Original Contributions

Framingham Stroke Risk Profile and Lowered Cognitive Performance

Merrill F. Elias, PhD; Lisa M. Sullivan, PhD; Ralph B. D'Agostino, PhD; Penelope K. Elias, PhD;
Alexa Beiser, PhD; Rhoda Au, PhD; Sudha Seshadri, MD; Charles DeCarli, MD; Philip A. Wolf, MD

Background and Purpose—The primary objective of this work was to describe the relationships between 10-year risk for stroke and multiple measures of cognitive performance for a large community-based sample of individuals who were free of clinical stroke and dementia at the time of risk assessment.

Methods—Participants were 1011 men and 1164 women from the Framingham Offspring Study. The Framingham Stroke Risk Profile was used to assess 10-year risk of stroke. Using a cross-sectional design, we assessed 10-year risk of stroke, the predictor variable, and cognitive performance, the outcome variable, at examination 7 of the Framingham Offspring Study. Multivariable linear regression models were used to relate 10-year risk of stroke to cognitive tests measuring multiple domains of cognitive functioning.

Results—With statistical adjustment for age, education, sex, and other correlates of both stroke and cognitive ability, an inverse association between increments in 10-year risk of stroke and cognitive performance level was observed for tests indexing visual-spatial memory, attention, organization, scanning, and abstract reasoning.

Conclusions—In stroke- and dementia-free individuals, higher 10-year risk for stroke is associated with performance decrements in multiple cognitive domains. (*Stroke*. 2004;35:404-409.)

Key Words: cognition ■ risk factors ■ stroke

Hypertension, diabetes, and other major cardiovascular risk factors for stroke have been associated with cognitive deficit in studies of persons who have not experienced either clinical stroke or dementia.[1–3] Therefore, we hypothesized that persons identified as being at higher risk for stroke on the basis of the presence of multiple stroke risk factors will exhibit greater cognitive deficits. The Framingham Stroke Risk Profile (FSRP)[4,5] allowed us to address this question because it is a validated stroke risk scale[4–6] that combines the major cardiovascular risk factors for stroke and weights them in such a way as to produce a score giving the 10-year probability, or risk, of stroke.

The FSRP has not been examined in relation to cognitive function for a large community-based sample of men and women. However, 1 investigation with 250 male Veterans Administration patients[7] used a composite stroke risk score based on weighted components of the FSRP, excluding age. Increments in the FSRP score were associated with decrements in test performance over a 3-year period for a measure of memory and executive function, verbal (category) fluency.[7] Several tests measuring memory and visual-spatial ability were unaffected by risk of future stroke. However, this study[7] did not include multiple measures of visual-spatial ability, placing demands on memory, organization, scanning, and speed of motor response. Silent stroke and cerebral ischemia affect areas of the brain that play a role in these cognitive domains,[8,9] and the major risk factors for stroke have been associated with these domains for persons free of clinically diagnosed stroke.[1–3] Consequently, we hypothesized that increments in 10-year risk for stroke, as defined by the FSRP score, would be inversely related to performance level on multiple cognitive tests for persons free of clinically defined stroke and dementia.

Methods

Subjects

The Framingham Offspring Study cohort, recruited in 1971, has been examined 7 times over a 30-year period to identify risk factors for cardiovascular and cerebrovascular disease. The primary criterion for enrollment was that at least 1 of the participant's biological parents or 1 of their spouse's parents was a member of the original Framingham cohort.

Using a cross-sectional design, we assessed stroke risk (FSRP) and cognitive performance at the seventh examination. The 3267 offspring who attended the seventh offspring examination (September 1998 through December 2001) were eligible. Of these, 923

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TABLE 1.   Description of the Cognitive Tests Administered to Participants of the Framingham Offspring Study and Mean and SD Obtained*

