

# Association of Duration and Severity of Diabetes Mellitus With Mild Cognitive Impairment

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**Background:** It remains unknown whether diabetes mellitus (DM) is a risk factor for mild cognitive impairment (MCI).

**Objective:** To investigate the association of DM with MCI using a population-based case-control design.

**Design:** Population-based case-control study.

**Setting:** Academic research.

**Participants:** Our study was conducted, among subjects aged 70 to 89 years on October 1, 2004, who were randomly selected from the Olmsted County (Minnesota) population.

**Main Outcome Measure:** We administered to all participants a neurologic examination, the Clinical Dementia Rating Scale, and a neuropsychological evaluation (including 9 tests in 4 cognitive domains) to diagnose normal cognition, MCI, or dementia. We assessed history of DM, DM treatment, and DM complications by interview, and

we measured fasting blood glucose levels. History of DM was also confirmed using a medical records linkage system.

**Results:** We compared 329 subjects having MCI with 1640 subjects free of MCI and dementia. The frequency of DM was similar in subjects with MCI (20.1%) and in subjects without MCI (17.7%) (odds ratio [OR], 1.16; 95% confidence interval [CI], 0.85-1.57). However, MCI was associated with onset of DM before age 65 years (OR, 2.20; 95% CI, 1.29-3.73), DM duration of 10 years or longer (OR, 1.76; 95% CI, 1.16-2.68), treatment with insulin (OR, 2.01; 95% CI, 1.22-3.31), and the presence of DM complications (OR, 1.80; 95% CI, 1.13-2.89) after adjustment for age, sex, and education. Analyses using alternative definitions of DM yielded consistent findings.

**Conclusion:** These findings suggest an association of MCI with earlier onset, longer duration, and greater severity of DM.

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**M**ILD COGNITIVE IMPAIRMENT (MCI) is a transitional stage between normal cognitive aging and dementia.<sup>1</sup> In the absence of curative treatments for dementia, identification of subjects at increased risk of dementia and modifiable risk factors may allow interventions that prevent progression from preclinical (MCI) to clinical disease (dementia). Findings from several studies have suggested an association between diabetes mellitus (DM) and cognitive impairment,<sup>2-4</sup> rapid decline in cognitive function,<sup>5,6</sup> and dementia.<sup>7-9</sup> In addition, DM has been associated with increased deposition and decreased clearance of amyloid  $\beta$ .<sup>10-12</sup> Poor glycemic control and long-term episodes of hypoglycemia or hyperglycemia may lead to microangiopathy, neuronal loss, and cognitive impairment.<sup>13</sup> Finally, DM is associated with increased cardiovascular risk and with macrovascular and microvascular cerebral disease,<sup>14</sup> all of which may independently increase the risk of cognitive impairment.

However, some studies<sup>15-17</sup> have not confirmed the association.

The inconsistency in findings may be due to differences in study design sources of study subjects, and variations in criteria for the diagnosis of DM or cognitive impairment. However, it may also be due to differences in the duration or severity of DM among study subjects. In this population-based case-control study, we investigated the association of DM and markers of DM severity (ie, age at onset, duration, treatment type, and complications) with MCI.

## METHODS

### IDENTIFICATION OF CASES AND CONTROLS

Identification of cases and controls was performed as part of a population-based study to estimate the prevalence of MCI in Olmsted County (Minnesota). Details of the study design and participant recruitment are described elsewhere.<sup>18</sup> The study protocol was approved by the insti-

tutional review boards of the Mayo Clinic and Olmsted Medical Center. Briefly, we used the medical records linkage system of the Rochester Epidemiology Project<sup>19</sup> to construct a sampling frame of Olmsted County residents aged 70 to 89 years on October 1, 2004. A total of 9953 unique individuals were identified, and 5233 were randomly selected and evaluated for eligibility. We excluded 263 subjects who died before they could be contacted and 56 subjects who were in hospice; 402 subjects with previously diagnosed confirmed dementia were identified by screening of their medical records and were also excluded. Furthermore, 114 subjects who could not be contacted were considered ineligible. Of 4398 eligible subjects, 2719 (61.8%) agreed to participate in a face-to-face evaluation (n=2050) or a telephone interview (n=669). This case-control study was based on subjects who participated in the face-to-face evaluation. Subjects underwent a neurologic evaluation, a nurse evaluation and risk factors assessment (including the Clinical Dementia Rating Scale), and a neuropsychological evaluation (including 9 tests and covering 4 cognitive domains [memory, executive function, language, and visuospatial function]).<sup>18</sup> An expert panel of physicians, neuropsychologists, and nurses then reviewed all the information collected for each participant to reach a consensus diagnosis of normal cognition, MCI, or dementia.

