Relation of Diabetes to Mild Cognitive Impairment

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Background: Type 2 diabetes mellitus is an important risk factor for Alzheimer disease and is more prevalent in elderly minority persons compared with non-Hispanic white persons.

Objective: To determine whether diabetes is related to a higher risk of mild cognitive impairment (MCI), a transitional stage between normal cognition and Alzheimer disease, in a multiethnic cohort with a high prevalence of diabetes.

Design: Longitudinal cohort study.

Setting: Northern Manhattan in New York, NY.

Participants: We studied persons without prevalent MCI or dementia at baseline and with at least 1 follow-up interval. Of 1772 participants with a complete neuropsychological evaluation, 339 (19.1%) were excluded because of prevalent dementia, 304 were excluded because of prevalent MCI (17.2%), and 211 were excluded because of loss to follow-up (11.9%), resulting in a final sample of 918 participants for longitudinal analyses.

Main Outcome Measures: We related diabetes defined by self-report to incident all-cause MCI, amnestic MCI, and nonamnestic MCI. We conducted multivariate analyses with proportional hazards regression adjusting for age, sex, years of education, ethnic group, apolipoprotein E (APOE) ε4 allele, hypertension, low-density lipoprotein level, current smoking, heart disease, and stroke.

Results: A total of 334 persons had incident MCI, 160 (47.9%) had amnestic MCI, and 174 (52.1%) had nonamnestic MCI. Diabetes was related to a significantly higher risk of all-cause MCI and amnestic MCI after adjustment for all covariates. Diabetes was also related to a higher risk of nonamnestic MCI, but this association was appreciably attenuated after adjustment for socioeconomic variables and vascular risk factors. The risk of MCI attributable to diabetes was 8.8% for the whole sample and was higher for African American persons (8.4%) and Hispanic persons (11.0%) compared with non-Hispanic white persons (4.6%), reflecting the higher prevalence of diabetes in minority populations in the United States.

Conclusion: Diabetes is related to a higher risk of amnestic MCI in a population with a high prevalence of this disorder.

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Among cardiovascular risk factors, type 2 diabetes mellitus has been consistently related to a higher risk of Alzheimer disease (AD).1-6 This association is presumed to be the result of the effects of peripheral hyperinsulinemia on the clearance of brain amyloid β,7,8 the putative main culprit in the pathogenesis of AD,9 or of other mechanisms such as advanced products of glycosylation.10 The prevalence of diabetes is more than 10% in the elderly population in the United States,11 is twice as high in African American and Hispanic populations compared with non-Hispanic white populations,12 and is more than 20% in persons 65 years or older in the predominantly minority population of northern Manhattan in New York, NY.13

Interest is growing in preclinical transitional states of AD as targets for treatment and prevention. Mild cognitive impairment (MCI), and particularly amnestic MCI, has been described as a transitional state between normal cognition and AD14-16 that is increasingly used in clinical and research settings. We previously demonstrated that diabetes is associated with an increased risk of AD and dementia.2,17 Thus, we hypothesized that diabetes is also related to a higher risk of MCI, particularly amnestic MCI.

METHODS

Participants and Setting

Participants were from a longitudinal cohort study of Medicare recipients 65 years or older residing in northern Manhattan (Washington
NEUROPSYCHOLOGICAL BATTERY

The neuropsychological measures used in this study have been previously described. The evaluation included measures of learning and memory, orientation, abstract reasoning, language, and visuospatial ability. Specific ability areas and tests administered included verbal list learning and memory (Selective Reminding Test), nonverbal memory (multiple-choice version of the Benton Visual Retention Test), orientation (items from the Mini-Mental State Examination), verbal reasoning (similarities subtest of the Wechsler Adult Intelligence Scale–Revised), nonverbal reasoning (identities and oddities subtest of the Mattis Dementia Rating Scale), naming (15-item version of the Boston Naming Test), letter fluency (Controlled Word Association), category fluency (animals, food, and clothing, using procedures from the Boston Diagnostic Aphasia Examination [BDAE]), repetition (high-frequency phrases of the BDAE), auditory comprehension (first 6 items of the complex ideational material subtest of the BDAE), visuospatial construction (Rosen Drawing Test), and visuoperceptual skills (multiple-choice matching of figures from the Benton Visual Retention Test). Norms for these tests to diagnose MCI have been previously described.

