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The Framingham Offspring Study

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Abstract—*Background:* Mid-life stroke risk factors have been related to late-life cognitive impairment. This association may result not only from clinical strokes but also from subclinical brain injury, such as a global atrophy demonstrable on quantitative brain MRI. *Methods:* The authors evaluated the community-based cohort of Framingham Offspring Study participants. A total of 1,841 subjects (mean age, 62 years; 857 men, 984 women) who underwent quantitative MRI and cognitive testing between 1999 and 2001 and were free of clinical stroke and dementia constituted our study sample. The authors used age- and sex-adjusted linear regression models to relate previous (1991 to 1995) and recent (1998 to 2001) Framingham Stroke Risk Profile (FSRP) scores to the total cerebral brain volume ratio (TCBVr) on follow-up MRI, and further to relate the TCBVr with education-adjusted scores on neuropsychological tests administered at the time of imaging. *Results:* There was an inverse association between FSRP scores and TCBVr. The TCBVr also showed a significant positive association with performance on tests of attention (Trails A), executive function (Trails B), and visuospatial function (visual reproduction, Hooper visual organization), but not with performance on tests of verbal memory or naming. *Conclusions:* The Framingham Stroke Risk Profile may identify subjects with smaller brains and poorer cognitive function among stroke- and dementia-free subjects, reinforcing the importance of managing stroke risk factors.

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Previous epidemiologic studies have demonstrated strong associations between individual stroke risk factors (elevations in blood pressure, diabetes) and cognitive impairment and dementia.[1-13] The mechanisms by which these stroke risk factors lead to cognitive impairment remain to be determined and likely include promotion of subclinical disease in addition to clinical stroke.

Generalized atrophy is the most conspicuous brain change associated with age.[14] Such atrophy may result from a variety of insults to the brain, such as the pathologic processes associated with Alzheimer disease (AD). Exposure to cerebrovascular risk factors can result in stroke,[15] which in turn may cause brain atrophy.[16] However, the etiology and clinical significance of generalized brain atrophy, in the absence of an underlying stroke or dementia, are uncertain. We hypothesized that exposure to elevated levels of vascular risk factors might be associated with lower brain volumes on MRI and that this subclinical brain "atrophy" might manifest as a lower level of cognitive function on targeted neuropsychological testing.

Previous studies of the relationship between vascular risk factors and subclinical changes in brain structure and function have several limitations. Several were restricted to highly select populations, such as "successful agers"[17] or men who were World War II veteran twins.[8,18] Other population studies, such as the Cardiovascular Health Study and the Rotterdam Scan Study,[19,20] have used semiquantitative rather than quantitative MRI techniques.

The Framingham Offspring Cohort is a middle-aged, community-based cohort that has been longitudinally evaluated for cardiovascular risk and the development of clinical stroke and dementia since 1971.[21] We studied participants who were free of clinical stroke and dementia using the Framingham Stroke Risk Profile (FSRP), a previously validated index of clinical stroke risk, as a single composite measure of exposure to a variety of vascular risk factors.[15,22] We related these FSRP scores to a measure of global brain atrophy, the total cerebral (parenchymal) brain volume ratio (TCBVr), determined from quantitative MRI. We also examined the functional significance of the observed differences in brain volume by relating the TCBVr to performance on a comprehensive battery of neuropsychological tests administered simultaneously with the MRI.

Methods. *Study subjects.* The Framingham Offspring cohort (n = 5,124) was enrolled in 1971 and has been evaluated seven

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Table 1 *Description of individual items in the neuropsychological (cognitive) test battery administered to Framingham Offspring Study subjects, simultaneously with quantitative MRI*

Neuropsychological test	Cognitive functions assessed	Variable(s) chosen to measure performance
Wechsler Memory Scale subtests[52]		
Logical memory*	Verbal memory	Immediate, delayed, and retained scores for total (verbatim and paraphrased) correct responses
Visual reproductions	Visual memory	Immediate, delayed and retained
Paired-associate learning	New learning	Total score (no. of hard pairs recalled + no. of easy pairs recalled/2)
Wechsler Adult Intelligence Scale subtest[53]		
Similarities (13 pairs)	Abstract reasoning	Total score—2 points per correct abstraction
Additional tests		
Trails A and B[54]	Attention, concentration; Trails B also measures executive function	Time to completion in minutes for each test
Hooper visual organization[55]	Visual perception	Total score—objects correctly identified
Boston Naming Test[56] (36 items presented)	Language—naming	Total items correctly named (spontaneously and/or with semantic or phonemic cues)
Wide Range Achievement Test—Reading 3[57]	Language—reading and vocabulary	Total score

