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Framingham Stroke Risk Profile is related to cerebral small vessel disease progression and lower cognitive performance in patients with hypertension

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The Framingham Stroke Risk Profile (FSRP) was developed to predict clinical stroke. We investigated if FSRP is associated with more "silent" effects of cerebrovascular disease, namely progression of cerebral small vessel disease (cSVD)-related brain damage and cognitive performance in hypertensive patients. Ninety patients with essential hypertension underwent a brain MRI scan and FSRP assessment at baseline, and a second brain MRI scan and neuropsychological assessment at 9-year follow-up. We visually rated progression of cSVD-related MRI markers. FSRP was associated with progressive periventricular white matter hyperintensities ($P = .017$) and new microbleeds ($P = .031$), but not after correction for the FSRP age component. FSRP was associated with lower overall cognitive performance ($P < .001$) and this remained significant after correction for the FSRP age component. A vascular risk score might be useful in predicting progression of cSVD-related brain damage or future cognitive performance in hypertensive patients. Age seems to be the most important component in FSRP.

1 | INTRODUCTION

Cerebral small vessel disease (cSVD) is a pathologic process involving the small arteries and arterioles in the brain, resulting in MRI abnormalities, such as white matter hyperintensities (WMH), lacunes, and microbleeds.[1] cSVD is a major cause of cognitive deficits and cognitive decline.[2,3] Hypertension is probably the most important risk factor for cSVD.[4] Other cardiovascular risk factors, including diabetes mellitus and smoking, have also been associated with cSVD[5-7] and lower cognitive function.[8-10]

The Framingham Stroke Risk Profile (FSRP) is a composite vascular risk score, which was originally developed to predict clinical stroke. Previous studies have investigated whether the FSRP is also associated with more "silent" cerebrovascular disease, such as MRI markers of cSVD. Several studies have shown that an increased FSRP is associated with the extent of WMH.[11,12] Other studies showed a higher FSRP in patients with silent cerebral infarcts or microbleeds compared to patients without these lesions.[13-15] Even though the FSRP is a prediction score, no longitudinal studies examining the

association with progression of cSVD or new cSVD lesions could be found.

A number of cross-sectional and longitudinal studies have examined the association between FSRP and cognitive performance or cognitive decline. For example, in the Framingham Offspring Cohort, an inverse association between FSRP and cognitive performance in several domains was shown.[16] Another study showed the FSRP to be associated with greater global cognitive decline over 10 years.[17]

Studies investigating the associations between FSRP and progressive cSVD and cognitive performance in patients with hypertension are lacking. More insight into the use of this composite vascular risk score in this population at high risk of cSVD and cognitive dysfunction is needed. Therefore, in a longitudinal, 9-year follow-up study, we investigated if the FSRP is associated with progression of MRI markers of cSVD and cognitive performance in patients with essential hypertension.

2 | METHODS

2.1 | Study population

Subjects were essential hypertensive patients who were included in a study on brain damage in patients with essential hypertension (HYBRiD).[18] Patients were recruited from the hypertension outpatient clinic of the Department of Internal Medicine of Maastricht University Medical Centre, the Netherlands. Hypertension was defined as an off-medication, clinically measured conventional systolic blood pressure (SBP) ≥140 mm Hg, diastolic blood pressure (DBP) ≥90 mm Hg, or both. Details about the HYBRiD study have been described before.[18] Exclusion criteria were: documented diabetes, ischemic or valvular heart disease, electrocardiographic evidence of atrial fibrillation, history of transient ischemic attacks or stroke, and obstructive sleep apnea syndrome. At baseline, all patients received a brain MRI and the FSRP was determined. Nine years later, patients were invited for a second brain MRI, a neuropsychological assessment, and a conventional on-medication office blood pressure measurement. The current study is a retrospective, secondary analysis of the HYBRiD study. The Medical Ethics Committee of the Maastricht University Medical Centre approved this study and all participants gave written informed consent.

