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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.[1–3,8,11–15] 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.

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From the Division of Neurology, Department of Medicine (T.J.), Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Canada; the Department of Neurology, School of Medicine (P.A.W., S.S.), the Department of Biostatistics (A.B., J.M.), School of Public Health, and the Department of Mathematics and Statistics (R.B.D.), Boston University, Boston, Mass; and the Department of Neurology and Center for Neuroscience (C.D.), University of California-Davis, Sacramento, Calif.

Reprint requests to Dr Philip A. Wolf, Department of Neurology, Boston University School of Medicine, 715 Albany St, B-608, Boston, MA 02118-2526. E-mail pawolf@bu.edu

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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.[28] 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.[29,30] 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 represented peripheral arterial disease or coronary heart disease. The FSRP has been shown to accurately predict probability of stroke in the Copenhagen City Heart Study as well and provides a single value that serves as a composite measure of cardiovascular risk.[31] We also related WMH to fasting blood sugar and hypertension status, although these are not component risk factors of the FSRP. Hypertension was defined as SBP >140 mm Hg, diastolic blood pressure >90 mm Hg, or medical treatment of blood pressure.

A Magnetom 1-T field strength machine (Siemens) was used. T2-weighted sequences were performed with double spin-echo coronal imaging, 4-mm contiguous slices from nasion to occiput with a repetition time of 2420 ms, an echo time (TE) of TE1 20/TE2 90 ms, an echo train length of 8, a field of view of 22 cm, and acquisition matrix of 192×256 interpolated to 256×256 with 1 excitation.

For quantitative analysis of WMHV, imaging data were transferred to the MRI reading center at the University of California at Davis. Analyses were performed using a custom-designed image analysis package (QUANTA 6.2) operating on a Sun Microsystems Ultra 5 workstation. Images were analyzed and interpreted blind to subject data and in random order. Semiautomated analysis of pixel distributions based on mathematical modeling of MRI pixel intensity histograms for cerebrospinal fluid (CSF) and brain matter (white matter and gray matter) were used to determine the optimal threshold of pixel intensity to best distinguish CSF from brain matter based on methods published previously.[32]

The intracranial vault above the tentorium was outlined manually to determine the total intracranial volume (TCV). 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 (after removal of CSF and correction of image intensity nonuniformities). A segmentation threshold for WMH was determined as 3.5 SDs in pixel intensity greater than the mean of the fitted distribution of brain parenchyma. These methods have been shown to have high inter-rater and intrarater reliabilities in previous studies.[8,32–35] For individuals analyzing data from the Framingham Study, inter-rater reliabilities range between 0.90 and 0.94 for TCV, TCB, and WMH, and intrarater reliabilities average 0.98 across all measures.

WMHV was expressed as a proportion of TCV to correct for head size, and this value designated WMHV. WMHV was not normally distributed and therefore was log transformed (LWMHV) for all regression analyses; and there was a clear linear relationship between age and LWMHV. A regression line was fitted with age as the independent variable and LWMHV as the dependent variable to determine the age-predicted value of LWMHV. Subjects with an LWMHV >1 age-specific SD greater than the age-predicted value based on the regression line were designated 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).

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-

TABLE 1. Comparison of Framingham Study Offspring Included in Current Analysis Versus Those Not Included

	Included	Not Included	*P*
n	1814	1748	
Age exam 5 (y)	53	55	<0.0001
Male (%)	47	45	NS
FSRP	0.040	0.047	<0.0001
SBP (mm Hg)	124.5	126.0	<0.0001
No. cigarettes per day	3.4	4.2	<0.0001
Current smoker (%)	16.3	22.3	<0.0001
Hypertension (%)	18.3	23.6	<0.0001
Diabetes (%)	5.0	6.8	0.0233
LVH (%)	1.73	1.98	NS
CVD (%)	5.8	9.7	<0.0001

icant 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.[8,12,13,16,27] In addition, we extend previous findings by showing that FSRP is significantly related to WMH, even among individuals ≤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 WMHV was robust even when WMHs were measured continuously or 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.[29,36] 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.[12,15] For continuous measures of WMH this relationship was only evident after

TABLE 2. Sample Characteristics Overall and by LWMHV-Large Status

	Overall	LWMHV-Large Yes	LWMHV-Large No
n	1814	240	1574
Age at exam 5 (y)	54.2±9.5	54.8±9.6	54.1±9.5
Age at MRI (y)	61.7±9.4	62.3±9.5	61.6±9.4
FSRP	0.040±0.04.7	0.048±0.054	0.039±0.046*
No. cigarettes per day	3.4±9.1	5.2±11.2	3.1±8.7†
WMHV (mL)	0.96±1.7	3.29±3.68	0.61±0.53‡
WMHV×100 (%)	0.077±0.13	0.26±0.29	0.049±0.042‡
SBP (mm Hg)	124.5±18.2	126.5±19.9	124.2±17.9
Diabetes (%)	5.0	5.0	5.02
Hypertension (%)	18.3	25.9	17.08†
CVD (%)	5.8	7.9	5.5
LVH (%)	1.7	3.8	1.4*

*$P<0.05$; †$P<0.01$; ‡$P<0.0001$.
Values followed by ± indicate means±SD.

TABLE 3. Linear Regression for Individual Stroke Risk Factors and LWMHV

	Crude		Adjusted for Age and Sex	
	Regression coefficient‡	*P*	Regression coefficient‡	*P*
Age (y)†	0.053	<0.0001*	0.053	<0.0001*
Male sex†	−0.039	0.4122	−0.058	0.1558
No. cigarettes per day	0.001	0.7369	0.006	0.0094*
Diabetes	0.277	0.0113*	0.023	0.8077
Fasting blood sugar	0.0028	0.0028*	0.00013	0.8766
CVD	0.604	<0.0001*	0.21	0.0198*
SBP (mm Hg)	0.012	<0.0001*	0.002	0.0631
LVH	0.706	0.0001*	0.324	0.0444*
Hypertension	0.473	<0.0001*	0.11	0.0498*

*Significant at $P=0.05$.
†Age adjusted for sex and sex adjusted for age.
‡Regression coefficient represents the change in log-WMHV for each 1 unit change in continuous risk factors and for a change from negative to positive for dichotomous risk factors.

TABLE 4. Logistic Regression for Individual Stroke Risk Factors and LWMHV-Large

	Crude		Adjusted for Age and Sex	
	OR (95% CI)†	*P*	OR (95% CI)†	*P*
No. cigarettes per day	1.021 (1.008 to 1.033)	0.0015*	1.021 (1.009 to 1.034)	0.0010*
CVD	1.469 (0.877 to 2.462)	0.1438	1.430 (0.842 to 2.430)	0.1856
Diabetes	0.996 (0.534 to 1.857)	0.990	0.970 (0.518 to 1.819)	0.9252
Fasting blood sugar	0.998 (0.993 to 1.004)	0.5573	0.998 (0.992 to 1.004)	0.4880
SBP	1.007 (1.000 to 1.014)	0.0667	1.007 (0.999 to 1.015)	0.0971
LVH	2.717 (1.236 to 5.973)	0.0129*	2.636 (1.188 to 1.850)	0.0172*
Hypertension	1.70 (1.238 to 2.336)	0.0016*	1.721 (1.229 to 2.409)	0.0016*

*Significant at $P=0.05$.

†OR for LWMHV-large status for each 1 unit increase in continuous risk factors and for a change in dichotomous risk factors from negative to positive.

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 WMHVs 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 WMHV. 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.

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