* The Anna Thompson story was used for testing logical memory.

times during the past 30 years. Participants who attended the fifth Offspring examination (between 1991 and 1995) and the seventh Offspring examination (between 1998 and 2001) were invited to participate in brain MRI studies and cognitive assessment using a neuropsychological test battery (n = 3,300). The Ethics Committee of Boston University approved the study protocol, and informed consent was obtained from all subjects. Subjects were excluded if they developed clinical stroke (n = 63) or dementia (n = 2) up to the date of the MRI, the neuropsychological evaluation, or the seventh Offspring examination (whichever was most recent), or if they had a contraindication to MRI, refused MRI, or refused neuropsychological testing (n = 1,394).

A total of 1,841 subjects (857 men and 984 women) underwent *both* MRI and neuropsychological evaluation, remained free of clinical stroke and dementia, and did not have any neurologic condition that could confound the interpretation of their MRI or neuropsychological test results. Seventeen subjects were excluded for a diagnosis of multiple sclerosis (MS), brain tumor, head injury, and other conditions. The subject's age at examination 5, the time of initial risk factor assessment, was mean (± SD) 54 ± 9 years (range, 35 to 74 years), and the MRI was undertaken after a mean interval of 7.5 years (SD 1.0; range, 4.5 to 10.8 years). The MRI and neuropsychological testing were done on the same day in most subjects and within 1 month in all but 21 subjects (99%).

The FSRP has been previously described and validated for predicting stroke risk both at Framingham and in other populations.[15,22,23] It provides an estimate of the 10-year risk of stroke for a given subject based on age, sex, and measurements of the systolic blood pressure (SBP), antihypertensive therapy, diabetes, smoking status, history of cardiovascular disease (CVD), and the presence of atrial fibrillation or left ventricular hypertrophy on the electrocardiogram (EKG-LVH). SBP was recorded as the average of two physician-recorded measurements. Subjects were classified as being "on medication for hypertension" or "not on

Table 2 *Characteristics of the study sample, sex-specific subsamples and excluded subjects with reference to component variables in the Framingham Stroke Risk Profile as recorded at the 5th Offspring Examination*

	Subjects included in current analysis			Excluded subjects
Stroke risk factors	Women, n = 984	Men, n = 857	Combined, n = 1,841	Sexes combined, n = 1,394
Age, y*	54 ± 9	54 ± 10	54 ± 9	56 ± 10‡
Systolic blood pressure, mm Hg*	122 ± 19	127 ± 16	124 ± 18	127 ± 19‡
Treatment with antihypertensive medication, %	14	17	15	20‡
Diabetes, %	4	7	5	6
Current smoker, %	16	16	16	22‡
History of cardiovascular disease, %	4	8	6	9‡
Atrial fibrillation, %	0.4	1.5	0.9	2.3‡
ECG-LVH, %	1	2	2	2
Framingham Stroke Risk Profile Score*†	0.029 ± 0.038	0.052 ± 0.053	0.040 ± 0.047	0.049 ± 0.056‡

* Plus-minus values are means ± SD.
† The Framingham Stroke Risk Profile Score provides the estimated stroke risk over the subsequent 10-year period.
‡ Excluded subjects were more likely to have the stroke risk factor ($p < 0.001$).