2.2 | Framingham Stroke Risk Profile

The FSRP is developed to predict 10-year probability of stroke and is derived from the Framingham study.[19,20] The gender-specific score is composed of age, SBP (with or without antihypertensive medication), diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. In our study, the FSRP factors were determined at baseline. SBP was determined by off-medication, conventional office blood measurements by sphygmomanometry. After at least 5 minutes of rest, 3 consecutive measurements were taken using the non-dominant arm with the participant seated. The mean of the second and third measurements was calculated. Electrocardiographic left ventricular hypertrophy was defined as a Sokolow-Lyons index (SV_1 + $RV_{5\text{-}6}$) >38 mm. Since diabetes mellitus and atrial fibrillation were exclusion criteria for our study, all patients received zero points for these factors in the FSRP.

2.3 | Neuropsychological assessment

Cognitive performance was measured at 9-year follow-up, with an extensive neuropsychological assessment; as has been described before.[21] Memory domain was measured with the Rey Auditory Verbal Learning Test[22] (immediate recall, delayed recall, and delayed recognition) and the Digit Span Forward (subtest of Wechsler Adult Intelligence Scale [WAIS]-III[23]). Executive function domain was measured with the Stroop Colour Word Test[24] (SCWT) interference score (time of part 3 minus mean time of parts 1 and 2), Trail Making Test[25] (TMT) interference score (time of part 2 minus time of part 1), category (animals and professions),[26] and letter fluency,[27] letter-number sequencing (subtest of WAIS-III), and digit span backward (subtest of WAIS-III). Information processing speed domain was measured with the symbol substitution—coding (subtest of WAIS-III), TMT part A, and SCWT parts 1 and 2. Test scores were transformed into standardized values (*z*-scores), by dividing the difference between the individual raw score and the sample mean by the sample standard deviation. For each patient, domain scores were calculated by averaging these *z*-scores of the tests within that domain. Finally, the overall cognition score was calculated by averaging the domain scores of memory, executive function, and information processing speed.

The Dutch Adult Reading Test (DART) was used as a measure of prior cognitive ability.[28] The Rotterdam-Cambridge Cognitive Examination (R-CAMCOG) was used to determine the presence of possible dementia, defined as a score <34.[29] The Hospital Anxiety and Depression Scale (HADS) total score (range 0-42) was used to determine symptoms of depression and anxiety. Since symptoms possibly caused by physical problems (eg, insomnia or weight loss) are not included in the HADS, the scale is considered to be suitable to use in somatic populations.[30]

2.4 | MRI data

We used the same MRI scanner (Intera 1.5-T; Philips Medical Systems, Best, the Netherlands) and the same protocol (standard axial T2-weighted, FLAIR and T2* gradient echo sequences) with the same sequences parameters at baseline and follow-up. On these brain MRI scans at baseline and after 9 years, 2 experienced vascular neurologists rated baseline MRI markers, and one rated progression of markers, after reaching satisfactory inter-rater agreements. The inter-rater agreement statistics have been previously reported.[31] Baseline WMH were assessed according to the Fazekas scale.[32] Presence of extensive periventricular WMH was defined as periventricular WMH Fazekas score 3 (irregular hyperintensities extending into the deep matter) and presence of extensive subcortical/deep WMH was defined as deep WMH Fazekas score 2 or 3 (confluent hyperintensities). Lacunes and cerebral microbleeds were assessed according to international consensus definition.[33] An overall score for the baseline MRI total burden of cSVD was composed, as described earlier.[34]

Progression of periventricular and subcortical WMH were scored according to the WMH change scale, as proposed by Prins and colleagues.[35] Progression of periventricular WMH was scored in 3 regions (frontal caps, lateral band, and occipital caps) and progression of subcortical WMH was scored in 4 regions (frontal, parietal, temporal, and occipital). New lesions or increase of existing lesions was scored in each region as +1 and disappeared lesions or decrease of existing lesions was scored as −1. This adds up to a progression score ranging from −3 to +3 for periventricular WMH and −4 to +4 for subcortical WMH. We defined progression of periventricular or subcortical WMH as a score of ≥1. Progression of lacunes or microbleeds was defined as any new lacune or microbleed.

2.5 | Statistical analysis

Differences between included and excluded patients were examined with independent sample *t*-test or chi-square test.

