Several longitudinal population-based studies have suggested that white matter hyperintensities (WMHs) and MRI-defined brain infarcts (BIs) are associated with an increased risk of stroke,\textsuperscript{1-6} dementia,\textsuperscript{7} and death.\textsuperscript{8,9} Some studies observed an association only for certain subtypes of outcomes such as vascular dementia\textsuperscript{10} or certain types of WMH such as periventricular hyperintensities.\textsuperscript{4,11}

The majority of these studies were performed in older individuals over age 65 years.\textsuperscript{2,3,7-11} Furthermore, all studies, except 2,\textsuperscript{6,9} have measured WMH volume (WMHV) using visual semiquantitative rating scales. Finally, only few studies have assessed the relative contribution of WMH and BI to the risk of stroke, dementia, and mortality in elderly people.\textsuperscript{9} Disentangling the relative effects of WMH and BI on these outcomes in middle-aged adults could improve our understanding of the underlying mechanisms and help refine risk prediction.

Our aim was to assess simultaneously the relation of both a quantitative measure of WMHV and the presence of BI with the risk of incident stroke, mild cognitive impairment (MCI), dementia, and death in a middle-aged community-based cohort.
dementia, and mortality in a large community-based sample of middle-aged adults.

Methods

Population

The Framingham Heart Study is a community-based, prospective cohort study that was initiated in 1948 and now comprises 3 generations of participants. The present study includes participants from the intermediate generation, the Framingham Offspring Cohort, comprising 5124 persons examined approximately once every 4 years since enrollment (1971).12

Offspring participants who survived to the seventh examination (1998 to 2001) and had attended at least 1 among the fifth, sixth, or seventh examinations or had moved away from Framingham but continued to be followed up offline were invited to take a neuropsychological test battery (NP) and undergo volumetric brain MRI (1999 to 2005). Among the participants who were invited (n=3623), 2229 participants were available for this study (see flow diagram, Supplemental Figure I; available at http://stroke.ahajournals.org).

Since 2005, all participants included in the ancillary study have been invited to undergo a second NP and MRI. Examinations performed between 2005 and 2007 (n=1694) could be used for the analysis of incident MCI (data from 2008 to 2009 are still being processed at this time).

MRI Scans

MRI techniques used in the Framingham Offspring Study have been described previously.13,14 Briefly, participants were evaluated with a 1- or 1.5-T Siemens Magnetom. Three-dimensional T1 and double-echo proton density and T2 coronal images acquired in 4-mm contiguous slices were performed. All images were transferred to a centralized reading center (University of California–Davis Medical Center) and analyses were performed on QUANTA 6.2, a custom-designed image analysis package operating on a Sun Microsystems Ultra 5 workstation. Semiautomated analysis of pixel distributions based on mathematical modeling of MRI pixel intensity histograms for cerebrospinal fluid and brain matter (white matter and gray matter) were used to determine the optimal threshold of pixel intensity to best distinguish cerebrospinal fluid from brain matter based on methods published previously.15 For segmentation of WMH from other brain tissues, the first and second echo images from T2 sequences were summed and a log-normal distribution was fitted to the summed data. A segmentation threshold for WMH was determined as 3.5 SDs in pixel intensity greater than the mean of the fitted distribution for brain parenchyma.14 WMHV was computed as the ratio of total WMH volume to total intracranial volume using a previously validated method.14 WMHV was not normally distributed and was log-transformed for all analyses. In addition, we created (5-year) age group-specific z-scores, zWMHV, and participants with zWMHV >1 were designated as having extensive WMHV (EXT-WMHV; Figure 1A–B; see Supplemental Table I for age-specific thresholds). BI was defined as an area of abnormal signal intensity in a vascular distribution, at least 3 mm in size with a cerebrospinal fluid density on the subtraction image and, for lesions in the basal ganglia area, distinct separation from the circle of Willis vessels (Figure 1C).13,16 We used size, location, shape, and tissue contrast to distinguish BI from dilated perivascular spaces. Indeed, our analysis method allows for the superimposition of T1, proton density, and T2 images and using this method, vessels can often be seen within perivascular spaces, particularly on T2 images.