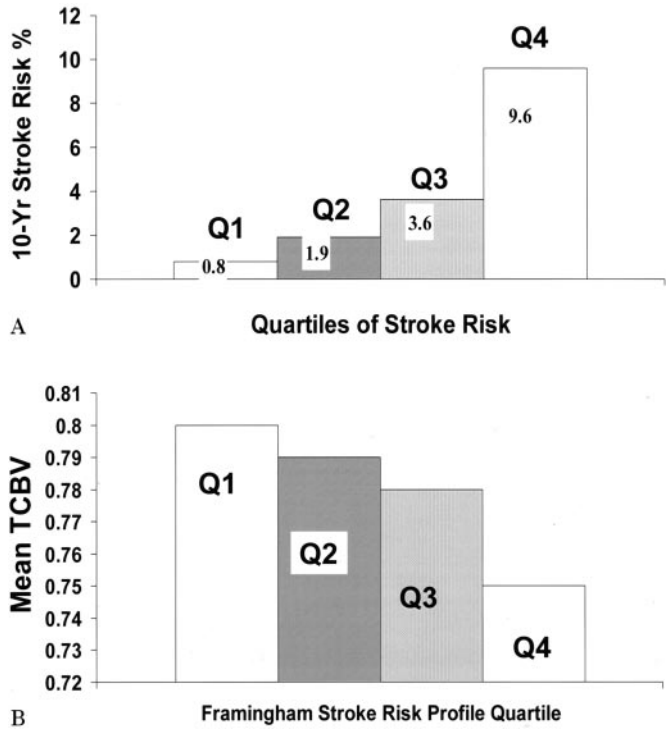

Figure 1. (A) Mean Framingham Stroke Risk Profile (FSRP) score within each quartile of stroke risk profile. (B) Mean total cerebral brain volume ratio (TCBVr) for subjects within each quartile. When FSRP scores were defined within 5-year age- and sex-specific quartiles, mean TCBVr values for subjects in each quartile were 0.79 (Q1), 0.78 (Q2), 0.78 (Q3), and 0.77 (Q4).

medication for hypertension" at each examination. Diabetes mellitus was defined by a recorded random blood glucose >200 mg/dL (11.1 mmol/L), a previous diagnosis of diabetes mellitus, or the use of a hypoglycemic agent or insulin. Subjects were categorized with regard to their cigarette smoking status as current smokers or nonsmokers. Previous CVD events included a diagnosis of coronary heart disease, congestive heart failure, or peripheral vascular disease. The diagnosis of atrial fibrillation and EKG-LVH was based on a standard 12-lead EKG obtained at or before the examination.

MRI acquisition. Subjects were imaged on a Siemens Magnetom (Munich, Germany) 1-T field strength machine using a double spin-echo coronal imaging sequence of 4-mm contiguous slices from nasion to occiput with a repetition time (TR) of 2,420 ms, an echo time (TE) of TE1 20 and TE2 90 ms, an echo train length of 8, a field of view (FOV) of 22 cm, and an acquisition matrix of 192 × 256 interpolated to a 256 × 256 with one excitation.

Image analysis. Imaging data were transferred to a central location for processing and analyses (CD). The images were analyzed by operators blinded to the subject's identity, age, sex, exposure to stroke risk factors, and cognitive performance on neuropsychological testing. Previously reported semiautomated analyses of pixel distributions based on mathematical modeling of MRI pixel intensity histograms for 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.[24] All analyses were performed using a custom-designed image analysis package, QUANTA 6.2, operating on a Sun Microsystems (Santa Clara, CA) Ultra 5 workstation.

Assessment of brain volume. Coronal sections were used for measurement of brain volume. Brain volume was determined by manual outlining of the intracranial vault above the tentorium to determine the total cranial volume (TCV) as a measure of head size. Once the skull and other nonbrain tissues were removed from the image, mathematical modeling was performed to determine total brain volume (TCB). The TCB measures comprised supratentorial gray and white matter, excluding the CSF. In this analysis, we report the TCBVr (i.e., the ratio of TCB to TCV as a measure of brain volume correcting for differences in head size). The inter-rater reliability for assessment of TCV and TCB has been previously reported.[24,25] For this study, repeat inter-rater reliabilities were calculated for all individuals analyzing the MRI data. Inter-rater reliabilities were, on average, 0.99 for the TCV and TCB estimations.

Measurement of other MRI variables. We adjusted our analyses for the following MRI variables that could potentially confound the association between the FSRP scores and TCBVr. The volume of abnormal white matter hyperintensity (WMH) was determined according to previously published methods of documented high reliability.[24] The presence or absence of silent cerebral infarcts (SCI) was determined manually by the operator based on the size (≥3 mm), location, and imaging characteristics of the lesion and using previously described methods.[18]

The neuropsychological (cognitive) test battery was a 40-minute battery that included 1) the majority of tests administered to the original Framingham cohort in 1976 to 1978,[26] so as to enable intergenerational comparisons; and 2) also tests designed to measure executive function and visual perception, domains shown to be sensitive to vascular cognitive impairment.[27,28] The individual components of the battery used are described in table 1. Tests were administered in a standardized fashion by trained interviewers and scored according to standard criteria as previously described.[3,26]