Neuropsychological Test	Latent Cognitive Ability Tested	Raw Scores	
		Mean	SD
WAIS			
Similarities	Abstract reasoning, general verbal intelligence	16.7	3.7
WMS			
Paired Associate Learning	New learning, memory	13.8	3.3
Logical Memory–Immediate Recall	Immediate recall of verbal passages	11.3	3.5
Logical Memory–Delayed Recall	Delayed recall–verbal passages	10.4	3.7
Logical Memory–Delayed Recognition	Recognition memory–verbal passages	9.5	1.3
Visual Reproductions–Immediate Recall	Immediate memory–visual-spatial	8.9	3.2
Visual Reproductions–Delayed Recall	Delayed recall–visual-spatial	8.1	3.4
Visual Reproductions–Delayed Recognition	Recognition memory–visual-spatial	3.0	1.0
HRB			
Trail-Making A	Attention, concentration, visual scanning, flexibility and motor speed	33.2	15.2
Trail-Making B	Attention, concentration, visual scanning and motor speed; flexibility, and executive function	83.5	45.3
Hooper Visual Organization	Visual organization; some demands on executive function	25.0	3.3

WAIS indicates Wechsler Adult Intelligence Test; WMS, Wechsler Memory Scale; and HRB, Halstead Reitan Neuropsychological Test Battery.

*Detailed test descriptions may be found in references 12 through 17.

participants declined. Of the remaining 2344 individuals, we excluded 66 because of a history of stroke, 4 because of a history of dementia, and 99 for missing information on the various covariates used in the study. The remaining 2175 individuals (1164 women) were subjects. Their mean age was 60.7 years (SD, 9.4; range, 33 to 89 years).

Stroke Risk Profile

The FSRP[5] is a function developed to predict stroke based on 427 initial stroke events observed over a 10-year follow-up for 3362 women and 2372 men in the Framingham study cohort. A 10-year probability (or risk) of stroke can be calculated for each subject with this function (previously described).[4,5] The function is based on the following stroke risk factors identified from 36 years of longitudinal study with the Framingham Heart Study cohort: age, systolic blood pressure (SBP), antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease (CVD), atrial fibrillation (AF), and left ventricular hypertrophy (LVH) as determined by ECG.[5,6] The FSRP was validated by following up Framingham Heart Study cohort participants, who were free of stroke at baseline, for 10 years to determine the 10-year incidence of stroke.[5] The FSRP has been shown to predict risk of stroke in other study populations.[6]

In the present study, the stroke risk factors were defined at the seventh Framingham Offspring Study examination. SBP was recorded as the average of 2 physician-recorded measurements in subjects in the sitting position. Subjects were classified as being on medication for hypertension or not on medication for hypertension at this examination. Diabetes mellitus was defined as a fasting blood sugar >140 mg/dL, a previous diagnosis of diabetes mellitus, or use of a hypoglycemic agent or insulin. Participants were categorized with respect to their cigarette smoking status as current smokers or nonsmokers. Consistent with the definition used in the construction of the FSRP, prior CVD events were defined as a diagnosis of coronary heart disease, congestive heart failure, or peripheral vascular disease. The diagnosis of atrial fibrillation and LVH was based on a standard 12-lead ECG.[10]

The risk factors constituting the FSRP, including age, were determined at examination 7, as was education level and the following additional covariates used in secondary regression analyses: total serum cholesterol (mm/dL), body mass index [BMI; weight (kg)/height (m)²], self-reported mean number of drinks per day converted to ounces of alcohol consumed per week, and depressed mood, defined as a score on the Center for Epidemiological Depression Scale >16.[11]

Neuropsychological Test Battery

Table 1 defines the test scores and shows the raw score means and SD for the study sample. To facilitate comparison of the regression coefficients for the different cognitive measures, raw scores on the neuropsychological test (with no correction for age and education) were first transformed to z scores. This linear transformation, based on the total distribution of scores after exclusions, had no effect on the distribution of test scores but allowed regression coefficients to be expressed in units of SD.

The battery is sensitive to cognitive impairment of vascular origin and dementia. It includes tests administered to the original Framingham cohort in 1974 to 1978[12] and newer clinical tests designed to measure visual organization ability,[13,14] visual scanning, and executive function under time constraints.[15,16] All tests were administered and scored via their standardized instructions[13] and by trained examiners.[12]

