Cognitive Function in Dementia-Free Subjects and Survival in The Old Age: The PROSPER Study

Running Head: Cognitive Performance and Survival in the Older Adults

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Abstract

BACKGROUND: Impairment in domain-specific cognitive function is associated with the increased risk of mortality. We prospectively evaluated the association of executive function and memory with the risk of long-term mortality in dementia-free older subjects. Moreover, we investigated the role of structural brain abnormalities in this association.

METHODS: We included 547 dementia-free participants (mean age 78 years, 56.5% male) from the nested magnetic resonance imaging sub-study of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER). Cox proportional hazard models were used to model 10-year risk of all-cause, cardiovascular and non-cardiovascular mortality in relation to performance in executive function and memory. Moreover, we evaluated the role of total brain parenchymal volume, cerebral blood flow, white matter hyperintensity and the presence of microbleeds and infarcts in the link between cognitive function and mortality.

RESULTS: In the multivariable model, lower performance in executive function was associated with greater risk of all-cause (hazard ratio [HR] 1.49, 95% confidence interval [CI] 1.31-1.70), cardiovascular (HR 1.69, 95%CI 1.36-2.11) and non-cardiovascular (HR 1.36, 95%CI 1.15-1.62) mortality. Similarly, poorer performance in memory tests associated with higher risk of all-cause (HR 1.47, 95%CI 1.29-1.68), cardiovascular (HR 1.45, 95%CI 1.15-1.83) and non-cardiovascular (HR 1.49, 95%CI 1.27-1.76) mortality. The associations were similar in subjects with various levels of brain structural abnormalities and cerebral blood flow (all p for interaction >0.05).

CONCLUSIONS: Poorer performance in both executive function and memory tests associates with all-cause, cardiovascular and non-cardiovascular mortality in elderly individuals. This association is independent of cardiovascular risk factors and diseases, brain structural abnormalities and cerebral blood flow.

KEYWORDS: Executive Function, Memory, Mortality, Structural Brain Abnormalities, Older Subjects

Background

Patients with advanced dementia have a higher mortality rate and are at excess risk for cardiovascular events [1-3]. Although the link between global cognitive impairment and mortality is well-established, only a few studies have investigated the relation of domain-specific cognitive function and mortality, with conflicting findings [4, 5]. It has been suggested that different domains of cognitive function provide heterogeneous information in relation to health and survival. For instance, executive function, as compared to other cognitive domains, might better identify subjects at an increased risk for cardiovascular events [4-7].

Neuroimaging studies have shown that older subjects with cognitive dysfunction have greater loads of subclinical structural brain abnormalities including white matter hyperintensity, atrophy, microbleeds and infarcts [8-13]. Such brain structural abnormalities are also related to a shorter survival. Hence, it has been hypothesized that cognitive impairment might be an early manifestation of clinically unrecognized cerebral and systemic vascular pathologies which signals future risk of cardiovascular events and mortality [3, 6, 14].

In this study we aimed, firstly, to evaluate the risk of all-cause, cardiovascular and non-cardiovascular mortality in relation to performance in cognitive domains of executive function and memory; and secondly, to determine this association is independent of structural brain abnormalities and cerebral blood flow.

Methods

Study participants

Data were extracted from the magnetic resonance imaging (MRI) sub-study of the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a prospective randomized controlled trial that of elderly men and women over 70 years old.

At the initial visit, all participants gave their informed consent and a brief medical history was taken. The vital signs recorded, and appropriate health and dietary advice given. Subjects who satisfied the eligibility criteria were invited to attend the other screening visits at the beginning of the trail and also during the follow-up period. In the next steps, a more detailed medical history was taken, a fasting venous blood sample for biochemical and hematologic factors checks were collected. Moreover, the subject's weight, height, and blood pressure were recorded and the mental and physical ability tests were controlled. Three national administrative centres, based in Scotland, Ireland and the Netherlands were responsible for recruiting participants, providing clinician support to the study nurses and investigators, managing the flow of trial medication and data, recording and reporting adverse events, and servicing the study committees. All data were preserved in the data centre, located at the university of Glasgow in the Robertson Centre for Biostatistics [15].

The original aim of PROSPER was to evaluate the effect of pravastatin in older participants with pre-existing or at high risk of cardiovascular diseases. Exclusion criteria included congestive heart failure (New York Heart Association class III/IV), arrhythmia and impaired cognition (Mini-Mental State Examination score lower than 24 points [16]). Detailed inclusion and exclusion criteria and data collection have been

described extensively elsewhere [15, 17]. In this sub-study of PROSPER, we included 547 Dutch participants with MRI measurements at the end of the official PROSPER trial, with complete follow-up for mortality and with at least one completed cognitive function measurement taken at the time of MRI. All participants in this MRI sub-study underwent cognitive assessment and brain MRI in 2002 and followed for 10 years.

Cognitive tests and settings

A battery of cognitive tests were administered to evaluate the performance of domain-specific cognitive function at baseline, during follow-up and at the end of the PROSPER trial [18]. The Stroop Colour-Word Test was used to test selective attention. Individuals were asked to read or name printed cards as quick as possible in three steps: (1) coloured names printed in black ink, (2) coloured patches, and (3) coloured names printed in incompatible coloured ink. The main outcome variable is the time needed to complete the third test. The Letter Digit Substitution Test is a paper-based task to test processing speed. Individuals are asked to fill in digits beside letters as quickly as possible, according to a key presented at the top of the test sheet. The main outcome variable is the number of correctly matched letter-digits during a 60-second test procedure.

The Picture Learning Test is used to test immediate and delayed memory performance. Fifteen pictures are presented sequentially, 2 seconds for each, after which subjects are asked to recall as many as picture as possible. To measure immediate memory, the same process is repeated 3 times. Delayed recall is tested after 20 minutes. The main outcome variable for both immediate and delayed memory is the average number of recalled pictures. For this study, tests were standardized and results were converted into Z-scores. By averaging the Z-scores of

the Stroop Colour-Word Test and the Letter Digit Substitution Test, a composite executive function was constructed and by averaging Z-scores of immediate and delayed memory, a composite memory score was created.