APOE genotype was determined using standard techniques of DNA amplification and restriction isotyping.[29]

Statistical analysis. Using multivariable linear regression models, initial analyses examined the association between FSRP score and TCBVr in sex-specific analyses with adjustment for age (at MRI evaluation) and age squared. We chose FSRP scores at the fifth Offspring examination as our primary predictor variable because we believed that a prolonged exposure to vascular risk factors was more likely to be reflected in changes on MRI brain volume. Because vascular risk factors might be associated with an increased volume of WMH and a higher prevalence of SCI, we re-examined the relation between FSRP score and TCBVr after accounting for the volume of WMH (adjusting for intracranial volume and using a logarithmic transformation to normalize the distribution of WMH in subjects), and the presence or absence of SCI on brain MRI (in a subset of 1,436 subjects in whom measurements of SCI had been completed). Similarly we examined the effect of adjusting for presence or absence of an *APOE*-ϵ4 allele on the observed association between the FSRP score and TCBVr.[30] Finally, we adjusted our analyses for time elapsed in each subject between examination 5 and date of brain MRI. As a secondary analysis, we also examined the relation between FSRP scores at the seventh Offspring examination and MRI parameters.

We used linear regression models to analyze the association between TCBVr and each of the neuropsychological tests in our battery, and these analyses were adjusted for age, sex, and educational achievement. The raw score for each test was transformed into a Z score (individual test score minus mean test score divided by the SD), thus permitting us to standardize performance across the various cognitive measures. All analyses were performed using Statistical Analyses System software (SAS Institute, Cary, NC).

Results. *Baseline characteristics.* Demographic and vascular risk factor characteristics of men and women in the study sample are summarized in table 2. There were differences between men and women ($p < 0.05$) in the prevalence of SBP >140 mm Hg, EKG-LVH, CVD, prevalence of atrial fibrillation and diabetes mellitus, but no significant differences in age, prevalence of current smoking, or treatment for hypertension. Men had significantly higher FSRP scores than women. For illustrative purposes, the FSRP scores were grouped into quartiles. Mean FSRP scores for each sex-pooled quartile are shown in figure 1A.

Characteristics of subjects not included in the analysis. Table 2 also compares participants in the present investigation with other Framingham subjects (n = 1,394) who were alive and free of prevalent dementia and stroke at the sev-

Table 3 *Results of multivariable regression analyses of the Framingham Stroke Risk Profile (FSRP) score and its components on the total cerebral brain volume ratio: without and with adjustment for white matter hyperintensity (WMH), silent cerebral infarcts, APOE4 genotype, and time elapsed between FSRP score estimation and brain MRI*

	Women								
	FSRP estimated at 5th Offspring Examination (1991–1995)						Estimated at 7th Offspring Examination (1998–2001)		
	Total			<55 at time of MRI					
Predictor variable	beta*	SE†	*p*	beta*	SE†	*p*	beta*	SE†	*p*
Log FSRP score‡ (per 10% increase in log FSRP score)	−10	2.9	<0.001	−5.4	2.6	0.038	−6.8	1.8	<0.001
FSRP score (per 10% increase in 10-year stroke risk)	−6.7	1.8	<0.001	−39	13.1	0.003	−5.6	1.8	0.002
Systolic blood pressure (per 10 mm Hg increase)	−0.9	0.5	0.07	−0.6	0.7	0.387	−1.1	0.5	0.016
Antihypertensive medication	−9.2	2.5	<0.001				−7.5	1.9	<0.001
Diabetes (diabetics v non-diabetics)	−11	4.3	0.013	−19	0.7	0.006	−6.3	3.4	0.069
Smoking (current smokers v non-smokers)	−3.5	2.2	0.116	−1.9	0.3	0.473	−3.5	2.2	0.116
Cardiovascular disease	−14	4.4	0.001	−19	0.9	0.031	−10	3.6	0.005
Atrial fibrillation	−1.9	12.8	0.885						
EKG-Left ventricular hypertrophy	−2	8.2	0.805						
FSRP score (adjusted for WMH)§	−6.8	1.8	<0.001				−6.9	1.8	<0.001
FSRP score (adjusted for presence or absence of SCI)¶	−6.2	2	0.002				−6.8	2	<0.001
FSRP score (adjusted for presence or absence of *APOE ε4* allele)‖	−6.5	2	0.002				−5.8	2	0.004
FSRP score (adjusted for interval between exam 5 and MRI)	−7.3	1.8	0.001						

All analyses are adjusted for age and age-squared.