## CASES

All subjects who participated in the face-to-face evaluation and were found to be affected by MCI were included as MCI cases (prevalent series of MCI cases). Mild cognitive impairment was defined according to the following published criteria: cognitive concern by physician, subject, or nurse; impairment in at least 1 of 4 cognitive domains; essentially normal functional activities; and not demented.<sup>1</sup> Subjects with MCI were classified as having amnesic MCI if the memory domain was impaired or nonamnesic MCI if there was no impairment in memory.

## CONTROLS

All subjects who participated in the face-to-face evaluation and were found to be cognitively normal were included as controls. A diagnosis of normal cognition was assigned according to published criteria.<sup>1,20</sup> Therefore, controls were free of MCI and dementia. A diagnosis of dementia was based on the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition).<sup>21</sup>

## MEASURE OF DM

Diabetes mellitus was defined using 3 sources of information—self-reports, fasting blood glucose levels, and medical index diagnoses.

## SELF-REPORT OF DM

As part of the nurse interview and risk factor assessment, participants were asked if they had ever been diagnosed as having DM or “borderline DM” by a physician or if they had ever had DM nerve problems in their legs or feet (neuropathy), ulcers or sores on their feet that were difficult to heal or that a physician said were related to DM (neuropathy), eye problems or eye surgery attributed to DM (retinopathy), or kidney problems that had been attributed to DM (nephropathy). They were also asked about all medications used on a daily basis. Medication use was validated by reviewing the bottles of medications brought to the evaluation (subjects were instructed to bring these with them). Subjects who reported a physician diagnosis of DM, treatment for DM using oral anti-DM agents or insulin, or DM complications were classified as having DM.

## FASTING BLOOD GLUCOSE LEVEL

Each participant underwent a blood draw, and a fasting blood glucose level was measured using a photometric rate reaction (Roche/Hitachi Modular Systems, Indianapolis, Indiana). The coefficient of variation of the test was 0.87 at a mean of 88 mg/dL and 0.63 at a mean of 289 mg/dL (to convert glucose level to millimoles per liter, multiply by 0.0555). A qualifying fasting blood glucose level for DM was defined as 126 mg/dL or higher after a 10- to 12-hour fast for subjects evaluated in the morning<sup>22</sup> or a fasting blood glucose level of 114 mg/dL or higher after a 4- to 6-hour fast for subjects evaluated in the afternoon.<sup>23</sup> The latter cut point was used because 4- to 6-hour fasting glucose levels measured in the afternoon are lower than 10- to 12-hour fasting levels measured in the morning.<sup>23</sup> Using a technique described in a previous study,<sup>23</sup> we first determined the proportion of subjects with DM based on a 10- to 12-hour fasting blood glucose level measured in the morning and a cut point of 126 mg/dL. We then determined the fasting blood glucose cut point that would yield a similar proportion of subjects with DM based on a 4- to 6-hour fasting blood glucose level measured in the afternoon. We arrived at the same cut point of 114 mg/dL reported by other investigators.<sup>23</sup>

## MEDICAL RECORDS ASCERTAINMENT

Diabetes mellitus was also ascertained from the medical index of the medical records linkage system serving Olmsted County.<sup>19</sup> Subjects were considered to have DM if they had at least one *International Classification of Diseases* code for DM (not otherwise specified), DM with or without mention of complications (neuropathy, retinopathy, or nephropathy), or type 1 DM (either *International Classification of Diseases, Eighth Revision, Adapted Codes for Hospitals*<sup>24</sup> or *International Classification of Diseases, Ninth Revision*).<sup>25</sup> Subjects who only had a code for hyperglycemia or borderline DM were considered unaffected. The date of first appearance of a DM code in the medical records was used to estimate the age at onset of DM.

## MEASURE OF POTENTIAL CONFOUNDERS

Date of birth; educational status; cigarette smoking; and medical history of depression, hypertension, stroke, or transient ischemic attack (TIA), and coronary heart disease (angina, myocardial infarction, coronary revascularization, or coronary artery bypass grafting) were ascertained by interview. Surgical procedures for coronary heart disease were also ascertained by searching the surgical index of the medical records linkage system.<sup>19</sup> Current symptoms of depression were assessed through the Neuropsychiatric Inventory questionnaire administered to a study partner.<sup>26</sup> DNA extraction and apolipoprotein E (APOE) genotyping was performed for each subject using standard methods.<sup>27</sup>

## STATISTICAL ANALYSIS

In the first set of case-control analyses, we defined DM as a self-reported physician's diagnosis of DM, DM treatment, or DM complications. The associations of MCI with type of treatment for DM and DM complications were evaluated. We used logistic regression models with adjustment for age (expressed as a continuous variable), sex, and educational status (expressed as a continuous variable) because these 3 variables have been shown to be strongly associated with cognitive function. Potential confounding by hypertension, stroke or TIA, depression, coronary heart disease, smoking (ever vs never), APOE genotype ( $\epsilon 4\epsilon 4$  or  $\epsilon 3\epsilon 4$  vs  $\epsilon 2\epsilon 2$ ,  $\epsilon 2\epsilon 3$ , or  $\epsilon 3\epsilon 3$ ), and body mass index ( $\geq 30$  vs  $< 30$  [calculated as weight in kilograms divided

