Stroke Risk Profile Predicts White Matter Hyperintensity Volume: The Framingham Study
Tom Jeerakathil, Philip A. Wolf, Alexa Beiser, Joseph Massaro, Sudha Seshadri, Ralph B. D’Agostino and Charles DeCarli
Stroke 2004;35;1857-1861; originally published online Jun 24, 2004;
DOI: 10.1161/01.STR.0000135226.53499.85
Stroke is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
Copyright © 2004 American Heart Association. 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/cgi/content/full/35/8/1857

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

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, 351 West Camden Street, Baltimore, MD 21202-2436. Phone 410-5280-4050. Fax: 410-528-8550. Email: journalpermissions@lww.com

Reprints: Information about reprints can be found online at
http://www.lww.com/static/html/reprints.html
Stroke Risk Profile Predicts White Matter Hyperintensity Volume
The Framingham Study

Tom Jeerakathil, MD; Philip A. Wolf, MD; Alexa Beiser, PhD; Joseph Massaro, PhD; Sudha Seshadri, MD; Ralph B. D’Agostino, PhD; Charles DeCarli, MD

Background and Purpose—Previous studies of cardiovascular risk factors and white matter hyperintensity (WMH) on brain MRI have been limited by the failure to exclude symptomatic cerebrovascular disease and dementia or by the use of semiquantitative rather than quantitative methods to measure WMH volume (WMHV). We examined the relationship between Framingham Stroke Risk Profile (FSRP) and WMHV measured quantitatively in a stroke and dementia-free subset of the Framingham Offspring Cohort.

Methods—Brain MRI was performed in 1814 members of the Framingham Offspring Cohort. Pixel-based quantitative measures of WMHV corrected for head size were obtained using a semiautomated algorithm. WMHV was not normally distributed and therefore was log-transformed (LWMHV). The FSRP and its component risk factors measured a mean of 7.5 years before MRI were related to both continuous measures of LWMHV and to the presence of large volumes of LWMHV (LWMHV-large). All analyses were adjusted for age and sex.

Results—FSRP was strongly associated with LWMHV and LWMHV-large. Age, smoking, history of cardiovascular disease, hypertension, and left ventricular hypertrophy by electrocardiogram were all significantly related to LWMHV or LWMHV-large.

Conclusions—FSRP and several cardiovascular risk factors were related to both WMHV measured continuously and to a categorical designation of large volumes of WMH. These findings provide strong evidence of a vascular basis for WMH. (Stroke. 2004;35:1857-1861.)

Key Words: risk factors ■ magnetic resonance imaging ■ white matter ■ cerebrovascular disorders

White matter hyperintensities (WMHs) are areas of increased signal on T2-weighted and fluid-attenuated inversion recovery MRI sequences of the brain.1–3 These phenomena may not be benign because they are seen in up to 70% of persons with vascular dementia and Alzheimer’s disease.4 Other studies have found adverse associations between WMH and neuropsychological function, gait and balance, lower extremity function, depression, and recurrent stroke and death.5–10

Increasing age is a potent risk factor for WMH, suggesting that the phenomenon is a consequence of the aging process.1,3,6,8,11–15 After age, a history of cardiovascular disease (CVD) and hypertension have been the most consistent risk factors across most studies.6–8,12,13,15–17 Associations are less consistently demonstrated for other risk factors such as diabetes, serum glucose levels, and smoking status.7,8,12,15,18

Most large community-based MRI studies examining the relationship between cardiovascular risk factors and WMH have used semiquantitative methods to measure WMH volume (WMHV) on graded ordinal scales.12,13,15–17,19–24 Despite the advantages of ease of use and minimal technical requirements, semiquantitative methods have a number of limitations, including variable inter-rater reliability and questionable ability to detect WMH progression.25,26 Studies that used quantitative methods have been limited by (1) restriction to elderly male World War II veteran twins; (2) a relatively small sample size; or (3) failure to exclude subjects with a history of symptomatic stroke or dementia.1,7,8,27 Stroke and dementia are associated with elevated WMH burden and may confound relationships between WMH and cardiovascular risk factors.

Previous studies have related WMH to individual cardiovascular risk factors. Relating WMH to stroke risk prediction scores may have advantages over the use of individual risk factors because a risk score provides a quantitative probability of stroke accounting for the cumulative cardiovascular risk factor burden.
The current study examines the relationship between the Framingham Stroke Risk Profile (FSRP) and individual cardiovascular risk factors and WMHV in a community-based sample of individuals free of stroke and dementia using quantitative MRI methods.

