people without cognitive impairment, 597 with MCI, 296 with AD, and 20 with other forms of dementia completed the clinical evaluation. As shown in Table 1, those with dementia were slightly older and less educated than those without dementia.

DEMENTIA DIAGNOSIS AND MORTALITY

Vital status was monitored for up to 10 years (mean [SD], 4.7 [3.0]). During this period, 634 individuals died.
(37.0%), including 25.8% of those without cognitive impairment, 40.4% of those with MCI, 59.1% of those with AD, and 60.0% of those with other forms of dementia. We examined the relationship of diagnosis to risk of death in a series of proportional hazards models. These and all subsequent analyses were adjusted for the potentially confounding influences of age, sex, race, and educational level. Individuals without cognitive impairment served as a reference group that was contrasted with each of the other diagnostic groups (ie, participants with MCI, AD, or other dementia). As shown in Table 2, compared with those without cognitive impairment, risk of death was about 50% higher among those with MCI and nearly 3 times higher among those with AD or other forms of dementia. Results were similar after controlling for common chronic medical conditions (ie, heart disease, hypertension, stroke, diabetes mellitus, and cancer) (hazard ratio [HR] for MCI group [95% confidence interval [CI]], 1.44 [1.19-1.75]; AD group, 2.81 [2.25-3.50]), possession of at least 1 apolipoprotein E ε4 allele (MCI group, 1.45 [1.19-1.77]; AD group, 2.91 [2.32-3.65]), or socioeconomic indicators (ie, occupation and income) (MCI group, 1.49 [1.21-1.82]; AD group, 2.81 [2.23-3.55]).

Because little is known about racial differences in survival rates among people with AD, we conducted separate analyses for African Americans and whites. In these analyses, the associations of MCI and AD with risk of death among African Americans appeared slightly weaker than the same associations in whites (Table 2 and Figure). This apparent difference was not significant, however; in an analysis that included terms for the interactions of race with the indicators for MCI and AD, neither interaction was significant (race × MCI: estimate [SE], −0.29 [0.19], P = .13; race × AD: −0.36 [0.21]; P = .08).

**COGNITIVE IMPAIRMENT AND MORTALITY WITHIN DIAGNOSTIC GROUPS**

Both MCI and AD are clinically heterogeneous conditions. One important way in which affected persons differ is in overall severity of cognitive impairment. To determine whether individual differences in the severity of these conditions aided in the prediction of mortality, we conducted separate analyses within the MCI and AD groups. Each analysis used a baseline score on the composite measure of global cognition (full cohort mean [SD], 0.35 [0.59]) as an indicator of severity of cognitive impairment. A lower global cognition level was associated with increased risk of death in the MCI (HR [95% CI], 2.65 [1.68-4.16]) and AD (2.29 [1.65-3.19]) groups. Thus, in participants with MCI, a relatively low global cognitive score (25th percentile; 0.01) was associated with a 58% increase in risk of death compared with a relatively high score (75th percentile, 0.48). Risk of death
among participants with AD was increased by about 58% for a low score (−0.70) vs a high score (−0.15).

To determine whether these effects varied by race, we conducted separate analyses for African Americans and whites. In participants with MCI, the correlation of severity of cognitive impairment with mortality was equivalent for African Americans (HR [95% CI], 2.54 [1.31-4.94]) and whites (2.44 [1.30-4.57]). In participants with AD, severity of cognitive impairment had a slightly stronger association with mortality for African Americans (HR [95% CI], 3.38 [2.06-5.53]) than for whites (1.62 [1.01-2.59]), confirmed by an interaction between race and global cognitive score in a subsequent analysis (estimate [SE], −0.64 [0.31]; P = .04).

Persons with MCI and AD also vary in the cognitive domains that are most compromised. Therefore, we conducted a final series of analyses to assess whether the association of severity of cognitive impairment with mortality in these conditions varied across domains of cognition. Within each diagnostic group, we related baseline level of function in each of 5 cognitive domains to mortality, first with a separate model for each domain and then with all 5 domain scores simultaneously analyzed (Table 3). In the separate models, lower levels of function in nearly all cognitive domains were associated with increased risk of death in the MCI and AD groups, consistent with a global severity effect. By contrast, in the simultaneous models, only perceptual speed was related to increased mortality in both groups, and there were no other associations in the other cognitive domains, suggesting a much more selective effect.

