Depression, Apolipoprotein E Genotype, and the Incidence of Mild Cognitive Impairment

A Prospective Cohort Study

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Background: It remains unknown whether depression and apolipoprotein E genotype are risk factors for incident mild cognitive impairment (MCI).

Objective: To determine whether elderly individuals with depression (measured by the short Geriatric Depression Scale) are at increased risk of developing incident MCI.

Design: Prospective cohort study.

Setting: Primary care clinic.

Participants: A cohort of 840 cognitively normal elderly subjects without depression at recruitment who were followed up prospectively for a median of 3.5 years (range, 0.4-12.8 years). Subjects who developed depression (score of ≥6 on the short Geriatric Depression Scale; depression cohort) were compared with all remaining subjects (referent cohort).

Main Outcome Measures: Incidence of MCI (primary outcome) and incidence of MCI or dementia (composite secondary outcome).

Results: Individuals in the depression cohort were at significantly increased risk of subsequent incident MCI (hazard ratio [HR], 2.2; 95% confidence interval [CI], 1.2-4.1) after adjusting for age (time scale), sex, and education, and considering dementia as a competing outcome. The association was stronger in men but did not vary by severity of depression. We observed a synergistic interaction between apolipoprotein E genotype (ε3/ε4 or ε4/ε4) and depression (joint effect HR, 5.1; 95% CI, 1.9-13.6; test for additive interaction, P = .03). We found a similar association between depression and the subsequent composite outcome of incident MCI or dementia (HR, 2.6; 95% CI, 1.6-4.3).

Conclusions: Cognitively normal elderly individuals who develop depression are at increased risk of subsequent MCI. We found a synergistic interaction between depression and apolipoprotein E genotype.

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The cognitive spectrum, ranging from normal aging to dementia, has increasingly become the focus of contemporary research on aging and dementia. Various terms are used to describe this entity, including mild cognitive impairment (MCI).1-4 Although much progress has been made in characterizing the cognitive aspects of MCI, there has been less work focusing on the neuropsychiatric aspects.5-7 In a recent cohort study,8 depression (as measured by the Geriatric Depression Scale [GDS]) doubled the risk of progressing from MCI to dementia.8 However, it remains unknown whether depression is also a risk factor for MCI. Similarly, apolipoprotein E (APOE) genotype is a risk factor for Alzheimer disease10,11; however, its role in MCI remains unknown. We tested the hypothesis that elderly individuals with depression as measured by the short GDS are at increased risk of developing incident MCI.12,13

STUDY PARTICIPANTS

Normal elderly persons have been recruited by the Mayo Alzheimer Disease Patient Registry for longitudinal studies of cognitive aging since 1986. This cohort has been described in detail in previous publications.2,14 All subjects were residents of Olmsted County, Minnesota, and were receiving their routine medical care at the Division of Primary Care Medicine of the Mayo Clinic, Rochester, Minn. Potential normal individuals were referred to Alzheimer Disease Pa-
tient Registry personnel by primary care physicians. On referral to the Alzheimer Disease Patient Registry, each research participant was thoroughly evaluated by one of several behavioral neurologists (primarily R.C.P., D.S.K., and B.F.B.), who obtained a medical history from the participant and from an informant, completed the short test of mental status examination and the Hachinski Ischemic Scale, and performed a neurologic examination. Study personnel obtained other data, including the Record of Independent Living, the short version of the GDS, and additional family history information. Laboratory studies included standard hematologic tests; vitamin B12, folate acid, and sensitive thyroid stimulating hormone levels; and syphilis serologic testing. All participants underwent brain imaging (computed tomography or magnetic resonance imaging).

An extensive neuropsychological battery was administered on enrollment, and a briefer version was administered at subsequent follow-up visits every 12 to 18 months. These tests included the Wechsler Adult Intelligence Scale–Revised, the Wechsler Memory Scale–Revised, the Auditory Verbal Learning Test, and the Wide-Range Achievement Test–III. Additional tests were the Mini-Mental State Examination, the Dementia Rating Scale, the Free and Cued Selective Reminding Task, the Boston Naming Test, the Controlled Oral Word Association Test, and the category fluency procedures. At the completion of the clinical, neuropsychological, and neuroimaging evaluations, a consensus meeting was held involving behavioral neurologists, a geriatrician, neuropsychologists, nurses, and other study personnel who had evaluated the participant. The consensus team also assigned a Clinical Dementia Rating score and a Global Deterioration Scale score.