**Table 1. Demographic and Clinical Characteristics of Cases With Mild Cognitive Impairment (MCI) and Controls**

| Variable                              | No. (%)                                |                                   | Odds Ratio<br>(95% Confidence Interval) <sup>b</sup> | P<br>Value |
|---------------------------------------|----------------------------------------|-----------------------------------|------------------------------------------------------|------------|
|                                       | Cases With MCI<br>(n=329) <sup>a</sup> | Controls<br>(n=1640) <sup>a</sup> |                                                      |            |
| Age at evaluation, y                  |                                        |                                   |                                                      |            |
| 70-79                                 | 103 (31.3)                             | 847 (51.6)                        | 1 [Reference]                                        | ...        |
| 80-89                                 | 226 (68.7)                             | 793 (48.4)                        | 2.73 (2.07-3.59)                                     | <.001      |
| Sex                                   |                                        |                                   |                                                      |            |
| Women                                 | 137 (41.6)                             | 830 (50.6)                        | 1 [Reference]                                        | ...        |
| Men                                   | 192 (58.4)                             | 810 (49.4)                        | 1.67 (1.30-2.13)                                     | <.001      |
| Educational status, y                 |                                        |                                   |                                                      |            |
| <9                                    | 48 (14.6)                              | 92 (5.6)                          | 2.65 (1.78-3.96)                                     | <.001      |
| 9-12                                  | 140 (42.6)                             | 641 (39.1)                        | 1.42 (1.09-1.84)                                     | .008       |
| >12                                   | 141 (42.9)                             | 907 (55.3)                        | 1 [Reference]                                        | ...        |
| Stroke or transient ischemic attack   | 89 (27.1)                              | 205 (12.6)                        | 2.30 (1.72-3.08)                                     | <.001      |
| Coronary heart disease <sup>c</sup>   | 121 (36.8)                             | 490 (29.9)                        | 1.17 (0.91-1.52)                                     | .23        |
| <i>APOE</i> ε3ε4 or ε4ε4 <sup>d</sup> | 89 (29.2)                              | 334 (21.9)                        | 1.55 (1.17-2.05)                                     | .002       |
| Depression                            | 86 (27.0)                              | 182 (11.4)                        | 2.88 (2.13-3.88)                                     | <.001      |
| BMI ≥30                               | 74 (23.3)                              | 457 (28.4)                        | 0.87 (0.65-1.16)                                     | .35        |
| Hypertension <sup>e</sup>             | 234 (71.1)                             | 1154 (70.4)                       | 0.99 (0.76-1.29)                                     | .92        |
| Cigarette smoking <sup>f</sup>        |                                        |                                   |                                                      |            |
| Never                                 | 164 (49.8)                             | 834 (50.9)                        | 1 [Reference]                                        | ...        |
| Former                                | 152 (46.2)                             | 739 (45.1)                        | 1.02 (0.79-1.31)                                     | .91        |
| Current                               | 13 (4.0)                               | 66 (4.0)                          | 1.17 (0.62-2.19)                                     | .63        |

Abbreviations: *APOE*, apolipoprotein E; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

<sup>a</sup>Totals do not sum to 329 or 1640 because some information is missing.

<sup>b</sup>Adjusted for age, sex, and education (where applicable).

<sup>c</sup>Myocardial infarction, angina pectoris, coronary artery bypass surgery, or coronary angioplasty.

<sup>d</sup>Subjects with ε2ε4 genotype were excluded from the percentages because they are of uncertain risk (*APOE* genotype was missing or excluded for 136 subjects).

<sup>e</sup>Self-report or the use of medications for hypertension.

<sup>f</sup>Cigarette smoking was defined as having smoked more than 100 cigarettes ever in life.

by height in meters squared]) were examined, with each variable entered separately in the models. Subjects with *APOE* genotype ε2ε4 were excluded because ε2 is considered protective, while ε4 is considered a risk factor, and also because that genotype was rare (2.3%). The association of DM with MCI was also examined with these variables entered simultaneously in the model. Effect modification by these variables was examined in stratified analyses and by inclusion of an interaction term for DM and the variable in the model.

In the second set of case-control analyses, the definition of DM was broadened by also including subjects who did not report a diagnosis of DM, DM treatment, or DM complications but who had a qualifying fasting blood glucose level (≥126 mg/dL after a 10- to 12-hour fast for subjects evaluated in the morning or ≥114 mg/dL after a 4- to 6-hour fast for subjects evaluated in the afternoon). In sensitivity analyses, subjects were characterized as having DM if they had a self-report of DM and were found to have at least 1 code for DM in the medical records linkage system. For these sensitivity analyses, duration of DM was estimated using information on age at onset abstracted from the medical records.