**Subjects and Methods**

The Framingham Offspring Cohort were recruited in 1971 and consisted of 5124 children and spouses of children of the original Framingham Cohort. Offspring subjects have been examined 7 times since 1971, and between 1999 and 2001, they were invited to undergo a brain MRI using a standard protocol. For the current analysis, only subjects attending examination 5 were included, and risk factor data from this examination were related to findings from brain MRI examinations. Data from examination 5 were used because a larger number of subjects had risk factor and MRI data available than from exam 6 or 7. Subjects were excluded from MRI examination if they had metal in the eyes or central nervous system, claustrophobia, valvular prosthesis, cardiac pacemaker, vascular clip, cochlear implant or other implantable device, or if they refused.

Of those offspring who attended examination 5, 3562 were alive as of September 2001, the cutoff for the analysis. Of them, 1939 had an MRI examination of the brain as of September 2001. MRI exams were scheduled based on the date of attendance at previous exams, but otherwise in no particular order. Of 1939 subjects who had a brain MRI scan, data on 1860 subjects were available for analysis. Individuals with symptomatic stroke or dementia were excluded, as were subjects with other medical diagnoses that might confound or interfere with the analysis of WMHs, such as multiple sclerosis, agenesis of the corpus callosum, hydrocephalus, brain tumors, sarcoidosis, Lyme disease, or a history of head trauma severe enough to produce loss of consciousness for >24 hours. Of 1860 subjects with available data, 30 were excluded because of stroke or dementia, 5 because of multiple sclerosis, and 11 for a variety of other cited neurological conditions, leaving a final study group of 1814 subjects. All subjects provided informed consent, and the research was approved by the institutional review board at Boston Medical Center.

The FSRP was developed using subjects from the Framingham Study Original Cohort. The contribution of individual risk factors to the 10-year probability of stroke events was determined using sex-specific Cox proportional hazard models. Component risk factors are (1) age in years; (2) systolic blood pressure (SBP) in mm Hg; (3) use of antihypertensive medication; (4) diabetes; (5) number of cigarettes smoked per day; (6) other CVD; (7) atrial fibrillation; and (8) left ventricular hypertrophy (LVH) by electrocardiogram (EKG). For the current stroke-free study sample, CVD factors to the 10-year probability of stroke events was determined as having a large value for LWMHV relative to age (LWMHV-large). We used linear regression to examine the relationship between FSRP and LWMHV and logistic regression to relate FSRP to LWMHV-large. If stroke probability was found to be related to WMHV, we then planned to examine the individual stroke risk factors to determine which were most important in explaining this relationship. We used linear regression to relate age, sex, CVD, number of cigarettes smoked per day, LVH, diabetes, fasting blood sugar, and hypertension to LWMHV and logistic regression to relate the variables to LWMHV-large. Analyses were adjusted for age and sex. All analyses were performed with SAS software 8.2 (SAS Institute).

**Results**

Mean age (range) of the study sample was 53 (26 to 81). Mean values and prevalence of risk factors are presented for the study group and for the 1748 offspring not included in these analyses. Nonparticipants were older, had a higher mean FSRP, smoked more, and had a greater prevalence of hypertension, diabetes and CVD than the 1814 included in the analysis (Table 1).

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Study Group</th>
<th>Nonparticipants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 ± 12</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>CVD</td>
<td>53%</td>
<td>58%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7%</td>
<td>10%</td>
</tr>
<tr>
<td>Fasting Blood Sugar</td>
<td>108 ± 25</td>
<td>112 ± 25</td>
</tr>
<tr>
<td>SBP</td>
<td>128 ± 18</td>
<td>132 ± 18</td>
</tr>
<tr>
<td>LVH</td>
<td>10%</td>
<td>13%</td>
</tr>
<tr>
<td>Cigarettes smoked/day</td>
<td>12 ± 8</td>
<td>15 ± 8</td>
</tr>
<tr>
<td>Other CVD</td>
<td>5%</td>
<td>8%</td>
</tr>
</tbody>
</table>

Compared with those without, subjects with LWMHV-large status smoked significantly more cigarettes, had a higher mean FSRP, and had a greater prevalence of hypertension, LVH, and smoking (Table 2). As expected, because derivation of LWMHV-large status was age specific, there was no difference in age between these 2 groups.

In univariate analysis, FSRP was associated with LWMHV (regression coefficient 0.679; \( P < 0.0001 \)) and remained so after adjustment for age and sex (regression coefficient 0.153; \( P = 0.0058 \)). The FSRP was similarly associated with LWMHV-large status (odds ratio [OR], 1.349 [95% CI, 1.067 to 1.705]; \( P = 0.0124 \)) and remained so after adjustment for age and sex (OR, 1.438 [95% CI, 1.078 to 1.920]; \( P = 0.0136 \)). There was no significant interaction between age and sex in any of these analyses.

