**Are different vascular risk scores calculated at midlife uniformly associated with subsequent poor cognitive performances?**

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**Abstract**

**Background:** Research concerning the link between individual vascular risk factors and cognition is plentiful but few studies have investigated the role of global vascular risk. We examined the cross-time associations of several vascular risk scores with cognitive performance during aging.

**Methods:** Using data from the French SU.VI.MAX cohort, we studied a sample of 3,061 participants. Framingham coronary heart disease, cardiovascular and stroke risk profiles were computed using baseline data (1994-1996). Cognitive performance was assessed after a mean of 13 years via a battery of six validated instruments. Principal component analysis identified scores for verbal memory and working memory.

Associations between risk profiles (as continuous variables and in quartiles (Q)) and subsequent poor performance (defined as poor cognitive score, i.e. $<10^{th}$ percentile) were examined via logistic regression (odds ratios, 95% CI).

**Results**: All continuous-scale Framingham risk scores assessed at midlife were inversely and uniformly associated with subsequent poor global cognitive performance, especially in terms of verbal memory. Considering risk score Q, higher quartiles were associated with poorer performance in verbal memory: The fully-adjusted odds ratios (95% CI), comparing Q4 versus Q1, were 2.84 (1.70, 4.75), 2.31 (1.43, 3.73) and 1.77 (1.13, 2.76) for Framingham coronary heart disease, cardiovascular and stroke risk profiles, respectively. Similar findings were observed when modeling cognitive outcomes as continuous variables using covariance analyses.

**Conclusion:** This study supports the existence of an inverse cross-time association between midlife vascular risk profiles and subsequent poor cognitive performance in memory. Beyond their importance as regards vascular risk, such risk scores may help primary prevention efforts in identifying and targeting individuals at high risk of cognitive aging.

## 1. Introduction

Cardiovascular (CV) disease is a major public health challenge in the western world, likely to worsen with the increasing prevalence of obesity and type 2 diabetes [1]. Owing to common mechanistic pathways, a growing body of evidence supports a role of CV risk factors in cognitive decline etiology [2-4].

Over the past few decades, multicomponent CV risk scores based on the Framingham Risk equations and accounting for joint effects have been elaborated in order to predict CV events and to characterize CV profiles in a quantitative manner [5]. According to a recent meta-analysis, interventions using such validated scores to identify high-risk individuals may help decrease CV morbidity and mortality risk [6].

Recent clinical research using quantitative MRI reported an inverse association between total cerebral brain volume ratio and Stoke Risk Profile, while a positive association was observed between total cerebral brain volume ratio and cognitive function [7].

As recently reviewed [8], most of epidemiological studies investigating the link between CV risk scores and subsequent cognitive outcomes are cross-sectional [7;9-12] or have considered only the Framingham Stroke risk profile (FSRP) [7;9;10;12-16]. To our knowledge, only one study compared different Framingham risk profiles in the same population [17]. Furthermore, there is a large heterogeneity in the neuropsychological tests employed, which limits the possibility to compare the respective studies [8]. Accordingly, researchers have underlined the need to summarize individual cognitive scores via multidimensional techniques (principal component analysis, PCA; factor analysis) and to use such summary cognitive scores as primary outcomes- rather than only investigating performances on specific tests [2].

The aims of the present study were to estimate the cross-time association between different Framingham risk scores assessed in midlife using accurate data and subsequent poor performance in large sample. Accounting for previously reported limitations, we focused on

different cognitive domains characterized by summary scores, and we test if the associations differed by the risk profile score used accounting for follow-up bias.

## 2. Materials and methods

### 2.1 Population

The SU.VI.MAX study (SUpplémentation en VItamines et Minéraux AntioXydants, 1994-2002) was a randomized, double-blind, placebo-controlled primary prevention trial including 12,741 individuals for a planned follow-up of 8 years. It tested the efficacy of daily nutritional-dose supplementation with antioxidant vitamins and minerals (ascorbic acid, vitamin E, β-carotene, selenium, zinc) on the incidence of cancer, CV morbidity and overall mortality [18].

Following the trial phase, participants were invited for an additional follow-up. From the initial sample, 6,850 participants were (on a voluntary basis) included in the SU.VI.MAX 2 observational study (2007-2009), which investigated the impact of nutrition on quality of aging [19].

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the guidelines laid down in the Declaration of Helsinki and were approved by the Ethics Committee for Studies with Human Participants of Paris-Cochin Hospital (CCPPRB n° 706 and n° 2364, respectively) and the Comité National Informatique et Liberté (CNIL n° 334641 and n° 907094, respectively). Written informed consent was obtained from all participants.

### 2.2 Selection of the sample

From the 6,850 participants in the SU.VI.MAX 2 study, we excluded women < 45 years at baseline ($n$=1,267) to obtain a similar age range across genders, those with missing neuropsychological data ($n$=1,136), with missing data for Framingham risk profile computation ($n$=891) or with missing covariate data ($n$=295). The final sample included 3,261 participants.

