Association of Depression With Accelerated Cognitive Decline Among Patients With Type 2 Diabetes in the ACCORD-MIND Trial

Mark D. Sullivan, MD, PhD; Wayne J. Katon, MD; Laura C. Lovato, MA; Michael E. Miller, PhD; Anne M. Murray, MD; Karen R. Horowitz, MD; R. Nick Bryan, MD; Hertzel C. Gerstein, MD; Santica Marcovina, MD; Basil E. Akpunonu, MD; Janice Johnson, BA; Jean Francois Yale, MD; Jeff Williamson, MD; Lenore J. Launer, PhD

IMPORTANCE Depression has been identified as a risk factor for dementia among patients with type 2 diabetes mellitus but the cognitive domains and patient groups most affected have not been identified.

OBJECTIVE To determine whether comorbid depression in patients with type 2 diabetes accelerates cognitive decline.

DESIGN A 40-month cohort study of participants in the Action to Control Cardiovascular Risk in Diabetes–Memory in Diabetes (ACCORD-MIND) trial.

SETTING Fifty-two clinics organized into 6 clinical networks across the United States and Canada.

PARTICIPANTS Two thousand nine hundred seventy-seven participants with type 2 diabetes at high risk for cardiovascular events.

INTERVENTION The Digit Symbol Substitution Test, Rey Auditory Verbal Learning Test, and the modified Stroop test were used to assess cognition. The 9-item Patient Health Questionnaire was used to assess depression.

MAIN OUTCOMES AND MEASURES Mixed-effects statistical models were used to analyze cognitive test outcomes incorporating depression as a time-dependent covariate.

RESULTS Participants with scores indicative of depression (9-item Patient Health Questionnaire, \( \geq 10 \)) showed greater cognitive decline during 40-month follow-up on all tests, with the following differences in estimated least squares means: Digit Symbol Substitution Test, 0.72 (95% CI, 0.25 to 1.19; \( P = .003 \)), Rey Auditory Verbal Learning Test, 0.18 (95% CI, 0.07 to 0.29; \( P = .001 \)), and Stroop interference, −1.06 (95% CI, −1.93 to −0.18; \( P = .02 \)). This effect of depression on risk of cognitive decline did not differ according to previous cardiovascular disease; baseline cognition or age; or intensive vs standard glucose-lowering treatment, blood pressure treatment, lipid treatment, or insulin treatment. Addition of demographic and clinical covariates to models did not significantly change the cognitive decline associated with depression.

CONCLUSIONS AND RELEVANCE Depression in patients with type 2 diabetes was associated with greater cognitive decline in all domains, across all treatment arms, and in all participant subgroups assessed. Future randomized trials will be necessary to determine if depression treatment can lower the risk of cognitive decline in patients with diabetes.
Depression and diabetes are among the most common illnesses in older primary care populations. Up to 20% of adult patients with type 2 diabetes meet criteria for comorbid major depression. Furthermore, each of these disorders is associated with an increased risk of the other, with depression being associated with an increased risk of diabetes 1,2 and adult-onset diabetes being associated with an increased risk of subsequent depression. 7

Both depression and diabetes appear to be associated with an increased risk of dementia. Lu and colleagues 3 reviewed 16 studies and found that persons with diabetes had a 47% increased risk of all-cause dementia, a 39% increased risk of Alzheimer disease, and a 200% increased risk of vascular dementia compared with those without diabetes. Two recent systematic reviews found that depression was associated with a doubling 8 of the risk of subsequent Alzheimer disease and all-cause dementia in the general population of older adults. 4,5

In the Cardiovascular Health Study population, this association between depression and incident mild cognitive impairment was independent of underlying vascular disease. 6

Two recent studies in health maintenance organization populations examined whether depression was associated with an increase in the risk of all-cause dementia among patients with diabetes. The first study, among nearly 4000 patients with type 2 diabetes, found a doubling of the risk of dementia diagnosis for patients with depression after 3 to 5 years of follow-up. 7 The second study of nearly 20,000 patients with type 2 diabetes also found a doubling of the risk of a dementia diagnosis for patients with depression after 3 to 5 years of follow-up. 8 These studies were limited by their reliance on medical record diagnoses of dementia, which lack sensitivity and are prone to ascertainment bias. For example, clinicians often notice and diagnose only more severe cases of dementia.

The Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes (ACCORD-MIND) study offers the opportunity to prospectively examine the effects of depression on cognitive decline in a well-characterized and well-managed cohort of participants prospectively assessed with a rigorous battery of cognitive tests. Our hypothesis was that depression (9-item Patient Health Questionnaire [PHQ-9] score ≥10) as a time-dependent covariate would be associated with subsequent decline in cognitive function after controlling for relevant clinical variables.

Methods

The ACCORD trial design is described elsewhere. 9 Briefly, ACCORD was a randomized, multicenter, double 2 × 2 factorial design trial of 10,251 middle-aged and older participants with type 2 diabetes who are at high risk for cardiovascular disease (CVD) events because of existing CVD (secondary prevention) or additional cardiovascular risk factors (primary prevention). All participants were enrolled into the glycemia trial, which compared a therapeutic strategy targeted to a glycated hemoglobin level of less than 6.0% (to convert to proportion of total hemoglobin, multiply by 0.01) (intensive arm) with a strategy that targeted a glycated hemoglobin level of 7.0% to 7.9% (standard arm). The lipid trial (54% of the total sample) compared the masked administration of either placebo or fenofibrate to persons taking simvastatin. The blood pressure trial included the other 46% of participants and compared a therapeutic strategy targeting a systolic blood pressure of less than 120 mm Hg (intensive) with one targeting a systolic blood pressure of less than 140 mm Hg (standard).

In February 2009, the intensive glycemic intervention was stopped because an increased risk for mortality was detected in that arm. 10 At that time, all intensive glycemic control subjects were transitioned to the standard glycemic treatment, but MIND evaluations continued according to the original protocols. The lipid and blood pressure trials continued to the planned completion date in June 2009. The trial was sponsored by the National Heart, Lung, and Blood Institute, and the protocol was approved by a review panel at the National Heart, Lung, and Blood Institute as well as by the institutional review board or ethics committee at each center. The MIND substudy was sponsored by the National Institute on Aging in collaboration with the National Heart, Lung, and Blood Institute and was approved by the institutional review boards of all participating institutions (eTable in Supplement). Separate informed consent for MIND was signed by participants.

The design of the MIND substudy has been described previously. 11 Cognitive function was assessed with a test battery of cognitive functions typically affected in type 2 diabetes in baseline (targeted to be within 45 days of randomization) and 20 months and 40 months after baseline. The choice of specific tests was based on several factors, including the distribution of the test scores in adult populations without dementia, the ease of standardizing and monitoring the quality of test administration in multiple study sites, the time required to administer the test, and the frequency with which other studies have used the test.

Cognitive Function

The primary cognitive outcome for MIND was the number of correctly completed cells on the Digit Symbol Substitution Test (DSST), which is an omnibus test of psychomotor speed. 12 Secondary cognitive outcomes were verbal memory and executive function. Memory was measured with the Rey Auditory Verbal Learning Test (RAVLT) 13 and is reported as the average number of words recalled (0-15) over the immediate, short, and delayed recall trials. Higher scores on the DSST and RAVLT indicate better cognitive functioning. Executive functioning was measured with the modified Stroop test 14 and is reported as the interference score; a higher score is indicative of worse function. The Mini-Mental State Examination was administered to allow comparison of the MIND sample with other samples, but it was not a study outcome because of its lack of sensitivity to cognitive decline. In addition to the cognitive tests, the PHQ-9 14 was administered to screen for depression, a frequent comorbidity in type 2 diabetes and potential confounder.

Participants were tested in a quiet setting during a scheduled ACCORD clinic visit. Before testing, capillary blood glucose level was measured and if it was less than 60 mg/dL (to convert to millimoles per liter, multiply by 0.0555), a snack was...
given to the participant, who then rested for 15 minutes before the battery was started. Quality control was monitored by the MIND Coordinating Center at the Roena B. Kulynych Center for Memory and Cognition Research, Department of Internal Medicine, Wake Forest University. To ensure quality control, we (1) certified testers at baseline and semiannually thereafter, (2) reviewed a 10% random sample of tape recordings acquired during testing, (3) did random reviews comparing test forms with data entered into the database, and (4) checked test and tester score distributions for unusual trends. Staff from the Coordinating Center were available throughout the study to answer testers’ questions.

**Depression Assessment**

Depressive symptoms were measured in ACCORD-MIND using the PHQ-9, the self-report version of the PRIME-MD, a well-validated psychiatric diagnostic interview for use in primary care settings. A score of 10 or more on the PHQ-9 has been shown to have 77% sensitivity and 94% specificity to the diagnosis of major depression by structured psychiatric interview. In patients with type 2 diabetes, a PHQ-9 score of 10 or more has been associated with higher risk of mortality and dementia as well as macrovascular and microvascular complications. A recent review of the reliability and validity of depression screening tools in patients with diabetes gave the PHQ-9 generally higher rates of sensitivity (66%-100%) but lower rates of specificity (52%-85%).