MRI scanning

MRI was performed at baseline and after three years of follow-up at 1.5 Tesla field strength on a clinical MR-system operating (Philips Medical Systems, Best, The Netherlands). Dual fast spin echo (repetition time=3,000 milliseconds; echo time=27/120 milliseconds; flip angle=90°; slice thickness=3 millimetres; 48 slices; no inter slice gap; field of=220×220 millimetres; matrix=256×204), fluid-attenuated inversion recovery (FLAIR) (repetition time=8,000 milliseconds; echo time=100 milliseconds; flip angle= 90°; slice thickness=3 millimetres; 48 slices; no inter slice gap; field of view=220×176 millimetres; matrix=256×153), and T2* weighted images (multi slice gradient echo sequence; repetition time=2593 milliseconds; echo time=48 milliseconds; flip angle=60°; slice thickness=6 millimetres; 22 slices; inter slice gap=6 millimetres; whole-brain coverage; field of view=220×198 millimetres; matrix=256×176) were obtained. In addition, single slice phase contrast MR angiography (TR/TE=16/9 milliseconds; flip angle=7.5°; slice thickness=5millimetres; FOV=250; RFOV=75%; scan percentage=80%; matrix=256; 8 signal averages) with a velocity encoding of 100 centimetres per second was used for flow measurements [19].

MRI analyses

The SIENAX (Structural Image Evaluation using Normalization of Atrophy) technique was used to obtain estimates of total parenchymal brain volume. By using Software for Neuro-Image Processing in Experiment Research (SNIPER), an in-house

developed program for image processing, quantification and presence of white matter hyperintensities, cerebral microbleeds and infarcts were automatically computed. Hyperintense lesions on T2*-weighted proton density images were defined as white matter hyperintensities. Focal areas of signal loss on T2*-weighted images that increased in size on the T2*-weighted gradients-echo planar images were defined as cerebral microbleeds. For cerebral blood flow assessment, images were analysed using the software package FLOW. The flow in vessels was summed giving the cerebral blood flow in millilitre per minute. Cerebral blood flow was also expressed in millilitre blood per 100 millilitres of brain parenchyma per minute [19-22].

Outcomes

Participants were followed-up for mortality for approximately 10 years after the official end of the PROSPER study. Dates of death were obtained from the Dutch municipal registry and specific causes of death were obtained from the Central Bureau of Statistics of The Netherlands. All endpoints were adjudicated by the independent local clinical events committee of PROSPER. The underlying cause of death from a death certificate was coded according to the International Classification of Diseases and Related Disorders, 10th revision, 1992. Death due to coronary heart diseases and cerebrovascular accidents were categorized as cardiovascular mortality and death from other complications including cancers, respiratory disorders, and neuropsychiatric diseases were categorized as non-cardiovascular mortality. All-cause mortality was defined as cumulative cardiovascular and non-cardiovascular mortality.

Covariates

Age, sex and educational attainment were recorded as socioeconomic characteristics of participants. Cardiovascular risk factors including history of smoking, systolic and diastolic blood pressures, body mass index, total cholesterol, creatinine, the presence of apolipoprotein 4, randomization to pravastatin treatment or placebo and antihypertensive treatment, history of diabetes and history of pre-existing vascular diseases (coronary, cerebral, or peripheral) were recorded at baseline, during follow-up time and at the end of the trail. The last available values measured during the follow-up time or at the end of the original study was considered as characteristics of this sub-study of the PROSPER. Cognitive performance and brain MRI measurements were measured at the end of the of the official trial at the same time with last cognitive test measurements.

Statistical analyses

Characteristics of subjects were reported as mean with standard deviation (SD) or median with interquartile range (if the data were skewed) for continuous variables and frequency with the percentage for categorical variables in the total population. Entry time variable in this study was the time each participant underwent cognitive assessment. Participants were censored at the end of follow up time or if death occurred, whichever comes first. In this study, no participant lost to follow-up. Mortality data was available for all participants; hence, no right censoring was present in this study.

Incident rates of mortality per 1000 person-years were calculated by dividing the number of deaths by person-years at risk. Cox proportional hazard models were used to model 10-year risk of all-cause, cardiovascular and non-cardiovascular mortality in relation to cognitive performance in composite executive function and

composite memory as well as each cognitive test independently. In addition, the relationships between cognitive function and all-cause, cardiovascular and non-cardiovascular mortality were analysed in categories of brain abnormalities including the presence of microbleeds, infarcts and thirds of total brain volume, white matter hyperintensities and cerebral blood flow. In fully adjusted models, we tested the interactions between cognitive measures and categories of brain measures in relation to mortality outcomes. Time to death was used as the outcome variable, whereby performances in the various cognitive functioning tests were used as determinants. Associations between cognitive impairment and mortality were reported as hazard ratios (HR) with 95% confidence intervals (CI). Hazard ratios were calculated for each unit decrease in standardized domain-specific cognitive function. Analyses were performed in multiple phases: First, crude analyses were performed. In the next step, analyses were adjusted for socioeconomic characteristics including age, sex and education. In the third phase, analyses were further adjusted for cardiovascular factors including body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, the presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of pre-existing vascular diseases (coronary, cerebral, or peripheral). Moreover, analyses were further adjusted for total brain parenchymal volume, cerebral blood flow, white matter hyperintensity and the presence of microbleeds and infarcts. The proportional hazard assumption was tested using scaled Schoenfeld residuals and graphical methods by plotting log(-log(S(t))) versus time and look for parallelism. In addition, we conducted stratified analyses to ensure that our findings were not different in various subgroups of participants. Kaplan-Meier curves were produced in order to compare risk of all-

cause, cardiovascular and non-cardiovascular mortality according to thirds of executive function and memory.

The association of cognitive performance and mortality was evaluated in interaction with total brain parenchymal volume, white matter hyperintensity load, cerebral blood flow, and the presence of microbleeds or infarcts. Interaction terms were produced by multiplying cognitive functioning test scores and brain MRI measurements.

Moreover, all statistical analyses were performed using SPSS software (version 23.0.0; SPSS Inc., Chicago, IL). Curves and plots were produced by GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, CA).

Results

Table 1 shows socioeconomic characteristics, cardiovascular factors, cognitive performance and brain MRI measurements of the participants. The mean age was 78 (SD: 3.2) years and 56.5% were male.

At the end of 10-year follow-up, 268 (49.0%) of participants had died. Among those, 87 (15.9%) individuals deceased due to cardiovascular events and 179 (32.7%) subjects due to non-cardiovascular bases. Cause of mortality in two (0.4%) participants was unknown.

The crude incidence rate of all-cause mortality was 62.7 (95%CI 55.7-70.3) deaths per 1,000 person-years. The incidence rates of cardiovascular and non-cardiovascular mortality were 20.5 (95%CI 16.6-25.2) and 42.2 (95%CI 36.4-48.6) per 1,000 person-years respectively.

