Late-Life Depression, Mild Cognitive Impairment, and Dementia

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Objective: To evaluate the association of late-life depression with mild cognitive impairment (MCI) and dementia in a multiethnic community cohort.

Design and Setting: A cohort study was conducted in Northern Manhattan, New York, New York.

Participants: A total of 2160 community-dwelling Medicare recipients aged 65 years or older were included in the study.

Methods: Depression was assessed using the 10-item version of the Center for Epidemiological Studies Depression scale (CES-D) and defined by a CES-D score of 4 or more. We used logistic regression for cross-sectional association analyses and proportional hazards regression for longitudinal analyses.

Main Outcome Measures: Mild cognitive impairment dementia, and progression from MCI to dementia were the main outcome measures. We also used subcategories of MCI (amnestic and nonamnestic), and dementia (probable Alzheimer disease and vascular dementia, including possible Alzheimer disease with stroke).

Results: Baseline depression was associated with prevalent MCI (odds ratio, 1.4; 95% CI, 1.1-1.9) and dementia (2.2; 1.6-3.1). Baseline depression was associated with an increased risk of incident dementia (hazard ratio [HR], 1.7; 95% CI, 1.2-2.3) but not with incident MCI (0.9; 0.7-1.2). Persons with MCI and coexisting depression at baseline had a higher risk of progression to dementia (HR, 2.0; 95% CI, 1.2-3.4), especially vascular dementia (4.3; 1.1-17.0), but not Alzheimer disease (1.9; 1.0-3.6).

Conclusion: The association of depression with prevalent MCI and with progression from MCI to dementia, but not with incident MCI, suggests that depression accompanies cognitive impairment but does not precede it.


Depressive symptoms occur in 40% to 50% and major depression in 10% to 20% of patients with Alzheimer disease (AD).1 Depressive symptoms occur in 3% to 63% of individuals with mild cognitive impairment (MCI).2 This wide range is probably attributable to sample differences (hospital vs population based) and operationalization of MCI and depression criteria.2 Case-control studies and longitudinal studies have shown an increased dementia risk in persons with depression history,3 although a few longitudinal studies reported no increased dementia risk.4-6 Increased MCI risk in depression was recently reported in population-based studies,7,8 but this was not confirmed in 2 other population-based studies.9,10 Increased risk of progression to dementia in patients with MCI and depression has been reported in prospective studies in a memory clinic setting,11 but a population-based study found no association.9

The mechanisms behind the association between depression and cognitive decline have not been elucidated, and different mechanisms have been proposed.8,12,13 Depression could be a risk factor for dementia, an early dementia symptom, a reaction to cognitive and functional disability, or a symptom of a related risk factor, such as cerebrovascular disease. Vascular factors have been linked to late-life depression, and cerebrovascular disease might be an important contributor to MCI, dementia, and depression in late life.14-17 However, there is a paucity of data examining the association between depression and MCI. An association between depressive symptoms and AD was observed in a cohort of elderly individuals recruited in 1992-1994.18,19 Our aim in this study was to explore the cross-sectional and longitudinal associations of depression with
MCI and dementia and the progression from MCI to dementia in a newer cohort recruited in 1999-2001 in the same community.

METHODS

PARTICIPANTS

Participants were recruited by random sampling of healthy Medicare eligible persons older than 65 years in several low-income neighborhoods with a high proportion of Hispanics in Northern Manhattan. They were part of the Washington Heights–Inwood Columbia Aging Project (WHICAP)—a population-based cohort in which clinical and epidemiologic data are collected at regular intervals and vital status is continually updated. This report pertains to a cohort recruited in 1999 to 2001. The geographic study area was Manhattan north of 145th Street. Lists of persons in receipt of Medicare or Medicaid in this area were obtained from the Health Care Financing Administration. Potential participants were drawn by systematic random sampling into one of 6 strata formed on the basis of ethnicity (Hispanics, non-Hispanic blacks, and non-Hispanic whites) and age (65-74 and ≥75 years). Participants who reported a physician diagnosis of dementia were excluded. The total number recruited was 2183. Individuals who completed the baseline visit with neuropsychological and depressive symptoms information are included in this analysis (N=2160). Follow-up visits were scheduled with intervals of 18 to 24 months. Neuropsychological testing according to a standardized protocol was performed at baseline and then at 18- to 24-month intervals.