**ELIGIBILITY CRITERIA**

Normal cognitive status was defined using the published criteria of the Mayo’s Older American Normative Studies (MOANS) and required normal functioning in the community and no cognitive impairment. We excluded persons with a neurologic or psychiatric condition judged to interfere with cognitive assessment at the time of recruitment, such as depression. However, a history of depression was not an exclusion criterion. We also excluded persons receiving psychoactive medications in amounts that could compromise cognition. By contrast, persons with comorbid illnesses such as hypertension and coronary artery disease and those receiving medications for these disorders were included. However, if the primary care physician considered these illnesses or their treatments to interfere with cognitive functions, the persons were excluded.

**MEASURE OF DEPRESSION**

Participants were followed up longitudinally with repeated visits every 12 to 18 months. The follow-up visits included a clinical evaluation and the administration of an abbreviated neuropsychological battery. Depression was assessed by using the short version of the GDS (15 items). Study participants who developed depression (score of ≥6 on the GDS at least once) before reaching one of the outcomes of interest (MCI or dementia) were considered to be in the depression cohort starting on the date of the testing. All remaining participants who never developed depression (as per GDS score) were considered to be in the referent cohort. The depression and referent cohorts were followed up longitudinally to study the incidence of MCI. In addition, for each person in the study we obtained a history of depression preceding enrollment in the study. This historical information was obtained using the medical records–linkage system of the Rochester Epidemiology Project. Details about the system were reported elsewhere.

**APOE GENOTYPE**

Blood was drawn from the study participants after receiving informed consent. DNA was amplified by means of polymerase chain reaction, and APOE genotyping was determined by standard methods, as reported in detail elsewhere. The genotypes were determined by laboratory technicians who were kept unaware of clinical characteristics (eg, presence of depression or MCI).

**OUTCOME MEASURES**

The primary outcome was MCI. The adjudicating team diagnosed MCI on the basis of psychometric data collected during the follow-up visits and according to the criteria of Petersen et al (memory complaint, normal activities of daily living, normal general cognitive function, abnormal memory for age, mildly impaired performance on the MMSE). Because the follow-up visits occurred only every 12 to 18 months, a participant could develop dementia without any evidence of transition through an MCI status. Therefore, we considered as a secondary outcome measure the composite event of incident MCI or dementia. The adjudicating team diagnosed dementia according to Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition criteria.

**STATISTICAL ANALYSIS**

For survival analyses, baseline was the date of enrollment in the study for the referent cohort and the date on which depression was first measured (GDS score ≥6) for the depression cohort. Subjects were censored at death, loss to follow-up, or the end of the study (whichever came first). In analyses for MCI, dementia was considered a competing outcome. The association between the independent variable (depression measured by GDS) and the outcome of incident MCI was assessed using Cox proportional hazards models adjusted for sex and education (>12 vs ≤12 years). For more stringent age adjustment, age was used as the time scale in the survival analyses. However, graphic display of cumulative incidence curves was based on the more conventional time-to-event scale (accounting for competing outcomes). The same type of analysis was conducted for the composite event of incident MCI or dementia (secondary analysis). Stratified analyses were conducted for men and women separately and by level of severity of depression (GDS scores of 6 and 7-15 vs 0-5). Possible interaction effects with APOE genotype were examined using multivariate models to test for both multiplicative and additive interactions. This same method was also used to test for interaction between newly developed depression as measured by the GDS and a history of depression preceding enrollment in the study (preceding baseline). In addition, we compared the distribution of the individual GDS items in depressed subjects who developed MCI or dementia and in those who did not, to identify the most predictive items.

Statistical testing was conducted at the conventional 2-tailed α level of .05. Analyses were conducted using SAS (SAS Institute Inc, Cary, NC) and S-Plus (Insightful Corp, Seattle, Wash) statistical software.

**RESULTS**

Longitudinal data were available for 840 participants, who were free of both cognitive impairment and depression at the time of enrollment into the study and were followed up for a median of 3.5 years (range, 0.4-12.8 years). A total of 143 participants (17.0%) developed depression during follow-up (depression cohort), while 697 (83.0%) did not
(referent cohort). Of the 143 subjects in the depression cohort, 68 (47.6%) had a GDS score of 6, 72 (50.4%) had scores of 7 to 11, and 3 (2.1%) had scores of 12 to 15. The baseline characteristics of the depression and referent cohorts are summarized in Table 1. The depression cohort tended to be older than the referent cohort; however, this imbalance was controlled by using age as the time scale when modeling the survival data.