**Statistical Analyses**

All statistical analyses were conducted at the ACCORD Coordinating Center, Wake Forest School of Medicine, with SAS version 9.3 (SAS Institute). Participant characteristics are summarized with means, standard deviations, and percentages.

To test the effect of prior depression on change in cognitive function, we used a mixed-effects regression model with unstructured covariance to model 20-month change in cognitive outcome by prior depression status (baseline depression for the 0- to 20-month change; 20-month depression for the 20- to 40-month change). This model assumes the probability of missing outcomes depends only on previous recorded outcomes or factors in the model. For each cognitive outcome, we started with a basic model and added covariates to determine their effect on the relationship between depression and cognition. Model 1 (n = 2777) adjusted for baseline age (years), female (yes or no), race (white or nonwhite), education (4 levels), glycaemia group, blood pressure vs lipid trial, blood pressure group, lipid group, and Clinical Center Network (6 levels). Model 2 (n = 2766) adjusted for all variables in model 1 plus prior CVD event (yes or no), baseline body mass index, baseline glycated hemoglobin level, and baseline low-density lipoprotein cholesterol level. Model 3 (n = 2762) adjusted for all variables in models 1 and 2 plus current smoker at baseline (yes or no) and alcohol use at baseline (0 or >0). Model 4 (n = 2762) adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use (yes or no). We did not adjust for baseline levels of cognition in our primary analyses because this has been shown to introduce bias when exposures are associated with baseline health status. Analyses with adjustment for baseline cognition were conducted as a sensitivity analysis.

Using the adjustment factors from model 4 for DSST, interactions between depression and previous CVD, age, or intensive vs standard glucose-lowering treatment, blood pressure treatment, lipid treatment, and insulin treatment were tested. We also tested model 4 using the PHQ-9 score as a continuous variable. As prespecified, the main effect of depression on change in the cognitive primary outcome (DSST score) was tested at the 2-sided .05 significance level. All other hypothesis tests (interactions and analyses of secondary outcomes) were considered to be hypothesis generating and were also conducted at the .05 level. Since we present 12 tests of hypotheses each at the .05 level, there is a 46% chance (ie, 1 – (1 – .05)12) that at least 1 of these tests would be statistically significant at an α level of .05, assuming independence between tests.

**Results**

**Study Participants**

A total of 2977 participants were enrolled in the ACCORD-MIND substudy (eTable in Supplement). Of these, 2764 completed the 20-month cognitive assessment and 2664 completed the 40-month cognitive assessment. Among participants, 531 (18%) scored 10 or greater on the PHQ-9 Depression Scale at baseline assessment. These participants scoring 10 or more were younger, more likely to be female, and of non-Hispanic white ethnicity. They also had less education, were more likely to currently smoke cigarettes, but less likely to drink alcohol. They were more likely to have CVD and heart failure and had a higher mean body mass index and larger waist circumference. These participants also had higher baseline glycated hemoglobin, fasting glucose, low-density lipoprotein cholesterol, and total cholesterol levels. At baseline, participants scoring more than 10 were more likely to be treated with insulin and β-blockers and less likely to be treated with sulfonylureas, metformin, angiotensin-converting enzyme inhibitors, and aspirin. All other baseline measures were not statistically significant between depressed and nondepressed groups.

The proportion of participants scoring more than 10 on the PHQ-9 decreased slightly over the course of the study (Table 1). There were 62% of participants with all 3 assessments who never had a PHQ-9 score of 10 or more. Five percent had a PHQ-9 score of 10 or more at all 3 assessments. Five percent

<p>| Table 1. ACCORD-MIND Participants With PHQ-9 Score of 10 or More, by Assessment Time |
|-------------------------------|-------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Visit</th>
<th>Sample Size</th>
<th>PHQ-9 Score ≥10, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2977</td>
<td>531 (18)</td>
</tr>
<tr>
<td>20 mo</td>
<td>2775</td>
<td>471 (17)</td>
</tr>
<tr>
<td>40 mo</td>
<td>2648</td>
<td>415 (16)</td>
</tr>
<tr>
<td>Ever</td>
<td>2977</td>
<td>878 (29)</td>
</tr>
</tbody>
</table>