Statistical Analysis

Because the neuropsychological assessment consisted of multiple tests that theoretically measured related cognitive domains, the first analytical step was to derive composite scores that met the following criteria: (1) Each composite score was constructed from variables indexing a common factor; (2) the same test score was not included in >1 composite; and (3) the composites were theoretically meaningful. The Similarities Test is highly correlated with general intelligence.[17] The Wide Range Achievement Test–Reading is an index of reading achievement and premorbid intellect.[13] Consequently, both were excluded from the factor analysis a priori. To extract factors, we performed a principal-components analysis on the remaining 10 variables, followed by an orthogonal (Varimax) rotation.[18]

Next, we used multivariable linear regression analyses to examine relations between FSRP scores and composite scores. Finally, analyses of individual tests within the composite scores were undertaken to understand their relative contributions to the composite score. Associations between FSRP scores and the measures of

TABLE 2.   Demographic Characteristics and Covariables at Examination 7*

Variables	Women (n=1164)	Men (n=1011)	Combined (n=2175)
Framingham 10-y stroke risk†, %	5.0 (6.3)	8.2 (8.4)	6.5 (7.6)
Stroke risk components			
Age, y‡	60.5 (9.4)	61.0 (9.4)	60.7 (9.4)
Mean SBP†, mm Hg	124.7 (19.2)	127.0 (17.0)	125.8 (18.2)
Treatment with antihypertensive drugs†, %	28	35	31
Diabetes mellitus†, %	7	12	9
Smoker‡, %	12	11	12
History of CVD†, %	5	15	10
AF†, %	1	6	3
LVH†, %	1	3	2
Additional variables			
Mean educational level§	14.4 (2.4)	14.7 (2.6)	14.6 (2.5)
Mean diastolic blood pressure†, mm Hg	72.4 (9.3)	75.5 (9.5)	73.8 (9.5)
Mean alcohol consumption†, oz/d	1.7 (2.4)	3.4 (4.5)	2.5 (3.6)
Mean cigarettes smoked per day‡, n	2.0 (6.3)	2.2 (7.1)	2.1 (6.7)
Mean total cholesterol†, mg/dL‖	207.6 (37.1)	193.3 (37.0)	200.9 (37.8)
Obesity (BMI>30)†, %	28	36	32
Depressed mood (CESD>16)†, %	11	5	8
Mean BMI†, wt/ht^2	27.4 (5.9)	28.7 (4.5)	28.1 (5.3)

CESD indicates Center for Epidemiological Depression Scale. Values are mean (SD) when appropriate.

*Persons with a history of dementia and stroke were excluded.

†Difference between men and women is significant at $P<0.001$.

‡Difference between men and women is not significant.

§Difference between men and women is significant at $P<0.02$.

‖40 mg/dL=1 mmol/L.

cognitive functioning were adjusted for age, education, and sex. Age is a component of the FSRP, but we used it as covariate because of its very strong relationship to cognitive function and its significant influence on the FSRP profile scores. Secondary analyses added total serum cholesterol, BMI, mean number of drinks per day, and depressed mood to the basic covariate set. Trails A and B (time scores) were positively skewed. Natural log transformations were performed to normalize these distributions.

Results

Table 2 defines the characteristics of the sample. Men exhibited significantly higher FSRP scores than women ($P<0.001$). For the FSRP components, men also exhibited higher SBP and had a higher prevalence of antihypertensive drug treatment, diabetes, and history of CVD, atrial fibrillation, and LVH ($P<0.05$ for all).

A comparison between the final study sample and the 923 individuals who declined to participate indicated that the decliners had a higher prevalence of CVD ($P<0.001$), myocardial infarction ($P<0.01$), CHD ($P<0.01$), adult-onset diabetes ($P<0.001$), and hypertension ($P<0.001$). They had higher SBP ($P<0.0001$) and were taking more antihypertensive medications ($P<0.001$). The decliners were only slightly older (62.1 versus 60.6 years; $P<0.0002$) and less well educated (13.7 versus 14.1 years; $P<0.0001$).