Outcomes

Participants have been monitored since 1974 using previously described surveillance techniques for the development of stroke or dementia.17,18 Stroke was defined as an acute-onset focal neurological deficit of presumed vascular etiology lasting ≥24 hours. Ischemic stroke was diagnosed if a focal neurological deficit was documented and the imaging showed no hemorrhage, imaging showed an infarct that correlated with the clinical deficit, or an infarct was documented at autopsy. Dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition,19 and Alzheimer disease (AD) based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association for definite, probable, or possible AD.20

The diagnosis of MCI was based on the results of the NP. We defined 5 domain-specific composite cognitive factors (Supplemental Table II). Participants were defined as having MCI if they were nondenominated and scored ≥1.5 SD below the gender-specific mean of the distribution for ≥1 factor. Amnestic MCI was defined by a score ≥1.5 SD below the mean for factor 1 (verbal memory), factor 2 (visuospatial memory), or both. Incident MCI was defined as new-onset MCI on the second NP in participants without MCI at baseline. Incident amnestic MCI corresponded to new-onset amnestic MCI in participants without amnestic MCI at baseline (this included participants with nonamnestic MCI at baseline who developed a memory deficit during follow-up).

Vascular death was established on review of all available records if the cause of death was deemed most likely to be coronary heart disease (including sudden cardiac death), congestive heart failure, stroke, or any other vascular event and no other cause could be ascribed.21 Cardiovascular death was defined similarly but excluded stroke death.

Definition of Covariates

Vascular risk factors (systolic blood pressure, smoking, diabetes mellitus, and history of cardiovascular disease) were defined as in the Framingham Stroke Risk Profile.22 Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of antihypertensive medication.22 Educational achievement was studied as a 4-class variable (no high school degree; high school degree, no college; some college; college
degree). Participants were categorized according to the presence or absence of ≥1 Apolipoprotein E e4 (ApoEe4) allele.

Statistics
χ² tests for binary variables and t tests for continuous variables were used to compare baseline characteristics between persons with and without EXT-WMHV or BI.

We used multivariable Cox regression adjusted for gender and age at MRI to examine the associations of WMHV, EXT-WMHV, and BI with incident stroke, dementia, and mortality and logistic regression adjusted for gender, age at MRI, education, and interval regression adjusted for gender, age at MRI, education, and interval between first and second NP for the association with incident MCI. When analyzing associations with incident stroke, participants with prevalent stroke were excluded. Similarly, participants with prevalent dementia were excluded when testing associations with incident dementia and participants with prevalent MCI or dementia were excluded when looking at the association with incident MCI.

In secondary analyses, we adjusted for vascular risk factors, for ApoEe4 status in the analyses of cognitive outcomes, and we conducted analyses stratified on gender, age (<60 versus ≥60 years), and hypertension as well as ApoEe4 carrier status for incident MCI (given the small number of events, we did not perform any stratified analysis for incident dementia). To assess whether associations of WMHV or BI with dementia and MCI were mediated by intermediate variables, we ran regression models excluding prevalent stroke and adjusting for interim stroke as a time-varying covariate. Similarly, we ran a regression model excluding prevalent stroke and dementia and adjusting for interim stroke and dementia for the association with mortality. Finally, we tested for the presence of an interaction between WMHV and BI and EXT-WMHV and BI. In the absence of statistical interaction (P<0.05), we ran a multivariable regression model including both WMHV and BI (or EXT-WMHV and BI) as independent variables.

Analyses were performed using Statistical Analyses System software Version 9 (SAS Institute, Cary, NC).

Results
The baseline characteristics of the study population are presented in Table 1. Participants with EXT-WMHV were significantly older and more often had hypertension, prevalent stroke, and MCI. Participants with BI were significantly older and more often had hypertension, diabetes, and stroke. The mean duration of follow-up was 5.6±1.4 years for stroke, 5.9±1.4 years for dementia, and 5.2±1.5 years for mortality and 6.2±1.2 years between the first and last NP evaluation for MCI. During follow-up, 32 participants sustained a stroke (26 ischemic, 5 hemorrhagic, and 1 of unspecified type), 11 participants developed dementia (7 AD, 3 vascular dementia, 1 other), and 97 participants died (21 vascular deaths, of which 3 were stroke deaths). Between the first and second NP, 93 of the 1134 participants without cognitive deficit at baseline developed new-onset MCI, and 93 of the 1344 participants without memory deficit at baseline developed new-onset amnestic MCI. BI was correlated with WMHV (p=0.20, P<0.001) and EXT-WMHV (p=0.14, P<0.001).

Association of WMHV, EXT-WMHV, and BI With Incident Stroke
BI and EXT-WMHV, but not WMHV, were associated with an increased risk of incident stroke (Table 2; Figure 2), especially ischemic stroke (hazard ratio [HR]=3.49, 95% CI: 1.54 to 7.91 for BI and HR=2.97, 95% CI: 1.28 to 6.85 for EXT-WMHV). These associations were independent of vascular risk factors (Table 2) and were unchanged when stratifying on age, gender, and hypertension (data not shown). The associations were stronger for BI compared with EXT-WMHV (Table 2).

