Cardiovascular Risk Profile and Cognitive Function in Young, Middle-Aged, and Elderly Subjects

Hanneke Joosten, MD*; Marlise E.A. van Eersel, MD*; Ron T. Gansevoort, MD, PhD;
Henk J.G. Bilo, MD, PhD; Joris P.J. Slaets, MD, PhD; Gerbrand J. Izaks, MD, PhD

Background and Purpose—Cognitive decline occurs earlier than previously realized and is already evident at the age of 45. Because cardiovascular risk factors are established risk factors for cognitive decline in old age, we investigated whether cardiovascular risk factors are also associated with cognitive decline in young and middle-aged groups.

Methods—The cross-sectional study included 3778 participants aged 35 to 82 years (mean age, 54 years) and free of cardiovascular disease and stroke. Cognitive function was measured with the Ruff Figural Fluency Test (RFFT; worst score, 0; best score, 175 points) and the Visual Association Test (VAT; worst score, 0; best score, 12 points). Overall cardiovascular risk was assessed with the Framingham Risk Score (FRS) for general cardiovascular disease (best score, −5; worst score, 33 points).

Results—Mean RFFT score (SD) was 70 (26) points, median VAT score (interquartile range) was 10 (9–11) points, and mean FRS (SD) was 10 (6) points. Using linear regression analysis adjusting for educational level, RFFT was negatively associated with FRS. RFFT score decreased by 1.54 points (95% confidence interval, −1.66 to −1.44; $P<0.001$) per point increase in FRS. This negative association was not only limited to older age groups, but also found in the young (35–44 years). The main influencing components of the FRS were age ($P<0.001$), diabetes mellitus ($P=0.001$), and smoking ($P<0.001$). Similar results were found for VAT score as outcome measure.

Conclusions—In this large population–based cohort, a worse overall cardiovascular risk profile was associated with poorer cognitive function. This association was already present in young adults aged 35 to 44 years. (***Stroke**. 2013;44:1543-1549.*)

Key Words: amnesia ■ cardiovascular disease ■ cross-sectional analysis ■ executive function ■ risk assessment

It has become increasingly clear that the onset of cognitive decline is earlier than previously realized. Recently, it was found that cognitive decline is already evident at the age of 45 years.[1] This has led to the belief that poor cognitive function in old age is the result of a long-term pathological process that spans ≥2 to 3 decades. These findings have important consequences because interventions designed to prevent or postpone cognitive decline may be most effective when started at young age. However, effective interventions can only be designed when more insight is gained in mechanisms that underlie early cognitive decline. Because midlife cardiovascular risk factors, such as hypercholesterolemia and hypertension, are associated with cognitive decline in older age,[2] it is likely that cardiovascular risk factors are also associated with cognitive decline at younger age.

Despite the need for a better understanding of the determinants of early cognitive decline, data on the relationship of cardiovascular disease (CVD) with cognitive function at young age are still limited. Some data point toward a negative effect of modifiable risk factors, such as obesity and smoking,

on cognitive performance in young adults.[3,4] However, it is unclear at what age the negative effects of cardiovascular risk factors on the brain begin. Elias et al[5] showed that young adults may be as vulnerable as older adults to the negative effect of hypertension on cognitive function. Thus, there is some evidence that an adverse impact of cardiovascular risk factors on cognitive performance is not limited to older adults.

Cardiovascular risk is often underestimated in young persons because at a young age, individual risk factors may not exceed threshold values. However, risk factors for CVD, such as hypertension, dyslipidemia, and diabetes mellitus (DM), often cluster within subjects, and it is generally assumed that they act via shared biological pathways.[6] This has led to the development of multicomponent cardiovascular risk scores that can be used to predict an individual's risk of a cardiovascular event within the next years.[7–9] By accounting for the conjoint effects of risk factors, they can indicate an increase in cardiovascular risk even if separate risk factors are still subclinical.[8] Thus, cardiovascular risk scores reliably reflect the overall cardiovascular risk profile in young as well as older persons.

Therefore, the aim of this study was to evaluate the association of overall cardiovascular risk profile with cognitive function and to explore this association in various age groups. The study included a large community–based cohort of 3778 persons aged 35 to 82 years.

