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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tutional review boards of the Mayo Clinic and Olmsted Medical Center. Briefly, we used the medical records linkage system of the Rochester Epidemiology Project to construct a sampling frame of Olmsted County residents aged 70 to 89 years on October 1, 2004. A total of 9,953 unique individuals were identified, and 5,233 were randomly selected and evaluated for eligibility. We excluded 263 subjects who died before they could be contacted and 36 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 4,308 eligible subjects, 2,719 (61.8%) agreed to participate in a face-to-face evaluation (n = 2,050) 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 neuropsychological 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]). 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. Subjects with MCI were classified as having amnestic MCI if the memory domain was impaired or nonamnestic 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. 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).

**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. 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 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. The latter cut point was used because 4- to 6-hour fasting glucose levels measured in the afternoon were lower than 10- to 12-hour fasting levels measured in the morning. Using a technique described in a previous study, 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.

**MEDICAL RECORDS ASCERTAINMENT**

Diabetes mellitus was also ascertained from the medical index of the medical records linkage system serving Olmsted County. 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 or International Classification of Diseases, Ninth Revision). 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. Current symptoms of depression were assessed through the Neuropsychiatric Inventory questionnaire administered to a study partner. DNA extraction and apolipoprotein E (APOE) genotyping was performed for each subject using standard methods.

**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 (ε4εε0 or ε3ε4 vs ε2ε2, ε2ε3, or ε3ε3), and body mass index (≥30 vs <30) (calculated as weight in kilograms divided

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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 complete 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-

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases With MCI (n=329)a</th>
<th>Controls (n=1640)b</th>
<th>Odds Ratio (95% Confidence Interval)b</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at evaluation, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-79</td>
<td>103 (31.3)</td>
<td>847 (51.6)</td>
<td>1 [Reference]</td>
<td>.91</td>
</tr>
<tr>
<td>80-89</td>
<td>226 (68.7)</td>
<td>793 (48.4)</td>
<td>2.73 (2.07-3.59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Educational status, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9</td>
<td>48 (14.6)</td>
<td>92 (5.6)</td>
<td>2.65 (1.78-3.96)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>9-12</td>
<td>140 (42.6)</td>
<td>641 (39.1)</td>
<td>1.42 (1.09-1.84)</td>
<td>.008</td>
</tr>
<tr>
<td>&gt;12</td>
<td>141 (42.9)</td>
<td>907 (55.3)</td>
<td>1 [Reference]</td>
<td>.91</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>89 (27.1)</td>
<td>205 (12.6)</td>
<td>2.30 (1.72-3.08)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary heart diseasec</td>
<td>121 (36.8)</td>
<td>490 (29.9)</td>
<td>1.17 (0.91-1.52)</td>
<td>.23</td>
</tr>
<tr>
<td>APOEε3ε4 or ε4ε4d</td>
<td>89 (29.2)</td>
<td>334 (21.9)</td>
<td>1.55 (1.17-2.05)</td>
<td>.002</td>
</tr>
<tr>
<td>Depression</td>
<td>86 (27.0)</td>
<td>182 (11.4)</td>
<td>2.88 (2.13-3.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>74 (23.3)</td>
<td>457 (28.4)</td>
<td>0.87 (0.65-1.16)</td>
<td>.35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>234 (71.1)</td>
<td>1154 (70.4)</td>
<td>0.99 (0.76-1.29)</td>
<td>.92</td>
</tr>
<tr>
<td>GBR smokingf</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>164 (49.8)</td>
<td>834 (50.9)</td>
<td>1 [Reference]</td>
<td>.91</td>
</tr>
<tr>
<td>Former</td>
<td>152 (46.2)</td>
<td>739 (45.1)</td>
<td>1.02 (0.79-1.31)</td>
<td>.35</td>
</tr>
<tr>
<td>Current</td>
<td>13 (4.0)</td>
<td>66 (4.0)</td>
<td>1.17 (0.62-2.19)</td>
<td>.35</td>
</tr>
</tbody>
</table>

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

a Totals do not sum to 329 or 1640 because some information is missing.

b Adjusted for age, sex, and education (where applicable).

c Myocardial infarction, angina pectoris, coronary artery bypass surgery, or coronary angioplasty.

