White Matter Lesions Are Prevalent but Differentially Related With Cognition in Aging and Early Alzheimer Disease

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Background: White matter lesions (WMLs) are prevalent in nondemented aging and in Alzheimer disease (AD). Their relationship with cognition in the earliest stages of AD is unknown.

Objective: To assess the relationship between WMLs and cognition in nondemented aging and in early-stage AD.

Design: Cross-sectional study.

Setting: Alzheimer Disease Research Center, St Louis, Mo.

Participants: Participants were nondemented (n=88) or had very mild (n=48) or mild (n=20) AD.

Main Outcome Measures: Regression coefficients for deep WMLs and periventricular WMLs (PVWMLs) as predictors of cognition, after controlling for age, educational achievement, brain atrophy, and infarctlike lesions.

Results: White matter lesions were present in nondemented aging and in early-stage AD, with no group differences in deep WML burden and a modest PVWML burden increase in the AD group. The prevalence of infarctlike lesions was equivalent between groups. Age and hypertension were related to deep WML burden and PVWML burden. Deep WML burden and PVWML burden were associated with reduced global cognition in AD but not in nondemented aging. A PVWML × AD status interaction for global cognition suggests that the relationship between PVWMLs and cognition is modified by AD. In AD, global cognitive reductions were related to impairments in visual memory, processing speed, and executive function.

Conclusions: White matter lesions are prevalent in nondemented aging and in early-stage AD, and their presence influences cognitive impairment in the earliest stages of AD. Individuals with early-stage AD may be more vulnerable to the cognitive effect of WMLs than nondemented aging individuals with similar WML burden.

Arch Neurol. 2005;62:1870-1876
We examined WMLs in a sample of nondemented aging control subjects vs subjects with early-stage AD to determine the relative contribution of WMLs to the cognitive symptoms of early-stage AD. We also assessed whether the WML burden was increased in subjects with early-stage AD compared with nondemented aging controls.

**METHODS**

**PARTICIPANTS**

Participants were enrolled in the Washington University Memory and Aging Project and underwent brain magnetic resonance imaging between June 15, 2000, and August 15, 2003. Recruitment was based on media appeals for healthy and cognitively impaired individuals. Participants were nondemented (Clinical Dementia Rating [CDR] 0) or had a clinical diagnosis of AD in the very mild (CDR 0.5) or mild (CDR 1) dementia stage; participants who had a CDR 0.5 or CDR 1 together represent early-stage AD. At study enrollment, participants were free of non-AD disorders that could potentially cause dementia such as major depression, clinical history of stroke, Parkinson disease, and brain trauma. Twelve participants were excluded because of incomplete imaging protocols. Two participants were excluded because of the incidence of symptomatic infarctlike lesions during their longitudinal evaluation. Symptomatic infarctlike lesions were defined as the collateral source’s report of a clinical stroke or transient ischemic attack and neuroimaging evidence of an infarctlike lesion in an appropriate territory to explain the clinical symptoms. One hundred fifty-six participants were included in the study.

**CLINICAL ASSESSMENT**

The status of nondemented aging vs early-stage AD was based on clinical methods, without reference to psychometric performance. Experienced clinicians conducted semistructured interviews with each participant and with a collateral source who was knowledgeable about the participant. Diagnostic criteria for AD required the gradual onset and progression of impairment in memory and in at least 1 other cognitive and functional domain, comparable to standard diagnostic criteria for probable AD. These criteria have been validated and have a diagnostic accuracy for AD of 93%. In addition, longitudinal investigations have demonstrated that subjects with early-stage AD predictably progress to worse stages of cognitive impairment and that neuropathological examination of even CDR 0.5 AD brains overwhelmingly reveals AD pathologic features. A comprehensive health history was obtained from the collateral source and included the presence or a history of hypertension, stroke, or transient ischemic attack; diabetes mellitus; heart disease; and tobacco use. Trained registered nurses measured blood pressure at each annual visit using a manual cuff on the right arm or the left arm. The presence of apolipoprotein E alleles was determined for 132 participants (76 nondemented participants and 56 participants with early-stage AD) using restriction enzyme isotyping.