ASSESSMENT OF DEPRESSION

Presence of depressive symptoms was assessed at baseline and follow-up visits using the short version (Boston form) of the Center for Epidemiological Studies Depression (CES-D) scale. This is a 10-item questionnaire with questions to be answered by yes (1 point) or no (0 points), leading to a total score of 0 to 10. A cutoff of 4 points or more on this scale has been used to ascertain depression in studies, including a 1992 cohort. We used absent or mild depression as the reference for comparison. Change in depression was assessed at first follow-up. The CES-D comprises items that can be subclassified as depressed affect (I felt depressed, I felt lonely, I felt sad), positive affect (I was happy, I enjoyed life), somatic/vegetative signs (I felt that everything I did was an effort, my sleep was restless), and interpersonal distress (People were unfriendly, I felt people disliked me). Affirmative responses in these questions scored as yes (1) or no (0) were added, with the exception of the positive affect items, which were scored inversely. Symptoms of 1 cluster were scored as present if 1 or more of the questions were answered affirmatively. We used this classification of the CES-D items to conduct secondary analyses examining symptom type as the exposure.

ASSESSMENT OF MCI AND DEMENTIA

The diagnoses of dementia and MCI were made on the basis of all available clinical and neuropsychological information by consensus of a panel of neurologists, neuropsychologists, and psychiatrists according to international guidelines. A diagnosis of dementia was based on the Diagnostic and Statistical Manual of Mental Disorders (Third Edition Revised) criteria; AD, using the National Institute of Neurological Disorders and Stroke (NINDS)–Alzheimer’s Disease and Related Disorders Associa-

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RESULTS

There were 2160 of 2183 individuals (98.9%) with complete data on the CES-D at baseline; they were included in the study (Figure). Of these, 452 participants (20.9%) had a CES-D score of 4 or more and 1708 participants (79.1%) had a CES-D score less than 4. Individuals with depression were older, were more likely to be male, had fewer years of education, were more likely to be Hispanic, and were more likely to use antidepressants (Table 1). Five hundred fifty-nine participants (25.9%) did not have a follow-up visit after the baseline assessment. These people were older (78.3 vs 76.5 years, \( P < .001 \)) and less educated (9.5 vs 10.5 years, \( P < .001 \)) than the participants with follow-up, but there was no significant difference in depression (eTable 1; http://www.jamaneuro.com).

CROSS-SECTIONAL ANALYSES

Relationship of Depression With Prevalent MCI

At baseline, 429 participants fulfilled MCI criteria: 222 of these (51.7%) had amnestic MCI and 207 people (48.3%) had nonamnestic MCI. Participants with MCI were more often depressed than those who were cognitively intact (Table 2); this association was strongest for nonamnestic MCI but was not significant for amnestic MCI and was only slightly attenuated with adjustment for vascular burden (Table 2). The presence of depressive symptoms not meeting depression criteria (CES-D <4) was not associated with prevalent MCI.

Relationship of Depression With Prevalent Dementia

Dementia was diagnosed at baseline in 217 participants; 164 individuals (75.1%) received a diagnosis of possible or probable AD (probable, 126 [58.1%]), 33 received a diagnosis of VaD (15.2%), and 20 received a diagnosis of other dementia (9.2%; including dementia with Lewy bodies, toxic cause, and several rare causes of dementia). Participants with dementia were depressed twice as often as were those without dementia (odds ratio, 2.2; 95% CI, 1.6-3.1), and this association was stronger for VaD compared with AD (Table 2). There was marked attenuation of the odds ratio relating depression and VaD in the model adjusting for a vascular risk score. The presence of depressive symptoms not meeting the depression criteria was not associated with prevalent dementia.

LONGITUDINAL ANALYSES

Relationship of Baseline Depression With Incident MCI

Of 1514 participants without dementia or MCI at baseline, there were 1156 individuals (76.4%) with follow-up for longitudinal analyses with MCI as an outcome. During an average follow-up of 5.4 years (range, 1.1-10.1 years), MCI developed in 304 individuals, of
whom 151 (49.7%) developed amnestic MCI and 153 (50.3%) developed nonamnestic MCI. Depression was not associated with incident MCI or MCI subtype (Table 3). The presence of depressive symptoms not meeting the depression criteria was not associated with incident MCI.

