Magnetic Resonance Imaging White Matter Hyperintensities and Brain Volume in the Prediction of Mild Cognitive Impairment and Dementia

Eric E. Smith, MD, MPH, FRCPC; Svetlana Egorova, PhD; Deborah Blacker, MD, ScD; Ronald J. Killiany, PhD; Alona Muzikansky, MS; Bradford C. Dickerson, MD; Rudolph E. Tanzi, PhD; Marilyn S. Albert, PhD; Steven M. Greenberg, MD, PhD; Charles R. G. Guttmann, MD

Objective: To determine whether magnetic resonance imaging (MRI) white matter hyperintensities (WMH), whole-brain atrophy, and cardiovascular risk factors predict the development of cognitive decline and dementia.

Design: Subjects were recruited into this prospective cohort study and followed for incident cognitive decline for mean (SD) 6.0 (4.1) years. Magnetic resonance imaging dual-echo sequences, obtained at baseline, were used to determine the volume of WMH and the brain parenchymal fraction (BPF), the proportion of the intracranial cavity occupied by brain. White matter hyperintensity volume was analyzed as the percentage of intracranial volume (WMHr); “high WMH” was defined as a WMHr more than 1 SD above the mean.

Setting: General community.

Patients: Volunteer sample consisting of 67 subjects with normal cognition and 156 subjects with mild cognitive impairment (MCI).

Main Outcome Measures: Time to diagnosis of MCI (among those with normal cognition at baseline) or time to diagnosis of dementia, either all-cause or probable Alzheimer disease (AD) (among those with MCI at baseline). Cox proportional hazards models were used for multivariable analysis.

Results: High WMH was a predictor of progression from normal to MCI (adjusted hazard ratio [HR], 3.30; 95% confidence interval [CI], 1.33-8.17; \( P = .01 \)) but not conversion from MCI to all-cause dementia. Conversely, BPF did not predict progression from normal to MCI but did predict conversion to dementia (adjusted HR, 1.10 for each 1% decrease in BPF; 95% CI, 1.02-1.19; \( P = .02 \)). When conversion to AD dementia was considered as the outcome, BPF was likewise a predictor (adjusted HR, 1.16 for each 1% decrease in BPF; 95% CI, 1.08-1.24; \( P < .001 \)), but high WMH was not. Past tobacco smoking was associated with both progression from normal to MCI (adjusted HR, 2.71; 95% CI, 1.12-6.55; \( P = .03 \)) and conversion to all-cause dementia (adjusted HR, 2.08; 95% CI, 1.13-3.82; \( P = .02 \)), but not AD dementia.

Conclusions: These findings suggest that WMH are associated with the risk of progressing from normal to MCI. In persons whose cognitive abilities are already impaired, BPF predicts the conversion to dementia.

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Several lines of evidence suggest that so-called “silent” cerebrovascular disease is associated with cognitive impairment and may promote the development of dementia even in the absence of symptomatic stroke. Magnetic resonance imaging (MRI) abnormalities attributed to small-vessel disease, such as lacunar infarction and extent of white matter hyperintensities (WMH), have been associated with decreased brain volume, cognitive impairment, and cognitive decline, and an increased risk of dementia. Epidemiologic studies have shown that risk factors for vascular disease, including hypertension and diabetes, are also risk factors for dementia. The association of vascular risk factors with cognitive decline is not solely because of an increased risk of vascular dementia, but also because of an increased risk of Alzheimer disease (AD). Therefore, it has been suggested that vascular disease may confer an increased vulnerability to AD, either by damaging cortical or subcortical networks leading to decreased “cognitive reserve” or by interacting with the pathological processes of AD.

Because cerebral small-vessel disease has been linked with impaired cognition, we sought to determine whether WMH, a marker of white matter ische-
MCI18 as defined later in this section. The analyses presented were included in the analyses. The study population was in-  

brillation, or diabetes mellitus requiring insulin) were ex- 

have an informant as a collateral source of information. Those  

aces and Stroke–Alzheimer Disease and Related Disorders As-  

National Institute of Neurological and Communicative Dis-  

and Stroke–Association Internationale pour la Recherche´e t  

criteria from the National Institute of Neurological Disorders  

able AD was present. Vascular dementia was diagnosed using  

memory performance at baseline (34/156, 22%), defined as a  

minority of our subjects with MCI had poor objective  

objective memory performance below a defined threshold. A  

annual clinical follow-up visits.

in this article were performed using 67 subjects with normal  

as previously described.18,20 Apolipoprotein E (APOE) geno- 

types were determined using a previously described method.21  

A consensus diagnosis was assigned to participants with cogni- 

tive and functional impairment, incorporating clinical his- 

tory, medical records, laboratory evaluations, and neuroimag- 

studies. Incident all-cause dementia was diagnosed in accor- 

dance with criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).22 For subjects with  

MCI19 as defined later in this section. The analyses presented in  

this article were performed using 67 subjects with normal  

cognition and 156 subjects with MCI at baseline, who under- 

went MRI with dual-echo sequences and had 1 or more an- 

nual clinical follow-up visits.