**NEUROPSYCHOLOGICAL EVALUATION**

An annual psychometric battery was administered to all participants approximately 2 weeks after the clinical assessment. This battery included the MMSE, Short Blessed Test, Trail-Making Test (A and B), Boston Naming Test, Crossing-off, Benton Visual Retention Test (forms C and D), Wechsler Memory Scale Logical Memory (immediate and delayed), Wechsler Memory Scale Associate Memory, Wechsler Memory Scale Digit Span Backward, Wechsler Adult Intelligence Scale–Revised Information, Wechsler Adult Intelligence Scale–Revised Block Design, Wechsler Adult Intelligence Scale–Revised Digit Symbol, and Word Fluency (letters s and p). A principal components analysis of these measures in a sample of 82 nondemented older adults produced a single factor accounting for 34% of the variance. Cognitive factor scores for the present sample were computed and standardized using the weights, means, and standard deviations from the earlier sample of 82 nondemented older adults. The cognitive factor score broadly assesses cognition and is minimally susceptible to floor or ceiling effects. The MMSE was used as a secondary measure of global cognitive function. Psychometric test results were not used in the clinical diagnosis or severity staging of dementia.

**NEUROIMAGING**

All imaging was performed using a 1.5-T vision scanner (Siemens, Erlanger, Germany). Four $1 \times 1 \times 1.25$-mm T1-weighted (MP-RAGE) images were acquired in each individual (repetition time, 9.7 milliseconds; echo time, 4 milliseconds; flip angle, 10°; inversion time, 20 milliseconds; and delay time, 200 milliseconds). In addition, T2-weighted images were acquired using a turbo spin-echo sequence (repetition time, 6150 milliseconds; and echo time, 15 milliseconds), providing data at $1 \times 1 \times 2$-mm resolution. Proton density imaging was not performed. All image data were mutually coregistered, transformed to the atlas space of Talairach and Tournoux, and resampled to 1-mm$^3$ voxels as previously described. Two raters (J.M.B. and J.A.C.) blinded to dementia status, age, and clinical information assessed deep WMLs (DWMLs), periventricular WMLs (PVWMLs), and infarctlike lesions (Figure 1). White matter lesions were assessed using methods by Scheltens et al. White matter lesions were defined as hypointensity on T2-weighted images with corresponding T1-weighted hypointensity clearly discernible from the background. Periventricular WMLs were defined as WMLs located adjacent to the ventricle, while all other subcortical WMLs were considered DWMLs. Deep WMLs were rated semiquantitatively on a scale ranging from 0 to 6 in frontal, parietal, temporal, and occipital lobes. Total DWML burden represents the sum of the 4 regions (range, 0-24). Using these methods, interrater and intrarater intraclass coefficients exceeded 0.78. Periventricular WMLs were rated in the left and right frontal horns, posterior horns, and ventricular bodies on a semiquantitative scale ranging from 0 to 3. Each region’s PVWML score...
is the sum of the left-sided and right-sided scores, for a total ranging from 0 to 6. The total PVWML score represents the sum of the 3 regions (range, 0-18). Using these methods, interrater and intrarater intraclass coefficients exceeded 0.90. Infarctlike lesions were defined as nonmass defects greater than 3 mm in diameter with signal characteristics isointense to cerebrospinal fluid intensity on all sequences. We are developing and testing methods of automated quantification of WMLs. Our semiquantitative assessments will serve to validate these automated measures. Each rater recorded the number, size, and location of infarctlike lesions. A single rater (J.M.B.) blinded to all clinical information subsequently reviewed all suspected infarctlike lesions. Perivascular spaces were excluded as infarctlike lesions based on location, size, shape, and absence of a hyperintense border. Given the potential to incorrectly classify infarctlike lesions and perivascular spaces, we use the term infarctlike lesions rather than infarcts throughout the article. Normalized whole-brain volume was estimated by using the gray and white voxels—all voxels ratio in the atlas-registered brain mask based on a validated open-source segmentation algorithm.