Of the 143 subjects with depression, 17 (13.3%) developed MCI, whereas of the 697 referent subjects, only 33 (4.9%) developed MCI. Figure 1 shows cumulative incidence curves (using the conventional time-to-event scale and accounting for competing outcomes). The cumulative incidence curves for the depression and referent groups remained divergent throughout the follow-up for both the primary and secondary outcomes. The hazard ratio (HR) for MCI was 2.2 (95% confidence interval [CI], 1.2–4.1), after controlling for age (time scale), education, and sex, and considering dementia as a competing outcome. We also found a significant difference for the secondary outcome of incident MCI or dementia, with frequencies of 22.4% (32/143) for the depression cohort and 7.2% (50/697) for the referent cohort (HR, 2.6; 95% CI, 1.6–4.3).

We conducted analyses for the interaction between newly developed depression and history of depression by using subjects who did not develop depression during the study and did not experience depression before the study as the reference group. Compared with the reference group, subjects who developed depression but did not have a history of depression had an HR of 4.5 (95% CI, 1.9–10.9) for MCI, subjects who did not develop depression but had a history of depression before the study had an HR of 2.9 (95% CI, 1.5–5.8), and subjects with the joint effect of newly developed depression and a history of depression had an HR of 2.6 (95% CI, 1.1–6.3) (data not shown). A test for multiplicative interaction was significant (P = .008; antagonistic interaction), whereas a test for additive interaction was not (P = .3).

Persons with depression (GDS score ≥6) who subsequently developed MCI or dementia complained of “memory problems” more frequently (item 10 of the GDS; P = .04) and declared being “full of energy” less frequently (item 13; P = .04) than those who remained cognitively normal. All other items of the GDS were not significantly different between the 2 groups.

The association between depression and MCI was stronger in men (HR, 4.5; 95% CI, 1.8–11.3) than in women (HR, 1.5; 95% CI, 0.7–3.6); however, the difference was not statistically significant. The cumulative incidence of MCI did not increase with increasing severity of depression (GDS scores of 6 and 7-15 vs 0-5; data not shown). In addition, we found no significant difference in the duration of depressive symptoms between depressed subjects who developed incident MCI or dementia (median, 2.4 years; range, 0.6–8.2 years) and those who

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Table 1. Demographic and Clinical Characteristics of Study Subjects*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Referent Cohort (n = 697)</th>
<th>Depression Cohort (n = 143)</th>
<th>Overall Group (N = 840)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline, median (range), y‡</td>
<td>77 (50-98)</td>
<td>84 (65-102)</td>
<td>78 (50-102)</td>
</tr>
<tr>
<td>Education, median (range), y‡</td>
<td>13 (5-20)</td>
<td>12 (6-20)</td>
<td>13 (5-20)</td>
</tr>
<tr>
<td>Female, No. (%)</td>
<td>421 (60.4)</td>
<td>98 (68.5)</td>
<td>519 (61.8)</td>
</tr>
<tr>
<td>MMSE score, median (range)†</td>
<td>28 (22-30)</td>
<td>28 (14-30)</td>
<td>28 (14-30)</td>
</tr>
<tr>
<td>DRS score, median (range)‡</td>
<td>137 (107-144)</td>
<td>136 (88-144)</td>
<td>137 (88-144)</td>
</tr>
<tr>
<td>Follow-up time, median (range), y†</td>
<td>3.5 (1.0-12.8)</td>
<td>2.6 (0.4-12.3)</td>
<td>3.5 (0.4-12.8)</td>
</tr>
<tr>
<td>History of depression, No. (%)</td>
<td>184 (26.4)</td>
<td>82 (57.3)</td>
<td>266 (31.7)</td>
</tr>
<tr>
<td>APOE genotype, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ε4/ε4</td>
<td>12 (1.7)</td>
<td>2 (1.4)</td>
<td>14 (1.7)</td>
</tr>
<tr>
<td>ε3/ε4</td>
<td>164 (23.5)</td>
<td>24 (16.8)</td>
<td>188 (22.4)</td>
</tr>
<tr>
<td>ε3/ε3</td>
<td>412 (59.1)</td>
<td>84 (58.7)</td>
<td>496 (59.0)</td>
</tr>
<tr>
<td>Other‡</td>
<td>108 (15.5)</td>
<td>33 (23.1)</td>
<td>141 (16.8)</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; DRS, Dementia Rating Scale; MMSE, Mini-Mental State Examination.
*Subjects without depression constituted the referent cohort (Geriatric Depression Scale [GDS] score <6); subjects with depression, the depression cohort (GDS score ≥6).
†Baseline was the date of enrollment in the study for subjects in the referent cohort and the date on which depression was first measured (GDS score ≥6) for subjects in the depression cohort.
‡Information was missing for 3 subjects.
§Information was missing for 7 subjects.
¶History of depression preceding enrollment in the study.
‖Information was missing for 1 subject in the referent cohort.