### Relationship of Baseline Depression With Incident Dementia

Of 1943 participants without dementia at baseline, there were 1483 individuals (76.3%) with follow-up for longitudinal analyses with dementia as outcome. Two hundred seven developed dementia, of whom 167 individuals (80.7%) were classified as having possible or probable AD (133 [64.3%]) with probable AD), 29 (14.0%) as having VaD, and 11 (5.3%) as having other dementia.

Dementia risk was higher in persons with depression at baseline (Table 3) in all models. This risk was modestly higher for AD than for VaD. We conducted analyses examining probable AD cases as the outcome to exclude cases of AD with a cerebrovascular component, and the risk estimate was weaker and not statistically significant (HR, 1.3; 95% CI, 0.9-2.0). Depressive symptoms not meeting the depression criteria were not associated with incident dementia. When we repeated the analysis excluding the individuals with MCI at baseline, the risk of dementia in those with depression was attenuated (1.4; 95% CI, 0.9-2.0). We conducted additional analyses exploring whether the report of depression at first follow-up changed the association between depression and incident dementia. Persons with persistent depression (HR, 1.9; 95% CI, 1.3-2.8), depression at baseline but not at follow-up (HR, 1.6; 95% CI, 1.0-2.5), and persons with no depression at baseline but depression at follow-up (1.9; 95% CI, 1.3-3.0) all had increased risk of dementia compared with persons who persistently had no depression. We also conducted additional analyses exploring whether a particular type of depressive symptoms was more strongly related to dementia risk. We constructed a model with the 4 types of depressive symptoms in the CES-D adjusting for demographics, educational level, and APOE genotype. Only depressed affect was related to incident dementia (HR, 1.9; 95% CI, 1.4-2.7). Positive affect, somatic symptoms, and interpersonal distress had HRs close to 1 in relation to incident dementia that were not statistically significant. The relationship of depressed affect to dementia was stronger for VaD (HR, 4.1; 95% CI, 1.6-11.0) compared with AD (HR, 1.7; 95% CI, 1.1-2.5). Other types of depressive symptoms were not differentially related to AD or VaD.

### Relationship of Baseline Depression With Progression From Baseline MCI to Dementia

There were 320 participants with MCI at baseline who had at least 1 follow-up (mean follow-up, 5.1 years; range, 1.2-9.8 years): 160 with amnestic MCI, and 160 with nonamnestic MCI. Of these, 67 individuals progressed to dementia.

### Table 2. MCI and Dementia Outcomes for Participants From Cross-Sectional Analysis Using Logistic Regression

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td></td>
<td>At Risk</td>
<td>Cases</td>
</tr>
<tr>
<td><strong>MCI as Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All MCI (n = 429)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1567</td>
<td>326</td>
</tr>
<tr>
<td>Depression</td>
<td>376</td>
<td>103</td>
</tr>
<tr>
<td>Amnestic MCI (n = 222)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1383</td>
<td>174</td>
</tr>
<tr>
<td>Depression</td>
<td>314</td>
<td>48</td>
</tr>
<tr>
<td>Nonamnestic MCI (n = 207)</td>
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<tr>
<td>No depression</td>
<td>1361</td>
<td>152</td>
</tr>
<tr>
<td>Depression</td>
<td>321</td>
<td>55</td>
</tr>
<tr>
<td><strong>Dementia as Outcome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All dementia (n = 207)</td>
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<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1708</td>
<td>141</td>
</tr>
<tr>
<td>Depression</td>
<td>452</td>
<td>76</td>
</tr>
<tr>
<td>AD without vascular component (n = 164)</td>
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<td></td>
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<tr>
<td>No depression</td>
<td>1676</td>
<td>109</td>
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<tr>
<td>Depression</td>
<td>431</td>
<td>55</td>
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<tr>
<td>VaD, including AD with stroke (n = 33)</td>
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<tr>
<td>No depression</td>
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<td>21</td>
</tr>
<tr>
<td>Depression</td>
<td>388</td>
<td>12</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment; OR, odds ratio; VaD, vascular dementia.

*Model 1 was adjusted for age and sex; model 2 was additionally adjusted for educational level, ethnicity, and APOE genotype; and model 3 was additionally adjusted for vascular risk factors.

Based on a sample of 1645 individuals in whom the APOE genotype was available.