## RESULTS

### CHARACTERISTICS OF STUDY SUBJECTS

Of 2050 participants who were evaluated in person, 1969 subjects were found to be free of dementia and were included in this study. Eighty-one subjects were excluded as follows: 1 subject had lifelong impaired cognitive function not due to MCI or dementia, 13 subjects did not com-

plete the evaluation and could not be assigned a diagnosis, and 67 subjects received a diagnosis of dementia from the evaluation. Subjects with MCI were significantly older, were more likely to be men, and had a lower level of education than subjects without MCI (**Table 1**). Subjects with MCI were also more likely to have a history of stroke or TIA, an *APOE* ε3ε4 or ε4ε4 genotype, and depression.

### ASCERTAINMENT OF DM FROM SELF-REPORT ONLY

Overall, 356 subjects (18.1%) were characterized as having DM based on self-report of a physician's diagnosis of DM, treatment for DM, or DM complications. Of these, 148 (41.6%) reported treatment for DM only, 85 (23.9%) reported treatment and complications, and 18 (5.1%) reported complications only. Of 105 subjects (29.5%) who reported no treatment and no complications, 34 had at least 1 diagnostic code for DM in the medical records, 8 had a qualifying blood glucose level for DM, and 24 had both; there was no additional information about the remaining 39 subjects.

No significant associations were noted between DM and MCI overall or MCI subtypes (**Table 2**, footnotes); however, there were significant associations with type of DM treatment and DM complications. The odds ratio (OR) for treatment with insulin alone was significantly in-

**Table 2. Case-Control Analyses for Diabetes Mellitus (DM) Defined as Self-report of Physician's Diagnosis of DM, DM Treatment, or DM Complications**

| Variable                    | No. (%)                             |                                | Model 1 <sup>a</sup>                 |         | Model 2 <sup>b</sup>                 |         |
|-----------------------------|-------------------------------------|--------------------------------|--------------------------------------|---------|--------------------------------------|---------|
|                             | Cases With MCI (n=329) <sup>c</sup> | Controls (n=1640) <sup>c</sup> | Odds Ratio (95% Confidence Interval) | P Value | Odds Ratio (95% Confidence Interval) | P Value |
| DM                          |                                     |                                |                                      |         |                                      |         |
| No                          | 263 (79.9)                          | 1349 (82.3)                    | 1 [Reference]                        | ...     | 1 [Reference]                        | ...     |
| Yes                         | 66 (20.1)                           | 290 (17.7)                     | 1.16 (0.85-1.57) <sup>d</sup>        | .34     | 1.20 (0.86-1.67)                     | .28     |
| Treatment type <sup>d</sup> |                                     |                                |                                      |         |                                      |         |
| DM, no treatment            | 15 (4.6)                            | 108 (6.6)                      | 0.72 (0.41-1.26)                     | .24     | 0.75 (0.41-1.35)                     | .34     |
| Oral hypoglycemic           | 26 (7.9)                            | 118 (7.2)                      | 1.11 (0.70-1.76)                     | .65     | 1.14 (0.71-1.84)                     | .58     |
| Insulin                     | 25 (7.6)                            | 64 (3.9)                       | 2.01 (1.22-3.31)                     | .006    | 2.14 (1.25-3.66)                     | .005    |
| Complications <sup>e</sup>  |                                     |                                |                                      |         |                                      |         |
| None                        | 39 (11.9)                           | 214 (13.0)                     | 0.93 (0.64-1.35)                     | .69     | 0.97 (0.66-1.44)                     | .89     |
| DM                          | 27 (8.2)                            | 76 (4.6)                       | 1.80 (1.13-2.89)                     | .01     | 1.86 (1.12-3.08)                     | .02     |
| Neuropathy                  | 19 (5.8)                            | 49 (3.0)                       | 1.91 (1.09-3.34)                     | .02     | 1.87 (1.02-3.42)                     | .04     |
| Retinopathy                 | 13 (4.0)                            | 30 (1.8)                       | 2.15 (1.09-4.22)                     | .03     | 2.36 (1.17-4.79)                     | .02     |
| Nephropathy                 | 6 (1.8)                             | 21 (1.3)                       | 1.49 (0.58-3.82)                     | .40     | 1.58 (0.61-4.13)                     | .35     |

Abbreviation: MCI, mild cognitive impairment.