CLINICAL AND GENETIC ASSESSMENTS

A semistructured interview by an experienced clinician was used to evaluate the subjects at baseline and at each subsequent year as previously described.18,20 Apolipoprotein E (APOE) genotypes were determined using a previously described method.21

A consensus diagnosis was assigned to participants with cognitive and functional impairment, incorporating clinical history, medical records, laboratory evaluations, and neuroimaging studies. Incident all-cause dementia was diagnosed in accordance with criteria from the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition).22 For subjects with incident all-cause dementia, we next applied criteria from the National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA)23 to determine whether probable AD was present. Vascular dementia was diagnosed using criteria from the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l’Enseignement en Neurosciences (NINDS-AIREN).24

Nondemented individuals with CDR 0.5 were operationally defined as MCI. Therefore, in contrast with other studies, such as Petersen et al,25 our criteria for MCI did not require objective memory performance below a defined threshold. A minority of our subjects with MCI had poor objective memory performance at baseline (34/156, 22%), defined as a score on the delayed free recall measure of the California Verbal Learning Test that was more than 1.0 SD below the age-, sex-, and education-adjusted mean of our normal population.

CARDIOVASCULAR RISK FACTORS

We calculated each subject's individual stroke risk at baseline according to the updated, modified Framingham Stroke Risk Profile (FSRP).26 This prediction rule uses information on sex, age, systolic blood pressure, history of cardiovascular disease, left ventricular hypertrophy (determined from electrocardiogram), cigarette smoking, atrial fibrillation, and diabetes to estimate the individual probability of stroke within the next 10 years. For 4 subjects, we used the systolic blood pressure at the first follow-up visit because the systolic blood pressure at the baseline visit was not recorded. One subject did not have a systolic blood pressure measurement at either the first or second visit and was therefore excluded from analyses of FSRP.

MRT MEASUREMENTS

Subjects underwent MRI on either of two 1.5-T scanners (Signa, General Electric Medical Systems, Milwaukee, Wisconsin). A dual-echo sequence, yielding proton density–weighted and T2-weighted images of the whole head, was used for segmentation of volumes of WMH, gray matter, white matter, and cerebrospinal fluid. The sequence parameters were repetition time, 3000 milliseconds; echo time 1, 80 milliseconds (for proton density–weighted images); echo time 2, 80 milliseconds (for T2-weighted images); field of view, 24 cm; slice thickness, 3 mm interleaved; and matrix, 256 × 192. The half-Fourier tech- nique was applied to reduce imaging time to 11 minutes 36 sec- onds. Segmentation of the intracranial cavity, WMH, white matter, gray matter, and cerebrospinal fluid was performed using the previously described segmentation pipeline TDS + (template-driven segmentation “plus”).27 In brief, this methodology combines expectation-maximization tissue segmentation, template-driven segmentation, and partial volume effect correction algorithms to discriminate image voxels into predefined classes.27-29 High reproducibility and accuracy for this method has previously been reported.27,30,31

To account for variation in head size, WMH volume was ana- lyzed as the percentage of the intracranial cavity occupied by WMH (WMHr). Brain parenchymal fraction was calculated as the percentage of the intracranial cavity occupied by brain tissue.

STATISTICAL ANALYSES

The study population was divided into 2 groups for the pur- pose of analysis: those with normal cognition at baseline and those with MCI at baseline. Among the 26 subjects who pro- gressed from normal cognition to MCI, there were 5 who sub- sequently converted to dementia. Because these subjects did not have MCI at baseline, they were not included in analyses of the conversion from MCI to dementia.

Differences between the groups at baseline were analyzed by Fisher exact test (for categorical variables) or t test (for con- tinuous variables, with the exception of WMHr, which was ana- lyzed by Wilcoxon rank-sum test because of a nonnormal dis- tribution). We then examined baseline characteristics associated with WMHr, BPF, and FSRP by t test, Wilcoxon rank-sum test, Pearson correlation coefficient, or Spearman correlation coefficient, as appropriate.