* Regression coefficient - unstandardized beta weights adjusted for specified predictor variables; each row represents a separate multivariable model.

† SE refers to the standard error of beta.

‡ FSRP score was analyzed after a logarithmic transformation to normalize the distribution. Data were available for all 1,841 subjects.

§ WMH refers to white matter hyperintensity volume as measured on quantitative brain MRI. A logarithmic transformation was used to normalize the distribution. Data were available for all 1,841 subjects.

¶ SCI refers to "silent cerebral infarcts" as recorded on quantitative brain MRI. SCI data were available for 1,436 subjects.

‖ APOE genotype data were available in 1,509 subjects.

enth Offspring examination but are not included in the current analysis. The latter group includes all subjects who did not attend either the fifth or the seventh Offspring examination, those who attended these examinations but did not undergo brain MRI or neuropsychological testing and those who were excluded because of an unrelated neurologic problem, such as MS, brain tumors, or major head injury (n = 17). Subjects not included in the analysis were more likely to have a history of cardiovascular disease and atrial fibrillation, to be current smokers, and to be taking antihypertensive medication.

Distribution of TCBVr. The group mean TCB was 980 ± 108 cm^3, and the group mean TCV was 1,258 ± 132 cm^3, resulting in an average TCBVr of 0.78 ± 0.03. The mean TCB was lower in women (927 ± 87 cm^3) compared with men (1,041 ± 98 cm^3), but this was largely because of the smaller head size of women (1,184 ± 101 cm^3 in women vs 1,343 ± 109 cm^3 in men). TCBVr, the ratio of brain volume to head size, was not significantly different in the two sexes (0.78 ± 0.03 in women vs 0.77 ± 0.03 in men).

Age and TCBVr. The relation between age and TCBVr for the entire cohort was significant ($p < 0.0001$) and showed a 1.9% smaller TCBVr for each increasing decade of age. Age-related differences in TCBVr were less for women (1.5% per decade of age) than for men (2.3% per decade of age), resulting in an age-gender interaction for TCBVr ($p < 0.001$).

Association of the stroke risk profile and TCBVr. There was a strong, graded, inverse association between the FSRP score at baseline and TCBVr on subsequent MRI as seen in figure 1B. This association is partly attributable to age because stroke risk increased and TCBVr decreased with age. However, even after adjusting for age and age squared, the association between the residual TCBVr and the FSRP score remained significant ($p < 0.001$) and was seen in both sexes (table 3). Figure 2 shows that although the TCBVr decreases with age, at each age, in men and

***Table 3** Continued*

Men								
FSRP estimated at 5th Offspring Examination (1991–1995)						Estimated at 7th Offspring Examination (1998–2001)		
Total			<55 at time of MRI					
beta*	SE†	*p*	beta*	SE†	*p*	beta*	SE†	*p*
−6.7	2.1	<0.001	−16	2.9	<0.001	−9.3	1.8	<0.001
−11	2.1	<0.001	−42	7.2	<0.001	−5.4	1.2	<0.001
−1.5	0.6	0.009	−3.5	0.7	<0.001	−0.9	0.6	0.106
−5.5	2.4	0.025				−5.9	2	0.003
−22	3.5	<0.001	−17	0.6	0.002	−16	2.8	<0.001
−6.1	2.4	0.011	−5.8	0.3	0.033	−6.1	2.4	0.011
−8.1	3.4	0.016	−14	0.7	0.032	−11	2.7	<=0.001
−5	7.3	0.492						
−3.7	6	0.538						
−11	2.1	<0.001				−9.3	1.8	<0.001
−8.1	2.3	<0.001				−8.2	2	<0.001
−11	2.3	<0.001				−9.8	2	<0.001
−12	2.1	<0.001						