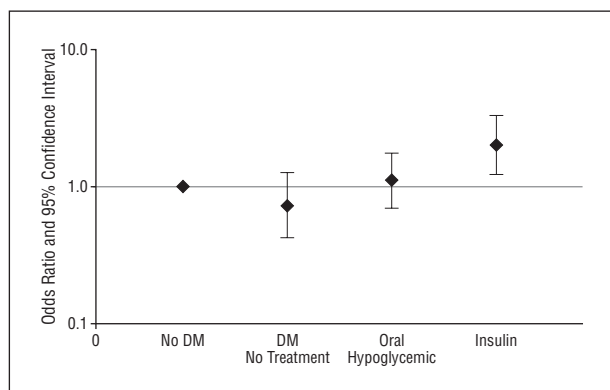
<sup>a</sup>Adjusted for age, sex, and educational status.

<sup>b</sup>Adjusted for age, sex, educational status, hypertension, stroke or transient ischemic attack, cigarette smoking, coronary artery disease, and body mass index (calculated as weight in kilograms divided by height in meters squared).

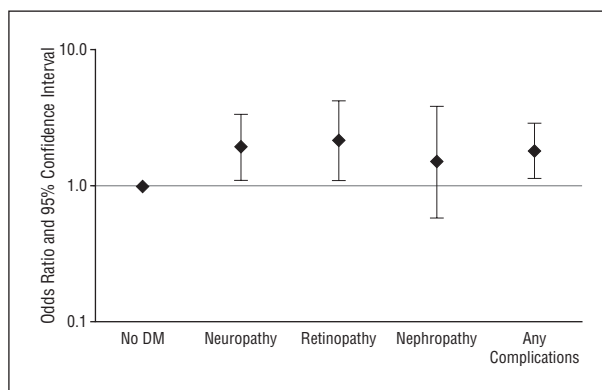
<sup>c</sup>Totals do not sum to 329 or 1640 because some information is missing.

<sup>d</sup>The odds ratios were 1.02 (95% confidence interval, 0.71-1.45;  $P=.94$ ) for amnesic MCI and 1.56 (95% confidence interval, 0.94-2.59;  $P=.08$ ) for nonamnesic MCI.

<sup>e</sup>The reference group included subjects without DM (same as the first line in the table).



**Figure 1.** Odds ratios and 95% confidence intervals (logarithmic scale) for the association of mild cognitive impairment with type of treatment for diabetes mellitus (DM) (no treatment, oral hypoglycemic agent, or insulin with or without oral hypoglycemic agent) compared with subjects without DM (odds ratio, 1).



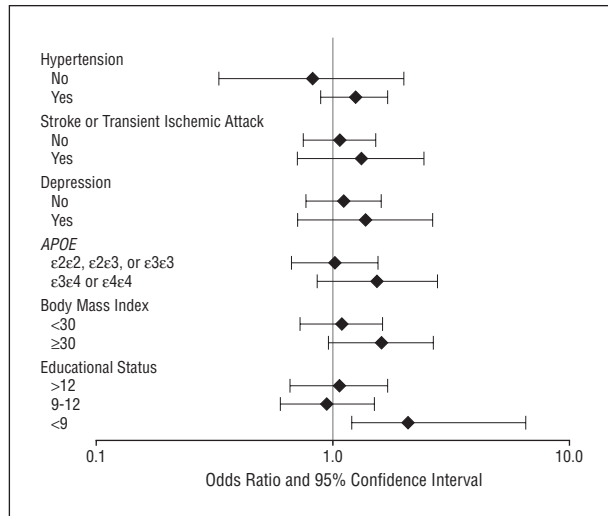
**Figure 2.** Odds ratios and 95% confidence intervals (logarithmic scale) for the association of mild cognitive impairment with diabetic neuropathy, retinopathy, nephropathy, or any of the 3 complications. Subjects without diabetes mellitus (DM) served as the reference group (odds ratio, 1).

creased (OR, 2.05; 95% confidence interval [CI], 1.20-3.49). Subjects receiving insulin and oral anti-DM agents (12 receiving metformin hydrochloride and 1 receiving pioglitazone hydrochloride) also had an elevated but non-significant OR (OR, 1.80; 95% CI, 0.48-6.71). The OR for any insulin treatment (insulin with or without an oral hypoglycemic agent) was significantly elevated (Table 2, model 1), but there was no significant association with oral hypoglycemic use only or with no treatment (**Figure 1**). There was also a significant association of MCI with the presence of any DM complications. Specifically, the ORs were significantly elevated 2-fold for neuropathy and retinopathy and 1.5-fold for nephropathy (Table 2, model 1), but the CIs for the latter estimate included 1 (**Figure 2**). The estimates were essen-

tially the same after adjustment for vascular risk factors (Table 2, model 2) and depression (data not shown).