Methods

Study Design

This study was part of the third survey of the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) cohort.[10] This survey included a total of 5862 participants. Data collection comprised assessment of demographic and cardiovascular risk factors, and measurements of hematologic and biochemical parameters. For further details, please see the online-only Data Supplement. All participants gave written informed consent. The PREVEND study was approved by the medical ethics committee (METc) of University Medical Center Groningen and conducted in accordance with the guidelines of the Helsinki Declaration.

Cognitive Function

The Ruff Figural Fluency Test (RFFT) was the primary outcome measure for cognitive function. The RFFT was introduced at the third survey of the PREVEND study and requires the participants to draw as many designs as possible within a set time limit, whereas avoiding repetitions.[11] The RFFT is generally seen as a measure of executive function but provides information about various cognitive abilities, such as initiation, planning, divergent reasoning, and the ability to switch between different tasks. The RFFT is sensitive to changes in cognitive performance in young and old persons.[11,12] The main outcome measure is the total number of unique designs, which range from 0 to 175 points (worst and best score, respectively).[11]

The Visual Association Test (VAT) was used as a secondary outcome measure for cognitive function. The VAT is a brief learning task that is designed to detect anterograde amnesia. The test consists of 6 drawings of pairs of interacting objects of animals. The person is asked to name each object and, later, is presented with 1 object from the pair and asked to name the other. The lowest (worst) score is 0 point, and the highest (best) score is 12 points.[13]

Cardiovascular Risk

Overall, cardiovascular risk was measured by the Framingham Risk Score (FRS) for general CVD,[8] a composite measure designed to predict the risk of developing a cardiovascular, cerebrovascular, or peripheral vascular event within the next 10 years. Calculation of the FRS is based on age, sex, DM, smoker status, systolic blood pressure, total cholesterol, HDL-cholesterol, and use of blood pressure–lowering agents. A higher FRS is associated with a higher risk of a new vascular event: the lowest score is −5 (risk <1%), and the highest score is 33 (risk >30%). For details on the measurements of the separate risk score components, please see the online-only Data Supplement.

Covariate Assessment

Educational level was divided into 4 groups according to the International Standard Classification of Education (ISCED): primary school level corresponded to 0 to 8 years of education (ISCED 0–1); lower secondary level to 9 to 12 years (ISCED 2); higher secondary level to 13 to 15 years (ISCED 3–4); and university level to ≥16 years (ISCED 5). Because it was recently found that the effect of cardiovascular risk on cognitive function might be modified by *APOE* ε4 carriership,[14] *APOE* ε4 genotype was also included as a covariate. Subjects were categorized as *APOE* ε4 carriers (allele ε2/ε4 or ε3/ε4 or ε4/ε4) or noncarriers (ε2/ε2 or ε2/ε3 or ε3/ε3).

Statistical Analysis

Normally distributed data are presented as means and SD, and skewed data are presented as medians and interquartile range. Differences were tested by *t* test or, if appropriate, Mann–Whitney *U* test. Trends were analyzed by ANOVA, and correlations between variables were analyzed by Pearson correlation coefficient.

The association of RFFT score with FRS was analyzed by 4 multiple linear regression models. In all models, RFFT score (points) was the dependent variable. In the first model, the association of RFFT score with FRS was investigated for the total study population and each separate age group (35–44, 45–54, 55–64, 65–74, and ≥75 years). The independent variables of this model were FRS (points) and educational level (categories). In the second model, it was investigated whether the association of RFFT score with FRS was dependent on age group. In this model, the independent variables were FRS (points), age group (categories), the product term FRS×age group, and educational level (categories). In the third model, the association of RFFT score with each separate component of the FRS was analyzed. The independent variables of this model were age (years), female sex (yes/no), DM (yes/no), current smoker (yes/no), systolic blood pressure (mm Hg), use of blood pressure–lowering agents (yes/no), total cholesterol (mmol/L), HDL-cholesterol (mmol/L), and educational level (categories). To investigate whether there was a dose–response effect of smoking, we also ran this model with smoking categorized into nonsmoking, light smoking (1–15 cigarettes/d), and heavy smoking (≥16 cigarettes/d). Finally, in the fourth model, it was evaluated whether the association of RFFT score with FRS was dependent on *APOE ε4* carriership. In this model, the independent variables were FRS (points), *APOE* ε4 carriership (yes/no), the product term FRS×*APOE* ε4 carriership, and educational level (categories).