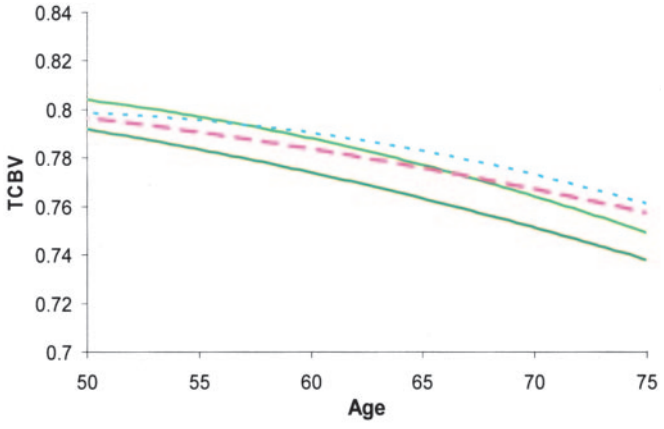

Figure 2. Distribution of mean total cerebral brain volume ratio (TCBVr) by age in four groups of subjects: men in highest quartile of Framingham Stroke Risk Profile (FSRP), men in lowest quartile of FSRP, women in highest quartile of FSRP, and women in lowest quartile of FSRP. Key: (light green solid line) TCBV in men within lowest age-, sex-adjusted FSRP quartile (Q1); (dark green solid line) TCBV in men within highest age-, sex-adjusted FSRP quartile (Q4); (blue dotted line) TCBV in women within lowest age-, sex-adjusted FSRP quartile (Q1); and (pink dotted line) TCBV in women within highest age-, sex-adjusted FSRP quartile (Q4).

women, the TCBVr is lower for subjects whose FSRP score falls in the highest quartile compared with subjects whose FSRP score falls in the lowest (healthiest) quartile. A 10% increase in the 10-year risk of stroke, as estimated using the FSRP score, was associated with a 1% lower TCBVr. The relation between the FSRP score and TCBVr remained robust after adjustment for the presence or absence of extensive WMH, the presence or absence of SCI, and the presence or absence of an *APOE*-ϵ4 allele (see table 3). This was true even in subjects aged <55 years at the time of the fifth Offspring examination (see table 3).

Because the FSRP score is a composite variable that summates several risk factors, we further examined the potential associations between the individual component factors of the FSRP score and the TCBVr. In multivariable analyses (adjusted for age and age squared), SBP, history of diabetes, and previous CVD were each significantly and inversely associated with TCBVr in either sex. In men but not in women current smoking status was also inversely related to TCBVr. In stepwise regression models, diabetes was a significant predictor of TCBVr in all subjects, men and women. Previous CVD was a significant predictor of TCBVr only in women, whereas SBP and current smoking were significant predictors only in men. In age-specific subgroup analysis, diabetes and EKG-LVH were inversely related to TCBVr in younger men and women aged <55 years, whereas current smoking and SBP were predictive in younger men as they had been in the larger group of all

Table 4 *Mean (and SD) of raw test scores of study subjects on individual tests in the neuropsychological battery*

Neuropsychological test	Women, n = 607	Men, n = 536	Combined, n = 1,147	*p* Value*
Logical memory (I)	11.8 (3.3)	11.0 (3.4)	11.4 (3.4)	<0.001
Logical memory (D)	10.9 (3.6)	10.0 (3.5)	10.5 (3.6)	<0.001
Logical memory—Percent retained	91.8 (19.0)	91.0 (21.1)	91.5 (20.0)	0.418
Visual reproduction (I)	9.0 (3.1)	9.2 (3.2)	9.1 (3.2)	0.141
Visual reproduction (D)	8.1 (3.3)	8.3 (3.5)	8.2 (3.4)	0.349
Visual reproduction (% retained)	91.3 (27.3)	90.3 (23.9)	90.9 (25.8)	0.395
Paired Associate Learning (total score)	14.6 (3.2)	13.0 (3.3)	13.8 (3.3)	<0.001
Trails A	0.53 (0.20)	0.57 (0.26)	0.55 (0.23)	0.002
Trails B	1.35 (0.71)	1.39 (0.73)	1.37 (0.72)	0.171
Hooper visual organization	25.3 (2.9)	24.9 (3.4)	25.1 (3.1)	0.002
Similarities	16.7 (3.4)	16.9 (3.8)	16.8 (3.6)	0.446
Boston naming (cued)	34.6 (1.6)	34.8 (1.6)	34.7 (1.6)	0.029
WRAT 3-R	49.1 (4.8)	48.2 (5.4)	48.7 (5.1)	<0.001

* Comparing mean values for men and women.

I = immediate; D = delayed; WRAT 3-R = Wide Range Achievement Test 3-Reading.

