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CLINICAL RESEARCH STUDY

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

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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 noncardiovascular 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 noncardiovascular (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 noncardiovascular (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 $\gg .05$).

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

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KEYWORDS: Executive function; Memory; Mortality; Older subjects; Structural brain abnormalities

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

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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 with 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 that signals future risk of cardiovascular events and mortality.[3,6,14]

CLINICAL SIGNIFICANCE

- Lower performance in cognitive domains of executive function and memory associates with the increased risk of long-term mortality in dementia-free older individuals with preexisting cardiovascular risk factors or diseases.
- The relationships between cognitive function and mortality outcomes were independent of a variety of brain structural abnormalities measured by magnetic resonance imaging.
- Cognitive assessment may identify individuals at higher risk of cardiovascular events and it can be used, alone or in combination with other predictors, to detect older adults at the greater risk of mortality.

In this study we aimed, firstly, to evaluate the risk of all-cause, cardiovascular, and noncardiovascular mortality in relation to performance in cognitive domains of executive function and memory; and secondly, to determine that 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 were 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 trial 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 centers, 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 center, 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 preexisting, 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 were followed for 10 years.

Cognitive Tests and Settings

A battery of cognitive tests was 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 quickly as possible in 3 steps: 1) colored names printed in black ink; 2) colored patches; and 3) colored names printed in incompatible colored 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 pictures 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 Color-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 3 years of follow-up at 1.5 Tesla field strength on a clinical MR operating system (Philips Medical Systems, Best, The Netherlands). Dual fast spin echo (repetition time = 3000 ms; echo time = 27/120 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no inter slice gap; field of = 220 × 220 mm; matrix = 256 × 204), fluid-attenuated inversion recovery (repetition time = 8000 ms; echo time = 100 ms; flip angle = 90°; slice thickness = 3 mm; 48 slices; no interslice gap; field of view = 220 × 176 mm; matrix = 256 × 153), and T2*-weighted images (multislice gradient echo sequence; repetition time = 2593 ms; echo time = 48 ms; flip angle = 60°; slice thickness = 6 mm; 22 slices; interslice gap = 6 mm; whole-brain coverage; field of view = 220 × 198 mm; matrix = 256 × 176) were obtained. In addition, single-slice phase contrast MR angiography (TR/TE = 16/9 ms; flip angle = 7.5°; slice thickness = 5 mm; field of view = 250; regional field of view = 75%; scan percentage = 80%; matrix = 256; 8 signal averages) with a velocity encoding of 100 cm per second was used for flow measurements.[19]

MRI Analyses

The Structural Image Evaluation using Normalization of Atrophy (SIENAX) 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 analyzed using the software package FLOW. The flow in vessels was summed giving the cerebral blood flow in mL per minute. Cerebral blood flow was also expressed in mL blood per 100 mL 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 noncardiovascular mortality. All-cause mortality was defined as cumulative cardiovascular and noncardiovascular 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 preexisting vascular diseases (coronary, cerebral, or peripheral) were recorded at baseline, during follow-up time, and at the end of the trial. The last available values measured during the follow-up time or at the end of the original study were considered as characteristics of this sub-study of the PROSPER. Cognitive performance and brain MRI were measured at the end 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 were 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 noncardiovascular 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 noncardiovascular mortality were analyzed 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 preexisting 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))) vs 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 noncardiovascular 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, Ill). Curves and plots were produced by GraphPad Prism 6 (GraphPad Software, Inc., La Jolla, Calif).

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 participants (49.0%) had died. Among those, 87 (15.9%) individuals deceased due to cardiovascular events and 179 (32.7%) subjects due to noncardiovascular bases. Cause of mortality in 2 (0.4%) participants was unknown.

The crude incidence rate of all-cause mortality was 62.7 (95% CI, 55.7-70.3) deaths per 1000 person-years. The incidence rates of cardiovascular and noncardiovascular mortality were 20.5 (95% CI, 16.6-25.2) and 42.2 (95% CI, 36.4-48.6) per 1000 person-years, respectively.

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, mm Hg, mean (SD)	155.8 (20.6)
Diastolic blood pressure, mm Hg, 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/100 mL/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.
cc = cubic centimeter; IQR = interquartile range; kg/m^2 = kilogram per meter squared; min = minute; mL = milliliters; mm Hg = millimeters of mercury; mmol/L = millimoles per liter; n = number; SD = standard deviation.