There were no statistically significant interactions between DM and demographic factors, clinical variables, or depression. However, for certain variables, the ORs were higher in subgroups of subjects exposed to variables that have been associated with cognitive impairment. Specifically, DM was significantly associated with MCI in subjects with fewer than 9 years of education (OR, 2.77; 95% CI, 1.17-6.57) but not in subjects with higher levels of education. After adjustment for age, sex, and education, the association of DM with MCI was stronger in subgroups with depression, hypertension, body mass index of 30 or higher, history of stroke or TIA, and APOE  $\epsilon 3\epsilon 4$  or  $\epsilon 4\epsilon 4$  genotype (**Figure 3**).





**Figure 3.** Odds ratios and 95% confidence intervals (logarithmic scale) for the association of diabetes mellitus with mild cognitive impairment across strata of potential confounders. For apolipoprotein E (*APOE*) analyses, subjects with  $\epsilon 2\epsilon 4$  genotype were excluded. Body mass index is calculated as weight in kilograms divided by height in meters squared.

#### ASCERTAINMENT OF DM FROM SELF-REPORT OR FASTING BLOOD GLUCOSE LEVEL

In this set of analyses, subjects were categorized as having DM based on self-report ( $n=356$ ) or based on having a fasting blood glucose level that met criteria for DM ( $n=54$ ), for a total of 410 subjects with DM. The ORs for DM were slightly greater than those found using only self-report; however, they were not statistically significant (**Table 3**). The association of DM with MCI was marginally significant after adjustment for vascular risk factors (OR, 1.33; 95% CI, 0.98-1.81;  $P=.07$ ) but did not change with adjustment for depression (data not shown). There was a significant association of DM with nonamnesic MCI (OR, 1.63; 95% CI, 1.01-2.63;  $P=.05$ ) but not with amnesic MCI (Table 3, footnotes). The associations with treatment type or complications were essentially the same as in the analyses for DM defined by self-report only (Table 3).

#### SENSITIVITY ANALYSES, INCLUDING ONLY DIAGNOSES OF DM CONFIRMED BY MEDICAL RECORDS

Of 356 subjects with a self-report of DM, 304 (85.4%) had at least 1 diagnostic code for DM from the medical records linkage system. The frequencies of DM were 17.6% in subjects with MCI and 15.0% in subjects without MCI (**Table 4**). The associations of DM and MCI were consistent with the primary and secondary analyses. In addition, we observed significant associations between age at onset and duration of DM and MCI. The adjusted ORs were significantly elevated 2-fold for subjects with DM onset before age 65 years, for subjects with duration of DM for 10 years or longer, for subjects treated with insulin, and for subjects with DM complications (Table 4, models 1 and 2).

In this population-based case-control study, onset of DM before age 65 years, longer duration of DM, treatment of DM with insulin, and the presence of DM complications were independently associated with MCI after accounting for age, sex, education, depression, and vascular risk factors. When we broadened the definition of DM to include subjects with a fasting blood glucose level that met criteria for DM, we observed marginally significant associations of MCI with DM overall. Our findings suggest that DM duration and severity, as measured by type of treatment and the presence of DM complications, may be important in the pathogenesis of cognitive impairment in subjects with DM. In contrast, late onset of DM, short duration of DM, or well-controlled DM may have a lesser effect. Long duration of DM may be associated with greater cerebral macrovascular disease, clinical cerebral infarctions, and subclinical infarctions that may impair cognitive function.<sup>28,29</sup> This is consistent with other findings in which vascular disease in midlife predicted late-life cognitive impairment or dementia.<sup>30</sup>

Severe DM is more likely to be associated with chronic hyperglycemia, which, in turn, increases the likelihood of cerebral microvascular disease<sup>31</sup> and may contribute to neuronal damage, brain atrophy,<sup>32-34</sup> and cognitive impairment. The 2-fold increased risk of MCI in subjects with diabetic retinopathy in the present study supports the potential effects of DM on cerebral microvascular disease and the pathogenesis of MCI.

Alternative mechanisms besides vascular disease may be involved in the pathogenesis of cognitive impairment in subjects with DM. It has been hypothesized that defects in insulin action may increase amyloid- $\beta$  aggregation.<sup>11,12,35</sup> In type 2 DM, insulin therapy may inhibit synaptic activity in the brain,<sup>36</sup> decrease insulin-degrading enzyme production, promote the development of amyloid plaques,<sup>11,12</sup> and increase production of advanced glycation end products associated with Alzheimer disease.<sup>10-12</sup> Recurrent or chronic hypoglycemia caused by treatment with insulin may also contribute to permanent cognitive impairment.<sup>37,38</sup> In the present study, the association of DM with MCI persisted after adjustment for vascular risk factors; this supports the hypothesis that additional pathologic mechanisms independent of vascular disease contribute to MCI in subjects with DM.