Separate Cox regression models were then constructed to determine the relationship of WMHr, BPF, and FSRP to the like- lihood of progression from normal to MCI and from MCI to dementia. Univariate Cox regression models with graphical display by Kaplan-Meier plots were used to determine which can- didate variables were associated with the following outcomes: (1) progression from baseline normal to MCI, (2) conversion
from baseline MCI to all-cause dementia, and (3) conversion from baseline MCI to AD dementia.

Multivariable Cox regression models were then constructed for each of these outcomes. For the analyses of AD dementia, subjects who converted to non-AD dementia were censored at the time of diagnosis of non-AD dementia. The model predictor variables included age, sex, education, APOE genotype, and any other variables associated with the outcome in the univariate analyses (P < .20). Age, education, CDR sum of boxes (CDR-SB), BPF, and FSRP were entered as continuous variables because there was no convincing evidence of a nonlinear relationship with the outcomes. In contrast, neither WMHR nor log-transformed WMHR showed a linear relationship with the hazard of progression from normal to MCI or conversion from MCI to dementia. Only subjects with higher amounts of WMH had an increased hazard ratio. Therefore, WMH was dichotomized, described herein as “high WMH” and “low WMH,” according to whether the log-transformed WMHR was greater than 1 SD above the study population mean.

Baseline characteristics for the 2 study groups are given in Table 1. None of the variables, with the exception of CDR-SB, differed between the groups. Characteristics associated with brain volumes and the FSRP were examined in the whole study population (ie, including those with normal cognition and those with MCI at baseline). The independent predictors of increased WMHR in a linear regression model were increased age (P = .005) and history of hypertension (P = .005). The independent predictors of lower BPF in a linear regression model were increased age (P < .001) and male sex (P < .001). There was little correlation between WMHR and BPF (Spearman r = −0.09, P = .17). Higher FSRP was correlated with increased WMHR (Spearman r = 0.27, P < .001) and decreased BPF (Pearson r = −0.42, P < .001). After controlling for age and sex, which are important elements of the FSRP, the relationship with WMHR remained significant (partial correlation coefficient = 0.26, P < .001), but the relationship with BPF did not (partial correlation coefficient = −0.10, P = .16). Subjects with high WMH as defined in the “Methods” section had an absolute 4% higher 10-year predicted probability of stroke than subjects without high WMH.

PROGRESSION FROM NORMAL TO MCI

Among 67 subjects with normal cognition at baseline, there were 26 who progressed to MCI during a mean (SD) 5.1 (4.0) years of follow-up. There were no subjects with incident strokes. High WMH was a significant predictor of progression (HR, 2.59; 95% CI, 1.07-6.25; P = .03), but BPF was not (HR, 1.03 for each decreased in BPF of 1%; 95% CI, 0.94-1.14; P = .54). Additional univariate predictors of progression to MCI were the absence of an APOE ε2 allele (P = .04) and past smoking (P = .03). The FSRP was not associated with progression from normal cognition to MCI (HR, 1.02 for each 1% increase in 10-year stroke risk; 95% CI, 0.96-1.07; P = .61).

High WMH remained an independent predictor of progression to MCI in a backward elimination model with the additional candidate variables age, sex, years of education, past smoking, and APOE genotype (adjusted HR, 3.30; 95% CI, 1.33-8.17; P = .01) (Table 2 and Figure 1).

CONVERSION FROM MCI TO DEMENTIA

Among 156 subjects with MCI at baseline, there were 54 who converted to dementia during a mean (SD) 6.4 (4.1) years of follow-up. There were 45 with AD dementia and 9 with non-AD dementia. Three subjects with MCI at base-
line subsequently reverted from MCI to normal cognition. Incident stroke during study follow-up occurred in 0 of 45 subjects with AD, 4 of 9 subjects with non-AD dementia, and 11 of 102 subjects who did not convert to dementia. The 4 subjects with incident stroke and dementia all had a clinical diagnosis of presumed vascular dementia based on NINDS-AIREN criteria.