Table 5 *Results of multivariate regression analyses describing the relation between the total cerebral brain volume ratio (TCBVr) on MRI, and the individual neuropsychological test scores (expressed as z-scores) for stroke and dementia-free subjects in the Framingham Offspring MRI study*

Test	Regression coefficient*	Se (beta)	*p* Value
Logical memory—immediate recall	−0.013	0.008	0.114
Logical memory—delayed recall	−0.008	0.008	0.329
Logical memory, % retained	0.017	0.009	0.054
Visual reproduction—immediate recall	0.021	0.008	0.011
Visual reproduction—delayed recall	0.029	0.008	<0.001
Visual reproduction, % retained	0.035	0.009	<0.001
Paired associates—total	0.013	0.008	0.121
Trails A	−0.044	0.008	<0.001
Trails B	−0.043	0.008	<0.001
Hooper visual organization	0.042	0.008	<0.001
Similarities	0.011	0.008	0.146
Boston Naming-cued	−0.001	0.008	0.930
WRAT 3-R	−0.001	0.008	0.928

* Regression coefficients are adjusted for age, sex and educational achievement and express change in '*z*' transformed test score per 10% change in TCBVr. Pooled data are presented as sex-specific analyses gave similar results.

WRAT 3-R = Wide Range Achievement Test 3-Reading.

men. We also examined the relation between FSRP scores (and the component variables) at the seventh Offspring examination and TCBVr on brain MRI and found similar results (see table 3).

Association of TCBVr with cognitive function. The mean raw test scores obtained by study subjects in each of the tests within the neuropsychological test battery are displayed in table 4. Performance on all tests in the neuropsychological battery was strongly associated with brain volume before adjustment for age, sex, and level of education ($p < 0.001$). Because of the strong association between age, TCBVr, and cognitive performance, we also adjusted for age and additional variables. After adjusting cognitive performance scores for age, sex, and education, a significant association remained between the TCBVr and tests of attention and executive function (Trails A and B), as well as with two tests of visuospatial function, one examining visual memory and construction (visual reproduction) and the second assessing visuospatial perception and organization (Hooper visual organization test; table 5).

Discussion. In the population-based, stroke- and dementia-free subjects of the Framingham Offspring cohort, an adverse stroke risk profile either at a baseline evaluation (4 to 11 years before brain imaging) or at a recent evaluation contemporaneous with the brain imaging was associated with a lower TCBVr on quantitative brain MRI. Among the various components of the stroke risk profile, hypertension, diabetes, smoking, and previous CVD were each independently and inversely associated with the TCBVr. This association was robust, consistent in men and women, and persisted after adjusting for multiple confounders, including WMH volumes, presence of SCI, and APOE genotype status. Furthermore, in our clinically disease-free subjects, lower TCBVr was associated with poorer performance on cognitive tests of attention, executive func-

tion, and visuospatial function, an association previously shown in individuals with overt vascular brain injury.[10,27,28,31]

The importance of these findings is fourfold. First, our results suggest that age-associated brain atrophy is associated with FSRP scores, a validated predictor of future stroke.[15,23] Second, the magnitude of these changes is large. The average difference in TCBVr between the lowest FSRP score quartile and the highest was 5%. We adjusted for the impact of age (a component in the FSRP score); the average difference in TCBVr remained substantial at 2%. This magnitude of effect corresponds to the change in TCBVr during a decade of brain aging (1.9%). Third, brain atrophy was associated with modest cognitive impairment in the absence of dementia or clinical stroke. Finally, these relations appear to begin at a relatively early age because they were observed in a population-based cohort with a mean age of 62 years at the time of MRI.

These results confirm and extend previous cross-sectional and longitudinal studies that have demonstrated strong associations between cerebrovascular risk factors and brain atrophy.[8,18,20,32-35] The potential pathophysiologic mechanisms for the observed atrophy remain speculative. PET studies suggest that hypertension is accompanied by regional reductions in cerebral metabolism, particularly in vascular watershed territories,[36] and brain atrophy has been recorded in spontaneously hypertensive rats.[37,38] Microvascular injury occurs with hypertension[39] and diabetes mellitus. Smoking may affect cerebral blood flow through direct vasoconstriction[40] or result in decreased cerebrovascular reactivity.[41] Because WMH has also been associated with cerebrovascular risk factors, injury of cerebral white matter with secondary axonal degeneration is an alternative possibility. However, our data show that the relation between FSRP scores and TCBVr persisted after adjusting for individual WMH volumes. Although hypertension, smoking, and diabetes may each decrease brain volume by promoting cerebral infarction, it is important to emphasize that none of the subjects in this study had experienced a clinical stroke. Additionally, adjustment for SCI in this cohort did not alter our findings, suggesting that the atrophy was independent of the presence or absence of SCIs.