2.3 Data collection

In 2007-2009, all participants were invited to undergo a clinical examination and (in a sub-sample) a neuropsychological evaluation by trained neuropsychologists. Episodic memory was evaluated using the RI-48 delayed cued recall test based on a list of 48 words belonging to 12 different categories. This test was designed to limit "ceiling effects" encountered in some list-learning tests. The total score was the number of words retrieved (maximum score of 48) [20]. Lexical-semantic memory was assessed by verbal fluency tasks, including a semantic fluency task (naming as many animals as possible), and a phonemic fluency task (citing words beginning with the letter P). The total score was the number of correct words produced during a 2-min period for each task [21]. Working memory was assessed with the forward and backward digit span. Participants were asked to repeat two sequences of digits, forwards or backwards. The number of digits increased by one until the participant failed two consecutive trials of the same digit span. One point was scored for each correct sequence repeated, with a maximum score of 14 points for digit span forward as well as backward. Mental flexibility was assessed through the Delis-Kaplan trail-making test (TMT) [22], consisting of connecting numbers and letters alternating between the two series. The score was the time in seconds needed to complete the task [23]. We thus reverse-coded this score so that higher scores would correspond to better performance, and further log-transformed it to improve normality. The cognitive test scores were converted into T scores (mean=50, SD=10). A composite cognitive score was defined as the mean of the standardized test scores [24].

Moreover, principal component analysis (PCA) with orthogonal rotation was performed in order to yield summary scores accounting for correlations among the cognitive tests as previously outlined[19]. Briefly stated, PCA factors are linear combinations of the initial

variables (the cognitive test scores in our case) that explain a maximum of the variance-covariance structure of these initial variables.

Habitually, PCA-factors are named after those initial variables with which they have the strongest correlations.

The extracted factors as well as the composite cognitive score were rescaled to have an SD of 10.

In order to account for multiple comparisons, results were hierarchically interpreted. We defined the composite cognitive score and the extracted PCA-factors as our main outcomes, and scores on the TMT (reflecting mental flexibility) as secondary outcome. Mental flexibility appeared to be of major interest in the context of our study as it presents a key domain of executive function, and previous studies argue for a role of the FSRP in subsequent executive functioning [7;9;10;13].

We defined the extracted PCA-factors as our main outcomes, but also investigated the specific association between mental flexibility (measured by the TMT in our study), a key domain of executive function and the risk profile scores, as previous studies argue for a role of the FSRP in subsequent executive functioning [7;9;10;13].

At baseline, information on sex, age, smoking (never, former, current smoker), alcohol use (g/day), physical activity (irregular, <1 h walking/day, ≥1 h walking/day), occupation (employees/office work, manual workers, homemakers/unemployed, white collar), education (primary, secondary, university level), self-reported medication use and self-reported memory troubles [“Do you have any memory complaints?“ (yes/no)] was collected by questionnaires.

At the first clinical examination (1995-1996), anthropometric measurements were collected. Blood pressure (BP) was measured using a standardized procedure with a mercury sphygmomanometer. It was taken once from each arm following a 10-min rest. The mean of

these two measurements was used for analyses. Blood samples were obtained after a 12-h fast, and all biochemical measurements were centralized.

The following biochemical indicators were measured at baseline: Fasting blood glucose, serum triglycerides and serum total cholesterol (Advia 1650 autoanalyzer; Bayer Diagnostics, Puteaux, France), as well as serum apolipoprotein B (nephelemetric assay, BNA Behring). HDL-cholesterol was calculated from total cholesterol and apolipoprotein B, using Planella's equation and the Friedewald formula [25;26].

Diabetes mellitus was defined as glucose concentrations ≥ 7 mmol/L or antidiabetic drug use.

Depressive symptoms were assessed during SU.VI.MAX 2 using the French version of the Center for Epidemiologic Studies Depression (CES-D) Scale [27].

2.4 Statistical analysis

Coronary heart disease (Framingham Coronary Heart Disease Risk Profile, FCHDRP), general CV disease (Framingham Cardiovascular Disease Risk Profile, FCVDRP) and stroke (FSRP) risk profiles were calculated using the Framingham equation system with SU.VI.MAX baseline data (1994-1996) [28]. The Framingham risk scores include baseline age, sex, systolic BP, HDL-cholesterol, total cholesterol, smoking (current versus former or never), and diabetes with specific weight. Left ventricular hypertrophy was not available in our sample, thus this parameter was not accounted for.

Framingham risk scores aim to predict 10-year probability of developing coronary heart disease, stroke and CV disease. Higher scores have been designed to be associated with a higher risk of new events.

Risk scores were divided into quartiles (Q1-Q4) for analysis and standardized continuous scores were also computed.

Included and excluded participants were compared using the $chi^2$ test or Wilcoxon rank test, as appropriate.

Descriptive baseline characteristics are reported as mean (SD) or percentages by sex as equations are different for men and women. Reported P-values refer to non-parametric Wilcoxon test or to the chi² test, as appropriate.