Similar analyses were performed for VAT score as cognitive outcome measure. Because of its skewed distribution, VAT score was dichotomized at the median into low performance (≤10 points) and high performance (≥11 points). Accordingly, the association of VAT performance with FRS was evaluated by logistic regression analysis (adjusted for educational level).

Sensitivity Analyses

Various a priori-defined sensitivity analyses were performed. For a detailed description, please see the online-only Data Supplement.

Results

Study Population

Overall, a total of 5862 subjects completed the third survey, of which 1271 participants (22%) refused to perform the RFFT and 433 participants (7%) had incomplete RFFT data.[15] Of those with a complete RFFT score, subjects with a history of CVD or stroke (n=311; 5%) or with missing data on components of the FRS or educational level (n=66; 1%) were excluded. Three participants aged <35 years were excluded because their number was too small to form a separate age group. Thus, the final study population included 3778 persons (51% men) with an age range from 35 to 82 years with mean (SD) age 54 (11) years (Table 1). Mean RFFT score (SD) was 70 (26) points. RFFT score decreased with increasing age and increased with each higher level of education (*P* for trend <0.001).[12] FRS ranged from −3 to +32 points with a mean (SD) of 10 (6) points and increased with increasing age (Table 2).

RFFT and Framingham Risk Score

The RFFT score was dependent on the FRS (Figure 1). The mean RFFT score (SD) decreased from 93 (20) points in persons with the lowest FRS to 44 (19) points in persons with the highest FRS (*P* for trend <0.001). The negative association of RFFT score with FRS persisted after adjustment for educational level: the RFFT score decreased 1.54 points (95%

Table 1.   Characteristics of the Study Population

	All
n (%)	3778 (100)
Age, y; mean (SD)	54 (11)
Sex, male (%)	1927 (51)
Age, n (%)	
35–44 y	900 (24)
45–54 y	1221 (32)
55–64 y	904 (24)
65–74 y	564 (15)
≥75 y	189 (5)
Cardiovascular risk factors	
Hypertension, n (%)	1173 (31)
Diabetes mellitus, n (%)	204 (5)
Smoker, n (%)	893 (24)
BMI, kg/m²; mean (SD)	27 (4)
Systolic blood pressure, mm Hg; mean (SD)	125 (17)
Total cholesterol, mmol/L; mean (SD)	5.42 (1.04)
HDL-cholesterol, mmol/L; mean (SD)	1.42 (0.38)
Non–HDL-cholesterol, mmol/L; mean (SD)	4.00 (1.02)
Elevated albuminuria, n (%)	493 (13)
APOE ε4 genotype, n (%)	
Carrier,* n (%)	1060 (28)
Noncarrier, n (%)	2472 (65)
Unknown, n (%)	246 (7)
Current medication, n (%)	
Blood pressure–lowering agents	721 (19)
Lipid-lowering agents	380 (10)
FRS (points)†, mean (SD)	10 (6)
RFFT score (points), mean (SD)	70 (26)
VAT score (points), median (IQR)	10 (9–11)
Low performance (≤10 points), n (%)	2176 (58)
High performance (≥11 points), n (%)	1530 (40)
Unknown, n (%)	72 (2)

BMI indicates body mass index; FRS, Framingham Risk Score; HDL, high-density lipoprotein; IQR, interquartile range; RFFT, Ruff Figural Fluency Test; SD, standard deviation; and VAT, Visual Association Test.

*Including ε2/ε4, ε3/ε4, and ε4/ε4.

†FRS for general cardiovascular disease and includes age, sex, DM, current smoker status, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol, and HDL-cholesterol. A higher FRS is associated with a higher risk of cardiovascular, cerebrovascular, and peripheral vascular events within the next 10 years.[8]

confidence interval [CI], −1.66 to −1.44; *P*<0.001) with each point increase in FRS.