Association of WMHV, EXT-WMHV, and BI With Incident Dementia and MCI
WMHV, EXT-WMHV, and BI were all associated with an increased risk of incident dementia, independently of vascular risk factors (Table 2; Figure 3) and of ApoEe4 (data not shown). The results were similar after excluding prevalent stroke and adjusting for interim stroke (Table 2). None of the MRI markers was associated with incident all MCI or amnestic MCI overall (Table 3). There was a significant interaction of EXT-WMHV and WMHV with age (P<0.05), EXT-WMHV and WMHV being associated with an increased risk of amnestic MCI only among participants aged ≥60 (OR=2.47, 95% CI: 1.31 to 4.66 for EXT-WMHV and OR=1.49, 95% CI: 1.14 to 1.97 for WMHV). There was also
a significant interaction of WMHV with gender (P<0.05), WMHV being associated with an increased risk of amnestic MCI only among women (OR = 1.43, 95% CI: 1.06 to 1.93).

**Association of WMHV, EXT-WMHV, and BI With Mortality**

Both WMHV and EXT-WMHV were associated with an increased risk of death (Table 2; Figure 4), especially vascular death (HR = 1.96, 95% CI: 1.31 to 2.92 for WMHV and HR = 4.18, 95% CI: 1.72 to 10.15 for EXT-WMHV) or cardiovascular death (HR = 1.86, 95% CI: 1.20 to 2.89 for WMHV and HR = 3.49, 95% CI: 1.30 to 9.37 for EXT-WMHV). These associations were not attenuated by adjustment for vascular risk factors, exclusion of prevalent stroke and dementia, and adjustment for interim stroke and dementia (Table 2). BI predicted an increased risk of death (Table 2), especially vascular death (HR = 3.42, 95% CI: 1.40 to 8.34) or cardiovascular death (HR = 2.76, 95% CI: 1.02 to 7.44), but these associations became nonsignificant after adjustment for vascular risk factors (Table 2 and data not shown). The associations of WMHV and EXT-WMHV with mortality were unchanged when stratifying on age and hypertension (data not shown).

**Discussion**

In 2229 middle-aged community-dwelling participants from the Framingham Offspring Study, BI and the presence of
excessive white matter hyperintensity for age (EXT-WMHV) were each associated with an increased risk of incident stroke, especially ischemic stroke, independently of vascular risk factors. WMHV as a continuous measure, EXT-WMHV, and BI were associated with an increased risk of incident dementia independent of vascular risk factors, prevalent, and interim stroke. WMHV and EXT-WMHV were associated with an increased risk of incident dementia independent of vascular risk factors, prevalent, and interim stroke. WMHV and EXT-WMHV were associated with an increased risk of death, particularly vascular death. The associations of WMHV and EXT-WMHV with mortality were also independent of concomitant vascular risk factors, and they were still significant but weakened after accounting for prevalent and interim stroke and dementia.

The strengths of this study are the prospective population-based setting with careful surveillance of clinical events and the quantitative measurement of WMHV. Original features are the younger age of the study sample compared with previous publications and the simultaneous assessment of the impact of WMH and BI on correlated outcomes, allowing estimation of the relative contribution of each risk marker. Our study also has limitations. Despite the substantial sample size, there were a limited number of events, especially for dementia. Although the acceptance rate was high, persons included in this study are not perfectly representative of the general population. Finally, we did not look at differential associations according to location, number, and size of BI or location of WMH.

Only a few community-based studies have assessed the relation of WMH with incident dementia,7,10,11 and these were in older adults (≥65 years). One study found an association of extensive WMH with an increased risk of all dementia, AD, and vascular dementia.7 A second study found an association of WMHV with vascular dementia only.10 A third study observed that increasing periventricular hyperintensities were associated with all dementia and AD.11 To our knowledge, our study is the first to test the association of BI and WMHV with incident dementia in middle-aged community-dwelling persons. It is also the first population-based study to test the association of these MRI markers with incident MCI. Small-vessel disease is commonly considered to be the main determinant of WMH.23,24 However, the fact

Table 3. Association of WMHV, EXT-WMHV, and BI With Incident MCI

<table>
<thead>
<tr>
<th>OR (95% CI) for Incident</th>
<th>Amnestic MCI</th>
<th>MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events/sample size</td>
<td>93/1134</td>
<td>93/1344</td>
</tr>
<tr>
<td>WMHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.06 (0.83–1.36)</td>
<td>0.617</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.06 (0.83–1.36)</td>
<td>0.635</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.04 (0.81–1.33)</td>
<td>0.750</td>
</tr>
<tr>
<td>Model 4*</td>
<td>1.09 (0.85–1.39)</td>
<td>0.516</td>
</tr>
<tr>
<td>EXT-WMHV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.27 (0.68–2.40)</td>
<td>0.452</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.26 (0.67–2.39)</td>
<td>0.471</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.13 (0.59–2.17)</td>
<td>0.719</td>
</tr>
<tr>
<td>Model 4*</td>
<td>1.35 (0.71–2.56)</td>
<td>0.363</td>
</tr>
<tr>
<td>BI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.76 (0.37–1.57)</td>
<td>0.456</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.77 (0.37–1.59)</td>
<td>0.478</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.68 (0.31–1.45)</td>
<td>0.314</td>
</tr>
<tr>
<td>Model 4†</td>
<td>0.73 (0.35–1.52)</td>
<td>0.400</td>
</tr>
</tbody>
</table>