Logistic regression was used to model the odds ratio (OR) and 95% confidence interval (CI) of poor cognitive performance (i.e., scoring ≤10th percentile on the cognitive assessment allowing to use OR as reliable proxy of relative risk) across Framingham risk score Q, using the lowest category as reference. P for trend was assessed, using linear contrast tests across the categories. OR of poor cognitive performance according to Framingham risk scores modeled as continuous variables (after standardization) were also estimated, i.e. for an increase of 1 SD of each risk score.

In the initial model, analyses were adjusted for age and sex. In the second model, analyses were adjusted for follow-up time (year), age at neuropsychological examination (year), sex and education (primary, secondary and post-secondary).

In the third set of models, analyses were further adjusted for occupation (employees manual workers, homemakers/ unemployed, white collar), intervention group (active group or placebo) during the trial phase (1994-2002), baseline alcohol consumption (g/d), baseline physical activity (irregular, <1h/day, ≥1 h /day), depressive symptoms (continuous score ranging from 0 to 60) concomitant with the cognitive evaluation, and baseline self-reported memory troubles (yes/no).

As an attempt to partly correct for selection bias, analyses were carried out using inverse probability weighting [29]. The probability of being included in the study was determined using baseline characteristics, including sociodemographic, lifestyle (alcohol, diet, physical activity) and health variables as well as interaction terms, among the original cohort after removing women younger than 45 years (N=10,090). The C statistic of the final model was 0.69 and the quality of the model was estimated through published recommendations (P-value

of the square of logit of the predicted value added in the model, Hosmer–Lemeshow test, absence of zero fitted probability in both included and excluded participants, comparison of the sum of the 10% highest weights in included participants to half of the total sum of weight) [29].

Data were analyzed using the inverse probability of inclusion as the respective weight.

To compare the predictive values of the different risk scores on cognition, we used the area under the receiver operating characteristic curves (AUC) [30]. AUC comparisons were fit using the SAS %add_predictive macro.

Effect modification by gender and antihypertensive treatment was also tested. Sensitivity analyses were also performed after excluding participant developing stroke during the follow-up (N=39).

In secondary analysis, covariance analyses were used to estimate the difference in mean cognitive scores (95% confidence interval, CI) with similar adjustment strategy for composite cognitive score, verbal memory score and working memory score.

All tests of statistical significance were two-sided and the type I error was set at 5%.

Statistical analyses were performed using SAS software (version 9.3, SAS Institute Inc, Cary, NC, USA).

**3. Results**

Among SU.VI.MAX participants > 45y at baseline (N=10,090), subjects excluded from the current study were more likely to be women, younger, more often smokers, with lower levels of education, less physically active. They also exhibited higher total cholesterol and fasting glucose concentration and higher systolic blood pressure. Excluded participants performed worse on some cognitive tests, i.e. digit span, and showed higher depressive symptoms (Supplemental table 1).

Participants were 65.5 (SD=4.6) years old at the neuropsychological evaluation. Mean follow-up was 13.4 (SD=0.6) years.

Characteristics of participants by sex are shown in **Table 1**. Men reported higher education, higher alcohol intake, were less likely to report memory troubles at baseline or depressive symptoms at follow-up, and were more physically active than were women. They also had higher BMI, BP, glycemia, total and LDL-cholesterol and lower HDL-cholesterol at baseline than did women. Men were also more often smokers (current and former). They presented higher Framingham risk scores overall.

Two cognitive factors were extracted with PCA, reflecting 61% of the initial variance. The first factor had the strongest correlations, i.e. factor loadings, with semantic (0.80) and phonemic fluency (0.66) and the RI-48 cued recall test (0.76), and thus primarily reflected language and lexical-semantic memory. The second factor had the strongest correlations with forward (0.84) and backward (0.84) digit span tasks, and thus primarily reflected working memory.

Associations between Framingham risk profiles (FCHDRP, FCVDRP and FSRP) in Q and subsequent poor cognitive impairment are presented in **Table 2**.

FCHDRP and FCVDRP were both associated with global cognitive impairment. Moreover, while all three Framingham risk profiles (FCHDRP, FCVDRP FSRP Q) were associated with poor performance in verbal memory, none of the risk profiles were associated with poor performance in working memory.

Concerning the association of the TMT with the risk profiles, a significant association with FCHDRP, FCVDRP and FSRP as standardized continuous scores was observed, with OR (95% confidence interval) comparing $4^{th}$ versus $1^{st}$ Q of 1.29 (1.12, 1.49), 1.27 (1.11, 1.46) and 1.22 (1.08, 1.38), respectively (data not tabulated).

No effect modification by gender or antihypertensive treatment was detected. Also, reanalysis of our data after removing participants developing stroke (N=39) provides similar findings. Associations between Framingham risk profiles (FCHDRP, FCVDRP and FSRP) - as modeled on a continuous standardized scale - and subsequent poor performance are presented in **Figure 1**.

Considering these continuous-scale standardized risk scores, all three risk profiles were significantly and negatively associated with global cognitive impairment and most specifically with poor performance in verbal memory, even after adjustment for confounders. AUC analysis (supplemental Table 1) revealed no differences in the prediction of poor cognitive performance according to risk score (All P >0.05).