Factor Analyses

Three factors were extracted through the use of a criterion of eigenvalues >1.00 (remaining eigenvalues <0.71). With a criterion of orthogonally rotated (Varimax) factor pattern scores >0.45, the following variables loaded on the 3 factors: factor 1: Hooper (0.49), Visual Reproductions–Delayed Recognition (0.75), Visual Reproductions–Delayed Recall (0.88), and Visual Reproductions–Immediate Recall (0.88); factor 2: Logical Memory–Delayed Recognition (0.78), Logical Memory–Delayed Recall (0.87), and Logical Memory–Immediate Recall (0.88); and factor 3: Trails A (0.88) and Trails B (0.79). Paired Associates Learning remained a single variable, independent of the 3 factors. When the factor analysis was repeated without including Paired Associates Learning in the analysis, the same 3 factors were identified with loadings highly similar to the initial analysis. The factors were labeled as follows: (1) Visual-Spatial Memory and Organization; (2) Verbal–Learning and Memory; and (3) Concentration, Visual Scanning, and Tracking. Composite scores based on factors 1, 2, and 3 were the means for the standardized (z) scores for those tests having significant factor loadings as reported above.

In a preliminary set of analyses, a sex×FSRP interaction term was added to the basic regression model. There were no statistically significant sex×FSRP interactions for the composite scores and the individual test scores that were not included in the composites ($P>0.24$ for all). Consequently, these interaction terms were deleted from the regression equations in further analyses.

TABLE 3. Regression Coefficients Expressing Performance Decrements (in SD Units) for Each 10% Increment in 10-Year Risk of Stroke*

Psychometric Test	β†	SE	P
Similarities (abstract reasoning ability)	−0.111	0.032	0.0005
Paired Associates Learning (new learning and memory)	−0.024	0.034	0.4879
Verbal Memory Composite‡	−0.041	0.029	0.1626
Visual-Spatial Memory and Organization Composite	−0.150	0.026	<0.0001
Visual Reproductions–Immediate Recall	−0.172	0.033	<0.0001
Visual Reproductions–Delayed Recall	−0.141	0.033	<0.0001
Visual Reproductions–Delayed Recognition	−0.139	0.034	<0.0001
Hooper Visual Organization Test	−0.138	0.033	<0.0001
Concentration, Visual Scanning and Tracking Composite	−0.138	0.029	<0.0001
Trail-Making Test A (log transformation)	−0.144	0.034	<0.0001
Trail-Making Test B (log transformation)	−0.129	0.032	<0.0001

Scores on the Wide Range Achievement Test–Reading were unrelated to FSRP.

*Persons with a history of dementia or stroke were excluded.

†Regression coefficients are adjusted for age, sex, and education level.

‡None of the tests of Logical Memory (Immediate Recall, Delayed Recall and Delayed Recognition) were associated with the FSRP ($P>0.12$).

The next analytical step was to use multiple linear regression analyses to examine relationships between FSRP scores and composite scores for the sample of men and women combined. The FSRP score represents the 10-year probability or 10-year risk of stroke. To facilitate interpretation, we expressed the risk of stroke as a percentage, 0% to 99%, rather than as a probability, 0.00 to 0.99. In the present study, we examined 10% increments in 10-year risk of stroke in relation to cognitive performance in units of SD (z scores).

Table 3 displays the sex-, age-, and education-adjusted multiple regression coefficients (β) expressing decrements in test performance (in SD units) for each 10% increment in 10-year risk for stroke. For example, each 10% increment in 10-year risk for stroke was associated with a decrement of −0.15 SD for the Visual–Spatial Memory and Organization composite score and a decrement of −0.14 SD for the Concentration, Visual Scanning, and Tracking composite score.

Statistically significant associations (Table 3) between 10% increments in 10-year stroke risk and level of cognitive functioning were observed for the single index of Abstract Reasoning Ability, the Similarities Test, and 2 of the composite scores: Visual-Spatial Memory and Organization and Concentration, Visual Scanning, and Tracking. A posteriori analyses of the individual scores within these composites indicated that the FSRP score was inversely related to each of the individual scores making up these 2 composite scores ($P<0.05$). The FSRP score was unrelated ($P>0.05$) to the Verbal Memory composite, its component scores, and the Paired Associates Learning test.

After analyses with the basic model, the additional covariates (described previously) were added to the basic covariate set: ounces of alcohol/week, BMI, total cholesterol, and depressed mood (Center for Epidemiological Depression Scale >16). Each of these covariates has been related to ≥1 stroke risk factors or to cognitive performance.[19–22] When adjusted for these covariates, the pattern of significant associations between the FSRP scores and cognitive tests was exactly the same as reported for the basic model in Table 3.