DIAGNOSIS OF DEMENTIA

Diagnosis of dementia and assignment of specific cause were made by consensus of 2 neurologists, 1 psychiatrist, and 2 neuropsychologists based on baseline and follow-up information. The diagnosis of dementia was based on Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria and required evidence of cognitive deficits on the neuropsychological test battery as well as evidence of impairment in social or occupational function (Clinical Dementia Rating of 1 or more). Diagnosis of AD was based on the National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorder Association criteria.

MCI DIAGNOSTIC CRITERIA

The MCI criteria were retrospectively applied among persons without dementia. Consistent with standard criteria, for all subtypes of MCI, those considered for MCI were required to have the following: (1) memory complaints; (2) objective impairment in at least 1 cognitive domain based on the average of the scores on the neuropsychological measures within that domain and a 1.5-SD cutoff using normative corrections for age, years of education, ethnicity, and sex; (3) essentially preserved activities of daily living; and (4) no diagnosis of dementia at the consensus conference.

To cast the widest net to determine prevalence of MCI and to determine which individuals were more likely to progress to dementia, we expanded the original Petersen criteria, which focus on memory impairment, to include mutually exclusive subtypes based on cognitive features. Our first subtype, amnestic MCI, corresponds most closely to the original definition used by Petersen and colleagues. Memory impairment was defined as a score of less than 1.5 SDs below the demographically corrected mean on an average composite measure that comprised the following learning and memory measures: (1) total recall from the Selective Reminding Test, (2) delayed free recall from the Selective Reminding Test, and (3) recognition from the Benton Visual Retention Test. Performance on composite scores from all other cognitive domains (ie, executive, language, and visuospatial) was required to be within normal limits (score must be ≥1.5 SDs below the demographically corrected mean). Other MCI subtypes were classified that allowed for impairment in a single nonmemory domain if performance on composite scores from all other cognitive domains was within normal limits. Executive MCI was assigned if impairment was demonstrated on an average composite measure that comprised the following measures: (1) letter fluency, (2) category fluency, and (3) the Wechsler Adult Intelligence Scale–Revised similarities subtest. Language MCI was defined as isolated impairment on an average composite measure that comprised (1) the Boston Naming Test, (2) the BDAE repetition test, and (3) the BDAE comprehension test. Visuospatial MCI was assigned if impairment was demonstrated on an average composite measure that comprised (1) Rosen Drawing and (2) Benton Visual Retention Test matching. Finally, we allowed for impairment in multiple cognitive domains in the absence of dementia. Multiple cognitive domains with memory impairment MCI (MCI-MCDM) was diagnosed if there was objective impairment on the memory domain composite score and if there was impairment on at least 1 other cognitive domain. Multiple cognitive domains without memory impairment MCI was assigned if there was impairment in 2 or more of the 3 nonmemory domains and if the memory domain composite score was within normal limits. Classification into the 6 subtypes was mutually exclusive. We used 3 outcomes for these analyses: (1) all-cause MCI; (2) amnestic MCI, which included amnestic MCI and MCI-MCDM; and (3) nonamnestic MCI. The rationale for grouping amnestic MCI and MCI-MCDM is that amnestic MCI and MCI-MCDM equally predict the development of AD and MCI-MCDM is thought to be a more advanced form of amnestic MCI involving other cognitive domains.

DEFINITION OF DIABETES AND OTHER COVARIATES

History of type 2 diabetes mellitus was ascertained by self-report or the use of diabetes medications at baseline and each follow-up visit. Hypertension, heart disease, and smoking were defined by self-report. Heart disease included a history of atrial fibrillation and other arrhythmias, congestive heart failure, myocardial infarction, and angina pectoris. Smoking was classified into never, current, and past smoking. Fasting
Table 1. Demographic and Other Relevant Characteristics of Persons With and Without Diabetes: The Washington Heights–Inwood Columbia Aging Project, 1992-2003*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Without Diabetes (n = 699)</th>
<th>With Diabetes (n = 219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.2 ± 6.1</td>
<td>75.3 ± 5.6†</td>
</tr>
<tr>
<td>Female sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>white</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, y</td>
<td>9.2 ± 4.6</td>
<td>7.8 ± 4.3‡</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>119.6 ± 36.1</td>
<td>122.0 ± 38.0</td>
</tr>
<tr>
<td>Current smoking</td>
<td>78 (11.2)</td>
<td>17 (7.8)</td>
</tr>
<tr>
<td>Stroke</td>
<td>85 (12.2)</td>
<td>53 (24.2)†</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6.0 ± 3.2</td>
<td>6.2 ± 3.1</td>
</tr>
<tr>
<td>MCI</td>
<td>241 (34.5)</td>
<td>93 (42.5)†</td>
</tr>
</tbody>
</table>

Abbreviations: LDL-C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment.

SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.

*Data are presented as number (percentage) of persons or mean ± SD.
†P < .05.
‡P < .001.

plasma total cholesterol and triglyceride levels were determined at the first follow-up using standard enzymatic techniques. High-density lipoprotein cholesterol levels were determined after precipitation of apolipoprotein B–containing lipoproteins with phosphotungstic acid. The low-density lipoprotein cholesterol level was recalculated using the formula of Friedewald et al. The apolipoprotein E (APOE) genotypes were determined as described by Hixson and Verrier with slight modification. We classified persons as homozygous or heterozygous for the APOE ε4 allele or as not having any ε4 allele.

STATISTICAL ANALYSIS

Bivariate analyses compared variables between persons with and without diabetes. Continuous variables were compared using analysis of variance, and categorical variables were compared using χ² tests. Cox proportional hazards regression models were used in multivariate analyses exploring the association of diabetes with incident all-cause MCI, amnestic MCI, and nonamnestic MCI. The time-to-event variable was age at diagnosis of MCI. Among individuals who did not develop MCI, those who developed dementia were censored at the time of dementia diagnosis, and those who did not develop dementia were censored at the time of last follow-up. We show the results of multivariate analyses for 3 models: 1 adjusted for age and sex; 1 adjusted also for education, ethnic group, and APOE ε4; and 1 additionally adjusted for hypertension, low-density lipoprotein cholesterol level, heart disease, stroke, and current smoking, with the caveat that some of these variables may be in the causal pathway between diabetes and cognitive disorders and attenuation of the hazard ratios (HRs) in this model should be considered evidence of mediation and not of confounding. The risk of MCI attributable to diabetes was calculated using the following formula:

\[ PAR = p(RR - 1)/(1 + p(RR - 1)) \]

where PAR is population attributable risk, RR is the adjusted HR obtained from the multivariate models, and p is the prevalence of diabetes in this sample. All analyses were conducted using SAS statistical software, version 9.1 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

There were 334 incident MCI cases, 160 amnestic MCI cases, and 174 cases of nonamnestic MCI in 5,556 person-years of follow-up (mean ± SD, 6.1 ± 3.2 years per person). The mean ± SD age of the sample was 75.9 ± 6.0 years, and the mean ± SD duration of education was 8.9 ± 4.6 years. Women represented 69.9% of the sample. 43.9% were Hispanic, 33.6% were African American, and 22.5% were non-Hispanic white. Diabetes was reported by 23.9% of persons, hypertension by 68.2%, coronary heart disease by 33.9%, and stroke by 15.0%; 28.3% of the sample carried the APOE ε4 allele. The mean ± SD low-density lipoprotein cholesterol level was 120.4 ± 36.7 mg/dL (3.12 ± 0.95 mmol/L).

Compared with persons without diabetes, persons with diabetes were younger, were more likely to be Hispanic, were less likely to be non-Hispanic white, had fewer years of education, and were more likely to have hypertension, heart disease, and stroke (Table 1). Persons with incident MCI were more likely to report diabetes and hypertension at baseline and had a longer study follow-up time (Table 2).

In multivariate analyses (Table 3), diabetes was related to a higher risk of all-cause MCI even after adjusting for age, sex, marital status, education, APOE ε4, hypertension, low-density lipoprotein level, heart disease, stroke, and current smoking (HR, 1.4; 95% confidence interval [CI], 1.1-1.8). When only amnestic MCI was considered the outcome of interest, the HR was unchanged (HR, 1.5; 95% CI, 1.0-2.2). When nonamnestic MCI was considered, diabetes was related to a higher risk in the model adjusted for age and sex (HR, 1.4; 95% CI, 1.0-1.9), but it became nonsignificant after adjusting for ethnic group, years of education, and APOE ε4 (HR, 1.3; 95% CI, 0.9-1.8). The HR attenuated further after adjusting for other vascular risk factors, heart disease, and stroke (HR, 1.2; 95% CI, 0.9-1.8).

The association between diabetes and MCI was not modified by the presence of APOE ε4. Compared with persons without diabetes and without APOE ε4, persons with diabetes and the APOE ε4 allele had an HR of 1.3 (95% CI, 0.8-2.1), whereas persons with diabetes without the APOE ε4 allele had an HR of 1.5 (95% CI, 1.1-1.9) in the full model. No effect modification by age (categorized by the median) or sex was found.