Despite our incomplete understanding of underlying pathology, the observed association between cerebrovascular risk factors and brain volume suggests that accelerated brain atrophy and stroke share common mechanisms. Longitudinal evaluation of those individuals with high FSRP scores and brain atrophy will be necessary to assess whether brain atrophy in the setting of cerebrovascular risk predicts future stroke or dementia and to determine the rate of brain atrophy in the setting of high FSRP scores. The degree of global brain atrophy appears to correlate with the clinical expression of dementia in some studies of individuals with vascular disease.[16,42,43]

Our findings are consistent with multiple previous studies showing moderate associations between brain atrophy and decreased cognitive performance.[8,31,35,44-47] Typically, these studies identified deficits in tests of attention, executive function, and visuospatial skills,[31,45-47] although impairments in memory and general intelligence have also been noted.[45] The majority of these reports, however, have been on older individuals. The Cardiovascular Health Study has reported a significant relationship between prevalent diabetes and cognitive decline in relatively young individuals.[13] Our data suggest that this relation may be partly the result of the brain atrophy noted here in association with exposure to stroke risk factors. This suggestion is reinforced by the similarity between the profile of cognitive impairment associated with brain atrophy and the pattern noted in previous studies of individuals with a high blood pressure.[2,10,46,48] Although the magnitude of the differences observed in this study may not be large enough to cause clinically detectable functional impairment and may not be recognized in routine clinical practice because of wide interindividual variability in neuropsychological test performance, the public health implications of small individual declines in cognitive function are likely to be substantial when applied to a large and growing population of elderly individuals.

The strengths of our investigation are the population-based sample, the previously documented accuracy of vascular risk factor determination in the Framingham Study, the use of a single composite measure of vascular risk (the FSRP score), the use of quantitative MRI techniques, and the use of a comprehensive neuropsychological test battery. Further, the MRI and neuropsychological measures were obtained simultaneously or within days of one another in most subjects, whereas in some studies the interval between MRI and neuropsychological evaluation was as long as 1 to 3 years.[49] The independent assessment of MRI volumes and neuropsychological testing by observers is an additional strength; MRI readers were blinded to demographic data such as age and gender, as well as to the clinical data.

Our study has several limitations. The Framingham Offspring cohort is predominantly white, thus our observations need to be investigated in other racial and ethnic groups. We did not address all potential variables that might affect TCBVr but rather focused our analysis on the vascular risk factors included in the FSRP score. Similarly, we focused in this study on global rather than regional brain volumes. Forty-three percent of subjects alive at the start of the seventh Offspring examination were excluded from the current analysis. These nonparticipants had a higher overall FSRP score. Exclusion of subjects with higher FSRP scores might be expected to decrease our power to detect an effect; despite this we did observe an association, and it is possible that the true magnitude of the association is larger than we observed. Last, we currently have only a single MRI and neuropsychological evaluation of these subjects, although participants have been undergoing follow-up MRI and neuropsychological evaluation

since 2002. We cannot comment on longitudinal changes in brain volume or cognitive performance at this time.

It is possible that we included a small number of subjects with preclinical dementia in our study sample, although we consider this unlikely. Our subjects had an average age of 62 years, an age group with a low prevalence of dementia. Further, all subjects who performed poorly on neuropsychological testing at the time of MRI were evaluated by neurologists for clinical dementia. Finally, we continued to follow study participants, and none developed dementia between the date of MRI and December 2002.

Stroke increases the risk of subsequent dementia.[50] Whether the lower brain volume and mild cognitive impairment observed in our study subjects with higher FSRP scores will translate into an increased risk of dementia can only be clarified by ongoing follow-up studies. Generalized brain atrophy and premorbid levels of cognitive function have been strongly associated with an increased risk of subsequent dementia.[25,51] The morphologic and functional changes we observed might represent accelerated brain aging. The fact that these associations were observed in subjects still in their fifth and sixth decades of life emphasizes the possible benefits of early preventive measures to identify and control stroke risk factors.

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