Abbreviations: ACCORD-MIND, Action to Control Cardiovascular Risk in Diabetes—Memory in Diabetes Study; PHQ-9, 9-item Patient Health Questionnaire.
Table 2. Estimated Least Squares Means for Change in DSST Score by Prior Depression Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior Depression Group</th>
<th>PHQ-9 Score &lt;10</th>
<th>PHQ-9 Score ≥10</th>
<th>Difference in Means (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.62 (−0.88 to −0.37)</td>
<td>−1.36 (−1.81 to −0.91)</td>
<td>0.74 (0.27 to 1.20)</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.61 (−0.87 to −0.36)</td>
<td>−1.34 (−1.79 to −0.88)</td>
<td>0.72 (0.25 to 1.19)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−0.62 (−0.88 to −0.36)</td>
<td>−1.35 (−1.80 to −0.90)</td>
<td>0.73 (0.26 to 1.20)</td>
<td>.003</td>
<td></td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−0.61 (−0.87 to −0.35)</td>
<td>−1.33 (−1.79 to −0.88)</td>
<td>0.72 (0.25 to 1.19)</td>
<td>.003</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: DSST, Digit Symbol Substitution Test; PHQ-9, 9-item Patient Health Questionnaire.

<sup>a</sup> Adjusted for baseline age (years), female (yes or no), race (white or nonwhite), education (4 levels), glycemia group, blood pressure vs lipid trial, intensive vs standard blood pressure-lowering treatment, fenofibrate or placebo, and Clinical Center Network.

<sup>b</sup> Adjusted for all variables in model 1 plus prior cardiovascular disease event (yes or no), baseline body mass index, baseline glycated hemoglobin level, and baseline low-density lipoprotein cholesterol level.

<sup>c</sup> Adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use.

<sup>d</sup> Adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use.

Table 3. Estimated Least Squares Means for Change in RAVLT Score by Prior Depression Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior Depression Group</th>
<th>PHQ-9 Score &lt;10</th>
<th>PHQ-9 Score ≥10</th>
<th>Difference in Means (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.25 (0.19 to 0.31)</td>
<td>0.07 (−0.03 to 0.17)</td>
<td>0.19 (0.08 to 0.29)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.25 (0.19 to 0.31)</td>
<td>0.07 (−0.04 to 0.17)</td>
<td>0.18 (0.07 to 0.29)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.25 (0.19 to 0.31)</td>
<td>0.07 (−0.04 to 0.17)</td>
<td>0.18 (0.07 to 0.29)</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.25 (0.19 to 0.31)</td>
<td>0.07 (−0.04 to 0.17)</td>
<td>0.18 (0.07 to 0.29)</td>
<td>.001</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; PHQ-9, 9-item Patient Health Questionnaire.

<sup>a</sup> Adjusted for baseline age (years), female (yes or no), race (white or nonwhite), education (4 levels), glycemia group, blood pressure vs lipid trial, intensive vs standard blood pressure-lowering treatment, fenofibrate or placebo, and Clinical Center Network.

<sup>b</sup> Adjusted for all variables in model 1 plus prior cardiovascular disease event (yes or no), baseline body mass index, baseline glycated hemoglobin level, and baseline low-density lipoprotein cholesterol level.

<sup>c</sup> Adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use.

<sup>d</sup> Adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use.

Table 4. Estimated Least Squares Means for Change in Stroop Interference Score by Prior Depression Status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prior Depression Group</th>
<th>PHQ-9 Score &lt;10</th>
<th>PHQ-9 Score ≥10</th>
<th>Difference in Means (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−0.89 (−1.38 to −0.40)</td>
<td>0.18 (−0.66 to 1.03)</td>
<td>−1.07 (−1.95 to −0.20)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Model 2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>−0.82 (−1.31 to −0.34)</td>
<td>0.27 (−0.57 to 1.11)</td>
<td>−1.09 (−1.97 to −0.22)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Model 3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>−0.84 (−1.33 to −0.35)</td>
<td>0.20 (−0.64 to 1.05)</td>
<td>−1.04 (−1.92 to −0.16)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Model 4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−0.81 (−1.30 to −0.32)</td>
<td>0.25 (−0.60 to 1.09)</td>
<td>−1.06 (−1.93 to −0.18)</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: PHQ-9, 9-item Patient Health Questionnaire.

<sup>a</sup> Reduction in scores is improvement on Stroop test, so means favor the nondepressed group.