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

Table 2 Domain-Specific Cognitive Function and Risk of 10-Year 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)	≪ .001	1.82 (1.52-2.17)	≪ .001	1.39 (1.19-1.61)	≪ .001
Adjusted model 1, HR (95% CI)	1.47 (1.30-1.67)	≪ .001	1.75 (1.43-2.13)	≪ .001	1.33 (1.14-1.56)	≪ .001
Adjusted model 2, HR (95% CI)	1.49 (1.31-1.70)	≪ .001	1.69 (1.36-2.11)	≪ .001	1.36 (1.15-1.62)	≪ .001
Memory						
Crude, HR (95% CI)	1.54 (1.37-1.72)	≪ .001	1.56 (1.28-1.92)	≪ .001	1.54 (1.32-1.79)	≪ .001
Adjusted model 1, HR (95% CI)	1.45 (1.28-1.64)	≪ .001	1.45 (1.18-1.82)	.001	1.47 (1.25-1.69)	≪ .001
Adjusted model 2, HR (95% CI)	1.47 (1.29-1.68)	≪ .001	1.45 (1.15-1.83)	.002	1.49 (1.27-1.76)	≪ .001

CI = confidence interval; CV = cardiovascular; HR = hazard ratio.
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.

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 Table 1, available online). Additionally, the risk of 10-year mortality in relation to performance in each standardized cognitive test was presented in Supplementary Table 2 (available online).

Figure 1 presents the cumulative risk of all-cause, cardiovascular, and noncardiovascular mortality in thirds of composite executive function score and composite memory score. Compared with subjects with higher performance in domain-specific cognitive functions, subjects with worse performance were at greater risk of all-cause, cardiovascular, and noncardiovascular 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 ≫ .05) (Figures 2A and 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 ($P = .033$). Individuals at the highest third of cerebral blood flow were at lower risk of all-cause mortality compared with 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, the difference between groups was not statistically significant (Figure 2C).

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

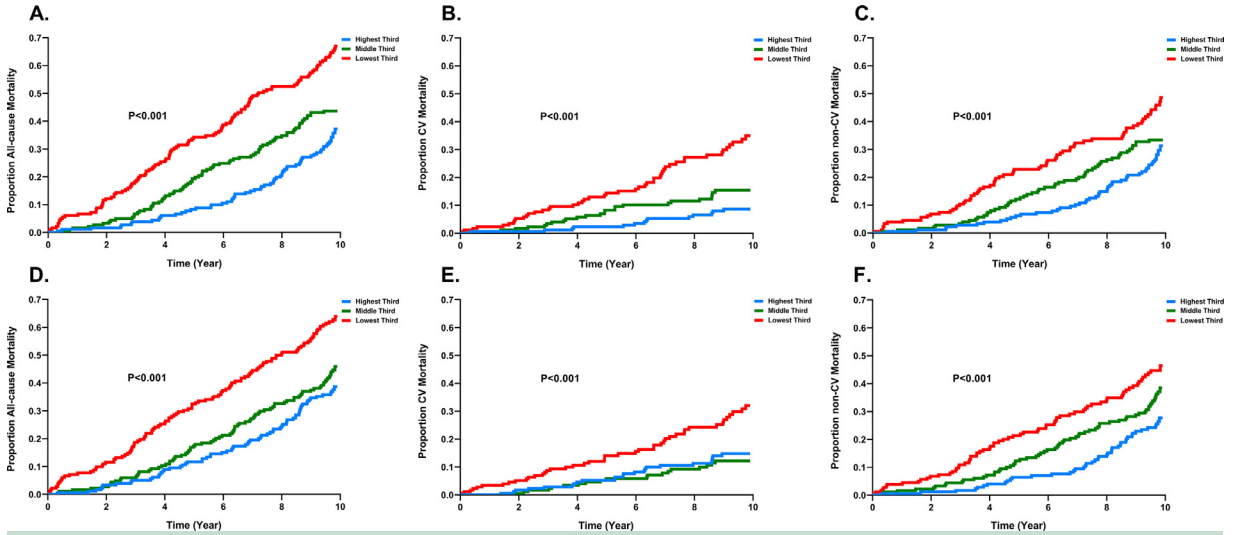

Figure 1 Risk of mortality in association with cognitive assessments. Risk of **(A)** all-cause, **(B)** cardiovascular, and **(C)** noncardiovascular mortality in thirds of composite executive score. Risk of **(D)** all-cause, **(E)** cardiovascular, and **(F)** noncardiovascular mortality in thirds of composite memory score. CV = cardiovascular.