Associations between FSRP and progression of MRI markers of cSVD were analyzed with simple logistic regression and thereafter with correction for baseline presence of the studied MRI marker. Associations between FSRP and cognitive performance in overall cognition and 3 separate cognitive domains (executive function, information processing speed, and memory) were first analyzed with simple linear regression analyses and second with multivariable linear regression with correction for DART and HADS score.

Exploratory analyses were performed to examine if associations between FSRP and progression of MRI markers or cognitive performance were explained by just the age or SBP component, as these are known to be important determinants of cSVD and cognition. Therefore, the associations between FSRP and progression of MRI markers (including correction for the baseline MRI marker) that were found to be significant were additionally adjusted for the FSRP age or SBP component (ie, the points awarded in the FSRP for age or SBP). Similarly, the significant associations between FSRP and cognitive performance, with correction for DART and HADS, were additionally adjusted for the age and SBP FSRP component separately. We also performed exploratory analyses, in which we adjusted the associations between FSRP and cognitive performance for baseline total burden of cSVD on MRI.

IBM SPSS Statistics 22 software was used for all analyses. Results were considered significant at $P < .05$.

3 | RESULTS

3.1 | Participants

Of the original 218 patients in the HYBRiD study, 90 (41.3%) completed the follow-up after 9 years. Reasons for exclusion during follow-up were: no consent to be contacted for follow-up (n = 20), not interested (n = 79), cerebrovascular event during follow-up (n = 7), death (n = 4), contra-indications for MRI (n = 5), neuropsychological assessment not possible (n = 4), unreachable (n = 4). and other reasons (n = 5).

The mean follow-up period was 9.06 years (SD = 0.14). Patients that were included (n = 90) did not differ from excluded patients (n = 128) in age (51.2 ± 11.9 vs 52.3 ± 13.1 years, respectively [$P = .498$]) or sex (male 57.8% vs 45.3%, respectively [$P = .070$]). There was a difference in presence of periventricular WMH at baseline between included patients and excluded patients (26.2% vs 44.9%, respectively [$P = .027$]), but there was no difference in presence of any of the other cSVD markers at baseline between included and excluded patients (all $P > .05$). Baseline and follow-up characteristics are shown in Table 1. Brain MRI of one patient was of insufficient quality to determine progression of WMH; therefore analyses for progression of WMH included 89 patients.

3.2 | Progression of cSVD markers on MRI

In simple regression analyses, FSRP was associated with progression of periventricular WMH and with new microbleeds (Table 2). These

TABLE 1 Patients' characteristics

	All patients (n = 90)
Baseline assessment	
Age, mean (SD), y	51.2 (11.9)
Male sex, No. (%)	52 (57.8)
Off-medication blood pressure	
Systolic blood pressure, mm Hg, median (IQR)	160.0 (148.75-180.5)
Diastolic blood pressure, mm Hg, median (IQR)	101.0 (94.0-108.25)
History of cardiovascular disease, No. (%)	24 (26.7)
Left ventricular hypertrophy, No. (%)	6 (6.7)
Smoking, No. (%)	14 (15.6)
FSRP total score, median (IQR)	8.5 (6.0-13.0)
Follow-up assessment	
On-medication blood pressure	
Systolic blood pressure, mm Hg, median (IQR)	142.75 (134.0-158.5)
Diastolic blood pressure, mm Hg, median (IQR)	83.5 (77.0-92.0)
Use of antihypertensive medication, No. (%)	77 (85.6%)
DART, median (IQR)	86 (74-94)
HADS total score, median (IQR)	6 (4-12)
Progression of periventricular WMH, No. (%)[a]	23 (25.8)
Progression of subcortical WMH, No. (%)[a]	44 (49.4)
New microbleeds, No. (%)	7 (7.8)
New lacunes, No. (%)	9 (10.0)

DART, Dutch adult reading test; FSRP, Framingham stroke risk profile; HADS, hospital anxiety and depression scale; IQR, interquartile range; SD, standard deviation; WMH, white matter hyperintensities.

[a]Information about progression of periventricular and subcortical WMH was missing for 1 patient.