Table 2 shows the risk of all-cause, cardiovascular and non-cardiovascular mortality dependent on the level of performance in executive function and memory. In the multivariable model, the risk of all-cause mortality was increased by 49 percent (HR 1.49, 95%CI 1.31-1.70) per one standard deviation decline in executive function and 47 percent (HR 1.47, 95%CI 1.29-1.68) per one SD decrease in memory domain. Cardiovascular mortality was increased by 69 percent (HR 1.69, 95%CI 1.36-2.11) in relation to executive function and 45 percent (HR 1.45, 95%CI 1.15-1.83) in relation to memory per one SD decline in performance of each domain-specific cognitive function. Similarly, non-cardiovascular mortality was elevated by 36 percent (HR 1.36, 95%CI 1.15-1.62) and 49 percent (HR 1.49, 95%CI 1.27-1.76) per one SD decline in performance of the executive function and memory respectively.

In order to minimize the heterogeneity of the participants and to remove potential confounders for accusation between cognitive performance and risk of mortality, we adjusted all analyses for structural brain abnormalities (supplementary data table S-1). Additionally, the risk of 10-year mortality in relation to performance in each standardized cognitive test was presented in the supplementary data table S-2.

Figure 1 presents the cumulative risk of all-cause, cardiovascular and non-cardiovascular mortality in thirds of composite executive function score and composite memory score. Compared to subjects with higher performance in domain-specific cognitive functions, subjects with worse performance were at greater risk of all-cause, cardiovascular and non-cardiovascular mortality.

Figure 2 shows the risk of 10-year all-cause mortality in thirds of total brain volume, white matter hyperintensities and cerebral blood flow in relation to performance in executive function and memory, adjusted for socioeconomic and cardiovascular risk factors. There was no statistically significant difference between thirds of total brain volume and white matter hyperintensities in the performance of both domains (all p for interactions >0.05) (Figure 2-A and 2-B). The risk of 10-year all-cause mortality in relation to the performance of memory was different in subjects at thirds of cerebral blood flow (p=0.033). Individuals at the highest third of cerebral blood flow were at lower risk of all-cause mortality compared to subjects at the lowest third. However, when the cause of death came into consideration, even in some points the association or the same trend were seen, but the difference between groups was not statistically significant (Figure 2-C).

Figure 3 presents the risk of 10-year mortality in the presence or absence of microbleeds and infarcts. All results were adjusted for socioeconomic and

cardiovascular risk factors. Similarly, the risk of 10-year mortality was not statistically different between groups. The risk of 10-year all-cause (table S-3 and S-4), cardiovascular (table S-5 and S-6) and non-cardiovascular (table S-7 and S-8) mortality in relation to structural brain abnormalities with the performance in each standardized cognitive test, adjusted for socioeconomic and cardiovascular risk factors, are presented as supplementary data.

Figure 4 shows the association of executive function and memory with the risk of mortality remained unchanged in various subgroups of participants with and without comorbidities.

Discussion

In this long-term prospective study of older individuals, we showed that poorer performance in various cognitive domains, independent of socioeconomic and conventional cardiovascular risk factors, was associated with greater risk of 10-year all-cause, cardiovascular and non-cardiovascular mortality. Moreover, we were not able to show that these associations could be explained by brain structural abnormalities or cerebral blood flow.

Our finding of the association between cognitive impairment and shorter survival is in line with previous reports [3, 23, 24]. Different explanations have been proposed for this association. Firstly, it was suggested that lower performance in cognitive function was associated with lower socioeconomic status and the higher burden of chronic medical conditions leading to an increased mortality [23]. In addition, individuals with cognitive deficits are at a higher risk for poorer self-care, such as medications adherence, health literacy and healthy lifestyle which might predispose them to cardiovascular and non-cardiovascular events [25-27]. Secondly, it was proposed that lower cognitive function, may be attributed to the effects of decreased biological vitality leading to lower survivals among elderly subjects [24]. Another explanation can be that cognitive performance in old age might be a reflection of vascular health. Cognitively impaired subjects are more likely to be exposed to life-long vascular risk factors [28, 29] and therefore, have greater vascular pathologies [30, 31], which increase the risk of mortality. The fourth possible explanation is related to the necessity of neural plasticity and integrity of the brain for the optimal brain and body functioning [32].

It has been demonstrated that existing structural brain abnormalities including white matter hyperintensities, infarcts, microbleeds and decreased cerebral blood flow are strongly related to worse cognitive performance [33-35]. On the other hand, we and others have shown that impaired brain structural integrity and lower cerebral blood flow are associated with higher risk of mortality in older adults [8, 36]. Hence, brain lesions and impaired cerebrovascular hemodynamics have been proposed as major mechanisms behind the link between cognitive impairment and mortality. However, in this study, we observed that the relationships between cognitive function and mortality outcomes were independent of a variety of brain structural abnormalities and cerebral blood flow. A possible explanation is that both cognitive dysfunction and structural brain abnormalities reflect the lack of brain structural and functional integrity which make subjects more vulnerable for morbidities and put individuals at an increased risk of mortality [37]. In addition, cognitive dysfunction and brain structural abnormalities have shared socioeconomic and cardiovascular risk factors and can be epiphenomenon which might explain that the link between impaired cognitive function and survival is not secondary to the established brain structural lesions or blood abnormalities. Hence, other mechanisms might play roles in this association which warrants further investigations [38-40]. This may call for earlier intervention in midlife and young adulthood to preserve brain health and integrity.

Several strengths and limitations of this study need to be acknowledged. As a strength, this study includes long follow-up time and availability of data for socioeconomic status, a wide range of cardiovascular factors, comorbidities and different cognitive domains. As a limitation, all participants in this study had relatively preserved cognitive function, which limits the generalizability of our findings to older adults with dementia. Furthermore, we included subjects with the history of

cardiovascular risk factors and pre-existing vascular diseases, which might also limit the generalizability of our findings, although a great number of older community-dwelling participants carry a high load of cardiovascular diseases. However, adjustment for cardiovascular factors did not alter the associations between cognition and mortality. In addition, by conducting sensitivity analyses, we showed that our findings were not dependent upon particular vascular risk factors and diseases. Patients with mild cognitive impairment (MCI) can be considered as a high-risk group which might benefit from early interventions to improve their survival and well-being in long-term. Future studies can address the links between various subtypes of MCI and cause-specific mortality.

Conclusions

Our results suggest that lower performance in domains of executive function and memory associates with all-cause, cardiovascular and non-cardiovascular mortality in elderly individuals. Hence, the cognitive assessment could be considered as a potential strategy, along with the other clinical tools, to identify elderly subjects at greater risk of mortality. Moreover, our data suggest that structural brain abnormalities per se do not play a key role in cognitive function-mortality link in dementia-free older subjects.

Declarations

Study funding

The original PROSPER clinical trial was founded by a grant from Bristol-Myers Squibb. The company had no involvement in the formulation of hypotheses, analysis of the data, or in any aspects of the preparation of this manuscript.