Model 1, logistic regression adjusted for age, sex, education, interval between examinations; Model 2, Model 1 additionally adjusted for systolic blood pressure, current smoking, diabetes, and history of cerebrovascular disease; Model 3, Model 1 additionally adjusted for interim stroke, after excluding participants with prevalent stroke at baseline; Model 4, Model 1 additionally adjusted for BI* or WMHV†.
that the associations between WMH and dementia persisted after adjusting for vascular risk factors, interim stroke, and BI could suggest that mechanisms other than arteriolosclerosis may be involved in the relation between WMH and cognition. Other potential mechanisms have been suggested such as amyloid angiopathy\(^{25}\) or wallerian degeneration due to cortical atrophy or AD-related pathological changes.\(^{26,27}\) Interestingly, WMHV and EXT-WMHV were associated with an increased risk of amnestic MCI in older participants only (aged ≥60 years). This could either suggest that increasing WMHV matters only above a certain absolute threshold, reached at an older age, or that other neurodegenerative lesions, which are more frequent in older persons, need to be present concomitantly to affect cognition.

The association of WMHV and EXT-WMHV with mortality in our middle-aged sample extends previous observations in elderly individuals.\(^{8,9}\) Although these associations were unchanged after adjusting for vascular risk factors, they became weaker after adjusting for interim dementia and stroke, suggesting that these events explain a substantial part of the increased mortality. Furthermore, the stronger associations with death due to vascular disease than with overall mortality, even after exclusion of stroke death, may imply that increasing amounts of WMH are correlated with vascular disease not only in the cerebral vasculature, but also in other territories such as coronary arteries. In line with these findings, a study conducted on patients aged 62 years on average with proven atherosclerotic disease had identified a significant association of periventricular WMHs (but not deep WMHs) with an increased risk of incident myocardial infarction.\(^{28}\) Interestingly, however, another more recent study did not observe any association of WMHV with the occurrence of major vascular events other than stroke (including myocardial infarction and nonstroke vascular death) in noninstitutionalized community-dwelling participants aged ≥65 years.\(^{6}\) A potential explanation for this discrepancy could be a selection bias, because participants with an increased risk of nonstroke vascular events, which generally occur earlier in life than stroke, may have been less likely to be included in the latter study due to death or institutionalization before the age of 65 years. In the present study, the association of BI with mortality disappeared when adjusting for vascular risk factors, suggesting that the association may be driven mainly by the presence of an increased burden of conventional vascular risk factors, whereas the association of WMH with mortality may be more complex, involving other factors such as an increased risk of death from dementia.

Overall, our findings show that, in middle-aged community-dwelling subjects, BI and WMH are important predictors of incident stroke, amnestic MCI, and dementia and also portend an increased risk of death. Interestingly, the associations of WMH with cognition and mortality were at least partly independent of concomitant vascular disease. Further epidemiological studies in middle-aged individuals are warranted to confirm or refute our findings as well as studies looking at the association of WMHV progression and incident BI with the risk of stroke, MCI, and dementia, because these MRI markers could potentially serve as intermediate end points in prevention trials.

Sources of Funding
This work was supported by the Framingham Heart Study’s National Heart, Lung, and Blood Institute contract (N01-HC-25195) and by grants from the National Institute of Neurological Disorders and Stroke (R01 NS17950) and from the National Institute on Aging (R01 AG16495, AG08122, AG033193, AG031287). S.D. is supported by a Fulbright grant and received an award from the Bettencourt-Schueller Foundation.

Disclosures
None.

References


Association of MRI Markers of Vascular Brain Injury With Incident Stroke, Mild Cognitive Impairment, Dementia, and Mortality: The Framingham Offspring Study
Stéphanie Debette, Alexa Beiser, Charles DeCarli, Rhoda Au, Jayandra J. Himali, Margaret Kelly-Hayes, Jose R. Romero, Carlos S. Kase, Philip A. Wolf and Sudha Seshadri

Stroke. 2010;41:600-606; originally published online February 18, 2010;
doi: 10.1161/STROKEAHA.109.570044
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/41/4/600

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/