Findings from the secondary analysis testing for the associations between Framingham risk profiles (FCHDRP, FCVDRP and FSRP) in Q and subsequent poor cognitive performances are presented in **Table 3**. Findings were similar to those of the primary analysis. All the Framingham risk profiles (FCHDRP, FCVDRP and FSRP) were negatively associated with verbal memory performances.

**4. Discussion**

Using a large sample of aging adults, this study showed a significant long-term role of all three Framingham CV midlife risk profiles in poor cognitive performance during aging, particularly in the domain of verbal memory. These findings persisted after accounting for many confounders, especially non-modifiable risk factors such as sex and age. Computing of area under the ROC curve argue for interchangeability of midlife risk scores in relationship with subsequent cognitive function.

Such scores, easily computable from non-invasive data, are great interest in clinical practice to identify very early population at elevated risk in poor cognitive performance in aging.

Besides, improvement of modifiable factors may help in maintaining cognitive performance in aging.

For comparison purposes, we modeled these three scores, reflecting heart disease, CV disease and stroke risk, as continuous variables. These scores were similarly associated with poor performance in the verbal memory domain. However, stroke risk, when modeled in Q, was less strongly associated with cognitive impairment than were the other two risk scores, which could be partly explained by the fact that stroke risk in our population was low, with small variability.

Only one study reported association between heart disease risk profile (FCHDRP) and cognitive outcome [31], especially with verbal fluency and recall what is concordant with our findings but only in women. As expected, findings related to FCVDRP and FCHDRP were very similar given the strong correlation between these two scores (Spearman r = 0.98).

A large body of literature argues for a role of vascular risk factors in cognitive health [2-4], especially executive function, regulated by the frontal cortex. Next, FSRP does not adequately encompass all risk factors. In particular, cholesterol, especially low HDL-cholesterol but also total cholesterol, which is not prominent in the FSRP computation, has been associated with cognitive dysfunction [2].

Our findings pertaining to FSRP are in line with previous research [8], albeit scarce, reporting a positive association between stroke risk and dysfunction in verbal memory [9;12;17]. In contrast, other studies did not detect a harmful impact of higher stroke risk on memory performance or decline [7;10;15;32].

Previous research has documented a role of FSRP in subsequent executive functioning despite a marked heterogeneity in the used neuropsychological tests [7;9;10;13]. Such findings are consistent with the observed association between FSRP and TMT in our study.

Available data pertaining to the role of FCVDRP in cognitive outcomes are more heterogeneous, especially concerning the range of investigated cognitive domains, with studies focusing on few tests [11] or on global cognitive function only [33]. While Kaffashian et al. reported that higher FCVDRP was associated with a more pronounced decline in ”reasoning” performance in particular [34], Dregan et al. reported a consistent, harmful role of higher FCVDRP- irrespective of the cognitive index [17].

No prior study investigating the relationship between FSRP and cognitive decline has yet compared the different risk scores with respect to the magnitude of their association with cognitive performance. Although Kaffashian et al. presented information comparing the predictive value of FCVDRP and FSRP against the CAIDE score, which was developed specifically to predict dementia, a direct comparison between FCVDRP and FSRP was not provided [34].

Underlying mechanisms linking vascular risk factors to cognitive aging are numerous. Vascular risk factors impair the structure and function of cerebral blood vessels and associated cells (neurovascular unit embracing neurons, glia, perivascular, and vascular cells) [35-37]. Specifically, impairment in the neurovascular unit may in turn alter regulation of the cerebral blood supply, disrupt blood-brain barrier function and the trophic function, as well as reduce autoregulation in the brain. Such alterations may also result in brain atrophy and degeneration of white matter. Underlying pathways for neurovascular dysfunction may also involve oxidative stress and inflammation [35].

Several limitations of our study should be stated. First, HDL cholesterol was not measured at baseline, but was calculated through validated equations [25;26]. Another limitation pertains to the unavailability of left ventricular hypertrophy measures which may have led to underestimated risk scores. Another limitation pertains to the evaluation of cognitive performance only at follow-up. Thus, we cannot rule out the possibility of pre-existing

differences in cognition according to risk profiles, limiting the potential for causal inference, and preventing the assessment of cognitive decline. Given the design of our study, caution is needed when generalizing the findings, as participants were relatively healthy volunteers involved in a long-term nutritional study [38]. An over selection of our sample may also occur as participants in the SU.VI.MAX 2 study are those who accepted to pursue the follow-up at the end of the SU.VI.MAX study. In turn these participants are also more likely to be health conscious.

Moreover, residual confounding cannot be excluded, despite the extensive adjustment for confounders and bias due to non-response or missing data may be an issue in our study but has been limited as we used inverse probability weighting.

In turn, our study also exhibits strengths and other original aspects including its large sample of community-dwelling subjects, long follow-up (focusing on midlife exposure) and the use of validated and sensitive tools designed to assess various cognitive domains while limiting floor/ceiling effects.