### Table 3. Relation of Baseline Level of Cognitive Function to Risk of Death

<table>
<thead>
<tr>
<th>Cognitive Measure</th>
<th>MCI Group Separate Models</th>
<th>MCI Group Single Model</th>
<th>AD Group Separate Models</th>
<th>AD Group Single Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodic memory</td>
<td>1.48 (1.08-2.04)</td>
<td>1.29 (0.92-1.80)</td>
<td>1.60 (1.19-2.14)</td>
<td>1.27 (0.87-1.86)</td>
</tr>
<tr>
<td>Semantic memory</td>
<td>1.75 (1.30-2.34)</td>
<td>1.31 (0.94-1.83)</td>
<td>1.47 (1.16-1.86)</td>
<td>0.95 (0.69-1.31)</td>
</tr>
<tr>
<td>Working memory</td>
<td>1.29 (1.03-1.62)</td>
<td>1.01 (0.79-1.29)</td>
<td>1.73 (1.35-2.23)</td>
<td>1.16 (0.84-1.62)</td>
</tr>
<tr>
<td>Perceptual speed</td>
<td>1.66 (1.32-2.09)</td>
<td>1.51 (1.14-2.00)</td>
<td>1.87 (1.43-2.43)</td>
<td>1.56 (1.10-2.21)</td>
</tr>
<tr>
<td>Visuospatial ability</td>
<td>1.12 (0.90-1.39)</td>
<td>1.03 (0.80-1.32)</td>
<td>1.49 (1.21-1.84)</td>
<td>1.12 (0.85-1.49)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment.

From proportional hazards models that controlled for age, sex, race, and educational level.

COMMENT

In this study, older persons sampled from an urban community were clinically classified and vital status was monitored for as long as 10 years. Persons with incident AD were nearly 3 times more likely to die than persons without cognitive impairment. This finding is consistent with previous population-based studies, further highlighting the malignant nature of the disease.

Mild cognitive impairment is widely recognized as a precursor to AD. In this study, risk of death was about 50% higher among those with MCI compared with those without cognitive impairment. This association has been previously observed in population-based samples. Negative results have also been reported, possibly because of the modest size of the association.

Knowledge about the consequences of MCI and AD in African Americans is limited. In this biracial sample, the presence of MCI and AD and the severity of cognitive impairment within these conditions were associated with risk of death in African Americans. These associations did not reliably differ from the associations observed among whites with one exception: the association of severity of cognitive impairment in AD with mortality was slightly stronger for African Americans than whites. Overall, these results do not suggest strong racial differences in survival for persons with MCI and AD. We are not aware of previous research on survival rates for African Americans with MCI. In national surveys of health care data, mortality rates among persons with AD have been reported to be higher for whites than for African Americans. Interpretation of these studies is difficult, however, because the quality of medical record data is unlikely to be uniform across racial subgroups, and results appear to depend in part on what data are used to establish dementia. In recent analyses of cataloged data from more than 30,000 patients at AD centers in the United States, African Americans were about 20% less likely to die than whites. These data are subject to bias, as the authors acknowledge, but they are not necessarily inconsistent with the present results because we probably lack the statistical power to detect an effect of this size. If there are racial differences in the consequences of AD, it will be important to determine whether they are due to diagnostic bias or whether they reflect actual differences in the underlying neurobiology of the disease or in how affected individuals are cared for.

Both MCI and AD are clinically heterogeneous. In prior research, severity of cognitive impairment in patients with AD has been associated with mortality. We replicated this finding and extended it by showing a comparable effect in participants with MCI that has not been observed in previous studies, possibly owing to lack of statistical power. Although risk of death was higher among persons with AD than with MCI, individual differences in severity of cognitive impairment within each group had comparable associations with mortality. Whether the association of severity of cognitive impair-
ment with mortality in persons with MCI and AD varies across domains of cognitive function has not been extensively studied. In this cohort, using continuous measures of multiple cognitive domains, we found that a lower level of functioning in any cognitive domain reduced the survival rate, but the effect was strongest for perceptual speed in the MCI and AD groups. Thus, survival in people with MCI and AD appears to depend in part on relative preservation of executive control processes, suggesting that interventions targeting these abilities should be considered in persons with these conditions or those at risk of developing them.

This study has important strengths and limitations. Participants were sampled from a defined population, making it more likely that a broad spectrum of affected persons was studied. Clinical classification of MCI, dementia, and AD was based on a uniform structured clinical evaluation and established criteria applied by an experienced physician, minimizing the likelihood that diagnostic imprecision affected results. The availability of previously established composite measures of cognition allowed us to estimate the associations of severity and type of cognitive impairment with survival. The main limitation is that, because individuals with evidence of cognitive impairment in the baseline phase of the study were eligible to be sampled for clinical evaluation, the MCI group includes prevalent and incident cases.

In summary, MCI and AD were associated with reduced survival rates to a similar extent in older African American and white persons. Further research is needed on the consequences of MCI and AD in racial and ethnic minorities.

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Author Contributions: Drs Wilson, Aggarwal, Barnes, and Mendes de Leon 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: Wilson and Evans. Acquisition of data: Wilson, Aggarwal, and Evans. Analysis and interpretation of data: Wilson, Barnes, Bienias, Mendes de Leon, and Evans. Drafting of the manuscript: Wilson. Critical revision of the manuscript for important intellectual content: Wilson, Aggarwal, Barnes, Bienias, Mendes de Leon, and Evans. Statistical expertise: Bienias, Mendes de Leon. Obtained funding: Evans. Administrative, technical, and material support: Wilson, Aggarwal, and Evans. Study supervision: Evans.

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