Availability of data and materials

Any data not published in this article are available at Leiden University Medical Centre. The datasets used and analysed regarding the present study will be shared on request from any qualified investigator for reasonable purposes.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

Authorship

All authors had access to the data and a role in writing this manuscript. SR, SH and BS designed and conceptualized the study. SR and SH analysed the data. SR drafted the manuscript for intellectual content. SR, SH, JG, MAB, IF, JWJ and BS interpreted the data and critically revised the manuscript for intellectual content. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Table 1: Characteristics of study participants (n=547)

Characteristics	Values
Socioeconomics Characteristics	
Male, n (%)	309 (56.5)
Age, mean (SD)	78.3 (3.2)
Age left school, mean (SD)	15.5 (2.9)
Cardiovascular Factors	
History of smoking, n (%)	378 (69.1)
Body mass index, kg/m^2, mean (SD)	26.6 (3.7)
Systolic blood pressure, mmHg, mean (SD)	155.8 (20.6)
Diastolic blood pressure, mmHg, mean (SD)	83.9 (9.8)
Total cholesterol, mmol/L, mean (SD)	4.9 (1.0)
Creatinine	95.4 (17.7)
Presence of apolipoprotein 4	150 (27.4)
History of vascular disease, n (%)	262 (47.9)
History of diabetes, n (%)	122 (22.3)
History of pravastatin treatment, n (%)	273 (49.9)
History of antihypertensive treatment, n (%)	346 (63.3)
Cognitive Performance	
Mini-mental state examination, points, median (IQR)	29 (28-30)
Stroop Colour-Word test, seconds, median (IQR)	50.6 (42.1-64.5)
Letter-Digit Substitution test, digits per minute, mean (SD)	26.3 (7.4)
Immediate Picture Learning test, words, mean (SD)	10.1 (2.2)
Delayed Picture Learning test, words, mean (SD)	11.1 (3.1)
Brain MRI Measurements	
Total brain volume, ml, mean (SD)	1359.2 (65.9)
Cerebral blood flow, ml/100ml/min mean (SD)	47.6 (8.9)
White matter hyperintensities, total volume, ml, median (IQR)	2.8 (0.8-9.2)
Infarcts, n (%)	180 (32.9)
Microbleeds, n (%)	104 (19.0)

All last available data measured at the end of the original PROSPER were considered as the characteristics of this study.

Abbreviations: n: number, SD: standard deviation, kg/m^2: kilogram per meter squared, mmHg: millimetres of mercury, mmol/L: millimoles per litre, cc: cubic centimetre; ml: millilitres; min: minute: IQR: interquartile range.

Table 2. Domain-specific cognitive function and risk of 10-years mortality (n=547)

	All-cause Mortality		CV Mortality		Non-CV Mortality	
Cognitive Domain	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Executive Function						
Crude, HR (95%CI)	1.54 (1.37-1.72)	<0.001	1.82 (1.52-2.17)	<0.001	1.39 (1.19-1.61)	<0.001
Adjusted model 1, HR (95%CI)	1.47 (1.30-1.67)	<0.001	1.75 (1.43-2.13)	<0.001	1.33 (1.14-1.56)	<0.001
Adjusted model 2, HR (95%CI)	1.49 (1.31-1.70)	<0.001	1.69 (1.36-2.11)	<0.001	1.36 (1.15-1.62)	<0.001
Memory						
Crude, HR (95%CI)	1.54 (1.37-1.72)	<0.001	1.56 (1.28-1.92)	<0.001	1.54 (1.32-1.79)	<0.001
Adjusted model 1, HR (95%CI)	1.45 (1.28-1.64)	<0.001	1.45 (1.18-1.82)	0.001	1.47 (1.25-1.69)	<0.001
Adjusted model 2, HR (95%CI)	1.47 (1.29-1.68)	<0.001	1.45 (1.15-1.83)	0.002	1.49 (1.27-1.76)	<0.001

Abbreviations: CV: Cardiovascular; HR: Hazard Ratio; CI: Confidence Interval.

Model 1: Adjusted for age, sex and education. **Model 2:** Model 1 adjusted further for body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

Cognitive Function in Dementia-Free Subjects and Survival in The Old Age: The PROSPER Study

Running Head: Cognitive Performance and Survival in the Older Adults

Somayeh Rostamian, MSc* [1,2]; Sandra de Haan, MSc [3]; Jeroen van der Grond, PhD [1]; Mark A van Buchem, MD, PhD [1]; Ian Ford, PhD [4]; J.Wouter Jukema, MD, PhD [5]; Behnam Sabayan, MD, PhD* [6].