Age, CVD, diabetes, fasting blood sugar, SBP, LVH, and hypertension were all significantly associated with LWMHV in crude analysis, but the number of cigarettes smoked per day was not (Table 3). After adjustment for age and sex, the number of cigarettes smoked per day and CVD were signif-
significant predictors of LWMHV with hypertension and borderline-significant LVH. There was no significant interaction between age and sex in any of the analyses. Age was a highly significant predictor in all of these models. LWMHV-large status was related to the number of cigarettes smoked per day, LVH, and hypertension in crude analysis (Table 4). Age was not associated with LWMHV-large status ($P=0.3503$). This suggests that the method of using $>1$ age-specific SD above the age-predicted value to define LWMHV-large status successfully controlled for the effects of age. However, age was still included in the analyses to control for any residual effect. After controlling for age and sex, the number of cigarettes smoked per day, LVH, and hypertension were still significantly associated with LWMHV-large status (Table 4).

**Discussion**

To our knowledge, this is the first large-scale community-based study to relate WMH to cardiovascular risk factors using quantitative MRI measures. Our findings confirm previous studies that showed significant relationships between various cardiovascular risk factors and WMH but were limited by use of semiquantitative methods to measure WMH or select subject samples. We also confirmed previous reports of a relationship between cigarette smoking and WMH. In addition, we extend previous findings by showing that FSRP is significantly related to WMH, even among individuals $\leq 55$ years of age in the absence of clinical disease because subjects with symptomatic stroke and dementia were excluded from this analysis. Moreover, the relationship between FSRP and WMH was robust even when WMHs were measured continuously and categorically. For example, each 10% increase in the 10-year risk of stroke increased the odds of having a large burden of WMHs by 44%. These observations support the notion that cardiovascular risk factors result in pernicious brain injury that may begin many years before clinical symptoms (eg, stroke or transient ischemic attack) are manifested and that this relationship may be continuous and not confined simply to individuals at substantial risk. Because FSRP is a composite measure that incorporates multiple stroke risk factors and predicts future cerebrovascular health, these findings also offer additional support for the use of WMH as a marker of vascular brain injury.

The FSRP also consists of a number of important component risk factors, particularly hypertension. Our results show that hypertension increased the odds of having large WMHVs by 70%, and LVH on EKG, a recognized measure of hypertensive end-organ disease, was associated with a 2.6-fold increased likelihood of large WMHVs. These findings support the notion that hypertension may be a leading factor in associating FSRP with WMH, possibly through the same mechanisms that link hypertension to stroke. Our findings predict an increasing burden of WMH as the population ages, given the increasing prevalence of systolic hypertension with age and the strong independent relationship between WMH and age.

We also confirmed previous reports of a relationship between cigarette smoking and WMH. For continuous measures of WMH this relationship was only evident after...
age adjustment because it is likely that cigarette smoking was negatively confounded by age. Younger subjects are more likely to smoke but because age is the strongest predictor of WMH, even older nonsmokers have higher WMHV than younger smokers. The relationship between smoking and WMH becomes apparent when age is controlled for. Conversely, we did not find significant associations between diabetes or fasting glucose levels and WMH. Our results are consistent with at least 1 other negative study, but this may reflect the relatively low prevalence of diabetes in the Framingham population (5%) compared with some other samples.7,12,15,18

Our study has a number of shortcomings. These findings might be of particular importance to vulnerable population groups with a high prevalence of cardiovascular risk factors such as Caribbean Hispanics or blacks. However, our ability to generalize is limited by restriction of our sample to a predominantly white and middle-class population. Also, although this was a prospective cohort study, analysis of cardiovascular risk factors and WMH was cross-sectional, limiting our ability to assess future cerebrovascular health in relation to our findings. Possible sampling bias is a third limitation. Although MRI scans were scheduled in no particular order based on attendance at examination 7, there is also the potential for sampling bias resulting from incomplete MRI study participation. However, those offspring who were not a part of the current analysis had a higher level of cardiovascular risk than those who were suggesting that our findings might underestimate the true relationship between FSRP and WMH.

In summary, we found a clear relationship between the FSRP and its component risk factors and WMH. Because of the adverse implications of WMH, it will be important to determine prospectively whether cardiovascular risk factors and control of risk factors influence WMH progression. Some of this work is already under way.27 Quantitative methods such as those used here will be important in future attempts to demonstrate changes in WMH over time in both observational studies and clinical trials.

Acknowledgments
This work was supported by the National Heart, Lung, and Blood Institute contract NO1-HC-25195; National Institute on Aging grant 5RO1-AG 16495–02; and National Institute of Neurological Disorders and Stroke grant 5RO1-NS17950-19. T.J. was supported by an American Academy of Neurology clinical research training fellowship. We acknowledge the staff of the Framingham Study and of the MRI reading center at the University of California-Davis for their continuing commitment to the MRI study.

References
15. Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G, Shahar E, Nieto J, Mosley T, Heiss G. The prevalence and severity of white matter lesions,