We calculated the risk of MCI attributable to diabetes for the whole sample and for each ethnic group. The prevalence of diabetes was 23.1% in African American persons, 30.8% in Hispanic persons, and 11.6% in non-Hispanic white persons, comparable to data from national surveys. The risk of MCI attributable to diabetes was 8.8% for the whole sample, 8.4% for African American persons, 11.0% for Hispanic persons, and 4.6% for non-Hispanic white persons, reflecting the differences in diabetes prevalence by ethnic group.

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Table 2. Relevant Characteristics Among Persons Without and With MCI, Amnestic MCI, and Nonamnestic MCI: The Washington Heights–Inwood Columbia Aging Project, 1992-2003*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No MCI</th>
<th>MCI</th>
<th>Amnestic MCI</th>
<th>Nonamnestic MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>584</td>
<td>334</td>
<td>160</td>
<td>174</td>
</tr>
<tr>
<td>Age, y</td>
<td>75.8 ± 6.2</td>
<td>76.3 ± 5.8</td>
<td>76.9 ± 5.8†</td>
<td>75.7 ± 5.7</td>
</tr>
<tr>
<td>Sex</td>
<td>406 (69.5)</td>
<td>233 (69.8)</td>
<td>112 (70.0)</td>
<td>121 (69.5)</td>
</tr>
<tr>
<td>African American</td>
<td>196 (33.6)</td>
<td>112 (33.5)</td>
<td>55 (34.4)</td>
<td>57 (32.8)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>251 (42.9)</td>
<td>152 (45.3)</td>
<td>65 (40.6)</td>
<td>87 (50.0)</td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>137 (23.5)</td>
<td>70 (20.9)</td>
<td>40 (25.0)</td>
<td>30 (17.2)</td>
</tr>
<tr>
<td>Education, y</td>
<td>9.0 ± 4.5</td>
<td>8.6 ± 4.6</td>
<td>9.0 ± 4.5</td>
<td>8.2 ± 4.6†</td>
</tr>
<tr>
<td>APOE ε4</td>
<td>147 (27.4)</td>
<td>97 (29.9)</td>
<td>50 (32.5)</td>
<td>47 (27.5)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>126 (21.6)</td>
<td>93 (27.8†)</td>
<td>43 (26.9)</td>
<td>50 (28.7†)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>368 (63.0)</td>
<td>258 (77.3†)</td>
<td>118 (73.8†)</td>
<td>140 (80.5)‡</td>
</tr>
<tr>
<td>Heart disease</td>
<td>197 (33.7)</td>
<td>114 (34.1)</td>
<td>54 (33.8)</td>
<td>60 (34.5)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>122.2 ± 36.6</td>
<td>117.0 ± 36.7</td>
<td>117.2 ± 34.1</td>
<td>116.8 ± 39.1</td>
</tr>
<tr>
<td>Current smoking</td>
<td>63 (10.8)</td>
<td>32 (9.6)</td>
<td>16 (10.0)</td>
<td>16 (9.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>87 (14.9)</td>
<td>51 (15.3)</td>
<td>27 (16.9)</td>
<td>24 (13.8)</td>
</tr>
<tr>
<td>Total follow-up</td>
<td>5.5 ± 3.2</td>
<td>6.9 ± 2.9‡</td>
<td>6.7 ± 2.9‡</td>
<td>7.2 ± 2.8‡</td>
</tr>
</tbody>
</table>

Abbreviations: LDL-C, low-density lipoprotein cholesterol; MCI, mild cognitive impairment. SI conversion factor: To convert LDL-C to millimoles per liter, multiply by 0.0259.

*Data are presented as number (percentage) of persons or mean ± SD. Persons without MCI are the reference for statistical testing. †P < .05. ‡P < .001.

Table 3. HRs and 95% CIs Relating Diabetes to MCI, Amnestic MCI, and Nonamnestic MCI*

<table>
<thead>
<tr>
<th>MCI Cases (Rate)</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>All-cause MCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>241 (7.2)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>93 (9.4)</td>
<td>1.4 (1.1-1.8)</td>
<td>.007</td>
</tr>
<tr>
<td>Amnestic MCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>117 (3.5)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>43 (4.4)</td>
<td>1.4 (1.0-1.9)</td>
<td>.05</td>
</tr>
<tr>
<td>Nonamnestic MCI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>124 (3.7)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>50 (5.1)</td>
<td>1.4 (1.0-1.9)</td>
<td>.04</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio; MCI, mild cognitive impairment. *Model 1 is adjusted for age and sex; model 2 is also adjusted for ethnic group, years of education, and APOE ε4; and model 3 is also adjusted for hypertension, low-density lipoprotein cholesterol level, current smoking, heart disease, and stroke. Rates are per 100 person-years.