<sup>b</sup> Adjusted for baseline age (years), female (yes or no), race (white or nonwhite), education (4 levels), glycemia group, blood pressure vs lipid trial, intensive vs standard blood pressure-lowering treatment, fenofibrate or placebo, and Clinical Center Network.

<sup>c</sup> Adjusted for all variables in model 1 plus prior cardiovascular disease event (yes or no), baseline body mass index, baseline glycated hemoglobin level, and baseline low-density lipoprotein cholesterol level.

<sup>d</sup> Adjusted for all variables in models 1 and 2 plus current smoker (yes or no) at baseline and alcohol use (0 vs >0) at baseline.

<sup>e</sup> Adjusted for all variables in models 1, 2, and 3 plus any baseline insulin use.

had a PHQ-9 score more than 10 at baseline but less than 10 at month 20 and month 40. Twenty-eight percent had other patterns of PHQ-9 scores or missing data.

Estimated least squares means for decline in cognitive function during the 40-month follow-up were consistently greater for participants scoring 10 or more on the PHQ-9 at the prior assessment for all cognitive tests (Tables 2, 3, and 4). On the DSST (Table 2), a statistically significant difference was apparent (P = .003). Adjustment for progressively more extensive lists of demographic and clinical covariates (models 1-4) did little to change the differences in means or statistical significance. On the RAVLT (Table 3), differences were approximately 0.2 unit in all models (P = .001) in all models. On the Stroop test (Table 4), differences between groups were approximately −1.06 (P = .02) in all models. If PHQ-9 score was entered into these models as a continuous variable, it remained significantly associated with cognitive decline on all 3 tests (DSST: β = −0.054; P = .004, RAVLT: β = −0.014; P = .001; STROOP: β = 0.079; P = .02). A depression × insulin interaction term added to model 4 was not statistically significant for any of the cognitive outcomes. Similarly, interactions with previous CVD, baseline cogni-
tion or age, or intensive vs standard glucose-lowering treatment, blood pressure treatment, and lipid treatment were not statistically significant.

Effects of depression on cognitive decline were larger and more statistically significant when the initial cognition level was included in the models for change (data not shown). Additional exploratory analyses revealed that subjects with PHQ-9 scores 10 or more at both baseline and 20 months showed the greatest cognitive decline on the DSST during both the 0- to 20-month (mean [SD] decline, −2.0 [7.4]) and 20- to 40-month (mean [SD] decline, −2.7 [8.0]) intervals. The group with a PHQ-9 score less than 10 at baseline but 10 or more at 20 months showed nearly as large a decline (mean [SD] decline, −2.5 [8.6]) in the 20- to 40-month interval. Patients with PHQ-9 scores of 10 or more at baseline were somewhat more likely to drop out before the 40-month assessment (n = 26), but omitting these individuals from the models did not significantly change the magnitude or significance of the changes noted. We have calculated a model $R^2$ value of 0.0249 using the method described by Edwards et al. 23

**Discussion**

In a sample of participants with type 2 diabetes for a mean of 9 years, depression was associated with accelerated decline on a battery of cognitive tests over 40 months of follow-up. Significant differences between depressed and nondepressed groups were found on the DSST, the RAVLT, and the Stroop test. Scores on the RAVLT and Stroop did improve slightly over time in the nondepressed group, possibly because of a learning effect. This effect of depression on cognitive decline did not differ according to any of the factors examined: previous CVD, baseline cognition or age, or intensive vs standard glucose-lowering treatment, blood pressure treatment, lipid treatment, or insulin treatment. To our knowledge, this is the clearest demonstration to date that depression constitutes a risk factor for cognitive decline in the population of patients with type 2 diabetes. It also demonstrates that this effect is not limited to specific cognitive tests or specific subgroups. Further, the fact that the relationship was detectable during the 40-month duration of the study suggests this interaction between cognition and depression develops over relatively short periods and needs to be monitored over time. The depression effect does not appear to be mediated by behaviors leading to poor glucose, blood pressure, or lipid control since all ACCORD-MIND participants received close follow-up and guideline-concordant care.