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

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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 essentially 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 ε3ε4 or ε4ε4 genotype (Figure 3).

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases With MCI (n=329)</th>
<th>Controls (n=1640)</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>No</td>
<td>263 (79.9)</td>
<td>1 [Reference]</td>
<td>. .</td>
<td>1 [Reference]</td>
<td>. .</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>66 (20.1)</td>
<td>1.16 (0.85-1.57)</td>
<td>.34</td>
<td>1.20 (0.86-1.67)</td>
<td>.28</td>
</tr>
<tr>
<td>Treatment type</td>
<td>DM, no treatment</td>
<td>15 (4.6)</td>
<td>0.72 (0.41-1.26)</td>
<td>.24</td>
<td>0.75 (0.41-1.35)</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>Oral hypoglycemic</td>
<td>26 (7.9)</td>
<td>1.11 (0.70-1.76)</td>
<td>.65</td>
<td>1.14 (0.71-1.84)</td>
<td>.58</td>
</tr>
<tr>
<td></td>
<td>Insulin</td>
<td>25 (7.6)</td>
<td>2.01 (1.22-3.31)</td>
<td>.006</td>
<td>2.14 (1.25-3.66)</td>
<td>.005</td>
</tr>
<tr>
<td>Complications</td>
<td>None</td>
<td>39 (11.9)</td>
<td>0.93 (0.64-1.35)</td>
<td>.69</td>
<td>0.97 (0.66-1.44)</td>
<td>.89</td>
</tr>
<tr>
<td></td>
<td>DM</td>
<td>27 (8.2)</td>
<td>1.80 (1.13-2.89)</td>
<td>.01</td>
<td>1.86 (1.12-3.08)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
<td>19 (5.8)</td>
<td>1.91 (1.09-3.34)</td>
<td>.02</td>
<td>1.87 (1.02-3.42)</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>Retinopathy</td>
<td>13 (4.0)</td>
<td>2.15 (1.09-4.22)</td>
<td>.03</td>
<td>2.36 (1.17-4.79)</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>Nephropathy</td>
<td>6 (1.8)</td>
<td>1.49 (0.58-3.82)</td>
<td>.40</td>
<td>1.58 (0.61-4.13)</td>
<td>.35</td>
</tr>
</tbody>
</table>

Abbreviation: MCI, mild cognitive impairment.

a Adjusted for age, sex, and educational status.
b 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).
c Totals do not sum to 329 or 1640 because some information is missing.
d The odds ratios were 1.02 (95% confidence interval, 0.71-1.45; P=.94) for amnestic MCI and 1.56 (95% confidence interval, 0.94-2.59; P=.08) for nonamnestic MCI.
e 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).
There was a significant association of DM with nonamnestic MCI and 15.0% in subjects without MCI. The frequencies of DM were 17.6% in subjects with amnestic MCI (Table 3, footnotes). The associations between vascular risk factors and nonamnestic MCI but not with amnestic MCI (Table 3, footnotes). The associations between vascular risk factors and nonamnestic 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).

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).
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 dementia. 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 compar...
The role of the Sponsors: The sponsors of this study had no role in the design or conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

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Author Contributions: Dr. Roberts takes full responsibility for the data, the analyses and interpretation, and the conduct of the research; she has full access to all of the data; and she has the right to publish any and all data, separate and apart from the attitudes of the sponsors. Study concept and design: Roberts, Knopman, Rocca, and Petersen. Acquisition of data: Geda, Knopman, Boeve, and Petersen. Analysis and interpretation of data: Roberts, Pankratz, Vella, and Rocca. Drafting of the manuscript: Roberts. Critical revision of the manuscript for important intellectual content: Geda, Knopman, Vella, and Rocca. Statistical analysis: Christianson and Pankratz. Study supervision: Roberts.

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REFERENCES


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