Differences in the association of DM across MCI subtypes raise questions regarding the role of DM in the origin and prognosis of MCI subtypes. When fasting blood glucose levels were considered, we observed a significant association of DM with nonamnesic MCI but not with amnesic MCI. Other investigators have reported stronger associations between vascular risk factors and nonamnesic MCI, suggesting that vascular risk factors may increase the risk of nonamnesic MCI. Nonamnesic MCI may be a prodromal stage for vascular dementia<sup>39</sup> or other nondegenerative dementias,<sup>40</sup> whereas amnesic MCI may be a prodromal stage for neurodegenerative dementias such as Alzheimer disease. However, this hypothesis is disputed by other authors who have found no difference in the association of vascular risk factors across MCI subtypes.<sup>41</sup>

**Table 3. Case-Control Analyses for Diabetes Mellitus (DM) Defined as Self-report or as Abnormal Fasting Blood Glucose Level**

| Variable                    | No. (%)                             |                                | Model 1 <sup>a</sup>                 |         | Model 2 <sup>b</sup>                 |         |
|-----------------------------|-------------------------------------|--------------------------------|--------------------------------------|---------|--------------------------------------|---------|
|                             | Cases With MCI (n=329) <sup>c</sup> | Controls (n=1640) <sup>c</sup> | Odds Ratio (95% Confidence Interval) | P Value | Odds Ratio (95% Confidence Interval) | P Value |
| DM                          |                                     |                                |                                      |         |                                      |         |
| No                          | 249 (75.7)                          | 1309 (79.9)                    | 1 [Reference]                        | ...     | 1 [Reference]                        | ...     |
| Yes                         | 80 (24.3)                           | 330 (20.1)                     | 1.24 (0.93-1.66) <sup>d</sup>        | .14     | 1.33 (0.98-1.81)                     | .07     |
| Treatment type <sup>e</sup> |                                     |                                |                                      |         |                                      |         |
| DM, no treatment            | 29 (8.8)                            | 148 (9.0)                      | 0.99 (0.64-1.52)                     | .96     | 1.10 (0.70-1.72)                     | .67     |
| Oral hypoglycemic           | 26 (7.9)                            | 118 (7.2)                      | 1.13 (0.72-1.80)                     | .59     | 1.18 (0.73-1.91)                     | .49     |
| Insulin                     | 25 (7.6)                            | 64 (3.9)                       | 2.05 (1.25-3.39)                     | .005    | 2.23 (1.30-3.81)                     | .004    |
| Complications <sup>e</sup>  |                                     |                                |                                      |         |                                      |         |
| None                        | 53 (16.1)                           | 254 (15.5)                     | 1.06 (0.76-1.49)                     | .72     | 1.16 (0.81-1.65)                     | .41     |
| DM                          | 27 (8.2)                            | 76 (4.6)                       | 1.84 (1.15-2.95)                     | .01     | 1.93 (1.16-3.21)                     | .01     |
| Neuropathy                  | 19 (5.8)                            | 49 (3.0)                       | 1.91 (1.09-3.34)                     | .02     | 1.87 (1.02-3.42)                     | .04     |
| Retinopathy                 | 13 (4.0)                            | 30 (1.8)                       | 2.15 (1.09-4.22)                     | .03     | 2.36 (1.17-4.79)                     | .02     |
| Nephropathy                 | 6 (1.8)                             | 21 (1.3)                       | 1.49 (0.58-3.82)                     | .40     | 1.58 (0.61-4.13)                     | .35     |

Abbreviation: MCI, mild cognitive impairment.

<sup>a</sup>Adjusted for age, sex, and education.

<sup>b</sup>Adjusted for age, sex, educational status, hypertension, stroke or transient ischemic attack, cigarette smoking, coronary artery disease, and body mass index (calculated as weight in kilograms divided by height in meters squared).

<sup>c</sup>Totals do not sum to 329 or 1640 because some information is missing.

<sup>d</sup>The odds ratios were 1.10 (95% confidence interval, 0.78-1.53; *P*=.59) for amnesic MCI and 1.63 (95% confidence interval, 1.01-2.63; *P*=.05) for nonamnesic MCI.

<sup>e</sup>The reference group included subjects without DM (same as the first line in the table).

**Table 4. Case-Control Analyses for Diabetes Mellitus (DM) Defined as Self-report but Also Confirmed by Medical Records Diagnosis**