TABLE 2 Associations between FSRP and progression of MRI markers

	Periventricular WMH		Subcortical WMH		Lacunes		Microbleeds	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Unadjusted logistic regression	1.19 (1.05-1.36)	.008	1.07 (0.96-1.20)	.196	1.08 (0.91-1.29)	.368	1.31 (1.04-1.64)	.022
Corrected for baseline MRI marker	1.18 (1.03-1.36)	.017	1.04 (0.92-1.16)	.549	1.02 (0.85-1.23)	.840	1.29 (1.02-1.64)	.031

CI, confidence interval; FSRP, Framingham stroke risk profile; OR, odds ratio; WMH, white matter hyperintensities.

TABLE 3 Associations between FSRP and cognitive performance

	Overall cognition		Executive function		Information processing speed		Memory	
	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*	B (95%CI)	*P*
Unadjusted linear regression	−0.10 (−0.13 to −0.06)	<.001	−0.07 (−0.11 to −0.03)	<.001	−0.12 (−0.16 to −0.09)	<.001	−0.09 (−0.12 to −0.06)	<.001
Corrected for DART & HADS	−0.09 (−0.12 to −0.06)	<.001	−0.07 (−0.10 to −0.03)	.001	−0.12 (−0.16 to −0.09)	<.001	−0.09 (−0.12 to −0.06)	<.001

CI, confidence interval; DART, Dutch adult reading test; FSRP, Framingham stroke risk profile; HADS, hospital anxiety and depression scale B, unstandardized regression coefficient.

results did not change after correction for baseline presence of the MRI marker. In both simple and multivariable regression analyses, no significant associations were found between FSRP and progression of subcortical WMH and new lacunes (Table 2).

3.3 | Cognitive performance

At follow-up, 3 patients had an R-CAMCOG score <34, indicating possible dementia.

Simple linear regression analyses showed that higher FSRP was associated with lower cognitive performance in overall cognition, executive function, information processing speed, and memory (Table 3). Correction for DART and HADS score did not change the results (Table 3).

For illustration, Figure shows mean *z*-scores of overall cognition for tertiles of FSRP. It can be seen that the first tertile (low FSRP) has a higher mean *z*-score (higher cognitive score), while the third tertile (high FSRP) has a lower mean *z*-score (lower cognitive score).

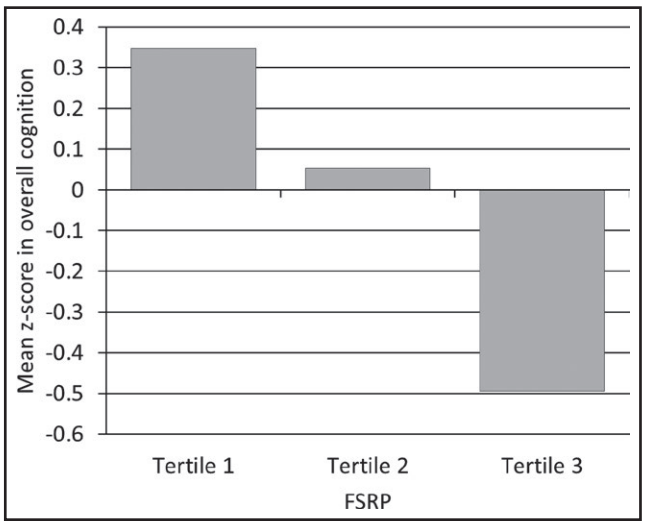

FIGURE Mean *z*-scores in overall cognition for tertiles of FSRP. FSRP, The Framingham Stroke Risk Profile

3.4 | Exploratory analyses

The association between FSRP and progression of periventricular WMH, corrected for baseline presence of periventricular WMH, lost significance after additional adjustment for the FSRP age component, but remained significant with correction for the FSRP SBP component. The association between FSRP and new microbleeds was no longer significant after adjustment for either the component of age or SBP.

The association between FSRP and cognitive performance in overall cognition, information processing speed, and memory (corrected for DART and HADS) remained significant after additional correction for the age or SBP component. Only for executive function, the association with FSRP lost significance after adjustment for age. All associations between FSRP and cognitive performance remained significant after additional correction for baseline total burden of cSVD.