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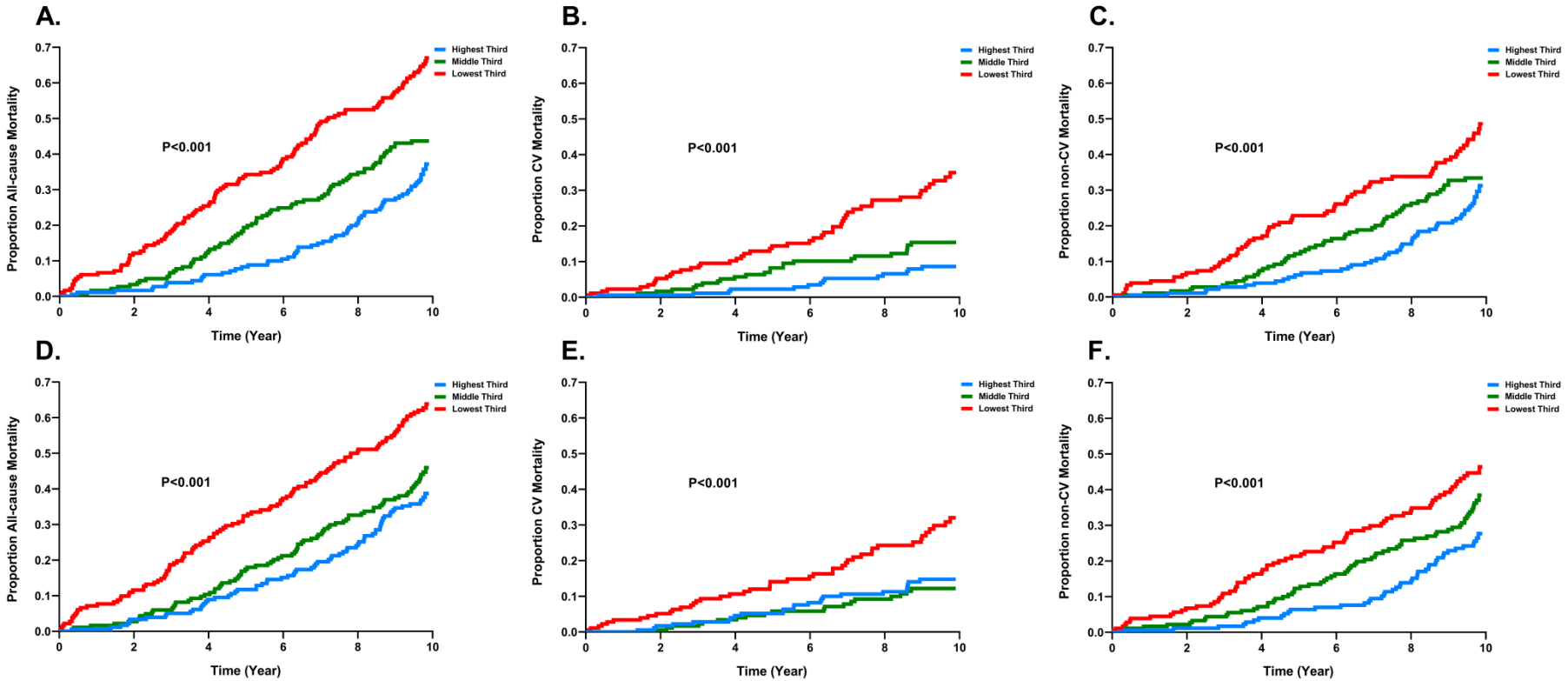
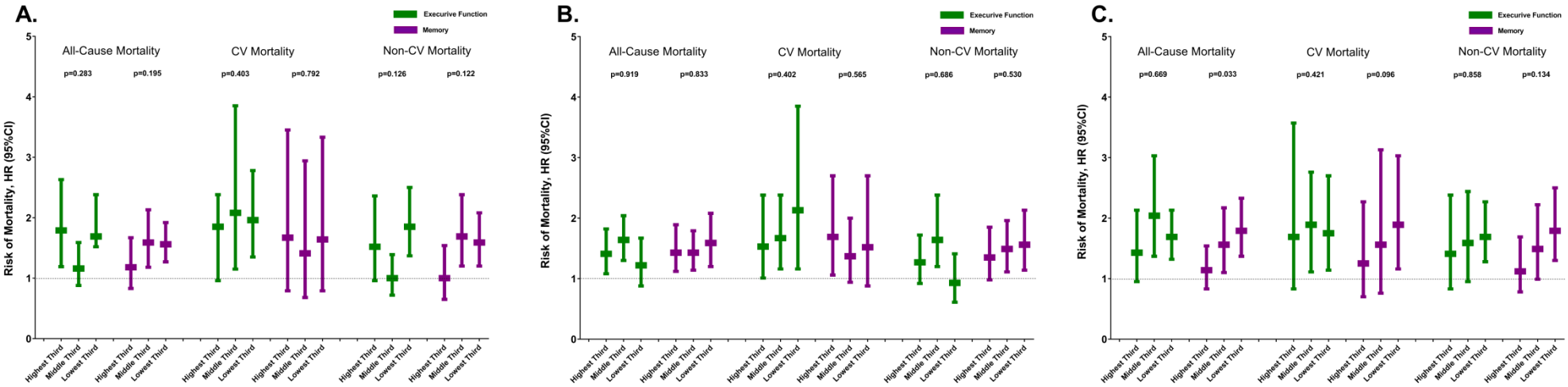
Figure 1. Risk of mortality in association with cognitive assessments



Abbreviation: CV: cardiovascular.

Risk of all-cause (1-A), cardiovascular (1-B) and non-cardiovascular (1-C) mortality in thirds of composite executive score. Risk of all-cause (1-D), cardiovascular (1-E) and non-cardiovascular (1-F) mortality in thirds of composite memory score.

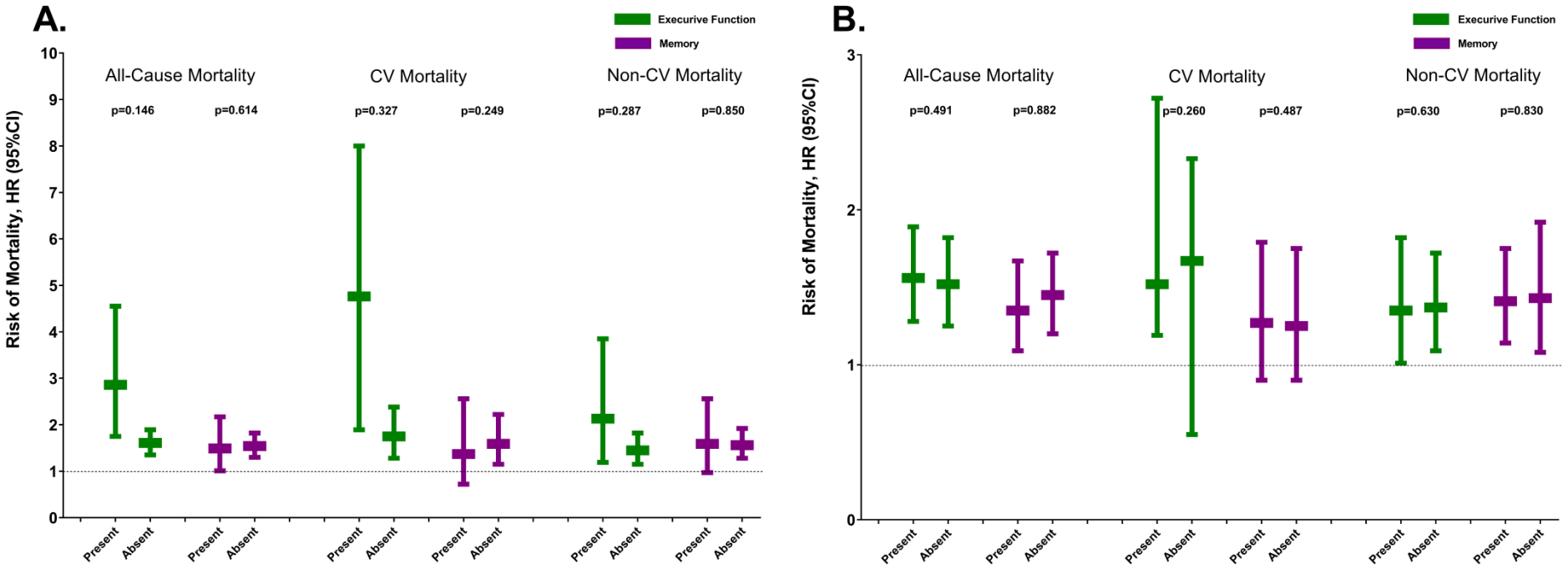
Figure 2. Risk of mortality in thirds of structural brain abnormalities in relation to cognitive assessments



Abbreviations: CV: cardiovascular; HR: Hazard Ratio; CI: Confidence Interval.