RFFT and Framingham Risk Score Per Age Group
The negative association of FRS with RFFT score was not only found in the overall study population, but also in all age groups, including the youngest (35–44 years). Figure 2 shows that the strength of the association was similar in all age groups. Indeed, there was no interaction between age group and FRS in their association with RFFT (*P*≥0.43). The correlation coefficients (95% CI) between RFFT score and FRS were comparable between the age groups and ranged from −0.20 (−0.25 to 0.15) to −0.13 (−0.19 to −0.07). Adjustment for educational level did not essentially change results.

RFFT and Separate Risk Factors
In univariate analyses, RFFT score was not only associated with the overall FRS, but also with each separate risk factor component of the FRS, except for sex (data not shown). However, in multiple linear regression analysis (with adjustment for educational level) only age, DM, HDL-cholesterol, and smoking were statistically significantly associated with RFFT score (Table 3). Compared with nonsmoking, smoking 1 to 15 cigarettes/d was associated with a decrease of 2.41 points in RFFT score (95% CI, −4.40 to −0.53; *P*=0.02), and smoking ≥16 cigarettes/d was associated with a decrease of 3.43 points in RFFT score (95% CI, −5.90 to −0.96; *P*=0.007).

Effect of *APOE* ε4 Carriership
The study population included 1060 *APOE* ε4 carriers and 2472 noncarriers (Table 1). The association of RFFT score with FRS was not dependent on *APOE* ε4 carriership (B-coefficient, 2.49; 95% CI, −0.77 to 5.74; *P*=0.13), and there was no statistically significant interaction between *APOE* ε4 carriership and FRS (*P*=0.84). Similar results were found if all *APOE* ε2 carriers were excluded.

VAT and Framingham Risk Score
Analysis of the association of VAT score with FRS yielded similar findings. VAT scores were obtained in 3706 subjects (98%). Overall, 58% (n=2176) had a VAT score of ≤10 (Table 1). The percentage with low performance gradually increased from 33% in the group with the lowest FRS to 78% in the group with the highest FRS (*P*<0.001; Figure I in the online-only Data Supplement). A similar increase was found in all age groups except one (Figure II in the online-only Data Supplement). The odds ratio for low performance on the VAT increased by factor 1.08 (95% CI, 1.07–1.10; *P*<0.001) per point increase in FRS (adjusted for educational level).

Sensitivity Analyses
Various sensitivity analyses gave essentially similar results. For further details, please see in the online-only Data Supplement.

Discussion
In this large population–based study, a worse general cardiovascular risk profile was associated with poorer cognitive function. Importantly, this negative association was not only found in older persons, but also already present in young and middle-aged subgroups. Cardiovascular risk profile was based on 8 individual risk factors. Within this composite risk score, the factors age, DM, smoking, and HDL-cholesterol proved to be the strongest determinants of cognitive function.

Biological Changes in Early Adulthood
It is generally assumed that the presence of cardiovascular risk factors at young age has important consequences later in life. Numerous studies showed that early presence of

Table 2. RFFT Score and Framingham Risk Score in Age Group Strata

Educational Levels	Age, y					P Value for Trend
	35–44	45–54	55–64	65–74	≥75	
Primary school						
RFFT (points)	67 (34)	59 (25)	49 (18)	40 (15)	39 (15)	<0.001
FRS (points)	5 (4)	11 (4)	13 (4)	17 (4)	19 (4)	<0.001
Lower secondary education						
RFFT (points)	73 (23)	64 (21)	57 (20)	49 (17)	43 (16)	<0.001
FRS (points)	5 (4)	9 (4)	13 (4)	16 (4)	19 (3)	<0.001
Higher secondary education						
RFFT (points)	82 (25)	74 (23)	66 (20)	54 (16)	46 (17)	<0.001
FRS (points)	4 (4)	9 (4)	12 (4)	16 (4)	19 (3)	<0.001
University						
RFFT (points)	93 (21)	87 (21)	75 (22)	61 (20)	55 (25)	<0.001
FRS (points)	3 (3)	7 (4)	12 (4)	16 (4)	19 (3)	<0.001
All						
RFFT (points)	85 (24)	76 (24)	64 (22)	50 (18)	45 (18)	<0.001
FRS (points)	4 (4)	9 (4)	12 (4)	16 (4)	19 (3)	<0.001

All values are listed as mean (SD). FRS indicates Framingham Risk Score for general cardiovascular disease and includes age, sex, DM, current smoker status, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol, and HDL-cholesterol; RFFT, Ruff Figural Fluency Test.