### STATISTICAL ANALYSIS

Differences in continuous demographic and imaging variables were determined using t tests. Mann-Whitney U test was used to compare categorical frequency distributions. Spearman rank correlations tested for associations between neuroimaging measures and clinical variables. Linear regression analyses were used to determine the effect of WML burden on cognitive performance measures after controlling for the effects of age, educational achievement, brain atrophy (normalized whole-brain volume), and presence of infarctlike lesions.

## RESULTS

### PARTICIPANT CHARACTERISTICS

Table 1 gives the demographic, clinical, and neuroimaging features of the 156 individuals in the study, including 88 nondemented aging participants and 68 participants with early-stage AD (48 were very mildly demented and 20 were mildly demented). There were no significant differences in age or sex between the nondemented aging and AD groups, although a trend was observed for more women in the nondemented aging group. The AD group had fewer years of formal education, had elevated systolic blood pressure, and were more likely to have an apolipoprotein E genotype than the nondemented aging group. No differences were observed in the histories of hypertension, stroke, diabetes mellitus, heart disease, tobacco use, or use of a lipid-lowering agent. The mean MMSE score for the AD group was 24.2.

### WML BURDEN

Periventricular WML burden was modestly higher in the AD group (Table 1 and Figure 2). Deep WML burden did not differ between the groups. Adjusting for age, sex, education, and brain atrophy did not change the results. The overall infarctlike lesion prevalence in the cohort was 42.3% and was comparable between the 2 groups.

Figure 3 shows the similar relationship between age and WMLs in the nondemented aging (DWML $r=0.26$ and PVWML $r=0.42$) and AD (DWML $r=0.27$ and PVWML $r=0.40$) groups (DWML $P<.05$ and PVWML $P<.001$ for both groups). Deep WML and PVWML burdens were related to a history of hypertension (DWML mean±SD burden of 13.7±3.6 in individuals with hypertension vs 12.2±3.0 without hypertension, $P<.01$; and PVWML burden of 9.3±4.9 with hypertension vs 7.7±3.8 without hypertension, $P<.05$) but not sex, heart disease, apolipoprotein E genotype, or use of a lipid-lowering agent. A history of diabetes mellitus was associated with increased DWML burden (mean±SD DWML burden of 14.1±1.9 for subjects with diabetes mellitus vs 12.6±3.5 for nondiabetics), although this relationship remained only a trend ($P=.09$) after controlling for

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Table 1. Demographic, Clinical, and Neuroimaging Features

<table>
<thead>
<tr>
<th>Feature</th>
<th>Nondemented Aging ($n = 88$)</th>
<th>Early-Stage Alzheimer Disease ($n = 68$)</th>
<th>$P$ Value</th>
<th>Total Cohort ($N = 156$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>76.9 ± 8.2</td>
<td>77.4 ± 7.1</td>
<td>.68</td>
<td>77.2 ± 7.7</td>
</tr>
<tr>
<td>Female sex</td>
<td>62 (70.5)</td>
<td>38 (55.9)</td>
<td>.06</td>
<td>100 (64.1)</td>
</tr>
<tr>
<td>Educational achievement, y</td>
<td>14.6 ± 2.9</td>
<td>13.3 ± 3.1</td>
<td>&lt;.01</td>
<td>14.0 ± 3.1</td>
</tr>
<tr>
<td>Mini-Mental State Examination score</td>
<td>29.0 ± 1.2</td>
<td>24.2 ± 3.8</td>
<td>&lt;.001</td>
<td>26.9 ± 3.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35 (39.8)</td>
<td>28 (41.2)</td>
<td>.95</td>
<td>63 (40.4)</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>135.8 ± 19.2</td>
<td>143.0 ± 21.1</td>
<td>&lt;.05</td>
<td>138.9 ± 20.3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>72.2 ± 10.3</td>
<td>74.4 ± 10.4</td>
<td>.22</td>
<td>73.2 ± 10.4</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10 (11.4)</td>
<td>6 (8.8)</td>
<td>.61</td>
<td>16 (10.3)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>30 (34.1)</td>
<td>24 (35.3)</td>
<td>.82</td>
<td>54 (34.6)</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>36 (40.9)</td>
<td>30 (44.1)</td>
<td>.84</td>
<td>66 (42.3)</td>
</tr>
<tr>
<td>Apolipoprotein E genotype†</td>
<td>21/76 (27.6)</td>
<td>31/56 (55.4)</td>
<td>&lt;.001</td>
<td>52 (39.4)</td>
</tr>
<tr>
<td>Lipid-lowering agent</td>
<td>26 (29.5)</td>
<td>12 (17.6)</td>
<td>.09</td>
<td>38 (24.4)</td>
</tr>
<tr>
<td>Deep WML burden‡</td>
<td>12.4 ± 3.0</td>
<td>13.3 ± 3.7</td>
<td>.12</td>
<td>12.8 ± 3.4</td>
</tr>
<tr>
<td>Periventricular WML burden‡</td>
<td>7.5 ± 4.2</td>
<td>9.5 ± 4.6</td>
<td>&lt;.01</td>
<td>8.4 ± 4.5</td>
</tr>
<tr>
<td>Infarctlike lesion prevalence</td>
<td>36 (40.9)</td>
<td>30 (44.1)</td>
<td>.69</td>
<td>66 (42.3)</td>
</tr>
</tbody>
</table>