In conclusion, our findings from an initially middle-aged and CV disease-free population provide new insights regarding the role of stroke risk profiles but also regarding general CV risk profiles in cognition. From a public health viewpoint, these risk scores may also help identify and target at-risk individuals, thus strengthening public health efforts aimed at cognitive function preservation.

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EKG carried out data checking and analyses and was responsible for drafting the manuscript. She takes full responsibility for the present work. CL, KAA, VAA, CJ, JB, LF, SH and PG were involved in interpreting results and editing the manuscript. EKG, PG and SH were responsible for developing the design and protocol of the study. All authors read and approved the final version of the manuscript.

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107 Table 1: Baseline characteristics of the sample, SU.VI.MAX study (except when otherwise
108 specified)

| Characteristic | Men | Women | P |
|---|---|---|---|
| N | 1,712 | 1,549 | |
| Age at cognitive evaluation, y | 65.9 (4.6) | 65.1 (4.6) | <.0001 |
| Age at baseline, y | 52.5 (4.6) | 51.7 (4.6) | <.0001 |
| Follow-up, y | 13.4 (0.6) | 13.4 (0.7) | 0.93 |
| Education,% | | | |
| Primary | 21.85 | 20.14 | <.0001 |
| Secondary | 35.51 | 44.67 | |
| Post-secondary | 42.64 | 35.18 | |
| Occupation | | | <.0001 |
| Employees | 24.72 | 30.85 | |
| Manual workers | 4.11 | 1.47 | |
| Homemakers/ unemployed | 0.28 | 7.08 | |
| White collar | 23.40 | 8.10 | |
| Physical activity,% | | | <.0001 |
| Irregular | 21.50 | 23.43 | |
| <1h/day | 25.82 | 36.28 | |
| ≥1 h /day | 52.69 | 40.28 | |
| Smoking status,% | | | |
| Non-smokers | 37.68 | 65.78 | <.0001 |
| Former smokers | 51.05 | 25.11 | |
| Current smokers | 11.27 | 9.10 | |

| | | | |
|---|---|---|---|
| Depressive symptoms (CES-D score) | 7.3 (6.5) | 10.5 (8.1) | <.0001 |
| Self-reported memory troubles,% | 27.16 | 45.00 | <.0001 |
| Alcohol, g/day | 24.8 (18.9) | 8.5 (9.7) | <.0001 |
| Systolic BP (mm Hg) | 128.5 (13.6) | 121.6 (13.8) | <.0001 |
| Total cholesterol (mmol/L) | 6.1 (1.0) | 6.0 (1.0) | <.0001 |
| HDL-cholesterol (mmol/L) | 1.7 (0.3) | 1.9 (0.3) | <.0001 |
| LDL-cholesterol (mmol/L) | 3.9 (0.7) | 3.7 (0.7) | <.0001 |
| Fasting glucose (mmol/L) | 5.9 (0.7) | 5.5 (0.7) | <.0001 |
| Heart disease 10y Framingham score (%) | 7.4 (3.7) | 3.2 (2.0) | <.0001 |
| CVD 10y Framingham score (%) | 11.2 (6.1) | 5.1 (3.4) | <.0001 |
| Stroke 10y Framingham score (%) | 1.7 (1.1) | 0.9 (0.7) | <.0001 |