Based on a sample of 1399 individuals in whom the vascular risk score could be determined, including all 5 risk factors.
were analyzed separately, the HRs relating depression to progression to dementia were similar (amnestic MCI: HR, 2.1; 95% CI, 1.0-4.3 vs nonamnestic MCI: 2.4; 1.1-5.7). There were no significant differences between amnestic and nonamnestic MCI in the HR relating depression to incident AD or VaD. In analyses with the CES-D as an ordinal scale, no association between a score of 0 or 1 or of 2 or 3 (some depressive symptoms) and incident dementia was found. Analysis using the different clusters of symptoms within the CES-D showed again that depressed affect was associated with increased incident dementia risk (HR, 2.1; 95% CI, 1.1-4.0).

**COMMENT**

We found that depression was related to a higher risk of prevalent MCI and dementia, incident dementia, and progression from prevalent MCI to dementia, but not to incident MCI. We also found that the association of depression with prevalent dementia and with progression from MCI to dementia was stronger for VaD compared with AD and was driven mostly by depressive affect.

Results of previous studies evaluating the association of late-life depression with incident dementia...
have been inconsistent. Studies evaluating the association of depression with MCI are inconsistent as well. An increased risk of MCI in individuals with depression was recently reported, although two other studies reported no association. Increased risk of developing dementia in MCI with depressive symptoms has been reported in a hospital-based series, but population-based studies until now could not confirm this association as we did. We found that depression was related to prevalent but not incident MCI. It seems reasonable to postulate that persons with prevalent MCI have a more advanced stage of cognitive impairment accompanied by depression, whereas persons with incident MCI have earlier cognitive impairment not accompanied by depression. This could explain our findings and some of the inconsistencies in the literature.

Our finding that depression was associated cross sectionally with both MCI and dementia and longitudinally only with dementia suggests that depression develops with the transition from normal cognition to dementia. This agrees with a study reporting that, in nondemented elderly persons, depression is more common with increasing cognitive impairment. This speculation is further supported by the observation that the association of depression with incident dementia was attenuated when persons with MCI at baseline were excluded and by our observation that persons with MCI and depression were more likely to develop dementia.

A potential link between depression and dementia in late life is through vascular factors, as postulated in the vascular depression hypothesis. Depression is associated with vascular risk factors and with cerebrovascular lesions on neuroimaging. Our findings that depression is more strongly associated with VaD than AD (both cross sectionally and longitudinally in participants with MCI at baseline) and that this relationship is attenuated in models adjusting for vascular burden suggest that cerebrovascular disease has a role in this association. Most studies that examined depression as a predictor of dementia generally did not attempt to separate AD from VaD. However, these results should be interpreted with caution because of the possibility of chance findings resulting from multiple subanalyses, because of the lack of neuroimaging data, and because we did not find an association of individual vascular risk factors with depression at baseline. Depressed mood seemed to drive the association, which is in line with reports that depressed mood alone predicts dementia. We could not confirm the association of apathy with an increased risk of progressing from MCI to dementia, but we did not perform an extensive apathy evaluation.

Our study has several limitations. Our results for subtypes of MCI and dementia in longitudinal analyses should be interpreted with caution because of relatively low cell sizes that could result in low power and chance findings. The CES-D inquires mainly about depressive symptoms within 2 weeks of its administration. Thus, the CES-D is likely to underestimate the presence of depressive symptoms and depression. To the extent that this measurement error is random (not related to the outcome), it will bias our results toward the null. In other words, our study may underestimate the true association between depressive symptoms and cognitive impairment (MCI or dementia).

Different explanations for the relationship between late-life depression and dementia have been suggested. Late-life depression could be an early symptom in the progression to dementia; depression could affect the threshold for dementia to become manifest or could be a reaction to cognitive impairment. Depression could also be a causal risk factor for dementia through hippocampal damage mediated by the influence of depression on the hypothalamic-pituitary-adrenal axis. Finally, common risk factors contributing to an increased risk of depression and dementia, such as cerebrovascular disease, could explain the association between the two. We could not address the exact mechanisms linking depression and dementia, but our results support the hypothesis that late-life depression accompanies the occurrence of cognitive decline and does not precede it. Our finding that the association of depression with probable AD was weaker compared with all AD (probable and possible) and VaD suggests that other pathologic conditions with AD may be more likely to manifest as depression.

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Online-Only Material: The eTable is available at http://www.jamaneuro.com.

REFERENCES