Finally, with multiple regression analyses, each of the individual risk factors included in the FSRP was related to the composite scores for which FSRP–cognitive performance associations were statistically significant. Within the context of the full covariate model (age, education, sex, depressed mood, alcohol consumption, smoker, and total cholesterol), all the individual risk factors were inversely and significantly related to the Concentration, Visual Scanning, and Tracking composite score (range, $\beta=-0.901$, $P<0.01$ to $\beta=-0.469$, $P<0.0001$) except for SBP; AF was related to the Similarities score ($\beta=-0.328$, $P<0.002$), and SBP was inversely related to the Visual-Spatial Memory and Organization performance composite ($\beta=-0.023$, $P<0.02$). However, with adjustment for age, education, and occupation alone (basic covariate model), CVD, LVH, smoking, AF, and diabetes were also inversely related to Visual-Spatial performance (range, $\beta=-0.114$, $P<0.03$ to $\beta=-0.264$, $P<0.002$).

Discussion

We found that 10% increments in 10-year risk for stroke were inversely related to performance level for tests placing demands on abstract reasoning, visual-spatial memory, visual organization, concentration, visual scanning, and tracking. They were not significantly related to the verbal memory composite or the verbal measures of memory making up the composite. These findings confirm a significant association between stroke risk and cognitive functioning for a large community-based sample of men and women. They indicate that the range of cognitive abilities related to stroke risk is even greater than reported previously.[7] Clearly, stroke risk–related deficits are not limited to measures of executive functioning in the verbal mode as previously suggested[7] but extend to a variety of cognitive domains, including executive functioning in the visual scanning and tracking modality, ie, Trails B performance. Moreover, they confirm many previous reports[1,2] and reviews[3] indicating that that individual risk factors for stroke are associated with lowered performance for a wide range of cognitive abilities.

Neither vascular dementia nor clinical vascular cognitive impairment (VCI) was an outcome variable in our study. However, the pattern of results we see in our study of stroke risk was not unlike that seen in vascular dementia or VCI. For example, patients with vascular dementia show deficits in tests of motor performance and visual spatial, visual organizational, and visual constructional abilities.[23] Similarly, in VCI, memory deficit is observed but is not predominant,[24,25] as was the case in the present study. Deficits in VCI also include attention, concentration, and speed of performance.[25] In the present study, selected tests within the visual-spatial memory and organization composite, as well as those within

the concentration, visual scanning, and tracking composite, place demands on these abilities.

Our results and those of a previous study[7] raise an important question: Why is risk of stroke associated with lowering of cognitive performance in the absence of clinical stroke and dementia? It is frequently postulated that subclinical vascular disease provides an important link between the major risk factors for stroke and cognitive functioning.[1,3,4,7] Even older adults in relatively good health experience ischemic changes in the brain before the development of clinically diagnosed cerebrovascular disease.[26–28] Consequently, we hypothesize that cerebrovascular-related brain injuries, accelerated brain atrophy, abnormalities of cerebral white matter, and clinically asymptomatic cerebral infarction[29–35] are possible mechanisms linking risk for future stroke and cognitive functioning.[36–38]

Limitations of our study were as follows. The sample was almost entirely white, and the mean education level was high. This work needs to be extended to an ethnically and educationally diverse study population. Less healthy, less well educated, and slightly younger individuals declined to participate in the study in greater numbers than did their healthier, more educated, and slightly older counterparts. This is a widely reported finding in longitudinal and cross-sectional studies[39] and may have contributed to an underestimation of the magnitude of the associations between the FSRP and lowered cognitive functioning. Finally, measures of cognitive functioning were not longitudinal. Thus, we cannot describe longitudinal change in cognitive functioning in relation to increased stroke risk, as has been done for a relatively small sample of men.[7]

Despite these limitations, it is reasonable to conclude that risk of future stroke is associated with temporally concurrent deficits in abstract reasoning, visual-spatial memory, visual-spatial organization, attention, and visual scanning and motor speed (tracking) deficits for persons who are currently free of diagnosed dementia and clinical stroke. Hopefully, our findings will stimulate investigations of the link between stroke risk and cognitive function and provide further emphasis to the potential role of prevention and management of stroke risk in the preservation of cognitive functioning.

Acknowledgments

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