cardiovascular risk factors leads to the acceleration of atherosclerosis in young people and increases the long-term risks of CVD.[16,17] Autopsy studies showed that hyperlipidemia, hypertension, smoking, and hyperglycemia are associated with the

Figure 1. Mean Ruff Figural Fluency Test (RFFT) score dependent on overall cardiovascular risk as measured by the FRS in the overall study population. For clarity, data are presented as mean and 95% CI (bars) per 10-year age group. FRS indicates Framingham Risk Score for general cardiovascular disease and includes age, sex, DM, current smoker status, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol, and HDL-cholesterol. [a]Framingham risk score for general cardiovascular disease (FRS).

prevalence and severity of atherosclerotic lesions in young people.[18] We showed that increased cardiovascular risk profile also associates with cognitive function at a young age. To our knowledge only 2 previous studies reported on the relationship between overall cardiovascular risk profile and cognitive function with disparate findings.[19,20] Beason et al[19] saw little effect of FRS on cognitive function in 97 cognitively normal middle-aged and elderly subjects, whereas Kaffashian et al[20] suggested that an adverse cardiovascular risk profile may be related to poorer cognitive function in a large population of middle-aged civil servants. Besides, the results cannot be extended toward subjects <50 years of age, because both study populations did not include younger adults. Our study shows a clear association between overall cardiovascular risk and cognitive function. Most importantly, this association was independent of age and was also found in young adults.
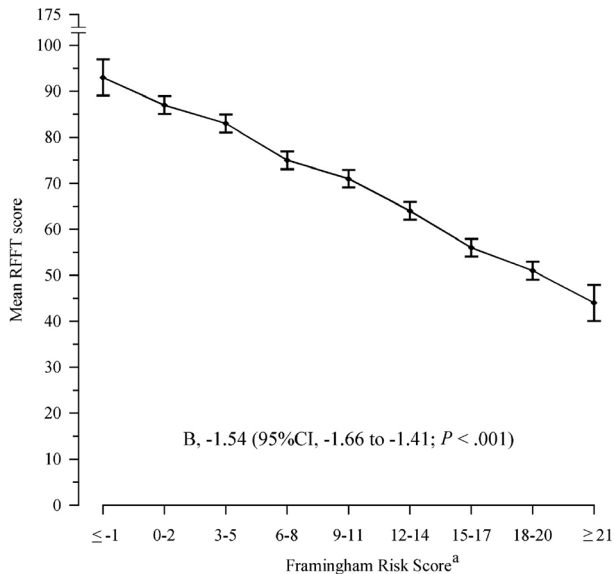
Interestingly, the association of cognitive function with cardiovascular risk in young adults matches the association of subclinical biological changes with cardiovascular risk in this age group. The most important biological changes indicating early CVD include increased intimal-media thickness, carotid coronary artery calcification, pulse pressure, and arterial pulse wave velocity.[21] Several studies showed that an adverse cardiovascular risk factor profile predicts increased intimal-media thickness, pulse wave velocity, and coronary artery calcification in young adults.[22,23] It seems plausible that the presence of these subclinical biological changes is associated with adverse outcome with respect to cognitive function later in life. Indeed, 3 previous large population–based studies showed that premature atherosclerotic changes predict clinically relevant cognitive decline,[24–26] although in 1 other study the results were equivocal.[27]

Implications

Many risk factors for premature atherosclerosis are modifiable. This strengthens the idea that early intervention at a young age may contribute to better cognitive function later in life. In this study, we found 2 risk factors, smoking and DM, that were strong determinants of cognitive function and can be changed or controlled by effective interventions.

Our data suggested a dose–response relationship between smoking and cognitive function because heavy smokers had lower performance on the cognitive test than light smokers and nonsmokers. However, nicotine dependence is still highly prevalent in young adults, and there has been no decline in smoking among young adults since 2003.[28] Nevertheless, it is likely that smoking cessation has a beneficial effect on cognitive function.[29] Therefore, our study underlines the need for effective smoking cessation treatments—not only for the prevention of cancer, cardiovascular events, and stroke, but also for the prevention of cognitive decline.