109 Table 2 Associations between different Framingham risk scores in quartiles (Q) and cognitive
110 impairment*

| **Global cognitive impairment** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
|---|---|---|---|---|---|---|
| FCHDRP | model 0 | ref | 1.21 (0.83, 1.77) | 1.20 (0.78, 1.85) | 1.46 (0.89, 2.39) | 0.17 |
| | model 1† | ref | 1.24 (0.85, 1.83) | 1.23 (0.79, 1.91) | 1.54 (0.93, 2.55) | 0.12 |
| | model 2‡ | ref | 1.27 (0.86, 1.87) | 1.30 (0.83, 2.04) | 1.72 (1.03, 2.87) | 0.05 |
| FCVDRP | model 0 | ref | 1.08 (0.74, 1.59) | 1.32 (0.88, 1.98) | 1.42 (0.89, 2.27) | 0.10 |
| | model 1† | ref | 1.15 (0.78, 1.70) | 1.39 (0.91, 2.11) | 1.53 (0.95, 2.47) | 0.06 |
| | model 2‡ | ref | 1.19 (0.80, 1.76) | 1.46 (0.96, 2.23) | 1.66 (1.02, 2.69) | 0.03 |
| FSRP | model 0 | ref | 0.87 (0.59, 1.27) | 0.98 (0.66, 1.45) | 1.17 (0.76, 1.82) | 0.30 |
| | model 1† | ref | 0.88 (0.60, 1.29) | 0.99 (0.66, 1.49) | 1.21 (0.77, 1.88) | 0.27 |
| | model 2‡ | ref | 0.90 (0.61, 1.33) | 1.03 (0.68, 1.55) | 1.26 (0.80, 1.98) | 0.20 |
| **Verbal memory impairment** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
| FCHDRP | model 0 | ref | 1.63 (1.09, 2.44) | 2.69 (1.74, 4.14) | 2.57 (1.56, 4.22) | 0.0001 |
| | model 1† | ref | 1.70 (1.13, 2.55) | 2.88 (1.85, 4.46) | 2.83 (1.71, 4.70) | <.0001 |
| | model 2‡ | ref | 1.66 (1.10, 2.50) | 2.82 (1.81, 4.40) | 2.84 (1.70, 4.75) | <.0001 |
| FCVDRP | model 0 | ref | 1.45 (0.98, 2.14) | 2.01 (1.33, 3.03) | 2.11 (1.32, 3.36) | 0.001 |
| | model 1† | ref | 1.56 (1.05, 2.32) | 2.17 (1.43, 3.30) | 2.34 (1.46, 3.77) | 0.0004 |
| | model 2‡ | ref | 1.56 (1.05, 2.32) | 2.12 (1.39, 3.22) | 2.31 (1.43, 3.73) | 0.001 |
| FSRP | model 0 | ref | 1.24 (0.86, 1.80) | 1.21 (0.81, 1.81) | 1.71 (1.11, 2.64) | 0.02 |
| | model 1† | ref | 1.29 (0.89, 1.88) | 1.27 (0.85, 1.91) | 1.81 (1.17, 2.82) | 0.01 |
| | model 2‡ | ref | 1.29 (0.89, 1.89) | 1.24 (0.82, 1.87) | 1.77 (1.13, 2.76) | 0.02 |
| **Working memory impairment** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
| FCHDRP | model 0 | ref | 1.21 (0.86, 1.68) | 0.91 (0.60, 1.37) | 1.13 (0.71, 1.81) | 0.91 |
| | model 1† | ref | 1.19 (0.85, 1.67) | 0.91 (0.60, 1.37) | 1.12 (0.69, 1.80) | 0.93 |
| | model 2‡ | ref | 1.26 (0.89, 1.77) | 1.01 (0.66, 1.54) | 1.28 (0.79, 2.07) | 0.52 |
| FCVDRP | model 0 | ref | 1.14 (0.82, 1.59) | 0.89 (0.60, 1.30) | 1.07 (0.69, 1.67) | 0.91 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | model 1† | ref | 1.15 (0.83, 1.61) | 0.89 (0.60, 1.31) | 1.06 (0.68, 1.67) | 0.89 |
| | model 2‡ | ref | 1.21 (0.86, 1.69) | 0.96 (0.65, 1.44) | 1.17 (0.74, 1.85) | 0.76 |
| FSRP | model 0 | ref | 1.02 (0.73, 1.42) | 0.85 (0.59, 1.24) | 1.05 (0.69, 1.59) | 0.97 |
| | model 1† | ref | 1.00 (0.72, 1.40) | 0.83 (0.56, 1.21) | 1.01 (0.66, 1.55) | 0.84 |
| | model 2‡ | ref | 1.05 (0.75, 1.47) | 0.89 (0.60, 1.31) | 1.09 (0.71, 1.68) | 0.88 |

FCHDRP: Framingham Coronary Heart Disease Risk Profile

FCVDRP: Framingham Cardiovascular Disease Risk Profile

FSRP: Framingham Stroke Risk Profile

*Values are adjusted odds ratios of cognitive impairment (95% confidence interval)

**Model 0 is adjusted for age and sex

†Model 1: adjusted for age, sex, education and follow-up time between baseline and cognitive evaluation

‡Model 2: further adjusted for occupational status, intervention group during the SU.VI.MAX trial phase (1994-2002), physical activity, alcohol consumption, depressive symptoms, baseline self-reported memory troubles

