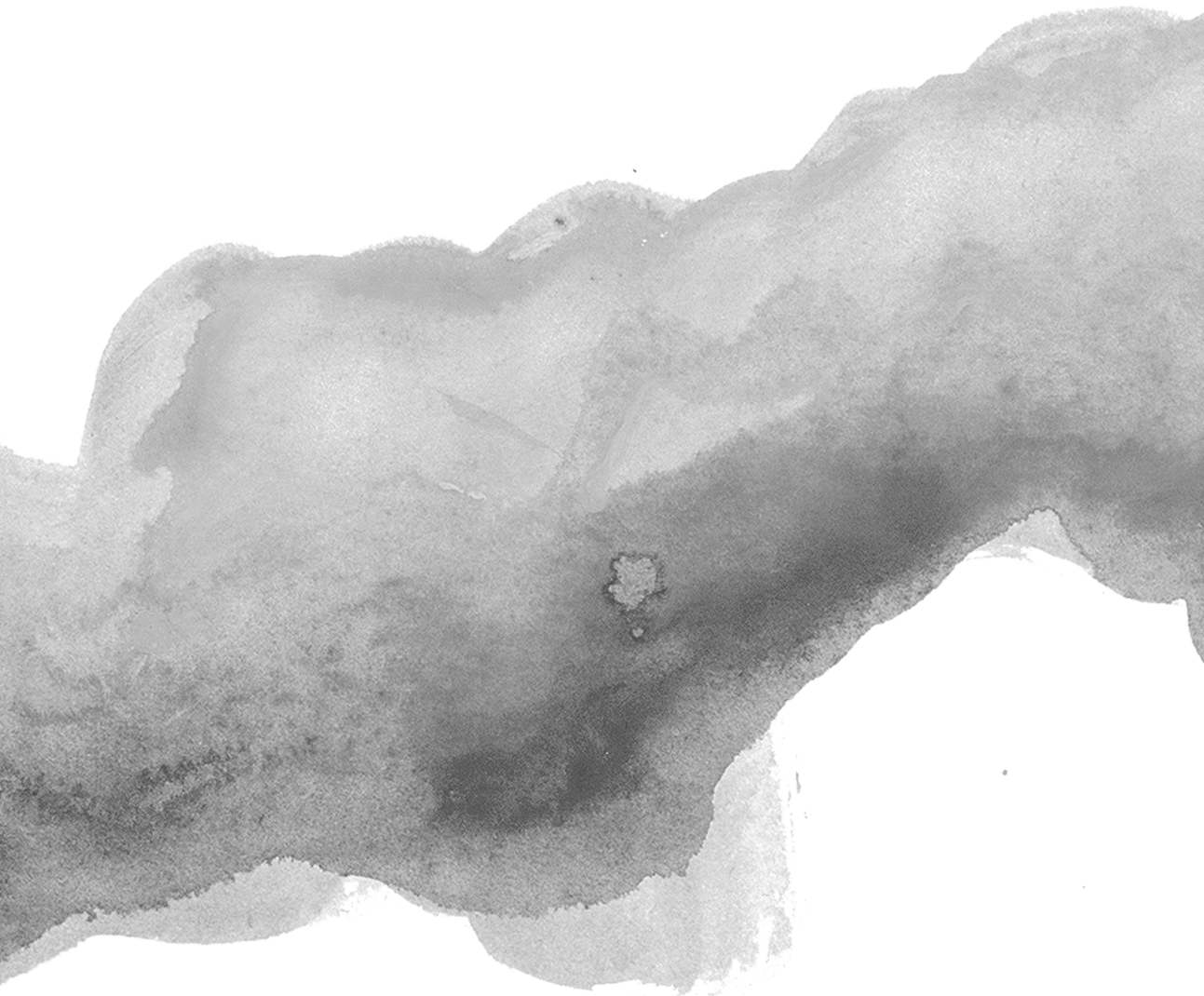

Part II

Cardiac biomarkers in cognitive function

Chapter 5

N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk

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Ann Neurol 2014; 76: 213–222

Abstract

Background Elevated levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are associated with cognitive impairment, which might be explained by cardiovascular diseases or risk factors. The aim of this study was to investigate the association of NT-proBNP with cognitive function and decline in older adults at high risk of cardiovascular disease.

Methods We studied 5,205 men and women (mean age 75 years) who were included in the PROspective Study of Pravastatin in the Elderly at Risk. All participants had pre-existing cardiovascular disease or risk factors thereof. Four domains of cognitive function were tested at baseline and repeated during a follow-up period of 3.2 years.

Results Participants with higher NT-proBNP (≥450 ng/L) had worse baseline cognitive function including reaction time (mean difference high vs. low group=3.07 seconds, 95% confidence interval (CI)=0.83 to 5.32), processing speed (-1.02 digits coded, 95% CI=-1.65 to -0.39) and immediate memory (-0.13 pictures remembered, 95% CI=-0.29 to 0.04). There was no significant difference in delayed memory (-0.14 pictures remembered, 95% CI =-0.38 to 0.10) between the NT-proBNP groups. Participants with higher NT-proBNP had a steeper cognitive decline, including reaction time (mean annual change high vs. low group=0.60 seconds, 95% CI=0.14 to 1.07), processing speed (-0.15 digits coded, 95% CI=-0.25 to -0.05), immediate memory (-0.05 pictures remembered, 95% CI=-0.09 to 0.00), and delayed memory (-0.05 pictures remembered, 95% CI=-0.11 to 0.01). Associations were independent of cardiovascular diseases and risks.