Diabetes was associated with a higher risk of incident all-cause MCI in a population with a high prevalence of this disorder. It was also related to a higher risk of amnestic MCI after adjustment for vascular risk factors, heart disease, and stroke, but the relation to nonamnestic MCI was attenuated after adjustment for these covariates.

Amnestic MCI has been described as a transitional stage between normal cognition and AD. Amnestic MCI may be related to cerebrovascular disease or other cognitive disorders and does not predict the onset of AD. Diabetes is related to a higher risk of AD and amnestic MCI through direct mechanisms, affecting the amyloid accumulation that is the putative culprit of AD, or indirect mechanisms, namely cerebrovascular disease, which is also related to a higher risk of AD. Hyperinsulinemia, which can precede and accompany diabetes, may disrupt brain amyloid clearance by means of the insulin degrading enzyme. Another potential mechanism is the generation of advanced products of glycosylation. We also expected that it would be related to a higher risk of nonamnestic MCI, which is more likely to be related to vascular cognitive syndromes. Diabetes could be related to a higher risk of AD and amnestic MCI through direct mechanisms, affecting the amyloid accumulation that is the putative culprit of AD, or indirect mechanisms, namely cerebrovascular disease, which is also related to a higher risk of AD. Hyperinsulinemia, which can precede and accompany diabetes, may disrupt brain amyloid clearance by means of the insulin degrading enzyme. Another potential mechanism is the generation of advanced products of glycosylation.
was appreciably attenuated and became nonsignificant after adjustment for stroke and vascular risk factors, suggesting that cerebrovascular disease may mediate the relation between diabetes and nonamnestic MCI.

Our findings have alternative explanations. Diabetes is more prevalent in African American, Hispanic, and lower socioeconomic groups. The risk of AD is also higher in African American and Hispanic populations and in persons with lower educational level; thus, confounding by ethnic group and socioeconomic status could contribute to our results. We adjusted for ethnic group and years of education without an appreciable change in our results for amnestic MCI. Bias related to the selection of an older cohort of community-dwelling survivors is also possible. Finally, it is possible that our results are explained by chance. However, our findings are consistent with published work relating diabetes to AD in the context of biologically plausible mechanisms.

The prevalence of diabetes was appreciably higher in our study compared with others that have examined the association between diabetes and cognitive impairment, which may raise the issue of sampling bias. However, the high prevalence of diabetes in our study is explained by the fact that it is twice as high in African American and Hispanic elderly persons, who constituted 77.5% of our sample. The prevalence of self-reported diabetes has increased at a 3-fold faster rate in minority compared with white populations. Thus, the high prevalence of diabetes in our sample would be expected in the elderly population of New York City and is in line with national estimates from the national surveys. However, most data on Hispanic populations from national surveys pertain to Mexican Hispanic populations. Virtually all of our Hispanic population is Caribbean Hispanic, mostly from the Dominican Republic, and our study is one of the few sources of information on diabetes prevalence in this population. One of the consequences of the higher prevalence of diabetes in African American and Hispanic people is that the risk of MCI attributable to diabetes in these groups is approximately twice that of non-Hispanic white populations, underscoring the importance of diabetes as a risk factor for MCI particularly in African American and Hispanic elderly populations.

The main limitation of our study is the ascertainment of diabetes by self-report. We did not have measures of glycemia and could not ascertain undiagnosed diabetes or glucose intolerance. Had we defined diabetes by self-report and fasting glycemia, our estimates of the prevalence of diabetes would have been higher than we report. Thus, it is likely that our results are biased toward the null hypothesis and that our findings underestimate the true association between diabetes and MCI.

Our results provide further support to the potentially important independent role of diabetes in the pathogenesis of AD. Diabetes may also be a risk factor for nonamnestic forms of MCI and cognitive impairment, but our analyses need to be repeated in a larger sample.

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Author Contributions: Study concept and design: Luchsinger. Acquisition of data: Luchsinger, Manly, and Mayeux. Analysis and interpretation of data: Luchsinger, Reitz, Patel, and Tang. Drafting of the manuscript: Luchsinger, Reitz, Patel, and Tang. Critical revision of the manuscript for important intellectual content: Luchsinger, Manly, and Mayeux. Statistical analysis: Luchsinger and Tang. Obtained funding: Luchsinger, Manly, and Mayeux. Administrative, technical, and material support: Mayeux.

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