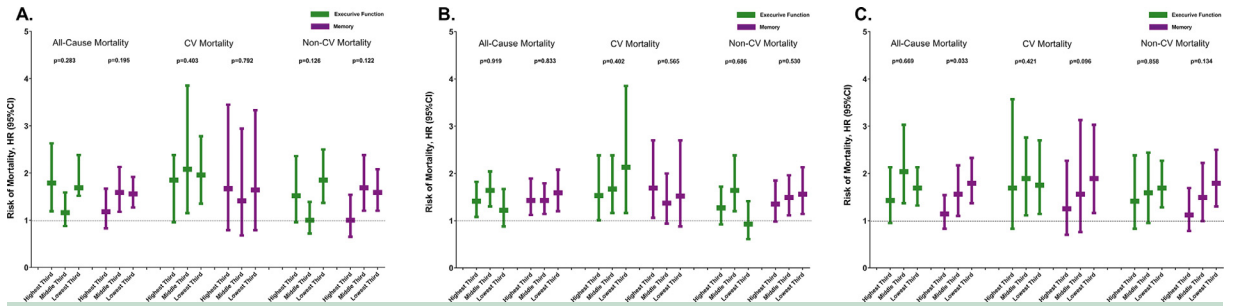

Figure 2 Risk of mortality in thirds of structural brain abnormalities in relation to cognitive assessments. Risk of 10-year all-cause mortality in **(A)** thirds of total brain volume, **(B)** white matter hyperintensities, and **(C)** cerebral blood flow in relation to performance in executive function and memory. All results were adjusted for socioeconomic and cardiovascular risk factors. CV = cardiovascular; HR = hazard ratio; CI = confidence interval.

statistically different between groups. The risk of 10-year all-cause (Supplementary Tables 3 and 4, available online), cardiovascular (Supplementary Tables 5 and 6, available online), and noncardiovascular (Supplementary Tables 7 and 8, available online) 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 remaining 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 noncardiovascular 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 noncardiovascular 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

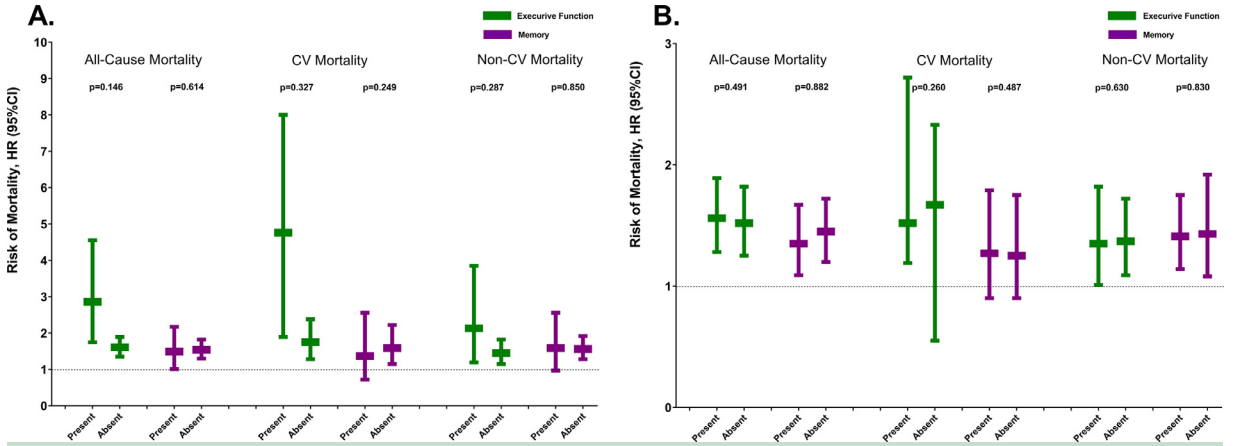

Figure 3 Risk of mortality in presence or absence of microbleeds and infarcts in relation to cognitive assessments. Risk of 10-year mortality in presence or absence of **(A)** microbleeds and **(B)** infarcts. All results were adjusted for socioeconomic and cardiovascular risk factors. CV = cardiovascular; HR = hazard ratio; CI = confidence interval.