DM was also negatively associated with cognitive function in our study. It is generally assumed that the effect of DM is at least partially modifiable because improved glucose regulation ameliorates important negative outcomes.[30] Until now, however, it was not clear whether improved glucose regulation also ameliorates cognitive decline. In 2 intervention studies, intensive glucose–lowering treatment was not associated with
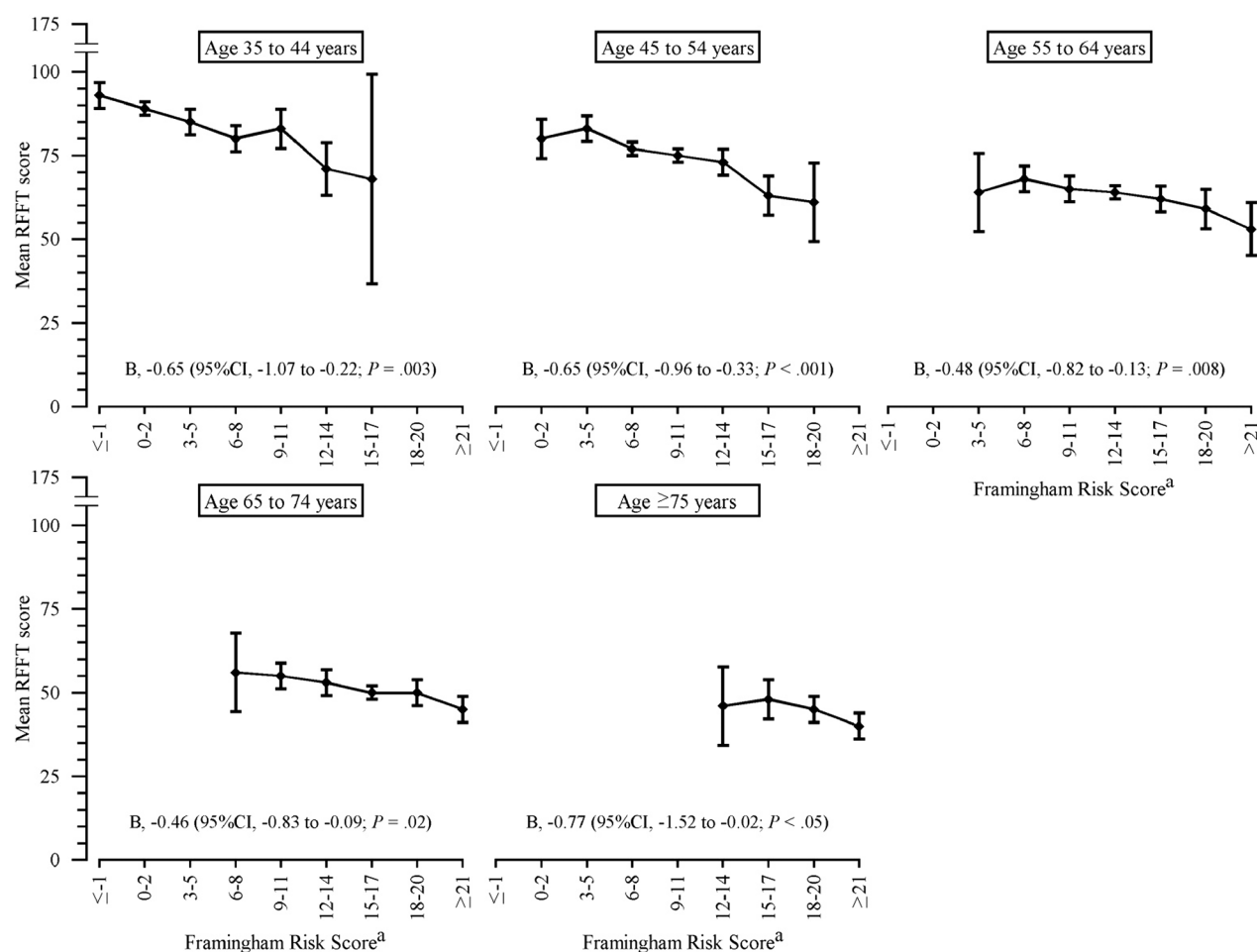
Figure 2. Mean Ruff Figural Fluency Test (RFFT) score dependent on overall cardiovascular risk as measured by the FRS per age group. For clarity, data are presented as mean and 95% CI (bars) per 10-year age group. FRS indicates Framingham Risk Score for general cardiovascular disease and includes age, sex, DM, current smoker status, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol, and HDL-cholesterol. [a]Framingham risk score for general cardiovascular disease (FRS).

better cognitive outcomes in middle-aged and elderly persons with type 2 DM.[31,32] However, both studies were of relatively short duration and, possibly, a longer time frame is necessary to show that stricter glucose regulation is beneficial for cognitive function.