Recent studies examining the risks associated with depressive symptoms in the population of patients with type 2 diabetes used clinically recognized dementia rather than cognitive testing as the outcome of interest. 7-8 These International Classification of Diseases, Ninth Revision dementia diagnoses have been found to be specific (few false positives) but have low sensitivity (many false negatives) for mild dementia. These retrospective studies are also prone to ascertainment bias. The cognitive testing protocol used in ACCORD-MIND is a more unbiased and sensitive outcome measure, allowing us to detect differences by depression status over a 40-month period as opposed to the 3- to 5-year period of these earlier studies. ACCORD-MIND also has very low rates of loss to follow-up, which reduces the chances of the ascertainment bias that characterizes studies based on medical record diagnoses. The ACCORD-MIND cognitive testing protocol also allowed us to demonstrate that depression accelerates decline in all cognitive domains assessed: psychomotor speed, verbal learning, and executive function. We were able to demonstrate that the effect of depression on cognitive decline was unaffected by previous CVD; baseline cognition or age; intensive vs standard glucose-lowering treatment, blood pressure treatment, and dyslipidemia; potentially depression-related health risk behaviors (body mass index, smoking, alcohol use), or intensive vs standard insulin treatment. We did not control for antidepressant treatment, because we did not have data on dose or duration of antidepressant treatment and did not have data on psychotherapy received.

It is difficult to comment on the clinical meaningfulness of these cognitive changes because we measured mean change and clinical meaningfulness is generally determined by whether a patient falls above or below an impairment threshold. However, the declines we observed can be compared with those noted in previous studies of cognitive decline in patients with diabetes. Over 40 months of follow-up in the MIND sample, nondepressed patients had a mean decline in unadjusted DSST scores of 1.7 points (0.51-point annual decline), while depressed patients declined 2.7 points (0.81-point annual decline). This compares with an approximately 0.49-point annual decline in the Atherosclerosis Risk in Communities Study sample with a mean age of 56.7 years at baseline 24 and approximately 0.87-point annual decline in the Health, Aging, and Body Composition Study sample of persons with a mean age of 74.2 years with prevalent diabetes.25 These studies did not compare declines by depression groups.

Most recent studies have demonstrated increased risk for dementia 26 and/or cognitive decline 27 in community-dwelling older adults with depressive symptoms (usually elevates scores on the Center for Epidemiologic Studies Depression Scale). Some of the recent studies have shown elevated risk specifically in those with recurrent 28 or persistent 29 depressive symptoms. This is consistent with our exploratory analyses that showed the greatest cognitive decline in participants with a score of 10 or more on the PHQ-9 at both baseline and 20 months. There have been persistent questions about whether depression represents a risk factor for cognitive decline or whether depression represents an early manifestation of dementia. In our study, no patients had dementia at baseline and the effect of depression did not differ by baseline cognitive impairment, also suggesting that depression is not simply an early manifestation of dementia.

There are a number of mechanisms that might be responsible for the acceleration of cognitive decline in those ACCORD-MIND subjects who also had depression. In patients with diabetes, depression is associated with poor adherence to diet, exercise, smoking, and medication recommendations, 30 poor glyemic control, 31 and an increased risk of microvascular and macrovascular complications. 32 Each of these may con-
Depression has been associated with an array of biological abnormalities that may mediate the effect of depression on cognitive decline. Dysregulation of the hypothalamic-pituitary axis associated with depression results in greater glucocorticoid secretion and impaired negative feedback. The resulting higher cortisol levels may damage brain areas involved in cognition such as the hippocampus. It may also decrease neurogenesis in brain areas essential for memory such as the hippocampus. Depression has also been linked to the hypothalamus. It may also be involved in cognitions such as the hypothalamus.

There are a number of important limitations to the current study. First, we lacked a control population of patients without diabetes and thus were unable to estimate the strength of the depression-cognitive decline association in nondiabetic patients. Second, there are a number of important differences in cardiovascular risk factors between depressed and nondepressed ACCORD-MIND participants that could account for the depression effect. We have attempted to control for these in our analyses. In general, these analyses showed little change in mean differences when these were added as covariates to our models. However, there may be residual confounding by these factors. Third, we used the PHQ-9 to assess depression. This is a self-report version of the PRIME-MD interview and does not yield a true depression diagnosis. Fourth, since this an observational study, we were not able to determine whether treatment of depression with pharmacotherapy or psychotherapy would reduce the risk of cognitive decline among similar patients with type 2 diabetes. To address this question, it will be necessary to conduct a depression treatment randomized clinical trial among patients with diabetes and monitor cognitive outcomes.

In summary, this epidemiological analysis of the effect of depression on risk for cognitive decline among participants in the ACCORD-MIND study showed that depression is associated with cognitive decline in all domains assessed and that this effect does not differ in important clinical subgroups. This suggests that a potentially reversible factor may be promoting general cognitive decline in the broad population of patients with type 2 diabetes. Since dementia is one of the fastest growing and most dreaded complications of diabetes, our findings may be important for public health.