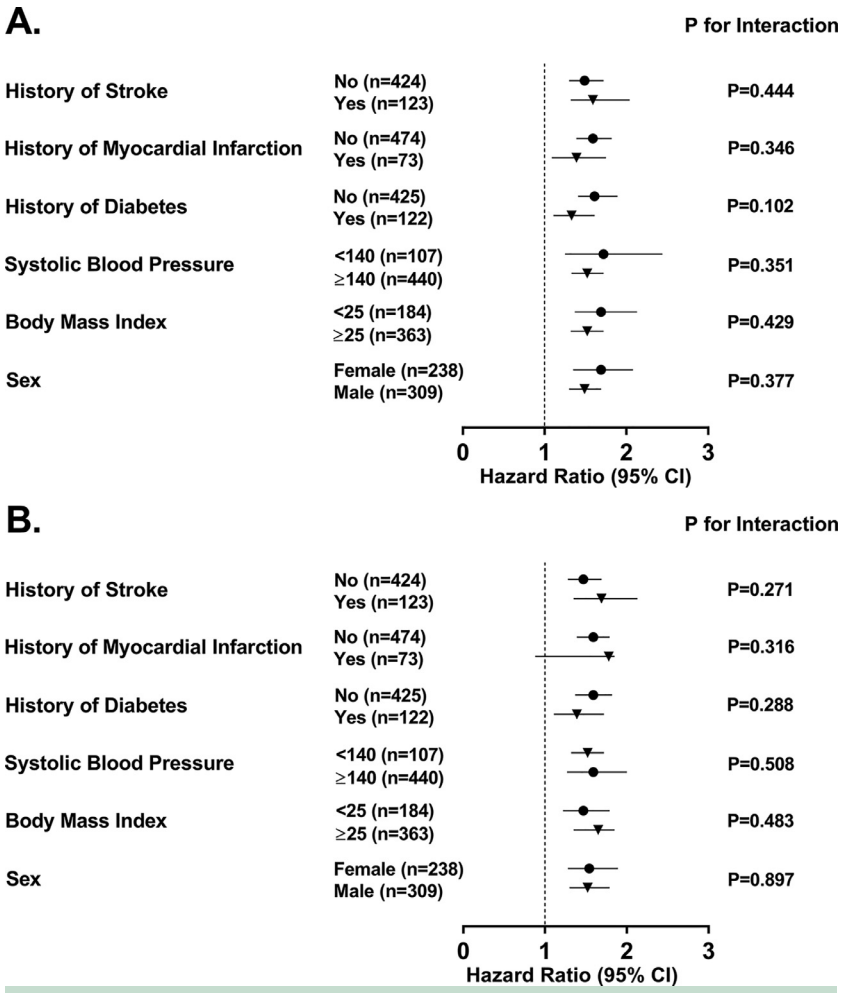

Figure 4 Subgroup analyses on the association of cognitive scores with all-cause mortality. Subgroup analyses on the association between **(A)** composite executive score and **(B)** composite memory score with all-cause mortality. CI = confidence interval.

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

preexisting 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 can be considered as a high-risk group that might benefit from early interventions to improve their survival and well-being in the long term. Future studies can address the links between various subtypes of mild cognitive impairment and cause-specific mortality.

CONCLUSIONS

Our results suggest that lower performance in domains of executive function and memory associates with all-cause, cardiovascular, and noncardiovascular 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.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2019.06.001.

SUPPLEMENTARY DATA

Table S-1 Domain-Specific Cognitive Function and Risk of 10-Year 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

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-Year 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

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-Year 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

CI = confidence interval; HR = hazard ratio.
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-Year 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

HR = 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-Year 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

CI = Confidence Interval; HR = hazard ratio.
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-Year 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

CI = Confidence Interval; HR = hazard ratio.
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

CI = Confidence Interval; HR = hazard ratio.
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-Year 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

CI = Confidence Interval; HR = hazard ratio.
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.