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Figure 1. Cumulative incidence curves of mild cognitive impairment (MCI) (A) (dementia was considered as a competing outcome) and MCI or dementia (B) for subjects with depression (depression cohort) and without depression (referent cohort). The graph does not correct for differences in age at baseline between the depression and referent cohorts (conventional time-to-event scale); however, the hazard ratio estimates reported in the text were corrected for age and for other potential confounders.
The association between depression and MCI increased when APOE genotype was included in the model (ε3/ε4, ε4/ε4, or otherwise). The HR for depression was 2.3 (95% CI, 1.2-4.3); for APOE ε4/ε4, 4.4 (95% CI, 1.0-19.0); and for APOE ε3/ε4, 1.7 (95% CI, 0.9-3.2).

Of 14 subjects with the ε4/ε4 genotype, 2 (14.3%) developed MCI and 1 (7.1%) dementia. Of 188 subjects with the ε3/ε4 genotype, 14 (7.4%) developed MCI and 15 (8.0%) dementia. Of 637 subjects with the ε3/ε4 or other rarer genotypes, 34 (5.3%) developed MCI and 31 (4.9%) dementia. We conducted analyses for interaction using subjects who did not carry either the ε3/ε4 or ε4/ε4 genotype and who did not have depression as the reference group. Compared with the reference group, subjects with depression but no ε3/ε4 or ε4/ε4 had an HR for MCI of 1.9 (95% CI, 0.9-4.1), subjects without depression but with ε3/ε4 or ε4/ε4 had an HR of 1.6 (95% CI, 0.8-3.4), and subjects with the joint effect of depression and ε3/ε4 or ε4/ε4 had an HR of 5.1 (95% CI, 1.9-13.6) (Table 2). A test for additive interaction was significant (P = .03; synergistic interaction), whereas a test for multiplicative interaction was not.

Table 2. Survival Analyses to Investigate the Possible Interaction Between Depression and APOE Genotype in Their Association With MCI*

<table>
<thead>
<tr>
<th>Sample or Stratum</th>
<th>No. at Risk</th>
<th>No. With MCI</th>
<th>Median Time in Study, y</th>
<th>HR (95% CI)†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No depression and no ε3/ε4 or ε4/ε4 genotype</td>
<td>512</td>
<td>22</td>
<td>3.6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>No depression but ε3/ε4 or ε4/ε4 genotype</td>
<td>167</td>
<td>11</td>
<td>3.5</td>
<td>1.0 (0.8-3.4)</td>
<td>.2</td>
</tr>
<tr>
<td>Depression but no ε3/ε4 or ε4/ε4 genotype</td>
<td>103</td>
<td>12</td>
<td>2.8</td>
<td>1.9 (0.9-4.1)</td>
<td>.08</td>
</tr>
<tr>
<td>Depression and ε3/ε4 or ε4/ε4 genotype</td>
<td>25</td>
<td>5</td>
<td>2.4</td>
<td>5.1 (1.9-13.6)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment.
*Data on APOE genotype were missing for 1 person.
†Calculated using Cox proportional hazards models considering dementia as a competing outcome, with age as the time scale and with adjustment for sex (male sex: HR, 1.8; 95% CI, 1.0-3.2; P = .07) and education (≥12 y: HR, 0.9; 95% CI, 0.4-1.9; P = .8). A test for additive interaction was significant (P = .03).