121 Table 3 Associations between different Framingham risk scores in quartiles (Q) and cognitive

122 functioning*

| **Composite cognitive score** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
|---|---|---|---|---|---|---|
| FCHDRP | model 0 | 0.00 (. - . ) | -0.01 (-1.03- 1.01) | -0.78 (-1.98- 0.43) | -0.75 (-2.16- 0.66) | 0.20 |
| | model 1† | 0.00 (. - . ) | -0.19 (-1.16- 0.78) | -1.01 (-2.15- 0.14) | -1.12 (-2.47- 0.23) | 0.06 |
| | model 2‡ | 0.00 (. - . ) | -0.44 (-1.40- 0.52) | -1.49 (-2.63- -0.36) | -1.73 (-3.07- -0.39) | 0.01 |
| FCVDRP | model 0 | 0.00 (. - . ) | -0.30 (-1.31- 0.71) | -0.83 (-1.96- 0.30) | -0.81 (-2.14- 0.51) | 0.17 |
| | model 1† | 0.00 (. - . ) | -0.69 (-1.65- 0.26) | -1.18 (-2.25- -0.10) | -1.27 (-2.53- -0.00) | 0.04 |
| | model 2‡ | 0.00 (. - . ) | -0.94 (-1.88- 0.01) | -1.57 (-2.64- -0.51) | -1.71 (-2.96- -0.46) | 0.01 |
| FSRP | model 0 | 0.00 (. - . ) | 0.21 (-0.78- 1.21) | 0.18 (-0.92- 1.28) | -0.48 (-1.75- 0.78) | 0.48 |
| | model 1† | 0.00 (. - . ) | 0.04 (-0.91- 0.99) | -0.08 (-1.13- 0.98) | -0.69 (-1.91- 0.52) | 0.27 |
| | model 2‡ | 0.00 (. - . ) | -0.19 (-1.13- 0.74) | -0.43 (-1.48- 0.61) | -0.98 (-2.18- 0.23) | 0.11 |
| **Verbal Memory** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
| FCHDRP | model 0 | 0.00 (. - . ) | -0.37 (-1.39- 0.66) | -2.07 (-3.28- -0.86) | -2.05 (-3.47- -0.64) | 0.001 |
| | model 1† | 0.00 (. - . ) | -0.58 (-1.57- 0.41) | -2.30 (-3.47- -1.13) | -2.45 (-3.83- -1.07) | 0.0001 |
| | model 2‡ | 0.00 (. - . ) | -0.70 (-1.69- 0.29) | -2.54 (-3.72- -1.37) | -2.77 (-4.15- -1.39) | <0.0001 |
| FCVDRP | model 0 | 0.00 (. - . ) | -0.30 (-1.32- 0.71) | -1.47 (-2.61- -0.34) | -1.83 (-3.16- -0.50) | 0.002 |
| | model 1† | 0.00 (. - . ) | -0.68 (-1.66- 0.29) | -1.82 (-2.92- -0.72) | -2.29 (-3.59- -1.00) | 0.0002 |
| | model 2‡ | 0.00 (. - . ) | -0.82 (-1.80- 0.15) | -2.03 (-3.13- -0.92) | -2.53 (-3.83- -1.24) | <0.0001 |
| FSRP | model 0 | 0.00 (. - . ) | 0.22 (-0.78- 1.23) | -0.42 (-1.53- 0.68) | -0.93 (-2.21- 0.34) | 0.10 |
| | model 1† | 0.00 (. - . ) | 0.03 (-0.94- 1.00) | -0.74 (-1.81- 0.34) | -1.20 (-2.44- 0.04) | 0.03 |
| | model 2‡ | 0.00 (. - . ) | -0.11 (-1.08- 0.86) | -0.94 (-2.02- 0.14) | -1.37 (-2.62- -0.12) | 0.02 |
| **Working memory** | **model** | **Q1** | **Q2** | **Q3** | **Q4** | **P for linear trend** |
| FCHDRP | model 0 | 0.00 (. - . ) | 0.36 (-0.68- 1.39) | 1.14 (-0.08- 2.37) | 1.13 (-0.30- 2.56) | 0.08 |
| | model 1† | 0.00 (. - . ) | 0.32 (-0.70- 1.34) | 1.07 (-0.14- 2.27) | 1.02 (-0.39- 2.44) | 0.10 |
| | model 2‡ | 0.00 (. - . ) | 0.09 (-0.92- 1.10) | 0.62 (-0.59- 1.82) | 0.49 (-0.92- 1.91) | 0.39 |
| FCVDRP | model 0 | 0.00 (. - . ) | -0.11 (-1.14- 0.91) | 0.44 (-0.71- 1.58) | 0.82 (-0.52- 2.16) | 0.17 |
| | model 1† | 0.00 (. - . ) | -0.28 (-1.28- 0.73) | 0.30 (-0.83- 1.43) | 0.67 (-0.65- 2.00) | 0.23 |
| | model 2‡ | 0.00 (. - . ) | -0.48 (-1.48- 0.51) | -0.06 (-1.18- 1.07) | 0.29 (-1.03- 1.62) | 0.55 |
| FSRP | model 0 | 0.00 (. - . ) | 0.11 (-0.90- 1.12) | 0.75 (-0.37- 1.86) | 0.36 (-0.92- 1.65) | 0.41 |
| | model 1† | 0.00 (. - . ) | 0.07 (-0.93- 1.06) | 0.72 (-0.38- 1.83) | 0.36 (-0.91- 1.63) | 0.41 |
| | model 2‡ | 0.00 (. - . ) | -0.12 (-1.11- 0.86) | 0.42 (-0.68- 1.52) | 0.14 (-1.13- 1.41) | 0.65 |

123 FCHDRP: Framingham Coronary Heart Disease Risk Profile

124 FCVDRP: Framingham Cardiovascular Disease Risk Profile

FSRP: Framingham Stroke Risk Profile

*Values are adjusted odds ratios of cognitive impairment (95% confidence interval)

**Model 0 is adjusted for age and sex

†Model 1: adjusted for age, sex, education and follow-up time between baseline and cognitive evaluation

‡Model 2: further adjusted for occupational status, intervention group during the SU.VI.MAX trial phase (1994-2002), physical activity, alcohol consumption, depressive symptoms, baseline self-reported memory troubles