4 | DISCUSSION

The results of the present study show that the Framingham Stroke Risk Profile is associated with progression of periventricular WMH

and with new microbleeds over 9 years of follow-up in patients with essential hypertension. We could not show associations between FSRP and progression of subcortical WMH and new lacunes. Furthermore, we showed that FSRP was associated with cognitive performance.

Previous studies showed that the FSRP is associated with presence of MRI markers of cSVD, but longitudinal results were lacking. We performed a longitudinal study into the association between FSRP and progression of cSVD. Our finding, that FSRP is associated with progression of periventricular WMH but not with progression of subcortical WMH, is in agreement with an earlier cross-sectional study.[12] Another study showed that FSRP was associated with total WMH, but did not differentiate between periventricular and subcortical WMH.[11] Even though baseline presence of WMH is a strong predictor of its progression,[36] we showed that the association between FSRP and progression of periventricular WMH was independent of baseline presence of periventricular WMH.

We also showed an association between FSRP and new microbleeds. Only 1 previous cross-sectional study investigated the association between FSRP and microbleeds and showed that FSRP was higher in patients with microbleeds compared to patients without microbleeds.[15] During our 9-year follow-up study, only a few patients developed new lacunes, which is quite low compared to other studies,[37] and we could not show an association between FSRP and new lacunes. Larger studies into the association between FSRP and new microbleeds and lacunes are needed.

We found that FSRP is associated with cognitive performance, which is in agreement with previous studies in other populations. In a cross-sectional study in the Framingham Offspring Cohort, Elias and colleagues[16] showed that the FSRP was associated with lower cognitive performance in several cognitive domains. Another cohort study showed that the FSRP, in midlife, was associated with cognitive decline over 10 years.[17] From our study, we can conclude that these results are similar in hypertensive patients, who have a higher risk for cSVD and cognitive deficits.

Age is generally considered the most important risk factor for cSVD and cognitive decline. In addition to age, hypertension is a major risk factor for cSVD. Therefore, the associations of FSRP with progressive cSVD and cognitive performance might be attributable to only age or SBP. Since our exploratory analyses showed that the association between FSRP and periventricular WMH lost significance after adjustment for the FSRP age component, this confirms the idea that age is probably the most important factor of the FSRP in the association with progression of periventricular WMH. In contrast, adjustment for SBP did not alter the association, which might be attributable to a reasonable blood pressure control during follow-up. For new microbleeds, the association with FSRP lost significance after adjustment for either age or SBP. For overall cognition, the association with FSRP remained significant after adjustment for any of the FSRP components. Therefore, we can conclude that the association between FSRP and cognitive performance is not explained by only age or SBP, but that multiple components are implicated in the association.

A major strength of our study is the longitudinal design with a 9-year follow-up, in which brain MRI scans are taken at both time points to determine the progression of markers. In addition, patients received an extensive neuropsychological assessment with multiple tests in 3 different cognitive domains. A limitation of the study is the lack of neuropsychological assessment at baseline, which withheld us from determining cognitive decline over the 9 years. However, since we used the DART to control for prior cognitive performance, results actually reflect associations with a lifetime change in cognitive performance. Second, although the long follow-up time was considered a strong point of our study, it was also coupled with a high dropout rate. Only 90 of the 218 patients included at baseline responded to the follow-up, possibly causing a selection bias. For example, patients excluded from follow-up might be those with worse cognitive function. Third, since diabetes mellitus and atrial fibrillation were exclusion criteria for our study, the entire spectrum of risk factors in the FSRP is not present in our sample. This might also cause the remaining factors, especially age and hypertension, to be more important in the FSRP in our cohort, possibly limiting the generalizability of the results.

In conclusion, our results show that the Framingham Stroke Risk Profile, a composite vascular risk score originally developed to predict symptomatic stroke, is also associated with more "silent" effects of cerebrovascular disease, such as progressive cSVD and cognitive performance in patients with hypertension. While we showed that the age component was the most important for progressive cSVD, this was not the case for cognitive performance. Our results support the importance of early detection of other vascular risk factors in patients with hypertension. Clinicians should be aware of the entire risk factor profile in attempting to preserve cognitive performance. Future studies are needed to examine if the predictive value of the risk factor profile could be improved by including more factors, such as education or prior cognitive ability.

CONFLICT OF INTEREST

None.

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