Risk of 10-year all-cause mortality in thirds of total brain volume (2-A), white matter hyperintensities (2-B) and cerebral blood flow (2-C) in relation to performance in executive function and memory. All results were adjusted for socioeconomic and cardiovascular risk factors.

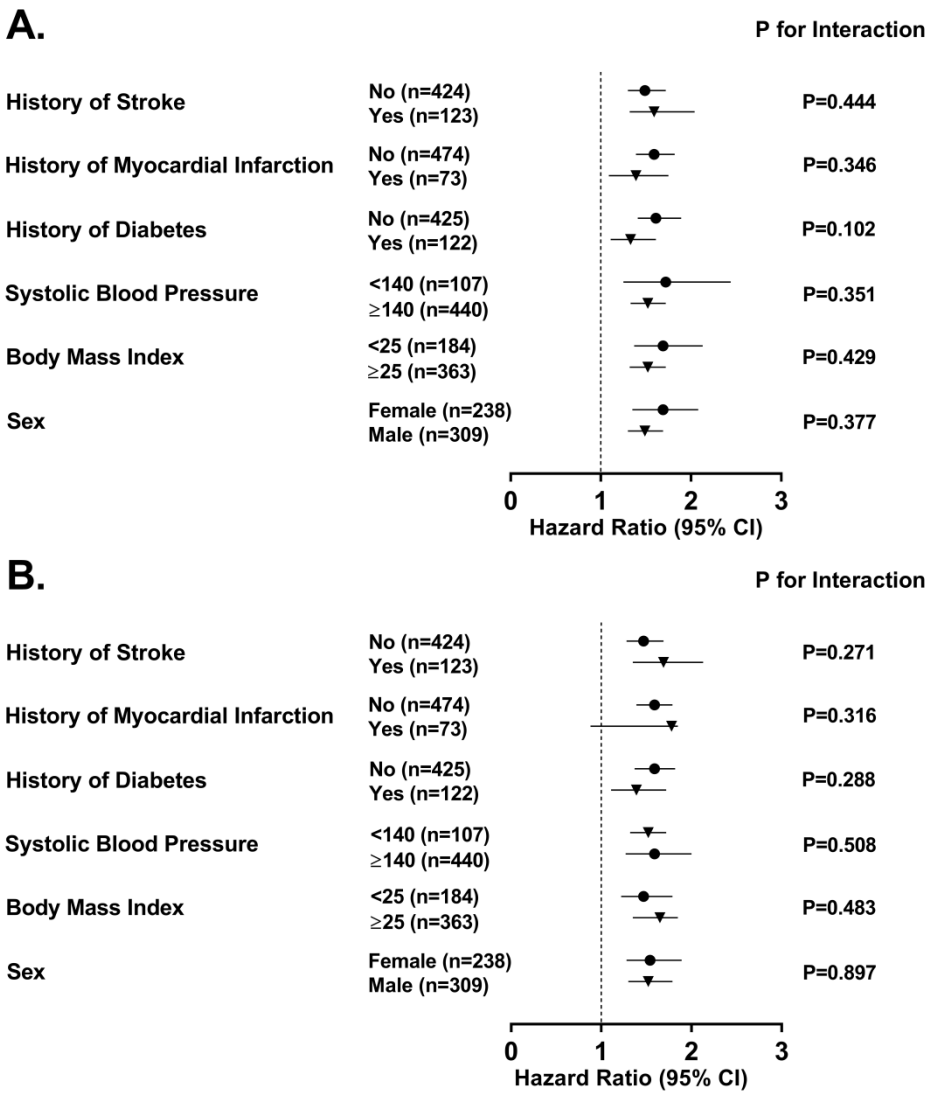
Figure 3. Risk of mortality in presence or absence of microbleeds and infarcts in relation to cognitive assessments



Abbreviations: CV: cardiovascular; HR: Hazard Ratio; CI: Confidence Interval.

Risk of 10-year mortality in presence or absence of microbleeds (3-A) and infarcts (3-B). All results were adjusted for socioeconomic and cardiovascular risk factors.

Figure 4. Subgroup analyses on the association of cognitive scores with all-cause mortality



Abbreviation: CI: Confidence Interval.

Subgroup analyses on the association between composite executive score (4-A) and composite memory score (4-B) with all-cause mortality.

Cognitive Function in Dementia-Free Subjects and Survival in The Old Age: The PROSPER Study

Running Head: Cognitive Performance and Survival in the Older Adults

Somayeh Rostamian, MSc* [1,2]; Sandra de Haan, MSc [3]; Jeroen van der Grond, PhD [1]; Mark A van Buchem, MD, PhD [1]; Ian Ford, PhD [4]; J.Wouter Jukema, MD, PhD [5]; Behnam Sabayan, MD, PhD* [6].

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Table S-1. Domain-specific cognitive function and risk of 10-years mortality in adjusted model containing structural brain abnormalities (n=547)

	All-cause Mortality		CV Mortality		Non-CV Mortality	
Cognitive Domain	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Executive Function	1.70 (1.40-2.07)	<0.001	1.86 (1.32-2.61)	<0.001	1.61 (1.26-2.07)	<0.001
Memory	1.50 (1.22-1.81)	<0.001	1.47 (1.05-2.04)	0.023	1.53 (1.22-1.92)	<0.001

Abbreviations: CV: Cardiovascular; HR: Hazard Ratio; CI: Confidence Interval.

Model is adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes, history of vascular diseases, total brain parenchymal volume, cerebral blood flow, white matter hyperintensity and the presence of microbleeds and infarcts.