Supplemental Table 1: Comparison between included and excluded participants for baseline characteristic and neuropsychologic tests (SU.VI.MAX 2) study, 1994–2007

| | Excluded participants | | Included participants | | |
|---|---|---|---|---|---|
| **variable** | **Values**[1] | ***N with available data*** | **Values**[1] | ***N with available data*** | **P**[2] |
| *General characteristics* | | | | | |
| Age at baseline, y | 51.2 ± 4.6 | 6829 | 52.1 ± 4.6 | 3261 | 0 |
| Male, % | 50.21 | 6829 | 52.5 | 3261 | 0.03 |
| Intervention group, % | 48.13 | 6829 | 53.73 | 3261 | <.0001 |
| Education, % | | 6829 | | 3261 | <.0001 |
| Primary | 24.60 | | 21.04 | | |
| Secondary | 39.87 | | 39.87 | | |
| Post-secondary | 35.52 | | 39.1 | | |
| Physical activity, % | | 6829 | | 3261 | <.0001 |
| Irregular | 29.17 | | 22.42 | | |
| < 1 h/day | 28.17 | | 30.79 | | |
| ≥ 1 h/day | 42.66 | | 46.8 | | |
| Smoking status, % | | 6829 | | 3261 | <.0001 |
| Never smokers | 41.63 | | 51.03 | | |
| Former smokers | 43.23 | | 38.73 | | |
| Current smokers | 15.14 | | 10.24 | | |
| Alcohol, g/day | 20.9 ± 23.1 | 3769 | 20.1 ± 20.4 | 2601 | 0.31 |
| Self-reported health quality | | 6829 | | 3261 | <.0001 |
| | 3.54 | | 0.49 | | |
| | 22.01 | | 26.1 | | |
| | 59.03 | | 62.13 | | |
| | 14.56 | | 10.86 | | |
| | 0.86 | | 0.43 | | |
| BMI, kg/m² | 23.8 ± 6.2 | 6829 | 24.4 ± 3.4 | 3261 | 0.44 |
| Total cholesterol (mmol/L) | 6.2 ± 1.1 | 6519 | 6.1 ± 1.0 | 3261 | 0.0003 |
| Fasting glucose (mmol/L) | 5.8 ± 1.1 | 6308 | 5.7 ± 0.7 | 3261 | 0.001 |
| Systolic BP (mm Hg) | 126.3 ± 14.6 | 4041 | 125.2 ± 14.1 | 3261 | |
| *Cognitive tests* | | | | | |
| Forward digit span | 6.9 ± 2.0 | 1266 | 7.0 ± 2.0 | 3261 | 0.03 |
| Backward digit span | 6.2 ± 2.1 | 1265 | 6.3 ± 2.1 | 3261 | 0.04 |
| Trail-making test (time in sec) | 95.1 ± 40.7 | 1230 | 92.6 ± 38.7 | 3261 | 0.09 |
| RI-48 cued-recall task (no. of words) | 26.2 ± 6.1 | 1237 | 26.3 ± 6.1 | 3261 | 0.72 |
| Phonemic fluency (no. of words) | 30.2 ± 16.4 | 2293 | 29.8 ± 16.0 | 3250 | 0.46 |
| Semantic fluency (no. of words) | 29.3 ± 8.2 | 1223 | 29.6 ± 8.1 | 3261 | 0.38 |
| CES-D score | 9.7 ± 8.2 | 2232 | 8.8 ± 7.5 | 3261 | 0.001 |

Abbreviations: CES-D, Center for Epidemiologic Studies–Depression Scale; RI–48, rappel indicé–48 items.

[1] Values are mean ± Sd as appropriate,

[2] P values were based on Kruskal-Wallis or chi-square-trend tests.

139 Supplemental Table 2: Discrimination and calibration analysis for different Framingham risk
140 profiles

| | Model A with Stroke risk profile | Model B with CHD risk profile | Model C with CVD risk profile | Model C versus Model A | Model B versus Model A | Model C versus Model B |
|---|---|---|---|---|---|---|
| **Global cognitive impairment** | | | | | | |
| AUC | 0.72 | 0.73 | 0.73 | | | |
| *P for difference in AUC* | | | | *0.39* | *0.36* | *0.49* |
| *P value Hosmer Lemeshow test for calibration* | *0.23* | *0.88* | *0.82* | | | |
| **Verbal memory impairment** | | | | | | |
| AUC | 0.68 | 0.68 | 0.68 | | | |
| *P for difference in AUC* | | | | *0.47* | *0.68* | *0.83* |
| *P value Hosmer Lemeshow test for calibration* | *0.38* | *0.62* | *0.34* | | | |
| **Working memory impairment** | | | | | | |
| AUC | 0.66 | 0.66 | 0.66 | | | |
| *P for difference in AUC* | | | | *1.00* | *0.95* | *0.88* |
| *P value Hosmer Lemeshow test for calibration* | *0.26* | *0.47* | *0.33* | | | |

141 AUC: area under the receiver operating curves

142