Abbreviation: WML, white matter lesion.

*Data are given as mean ± SD or as number (percentage) unless otherwise indicated.
†Apolipoprotein E genotype represents subjects with 1 or more alleles.
‡Semiquantitative burden, with higher scores representing more WMLs.

hypertension. Using Spearman rank correlation analyses, systolic and diastolic blood pressures were not associated with DWML or PVWML burden. Deep WML and PVWML burdens were highly correlated ($r=0.64$, $P<.001$).

**WMLs AND COGNITION**

Table 2 summarizes the relationship between WMLs and global cognition in nondemented aging and early-stage AD after adjusting for confounding variables of age, educational achievement, brain atrophy, and infarctlike lesions. In the AD group, DWMLs and PVWMLs were related to the cognitive factor score, the primary measure of global cognition. Adding hypertension and apolipoprotein E genotype to the model did not change the results. This relationship between WMLs and cognition was absent in the nondemented aging group. A PVWMLs × AD status interaction effect was present for the cognitive factor score ($P<.01$), indicating that the relationship between PVWMLs and cognition is different across groups (Figure 4). This interaction remained present after adjusting for age, education, brain atrophy, and infarctlike lesions ($P<.01$). There was no interaction effect for DWMLs × AD status for the cognitive factor score. Performance on secondary measures of global cognition, the MMSE and the Short Blessed Test, was related to PVWMLs but not DWMLs in participants with AD.

Given that the cognitive factor score combines performance on multiple psychometric tasks, we further examined the relationship between WMLs and performance on specific cognitive tasks (Table 2). Results of these analyses indicate that the observed relationship between overall global cognitive impairment and WMLs in early-stage AD was driven primarily by reductions in visual memory, processing speed, and executive function. In nondemented aging, PVWMLs were modestly associated with reduced associative memory and processing speed (Crossing-off), although multiple comparisons increase the risk of spurious associations. In nondemented aging, deep WMLs were not associated with performance on any measures.

**COMMENT**

Our results suggest that WMLs are prevalent in nondemented aging and in early-stage AD and that the earliest clinical stages of AD are influenced by the presence of...
WMLs, independent of brain atrophy and infarctlike lesions. The cross-sectional nature of our study limits the ability to infer causality, but the results suggest that in individuals in the early stages of AD may be more vulnerable to the cognitive influence of WMLs than nondemented aging individuals. Pathological studies demonstrate that AD and vascular-related lesions interact to increase the likelihood of expressing clinically significant cognitive decline. Our results conceptually replicate and extend these pathological observations by providing neuroimaging evidence suggesting that the co-occurrence of AD and vascular-related lesions is associated with greater cognitive impairment than either condition alone. The most parsimonious explanation is that WMLs are distinct from pathological changes associated with AD but, when combined with AD pathological changes, increase the level of cognitive impairment.