Univariate analyses showed that conversion to all-cause dementia was not predicted by high WMH (HR, 1.26; 95% CI, 0.61-2.59; \(P = .53\)) but was predicted by BPF (HR, 1.16 for each absolute 1% decrease in BPF; 95% CI, 1.08-1.23; \(P < .001\)). Additional predictors of conversion to all-cause dementia were increased age (\(P < .001\)), history of cardiovascular disease (\(P = .06\)), and baseline CDR-SB (\(P < .001\)). The FSRP was associated with conversion from MCI to all-cause dementia (HR, 1.07 for each absolute 1% increase in predicted 10-year stroke risk; 95% CI, 1.03-1.10; \(P < .001\)). Adjustment for age and sex attenuated this association to a trend (adjusted HR, 1.04; 95% CI, 0.99-1.08; \(P = .11\)). Past smoking showed a trend toward an association with conversion to all-cause dementia in bivariate analysis controlling for baseline CDR-SB (HR, 1.67; 95% CI, 0.94-2.96; \(P = .08\)) and was found to be an independent risk factor for dementia in the final model (HR, 2.08; 95% CI, 1.13-3.82; \(P = .02\)) (Table 3). Brain parenchymal fraction remained an independent predictor of conversion to dementia in the final backward elimination model with the candidate variables age, sex, years of education, baseline CDR-SB, APOE genotype, history of cardiovascular disease, and past smoking (adjusted HR, 1.10 for each 1% absolute decrease in BPF; 95% CI, 1.02-1.19; \(P = .02\)) (Figure 2 and Table 3).

Similar results were obtained when the outcome was restricted to the 45 of 54 subjects with dementia diagnosed as probable AD with the exception that past smoking was not a predictor of AD dementia in the multivariable analysis (\(P > .10\)). Brain parenchymal fraction was an independent predictor of AD dementia in the final model (HR, 1.16 for each 1% absolute decrease in BPF; 95% CI, 1.08-1.24; \(P < .001\)).

These data suggest that white matter damage, as measured by the volume of MRI T2 white matter hyperintensities, is a risk factor for progression from normal cognition to MCI but is not a major predictor of subsequent conversion to dementia (Table 2 and Figure 1). Conversely, BPF (a measure of whole-brain atrophy) is not a major predictor of progression from normal cognition to MCI but is a predictor of conversion to both all-cause dementia (Table 3 and Figure 2) and AD dementia. The observed association of WMH with MCI was not due to symptomatic stroke. Taken together, these data suggest that white matter damage, as measured by WMH, predisposes to forms of cognitive impairment that do not meet criteria for dementia.

### Table 2. Predictors of Progression From Normal Cognition to MCI in a Multivariable Modela

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>High WMH</td>
<td>3.30 (1.33-8.22)</td>
<td>.01</td>
</tr>
<tr>
<td>History of smoking</td>
<td>2.71 (1.12-6.55)</td>
<td>.03</td>
</tr>
<tr>
<td>ε2 allele</td>
<td>0.13 (0.02-0.96)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Abbreviations: APOE, apolipoprotein E; high WMH, log-transformed T2-weighted magnetic resonance imaging white matter hyperintensity volume, expressed as a percentage of total intracranial volume, greater than 1 SD above mean; MCI, mild cognitive impairment.

aResults of Cox regression model with backward elimination of predictors of progression to MCI. Eliminated candidate variables (\(P > .10\)) were age, female sex, years of education, and APOE ε4 allele.

### Table 3. Predictors of Conversion From MCI to All-Cause Dementia in a Multivariable Modela

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased BPF</td>
<td>1.10 (1.02-1.19)</td>
<td>.02</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td>3.49 (2.30-5.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age</td>
<td>1.07 (1.02-1.14)</td>
<td>.01</td>
</tr>
<tr>
<td>Education</td>
<td>0.93 (0.85-1.01)</td>
<td>.09</td>
</tr>
<tr>
<td>History of smoking</td>
<td>2.08 (1.13-3.82)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: BPF, brain parenchymal fraction, the proportion of the intracranial cavity occupied by brain; CDR, Clinical Dementia Rating; MCI, mild cognitive impairment.

aResults of Cox regression model with backward elimination of predictors of conversion from MCI to dementia. The hazard ratios represent the increased hazard for each 1-unit increase in that variable. Eliminated candidate variables (\(P > .10\)) were age, female sex, years of education, APOE ε4 allele, and history of cardiovascular disease.

bPer absolute 1% decrease in BPF.
cause dementia or AD dementia. In the Rotterdam study, WMH predicted the conversion from MCI to either all-cause dementia or AD dementia. In some cases, WMH may be less important in the later stages of cognitive decline, when normal cognition transitions to MCI, and may be most important in the early stages of cognitive decline, when MCI worsens into dementia. A potential explanation is that WMH are sufficient to produce mild to moderate cognitive impairment but that an additional process, such as superimposed AD, is necessary for the more severe cognitive and memory impairment that is seen in dementia. Another potential explanation for the finding that WMH did not predict the conversion from MCI to dementia is that WMH-associated cognitive impairment, which has been reported to preferentially involve executive function, may be less likely to meet criteria for dementia because of a relative lack of memory impairment. The relationship between WMH and subtypes of MCI and dementia merits further study.