Table S-2. Domain-specific cognitive function and risk of 10-years mortality (n=547)

	All-cause Mortality		CV Mortality		Non- CV Mortality	
Cognitive Domain	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
Stroop Colour-Word Test						
Crude, HR (95%CI)	1.29 (1.20-1.42)	<0.001	1.41 (1.24-1.61)	<0.001	1.24 (1.10-1.39)	<0.001
Adjusted model 1, HR (95%CI)	1.23 (1.21-1.35)	<0.001	1.32 (1.14-1.53)	<0.001	1.17 (1.04-1.32)	0.010
Adjusted model 2, HR (95%CI)	1.22 (1.10-1.36)	<0.001	1.29 (1.09-1.53)	0.002	1.19 (1.05-1.35)	0.011
Letter Digit Substitution Test						
Crude, HR (95%CI)	1.56 (1.37-1.75)	<0.001	1.96 (1.56-2.56)	<0.001	1.37 (1.16-1.59)	<0.001
Adjusted model 1, HR (95%CI)	1.56 (1.37-1.82)	<0.001	2.00 (1.59-2.56)	<0.001	1.37 (1.16-1.61)	<0.001
Adjusted model 2, HR (95%CI)	1.56 (1.36-1.81)	<0.001	2.01 (1.55-2.58)	<0.001	1.40 (1.15-1.65)	<0.001
Immediate Picture Learning Test						
Crude, HR (95%CI)	1.49 (1.33-1.69)	<0.001	1.59 (1.28-1.92)	<0.001	1.47 (1.27-1.69)	<0.001
Adjusted model 1, HR (95%CI)	1.43 (1.27-1.61)	<0.001	1.47 (1.20-1.82)	<0.001	1.41 (1.20-1.64)	<0.001
Adjusted model 2, HR (95%CI)	1.49 (1.32-1.70)	<0.001	1.45 (1.17-1.83)	<0.001	1.43 (1.20-1.69)	<0.001
Delayed Picture Learning Test						
Crude, HR (95%CI)	1.47 (1.32-1.64)	<0.001	1.45 (1.19-1.75)	<0.001	1.49 (1.30-1.69)	<0.001
Adjusted model 1, HR (95%CI)	1.39 (1.23-1.61)	<0.001	1.35 (1.10-1.64)	0.003	1.43 (1.23-1.64)	<0.001
Adjusted model 2, HR (95%CI)	1.48 (1.31-1.69)	<0.001	1.36 (1.10-1.63)	0.004	1.46 (1.24-1.69)	<0.001

Abbreviations: CV: Cardiovascular; HR: Hazard Ratio; CI: Confidence Interval.

Model 1: Adjusted for age, sex and education. **Model 2:** Model 1 adjusted further for body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-3. Domain-specific cognitive function and risk of 10-years all-cause mortality dependent on the level of brain MRI findings

	Thirds of Brain Abnormalities			
	Highest Third	Middle Third	Lowest Third	P for Interaction
Total Brain Volume				
Stroop: Fully adjusted, HR (95%CI)	1.65 (1.14-2.37)	1.00 (0.82-1.23)	1.53 (1.26-1.86)	0.395
Letter digit: Fully adjusted, HR (95%CI)	1.53 (1.09-2.15)	1.50 (1.09-2.10)	1.90 (1.53-2.38)	0.160
Immediate: Fully adjusted, HR (95%CI)	1.11 (0.79-1.54)	1.42 (1.05-1.90)	1.61 (1.32-2.01)	0.065
Delayed: Fully adjusted, HR (95%CI)	1.21 (0.85-1.64)	1.59 (1.21-2.09)	1.45 (1.17-1.77)	0.405
White Matter Hyperintensity				
Stroop: Fully adjusted, HR (95%CI)	1.24 (1.00-1.51)	1.31 (1.10-1.55)	1.05 (0.82-1.33)	0.359
Letter digit: Fully adjusted, HR (95%CI)	1.44 (1.10-1.82)	1.69 (1.32-2.17)	1.37 (1.00-1.92)	0.487
Immediate: Fully adjusted, HR (95%CI)	1.27 (1.00-1.59)	1.46 (1.19-1.82)	1.45 (1.11-1.92)	0.493
Delayed: Fully adjusted, HR (95%CI)	1.55 (1.21-1.96)	1.33 (1.06-1.66)	1.55 (1.24-1.96)	0.926
Cerebral Blood Flow				
Stroop: Fully adjusted, HR (95%CI)	1.37 (0.95-1.95)	1.66 (1.19-2.33)	1.35 (1.12-1.62)	0.293
Letter digit: Fully adjusted, HR (95%CI)	1.28 (0.90-1.80)	1.92 (1.30-2.86)	1.82 (1.41-2.33)	0.245
Immediate: Fully adjusted, HR (95%CI)	1.08 (0.80-1.47)	1.39 (1.02-1.92)	1.81 (1.40-2.43)	0.019
Delayed: Fully adjusted, HR (95%CI)	1.18 (0.88-1.56)	1.61 (1.14-2.27)	1.65 (1.28-2.08)	0.094

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-4. Domain-specific cognitive function and risk of 10-years all-cause mortality dependent on microbleeds and infarcts

	Brain Abnormalities		
	YES	NO	P for Interaction
Microbleeds			
Stroop: Fully adjusted, HR (95%CI)	1.89 (1.31-2.74)	1.34 (1.16-1.56)	0.288
Letter digit: Fully adjusted, HR (95%CI)	2.18 (1.45-3.23)	1.60 (1.32-1.93)	0.450
Immediate: Fully adjusted, HR (95%CI)	1.29 (0.90-1.88)	1.52 (1.28-1.83)	0.335
Delayed: Fully adjusted, HR (95%CI)	1.47 (1.06-2.04)	1.45 (1.24-1.70)	0.880
Infarcts			
Stroop: Fully adjusted, HR (95%CI)	1.27 (1.08-1.50)	1.27 (1.09-1.48)	0.558
Letter digit: Fully adjusted, HR (95%CI)	1.54 (1.23-1.96)	1.58 (1.28-1.91)	0.889
Immediate: Fully adjusted, HR (95%CI)	1.32 (1.08-1.62)	1.41 (1.18-1.69)	0.742
Delayed: Fully adjusted, HR (95%CI)	1.29 (1.06-1.60)	1.38 (1.15-1.65)	0.889

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-5. Domain-specific cognitive function and risk of 10-years cardiovascular mortality dependent on brain MRI findings

	Thirds of Brain Abnormalities			
	Highest Third	Middle Third	Lowest Third	P for Interaction
Total Brain Volume				
Stroop: Fully adjusted, HR (95%CI)	2.43 (1.06-5.46)	1.48 (0.98-2.23)	1.38 (1.01-1.88)	0.423
Letter digit: Fully adjusted, HR (95%CI)	2.64 (1.25-5.57)	2.35 (1.09-5.01)	2.35 (1.56-2.49)	0.668
Immediate: Fully adjusted, HR (95%CI)	1.48 (0.74-2.95)	1.31 (0.65-2.69)	1.65 (1.12-2.39)	0.964
Delayed: Fully adjusted, HR (95%CI)	1.63 (0.83-3.16)	1.36 (0.71-2.58)	1.45 (1.03-2.09)	0.697
White Matter Hyperintensity				
Stroop: Fully adjusted, HR (95%CI)	1.33 (0.94-1.87)	1.29 (0.98-1.68)	1.27 (0.86-1.86)	0.721
Letter digit: Fully adjusted, HR (95%CI)	1.68 (1.12-2.58)	2.06 (1.33-3.15)	3.70 (1.67-8.33)	0.248
Immediate: Fully adjusted, HR (95%CI)	1.44 (0.94-2.19)	1.47 (1.02-2.13)	1.61 (0.91-2.86)	0.892
Delayed: Fully adjusted, HR (95%CI)	1.86 (1.22-2.87)	1.24 (0.87-1.58)	1.43 (0.87-2.33)	0.308
Cerebral Blood Flow				
Stroop: Fully adjusted, HR (95%CI)	1.36 (0.74-2.52)	2.33 (1.17-4.64)	1.21 (0.86-1.69)	0.170
Letter digit: Fully adjusted, HR (95%CI)	1.55 (0.87-2.80)	3.33 (2.00-5.00)	2.44 (1.47-4.17)	0.291
Immediate: Fully adjusted, HR (95%CI)	1.14 (0.62-2.00)	1.53 (0.81-2.95)	2.01 (1.21-3.25)	0.047
Delayed: Fully adjusted, HR (95%CI)	1.29 (0.78-2.13)	1.45 (0.71-2.87)	1.61 (1.05-2.44)	0.236