Table 2. Relationship Between Global Cognition and White Matter Lesions (WMLs)*

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nondemented Aging</th>
<th>Early-Stage Alzheimer Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deep WMLs</td>
<td>Periventricular WMLs</td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive factor score</td>
<td>−.12</td>
<td>−.09</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>.07</td>
<td>.13</td>
</tr>
<tr>
<td>Short Blessed Test</td>
<td>.07</td>
<td>.07</td>
</tr>
<tr>
<td>Specific cognitive tasks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Logical Memory, immediate</td>
<td>−.12</td>
<td>−.10</td>
</tr>
<tr>
<td>Logical Memory, delayed</td>
<td>−.13</td>
<td>−.08</td>
</tr>
<tr>
<td>Associate Memory</td>
<td>.18</td>
<td>.32†</td>
</tr>
<tr>
<td>Digit Span Backward</td>
<td>.01</td>
<td>−.11</td>
</tr>
<tr>
<td>Benton Visual Retention Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Form C</td>
<td>.02</td>
<td>.10</td>
</tr>
<tr>
<td>Form D</td>
<td>−.01</td>
<td>.14</td>
</tr>
<tr>
<td>Trail-Making Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>.20</td>
<td>.03</td>
</tr>
<tr>
<td>B</td>
<td>.11</td>
<td>.23 (P = .06)</td>
</tr>
<tr>
<td>Crossing-off</td>
<td>−.21 (P = .07)</td>
<td>−.27‡</td>
</tr>
<tr>
<td>Word Fluency (letters s and p)</td>
<td>.07</td>
<td>.08</td>
</tr>
<tr>
<td>Animal Naming Test</td>
<td>−.03</td>
<td>.17</td>
</tr>
<tr>
<td>Boston Naming Test</td>
<td>−.12</td>
<td>−.01</td>
</tr>
</tbody>
</table>

*Data are given as standardized β values, representing the correlation of the WML burden with each cognitive measure after adjusting for age, educational achievement, brain atrophy, and infarctlike lesions. P values in parentheses represent trends.

†P<.01
‡P<.05
§P<.001.

The observation that WMLs may differentially modify cognitive impairment in early-stage AD highlights the complex relationship between AD neuropathological changes and vascular-related injury. Most reports attempt to describe homogeneous AD or vascular dementia syndromes. However, the clinical and neuropathological boundaries of the 2 entities often overlap. Alzheimer disease and vascular-related injury coexist at autopsy in up to 34% of the patients with dementia. Strokes alone rarely lead to full-blown dementia but are associated with an increased risk of vascular dementia and AD. In addi-
tion, a valid biomarker of AD neuropathological changes, hippocampal volume, predicts the development of post-stroke dementia and is the most predictive magnetic resonance imaging correlate of cognitive function in participants with subcortical ischemic vascular disease. Our data suggest that vascular dementia criteria requiring the combined presence of cognitive impairment and cerebrovascular disease may introduce a systematic selection bias for individuals most vulnerable to the cognitive effect of vascular-related injury, such as those with concomitant early neuropathological changes of AD.

The differential relationship between WMLs and cognition in nondemented aging and in early-stage AD may be related to the phenomenon of cognitive reserve. The theory of cognitive reserve postulates the existence of protective factors to account for the observation that some individuals are resilient to the clinical expression of brain lesions, while others are not. Proposed markers of cognitive reserve include higher education levels, occupation, brain size, and functional imaging measures. The presence of early-stage AD neuropathological changes in the brain may reduce the brain’s ability to compensate for the presence of WMLs and, in turn, accentuate the relationship between WMLs and cognition.