Strengths and Limitations

Some limitations of this study must be acknowledged. First, the primary outcome measure was based on a single cognitive test. However, the RFFT is a composite measure of very different cognitive abilities, such as initiation, planning, divergent reasoning, and the ability to switch between different tasks. In addition, because of its wide score range, the RFFT is not limited by a ceiling or floor effect and, thereby, sensitive to subtle changes in cognitive performance in young and old persons.[12] Also, the main findings were confirmed in the analyses with the VAT as cognitive outcome measure. Second, the PREVEND cohort is enriched for elevated albuminuria, which could induce selection bias, because albuminuria is a risk factor for CVD.[15] However, a sensitivity analysis in a subsample, representative for the general population, did not change results. Finally, the cross-sectional design of this study does not formally allow a firm conclusion on a causal

relationship. For example, it is possible that persons with low cardiovascular risk and poor cognitive performance were underrepresented in our study. However, there were no clear signs of selection bias. Moreover, the association of cardiovascular risk profile with cognitive function that we found in this study seems plausible on biological grounds and is supported by findings of other studies. Nevertheless, the causality of this relationship should be confirmed in longitudinal studies.

Despite these limitations, our study also has several strengths. We included a large community–based population with a wide age range, whereas others used selected populations, such as the elderly or subjects with DM. The generalizability of our data is, therefore, well preserved. In contrast to many previous studies, we explored the synergistic effects of cardiovascular risk factors instead of focusing on single risk factors that probably have complex interactions.[15,33–35] Risk score composites have the advantage to weigh multiple variables to generate optimal overall risk estimation. Additionally, they generate a single variable for overall cardiovascular burden, which limits the number of variables in small studies or extensive multivariate analyses. Using risk scores composites may, therefore, have advantages in both clinical practice and cardiovascular research.

Table 3. Multiple Linear Regression Analysis of RFFT Score With All Separate Components of the Framingham Risk Score*

	B-Coefficient	95% CI	Standardized β	P Value
Age, y	−0.88	−0.95 to −0.81	−0.38	<0.001
Sex				
Men	1.00	Reference		
Women	−0.98	−2.47 to 0.52	−0.02	0.20
Diabetes mellitus				
No	1.00	Reference		
Yes	−6.44	−9.55 to −3.33	−0.06	<0.001
Current smoker				
No	1.00	Reference		
Yes	−2.75	−4.35 to −1.15	−0.05	0.001
Systolic blood pressure, mm Hg	−0.03	−0.07 to 0.02	−0.02	0.20
Total cholesterol, mmol/L	−0.17	−0.84 to 0.50	−0.01	0.62
HDL-cholesterol, mmol/L	2.43	0.45 to 4.41	0.04	0.02
Use of blood pressure–lowering agents				
No	1.00	Reference		
Yes	−1.48	−3.37 to 0.42	−0.02	0.13

CI indicates confidence interval; FRS, Framingham Risk Score for general cardiovascular disease and includes age, sex, DM, current smoker status, systolic blood pressure, use of blood pressure–lowering agents, total cholesterol, and HDL-cholesterol; HDL, high-density lipoprotein; and RFFT, Ruff Figural Fluency Test.

*All components of the Framingham Risk Score were entered into the regression model. The model also included educational level (data not shown). Adjusted R^2 of the full model, 0.36; residual standard deviation, 21.

Conclusions

In this large population–based cohort, a worse cardiovascular risk profile was associated with poorer cognitive function. This association was already present in young adults. In our opinion, there is need for further investigation of cognitive function as a new clinical end point in the light of cardiovascular burden.

Sources of Funding

Disclosures

None.

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