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-6. Domain-specific cognitive function and risk of 10-years cardiovascular mortality dependent on microbleeds and infarcts

	Brain Abnormalities		
	YES	NO	P for Interaction
Microbleeds			
Stroop: Fully adjusted, HR (95%CI)	2.37 (1.23-4.55)	1.35 (1.03.75)	0.569
Letter digit: Fully adjusted, HR (95%CI)	3.43 (1.57-7.12)	2.02 (1.46-2.89)	0.631
Immediate: Fully adjusted, HR (95%CI)	1.19 (0.64-2.18)	1.63 (1.16-2.29)	0.092
Delayed: Fully adjusted, HR (95%CI)	1.40 (0.82-2.40)	1.45 (1.07-1.93)	0.549
Infarcts			
Stroop: Fully adjusted, HR (95%CI)	1.24 (0.95-1.60)	1.49 (1.15-1.93)	0.155
Letter digit: Fully adjusted, HR (95%CI)	2.09 (1.43-3.05)	1.83 (1.28-2.65)	0.859
Immediate: Fully adjusted, HR (95%CI)	1.19 (0.85-1.63)	1.80 (1.26-2.57)	0.111
Delayed: Fully adjusted, HR (95%CI)	1.30 (0.95-1.75)	1.31 (0.95-1.83)	0.849

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-7. Domain-specific cognitive function and risk of 10-years non-cardiovascular mortality dependent on brain MRI findings

	Thirds of Brain Abnormalities			
	Highest Third	Middle Third	Lowest Third	P for Interaction
Total Brain Volume				
Stroop: Fully adjusted, HR (95%CI)	1.50 (0.98-2.30)	0.94 (0.72-1.20)	1.64 (1.27-2.11)	0.167
Letter digit: Fully adjusted, HR (95%CI)	1.33 (0.90-1.96)	1.33 (0.90-1.94)	1.65 (1.22-2.25)	0.116
Immediate: Fully adjusted, HR (95%CI)	0.95 (0.64-1.42)	1.50 (1.10-2.10)	1.70 (1.25-2.21)	0.048
Delayed: Fully adjusted, HR (95%CI)	1.06 (0.75-1.57)	1.70 (1.25-2.35)	1.43 (1.11-1.85)	0.244
White Matter Hyperintensity				
Stroop: Fully adjusted, HR (95%CI)	1.20 (0.92-1.54)	1.32 (1.06-1.62)	0.92 (0.65-1.29)	0.254
Letter digit: Fully adjusted, HR (95%CI)	1.28 (0.93-1.70)	1.55 (1.14-2.08)	1.01 (0.68-1.46)	0.699
Immediate: Fully adjusted, HR (95%CI)	1.20 (0.90-1.61)	1.47 (1.13-1.97)	1.39 (0.99-1.92)	0.466
Delayed: Fully adjusted, HR (95%CI)	1.42 (1.04-1.93)	1.40 (1.07-1.87)	1.56 (1.19-2.08)	0.582
Cerebral Blood Flow				
Stroop: Fully adjusted, HR (95%CI)	1.45 (0.91-2.28)	1.43 (0.95-2.18)	1.41 (1.12-1.78)	0.821
Letter digit: Fully adjusted, HR (95%CI)	1.23 (0.82-1.86)	1.40 (0.92-2.15)	1.67 (1.22-2.27)	0.399
Immediate: Fully adjusted, HR (95%CI)	1.09 (0.76-1.56)	1.29 (0.88-1.85)	1.76 (1.27-2.45)	0.116
Delayed: Fully adjusted, HR (95%CI)	1.19 (0.83-1.68)	1.62 (1.08-2.39)	1.69 (1.22-2.23)	0.216

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.

Table S-8. Domain-specific cognitive function and risk of 10-years non-cardiovascular mortality dependent on the microbleeds and infarcts

	Brain Abnormalities		
	YES	NO	P for Interaction
Microbleeds			
Stroop: Fully adjusted, HR (95%CI)	1.64 (1.05-2.58)	1.32 (1.10-1.61)	0.371
Letter digit: Fully adjusted, HR (95%CI)	1.70 (1.03-2.79)	1.40 (1.11-1.74)	0.559
Immediate: Fully adjusted, HR (95%CI)	1.40 (0.88-2.25)	1.53 (1.23-1.85)	0.995
Delayed: Fully adjusted, HR (95%CI)	1.54 (1.01-2.39)	1.53 (1.23-1.84)	0.813
Infarcts			
Stroop: Fully adjusted, HR (95%CI)	1.28 (1.02-1.60)	1.19 (0.97-1.43)	0.981
Letter digit: Fully adjusted, HR (95%CI)	1.23 (0.92-1.67)	1.46 (1.17-1.84)	0.347
Immediate: Fully adjusted, HR (95%CI)	1.47 (1.09-1.95)	1.32 (1.06-1.61)	0.497
Delayed: Fully adjusted, HR (95%CI)	1.34 (1.02-1.58)	1.41 (1.15-1.72)	0.805

Abbreviations: Hazard Ratio; CI: Confidence Interval.

Model adjusted for age, sex, education, body mass index, history of smoking habit, systolic blood pressure, diastolic blood pressure, total cholesterol, creatinine, presence of apolipoprotein 4, antihypertensive treatment, statin treatment, history of diabetes and history of vascular diseases.

We used Z-score of each tests to increase the comparability of domain-specific cognitive function. In Stroop Colour-Word Test higher scores indicate worse cognitive performance, however, in other tests higher scores indicate better cognitive performance. In all tests best performance categorized as the highest third and worst performance as the lowest third.