| Variable                     | No. (%)                             |                                | Model 1 <sup>a</sup>                 |         | Model 2 <sup>b</sup>                 |         |
|------------------------------|-------------------------------------|--------------------------------|--------------------------------------|---------|--------------------------------------|---------|
|                              | Cases With MCI (n=329) <sup>c</sup> | Controls (n=1640) <sup>c</sup> | Odds Ratio (95% Confidence Interval) | P Value | Odds Ratio (95% Confidence Interval) | P Value |
| DM                           |                                     |                                |                                      |         |                                      |         |
| No                           | 271 (82.4)                          | 1393 (85.0)                    | 1 [Reference]                        | ...     | 1 [Reference]                        | ...     |
| Yes                          | 58 (17.6)                           | 246 (15.0)                     | 1.22 (0.88-1.68) <sup>d</sup>        | .23     | 1.28 (0.91-1.81)                     | .16     |
| Age at onset, y <sup>d</sup> |                                     |                                |                                      |         |                                      |         |
| <65                          | 21 (6.4)                            | 65 (4.0)                       | 2.20 (1.29-3.73)                     | .004    | 2.19 (1.25-3.82)                     | .006    |
| ≥65                          | 37 (11.2)                           | 181 (11.0)                     | 0.96 (0.65-1.41)                     | .82     | 1.03 (0.69-1.55)                     | .88     |
| Duration, y <sup>e</sup>     |                                     |                                |                                      |         |                                      |         |
| <10                          | 23 (7.0)                            | 147 (9.0)                      | 0.83 (0.52-1.33)                     | .44     | 0.93 (0.58-1.50)                     | .77     |
| ≥10                          | 35 (10.6)                           | 99 (6.0)                       | 1.76 (1.16-2.68)                     | .008    | 1.80 (1.14-2.84)                     | .01     |
| Treatment type <sup>f</sup>  |                                     |                                |                                      |         |                                      |         |
| DM, no treatment             | 8 (2.4)                             | 65 (4.0)                       | 0.64 (0.30-1.36)                     | .25     | 0.75 (0.35-1.62)                     | .46     |
| Oral hypoglycemic            | 25 (7.6)                            | 117 (7.1)                      | 1.10 (0.69-1.75)                     | .68     | 1.13 (0.70-1.83)                     | .62     |
| Insulin                      | 25 (7.6)                            | 64 (3.9)                       | 2.02 (1.23-3.33)                     | .006    | 2.16 (1.26-3.69)                     | .005    |
| Complications <sup>f</sup>   |                                     |                                |                                      |         |                                      |         |
| None                         | 32 (9.7)                            | 172 (10.5)                     | 0.96 (0.64-1.45)                     | .85     | 1.05 (0.68-1.60)                     | .84     |
| DM                           | 26 (7.9)                            | 74 (4.5)                       | 1.80 (1.11-2.90)                     | .02     | 1.83 (1.10-3.05)                     | .02     |

Abbreviation: MCI, mild cognitive impairment.

<sup>a</sup>Adjusted for age, sex, and educational status.

<sup>b</sup>Adjusted for age, sex, educational status, hypertension, stroke or transient ischemic attack, cigarette smoking, coronary artery disease, and body mass index (calculated as weight in kilograms divided by height in meters squared).

<sup>c</sup>Totals do not sum to 329 or 1640 because some information is missing.

<sup>d</sup>The odds ratios were 1.07 (95% confidence interval, 0.74-1.57; *P*=.71) for amnesic MCI and 1.58 (95% confidence interval, 0.93-2.70; *P*=.09) for nonamnesic MCI.

<sup>e</sup>Age at onset of DM (arbitrary cutoff at age 65 years) and duration of DM (upper 2 quintiles [≥10 years] vs lower 3 quintiles [<10 years]) were calculated from the first appearance of DM in the medical records. The reference group included subjects without DM (same as the first line in the table).

<sup>f</sup>The reference group included subjects without DM (same as the first line in the table).

We observed no significant interactions of DM with APOE ε4 genotype or depression. However, in our stratified analyses, the ORs for DM were stronger in the strata of subjects exposed to variables that have been reported to be associated with cognitive impairment or demen-

tia. We may have had insufficient power to detect significant interactions in these stratified analyses.

There are several strengths of this study. Participants were randomly selected from the community; therefore, the potential for selection bias was reduced in com-

parison with studies performed among subjects seen in referral practices or memory clinics. The availability of fasting blood glucose levels enabled us to identify subjects with undiagnosed or unreported DM and to reduce potential misclassification. In addition, using the medical records linkage system of the Rochester Epidemiology Project, we validated the self-report of DM and performed sensitivity analyses; these results confirmed our primary analyses.

There are potential limitations of our study. A comparison of participants and nonparticipants showed less participation among older men, subjects with lower educational status, and subjects with DM.<sup>18</sup> This underrepresentation of subjects with DM may have precluded our ability to detect a significant association between DM overall and MCI. Active follow-up of participants by second interviews and examinations and passive follow-up of nonparticipants through the medical records linkage system of the Rochester Epidemiology Project will enable us to determine whether these baseline differences are associated with differences in dementia incidence. Because MCI is typically not diagnosed in routine clinical practice, we may be unable to assess the effect on MCI incidence. Because of the cross-sectional design of the present study, we cannot be sure that DM preceded MCI. Finally, these findings were based on a primarily white sample representative of the Olmsted County community; therefore, extrapolation of findings to racial/ethnic groups not represented in our study should be performed with caution.

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