Whole-brain atrophy, as measured by BPF, did not predict progression from normal cognition to MCI in this study. A previous cross-sectional study found no differences between whole-brain volume in MCI and normal subjects. Prospective cohort studies have shown that higher rates of whole-brain atrophy over time, measured at baseline or longitudinally, are associated with the progression from normal cognition to MCI. Whether baseline whole-brain volume predicted progression to MCI was, however, not reported. Therefore, our findings suggest that a single baseline assessment of brain volume, in contrast to serial assessments, is of low value in the prediction of future MCI.

The conversion from MCI to dementia has been linked to baseline focal atrophy of specific cortical areas, and whole-brain atrophy, and an increased rate of focal and whole-brain atrophy over time. Our data (Table 3 and Figure 2), showing that a single baseline measurement of whole-brain atrophy predicts the conversion from MCI to dementia are therefore consistent with the prior literature.

Several findings from this study suggest that vascular risk factors may play a role in the transition from normal cognition to MCI and from MCI to dementia. A history of smoking was associated with both progression from normal to MCI and conversion from MCI to all-cause dementia but not AD dementia (Table 2 and Table 3). Some, but not all, prior studies have also suggested that smoking may be a risk factor for dementia and AD. The conversion from MCI to all-cause dementia and AD dementia was predicted by the FSRP, a composite measure of stroke risk that has previously been associated with decreased cognitive performance and lower brain volumes. The association between FSRP and incident dementia was mostly dependent, however, on age and sex.

The strengths of this study are the prospective design, relatively large sample size, and community recruitment with less likelihood of referral bias than recruitment from memory clinics. Even so, there are limitations. Study recruitment focused on memory loss; therefore, cognitive impairment in nonmemory domains may be relatively underrepresented. Information was not available on the amount of cumulative prior tobacco smoke exposure; therefore, we are unable to test for a dose response in the relationship of past smoking to cognitive decline. By design, potential study subjects with a history of stroke were excluded; therefore, we cannot make inferences about poststroke cognitive impairment. The exclusion of these subjects, however, allows us to focus more specifically on the impact of microvascular disease and vascular risk factors without confounding by
baseline symptomatic stroke. Our results may not apply to populations with high prevalences of atrial fibrillation or diabetes requiring insulin because such subjects were excluded from our study.

In summary, these findings suggest that white matter damage, attributed to cerebral microvascular disease, and vascular risk factors play a role in cognitive decline even in a population specifically selected to be free of baseline stroke and at relatively low risk for cardiovascular disease. With improved phenotyping of cerebrovascular disease, and the possibility of in vivo quantification of \( \beta \)-amyloid deposition, it may be possible in the future to better discriminate the relative contribution of each to cognitive decline, even in the setting of mixed-type dementia. A better understanding of the contribution of silent cerebrovascular disease is important because, unlike AD, cerebrovascular disease may be preventable with currently available therapies. In addition, awareness of the impact of cerebrovascular disease on cognition may enhance physician and patient compliance with prevention strategies for cardiovascular disease that are already part of recommended clinical practice.

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Correspondence: Eric Smith, MD, MPH, FRCP(C), Massachusetts General Hospital, 175 Cambridge St, Ste 300, Boston, MA 02114 (eesmith@partners.org).

Author Contributions: All the authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Smith, Blacker, Killiany, Tanzi, Albert, and Guttmann. Acquisition of data: Blacker, Albert, and Guttmann. Analysis and interpretation of data: Smith, Egorova, Blacker, Muzikansky, Dickerson, Albert, Greenberg, and Guttmann. Drafting of the manuscript: Smith. Critical revision of the manuscript for important intellectual content: Egorova, Blacker, Killiany, Muzikansky, Dickerson, Tanzi, Albert, Greenberg, and Guttmann. Statistical analysis: Smith, Blacker, Muzikansky, Dickerson, and Greenberg. Obtained funding: Blacker, Killiany, Tanzi, and Albert. Administrative, technical, and material support: Egorova, Tanzi, and Albert. Study supervision: Blacker, Albert, and Guttmann.

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