Inconsistencies in the literature regarding the association between WMLs and cognition are in part related to differences in study methods (ie, WML assessment and patient characteristics), as well as differences in data analysis. For instance, in our primary analysis (Table 2), the volumetric measure of brain atrophy was comparable to WMLs in predicting general cognition (brain atrophy $\beta = .39$ in the DWML model vs $\beta = .36$ in the PVWML model). This seems inconsistent with recent findings that hippocampal and gray matter volumes are stronger predictors of cognition than WMLs. That report, however, differed from ours because it assessed a cohort combining nondemented subjects and cognitively impaired individuals with subcortical ischemic vascular disease, while our primary analysis was confined to single groups of subjects with nondemented aging or early-stage AD. Combining our non-demented aging and AD groups (data not shown), we found similar results, with whole-brain atrophy as the strongest predictor of cognition ($\beta = .50$), while WML associations were weaker (DWML $\beta = -.27$ and PVWML $\beta = -.30$) ($P < .001$ for all). Therefore, well-defined differences in brain volume between controls and subjects with AD are likely responsible in part for the greater explanatory value of volumetric measures with cognition when analyses are conducted on combined control and AD groups. Conversely, confining the analysis to either group (ie, controls or AD) may result in reduced variability that might attenuate the demonstration of structural-functional relationships. Nevertheless, WML burden appears to be inversely related to cognitive performance, and our data suggest that this relationship is accentuated in AD.

This study has several limitations. The cross-sectional observational nature of the study limits the ability to infer causality. We plan to extend our findings with longitudinal analyses to determine the relative effect of WML progression on cognition. The sample consists of research participants who may not be representative of the general population. The imaging protocol did not include proton density scans, complicating the differentiation of infarctlike lesions from perivascular spaces. The slightly higher prevalence of infarctlike lesions in our sample (42.3%) compared with that reported in the literature ($\leq 33\%$) may be related in part to possible inclusion of perivascular spaces as infarctlike lesions. We subjected all suspected infarctlike lesions to a second level of review, and our results are consistent with the literature in terms of clinical associations (ie, hypertension). In addition, our imaging protocol provides high-resolution images that increase the sensitivity of detecting abnormal signals. Any difficulty in distinguishing perivascular spaces from infarctlike lesions or WMLs would be likely to attenuate associations with cognition. Furthermore, our T2-weighted sequence has a long repetition time, which may affect our ability to detect the full spectrum of WMLs. As in any study in which multiple analyses are performed on the same data, there is an increased chance of type I errors and spurious observations. The probability of a type I error is most likely for tests resulting in $P$ values that are close to .05, and the likelihood decreases with decreasing $P$ values. Last, we used clinical methods as the gold standard for determining a diagnosis of AD. Although these clinical criteria have been validated and are highly accurate, they remain imperfect in predicting pathological changes in AD.

Accepted for Publication: June 3, 2005.

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Author Contributions: Study concept and design: Burns and Buckner. Acquisition of data: Burns, Church, and Buckner. Analysis and interpretation of data: Burns, Church, Johnson, Xiong, Marcus, Fotenos, Snyder, Morris, and Buckner. Drafting of the manuscript: Burns. Critical revision of the manuscript for important intellectual content: Burns, Church, Johnson, Xiong, Marcus, Fotenos, Snyder, Morris, and Buckner. Statistical analysis: Burns, Johnson, and Xiong. Obtained funding: Morris and Buckner. Administrative, technical, and material support: Church, Marcus, Fotenos, Snyder, Morris, and Buckner. Study supervision: Burns, Morris, and Buckner.

Funding/Support: This study was supported by grant T32 NS070521 from the National Institutes of Health, Bethesda, Md (Dr Burns); by the Olin Fellowship for Women, Cambridge, Mass (Ms Church); by grants P01 AG03991 and P50 AG05681 from the National Institute on Aging, Bethesda (Dr Morris); by the Howard Hughes Medical Institute, Chevy Chase, Md (Dr Buckner); by the James S. McDonnell Foundation, St Louis (Dr Buckner); and by the Alzheimer’s Association, Chicago, Ill.

Acknowledgment: We thank Amy Sanders, Laura Girton, Jamie Parker, and Susan Larson for assistance with data collection, and Elizabeth Grant for assistance with data management. We also thank Martha Storandt for her valuable input, Alison Goate and the Washington University Alzheimer’s Disease Research Center Genetics Core for the apolipoprotein E data, as well as the Clinical Core for clinical and psychometric assessments.
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