Conclusion Higher NT-proBNP levels associate with worse cognitive function and steeper cognitive decline in older adults, independent of cardiovascular diseases and risks. Further studies to unravel the underlying mechanisms are warranted.

Introduction

Higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a neurohormone produced by cardiomyocytes in response to ventricular stretch, have been associated with cognitive impairment.(1-4) Evidence comes from several cross-sectional studies, which show that among community-dwelling older adults, higher NT-proBNP levels were associated with worse cognitive function, in particular memory.(1-4) There are limited numbers of longitudinal studies with relatively small sample sizes, which demonstrate that higher NT-BNP levels are also associated with steeper declines in Mini-Mental State Examination (MMSE) scores and higher incidence of dementia.(5, 6) A potential mechanism behind the relationship between higher NT-proBNP levels and cognitive function is clinical heart failure, resulting in left ventricular dysfunction with subsequent reduced cardiac output. It is hypothesized that reduced cardiac output causes inadequate cerebral perfusion, leading to a higher risk of cognitive impairment.(7-9) Improvements in cognitive function in patients following cardiac transplantation suggests that impaired cardiac function might be a reversible risk factor for cognitive impairment.(10, 11)

Recent evidence demonstrates that higher NT-proBNP levels in older adults are strongly associated with cardiovascular diseases and risk factors and predict an increased risk of atrial fibrillation, stroke, transient ischemic attack, myocardial infarction and mortality, even in the absence of clinical heart failure.(12-15) In addition, higher NT-proBNP levels have been related to left ventricular hypertrophy and systolic and diastolic dysfunction in adults without clinical heart failure.(16, 17) The relationship of cardiovascular diseases and risk factors with cognitive impairment is well-established.(18, 19) Hence, cognitive impairment might already be present in asymptomatic older adults at early stages of reduced cardiac function.

We hypothesized that elevated levels of NT-proBNP are associated with a steeper cognitive decline in older adults, which might be explained by cardiovascular diseases or risk factors. Therefore, we studied the cross-sectional and longitudinal association of NT-proBNP with cognitive function in a cohort of older men and women from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), in which all participants had either preexisting cardiovascular disease or were at risk of developing this condition.

Methods

Study design

Data were obtained from the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), a randomized, double-blind, placebo-controlled trial designed to investigate the effect of pravastatin in prevention of vascular events in older individuals with pre-existing cardiovascular disease or risk factors thereof. This trial was conducted between 1997 and 2002 and included 5,804 men and women aged 70-82 years old who were enrolled from three collaborating centers in Ireland, Scotland and the Netherlands. Approximately 50% of the participants had cardiovascular disease including stable angina, intermittent claudication, stroke, transient ischemic attack, myocardial infarction and/or vascular surgery. The rest of participants had one or more cardiovascular risk factor, defined as hypertension, smoking or diabetes mellitus. Primary outcome of the trial was the combined endpoint of definite or suspect death from coronary heart disease, non-fatal myocardial infarction and fatal or non-fatal stroke during a mean follow-up period of 3.2 years. The institutional ethics committees of the three collaborating centers approved the study and all participants gave written informed consent.(20, 21)

Study participants

All participants had pre-existing cardiovascular disease or risk factors thereof (defined as a history of hypertension, diabetes mellitus or current smoking). Participants with congestive heart failure, defined as New York Heart Association functional class III or IV, were excluded from the original PROSPER trial.(20) No information on NYHA class I or II was available. For the present study, we additionally excluded participants with heart failure hospitalization during follow-up (n=205).

NT-proBNP measurements

Blood samples were taken at 6 months after follow-up in EDTA tubes.(20) NT-proBNP was determined using electrochemiluminescence immunoassay on a Roche Modulator E170. A number of 394 participants had missing NT-proBNP measurements. In line with existing literature on cutoff values in this age group, we defined three groups of NT-proBNP: low (<100 ng/L), middle (100-450 ng/L) and high NT-proBNP (≥450 ng/L).(1) Furthermore, these cutoff values were chosen from a pragmatic approach, to allow direct interpretation for clinical practice.