In this prospective cohort study, depression more than doubled the risk of transition from normal cognitive aging to incident MCI after controlling for age (time scale), education, and sex. The risk was similarly increased when the composite outcome of incident MCI or dementia was considered. The association was stronger in men than women, but did not vary by severity of depression. It is surprising that there was no relationship between the severity of depressive symptoms and the risk of MCI. However, most of the subjects who developed depression in this cohort had mild or moderate depression (GDS scores of 6 or 7-11). In addition, the GDS may be inadequate to measure severity because the score increases by the number of items endorsed rather than by the severity of the items.

We found an antagonistic (negative) interaction between depression newly developed during the study and history of depression preceding the study. Subjects who developed depression during the study and also had a history of depression had a smaller risk of MCI than those who developed depression but had no history of depression. This pattern of interaction may suggest a protective effect of antidepressant medications used before recruitment by subjects with a history of depression. Unfortunately, we could not test this hypothesis because we did not collect data on antidepressant medications used before or during the study.

We also observed a synergistic (positive) interaction between APOE genotype and depression: the joint effect of depression and APOE genotype was significantly greater than the sum of the independent effects of the 2 factors. We propose the following 4 alternative mechanisms that may account for the observed association between depression (GDS score ≥6) and incident MCI (Figure 2).

1. **Causal factor.** Depression is in the chain of causality leading to MCI by virtue of its effect on the neuroendocrine axis. An important implication of this hypothesis is that an intervention targeting depression may lead to primary prevention of MCI.

2. **Shared risk factor or confounding.** Depression is non-causally associated with MCI because a third factor leads to the genesis of both MCI and depression. The third factor (confounder) could be genetic, environmental, or both.

3. **Reverse causality.** First, a person who is experiencing some degree of cognitive decline may develop depression as a reaction to the symptoms. Second, depressive symptoms may be an early noncognitive manifestation of dementia. Third, depression may “unmask” the clinical manifestations of MCI in individuals with limited cognitive reserve.

4. **Interaction.** Depression leads to cognitive decline only in the presence of a genetic susceptibility factor or another risk factor. We found evidence of a synergistic interaction between APOE genotype and depression.

These 4 mechanisms (and other possible mechanisms) are not mutually exclusive and may act in combination.

The individual items of the GDS that were significantly more endorsed by depressed subjects destined to later develop MCI or dementia were items 10 (memory) and 13 (energy). These 2 items refer to premonitory symptoms of later cognitive decline or illness in general rather than to mood symptoms per se.

Few prospective studies have investigated the association between depression and dementia, and the results of these studies have been inconsistent. To our knowledge, ours is one of the first studies to investigate...
the association between depression and incident MCI as measured by the criteria of Petersen et al.² Our secondary outcome of incident MCI or dementia is comparable to the outcome used in the Religious Orders Study³³ and in the Baltimore Longitudinal Study of Aging.³⁶ In those studies, subjects with depression were more likely than referent subjects to become demented or to experience cognitive decline.³⁵,³⁶

There are several strengths to our study. First, the longitudinal follow-up of a large cohort of elderly individuals free of both cognitive impairment and depression on enrollment enabled us to observe the association between the independent variable (depression) and the primary outcome of incident MCI. Second, the frequency of follow-up visits was high (every 12-18 months). This allowed us to detect depression and MCI or dementia near the time of their onset (incident events). Third, we adjusted for the difference in age at baseline between depressed and referent subjects by using age as the time scale in survival analyses.³¹ Traditional time-to-event survival analyses were also conducted for comparison and showed similar results (sensitivity analyses; data not shown).³¹ Fourth, available genotyping data allowed for the exploration of a possible interaction between APOE genotype and depression.

Our study also had limitations. First, we did not use a structured interview in the assessment of depression, and we did not collect information about treatments for depression. We measured depression using the short version of the GDS (15 items) rather than the original long version (30 items).⁹,¹²,¹³ However, the short version has been validated and shown to be comparable to the long version.¹² Second, because of our stringent eligibility criteria, the subjects included in our sample may have been healthier than a probability (random) sample of elderly individuals residing in the community. This may have reduced the external validity of our study. A future population-based study can rectify this weakness. Third, despite the high frequency of follow-up visits, we may have missed individuals who transitioned from normal cognition to dementia between 2 visits. To account for these incomplete assessments, we assumed that all subjects who developed dementia went through an MCI stage, and we used a composite secondary outcome measure of MCI or dementia.

Our study suggests that cognitively normal elderly individuals who develop depression are at increased risk of subsequent MCI. In addition, there may be a synergistic interaction between APOE genotype and depression.

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