Cognitive function

The MMSE was used to evaluate global cognitive function; participants with a baseline score below 24 points were not included in PROSPER. Cognitive function was tested at baseline and at 9, 18, 30 months and at the end of the study. The time-point of the measurement at the end of the study varied between 36 and 48 months; therefore, we performed the analysis with their individually varying time point, but report the results for the mean of these time points (at 42 months). Since PROSPER was conducted in three countries with in total two languages (Dutch and English), care was taken to select tests that are not sensitive to language. Furthermore, all analyses were adjusted for country.(22) Four different neuropsychological tests were used to assess executive function, attention, and immediate and delayed memory. The Stroop-Colour-Word-Test was used to test selective attention and reaction time. Participants were asked to read a color name which was displayed in a color different from the color it actually names. Outcome parameter was the total number of seconds to complete the test; a higher score indicates worse performance. General cognitive speed was tested by the Letter-Digit Coding Test. Participants had to match certain digits with letters according to a provided key. Outcome variable was the total number of correct entries in 60 seconds, therefore higher scores represented better performance. The Picture-Word Learning Test was used to assess immediate and delayed memory. Fifteen pictures were presented, and participants were asked to recall as many pictures as possible in three trials. After 20 minutes they were asked to repeat the pictures they remembered to measure their delayed recall. Outcome parameter was the accumulated number of correct recalled pictures, immediate and after 20 minutes. Higher scores thus indicate better performance. A detailed description of the cognitive tests has been published previously.(22) Since treatment with pravastatin did not influence cognitive function during follow-up, we included participants from both pravastatin and placebo groups.(23)

Statistical analysis

Baseline characteristics of the study participants are reported as number (percentage) for categorical variables and mean (standard deviation) for continuous variables for each group of NT-proBNP. Differences in categorical variables were tested by Chi-squared tests. Differences in continuous variables were tested with linear regression models. Since NT-proBNP levels were not normally distributed, we used log-transformed NT-proBNP levels to calculate p-values for continuous variables. To investigate the cross-sectional association of NT-proBNP with cognitive function, we used linear regression models. Log-transformed NT-proBNP levels were included as independent variable; outcome variable was the mean baseline score on each of the four cognitive function tests. Linear mixed models were

used to examine the association between NT-proBNP and cognitive decline over time. The models included log-transformed NT-proBNP levels, time (in years) and the interaction term between time and log-transformed NT-proBNP levels.

We performed our analyses in three steps. In the first step, crude analyses were performed, in which we only adjusted for cognitive test version where appropriate. In the second step, we added the variables age, sex, education (age left school), country and Apo E genotype to the model to investigate the potential influence of these factors on the associations (minimally adjusted model). Furthermore, in a fully adjusted model we also added the following potential confounders: cardiovascular diseases and risk factors at baseline (history of cerebrovascular and cardiovascular disease, hypertension, diabetes mellitus, smoking status, HDL and LDL cholesterol levels, triglycerides, systolic and diastolic blood pressure, body mass index), statin treatment and estimated glomerular filtration rate (eGFR). Since the associations did not essentially change in various models, we present the results of the minimally and fully adjusted models only.

To further explore the influence of cardiovascular diseases and risk factors, additional analyses were performed in which we stratified for history of cardiovascular diseases and risk factors. To test whether the difference between participants with or without a history of cardiovascular disease or risk factor was significant, we calculated a p-value for interaction by using linear regression models. Furthermore, we performed additional sensitivity analyses in which we excluded 1) participants taking pravastatin treatment during follow-up; 2) participants with incident stroke and/or transient ischemic attack; 3) participants with incident myocardial infarction; 4) participants with incident atrial fibrillation; 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA; 6) participants with NT-proBNP of ≥450 ng/L; and 7) participants taking loop diuretics, beta blockers or ace-inhibitors at baseline.

Results

Participants with heart failure hospitalization during follow-up were excluded (n=205). A number of 394 participants had missing NT-proBNP measurements, resulting in a total number of 5205 participants for the present study.

Table 1 shows characteristics of participants grouped by NT-proBNP levels. Participants with higher NT-proBNP levels were older and had a higher prevalence of hypertension,

myocardial infarction, vascular disease and smoking (all p-values <0.001). Body mass index was lower in participants with higher NT-proBNP levels (p-value <0.001). Systolic blood pressure, pulse pressure and mean arterial blood pressure were higher among participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and p=0.001 respectively). Furthermore, participants with higher NT-proBNP levels had a steeper decline in systolic and diastolic blood pressure during follow-up (p-values <0.001 and 0.001 respectively). Use of loop diuretics, beta blockers and ace-inhibitors was higher in participants with higher NT-proBNP levels (p-values <0.001, p<0.001 and p=0.031 respectively). Participants with higher NT-proBNP levels had lower eGFR (p <0.001).

Table 1. Characteristics of study participants grouped by NT-proBNP

	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Demographics				
Age (years), mean (SD)	74.42 (3.04)	75.53 (3.37)	76.59 (3.40)	<0.001
Female, n (%)	850 (46.8)	1490 (55.2)	360 (52.2)	<0.001
Education (age left school), mean (SD)	15.17 (2.06)	15.15 (2.06)	15.10 (2.08)	0.083
Vascular risk factors				
History of hypertension, n (%)	1056 (58.1)	1736 (64.3)	444 (64.4)	<0.001
History of diabetes mellitus, n (%)	245 (13.5)	245 (9.1)	57 (8.3)	<0.001
History of stroke or TIA, n (%)	189 (10.4)	301 (11.2)	85 (12.3)	0.371
History of myocardial infarction, n (%)	120 (6.6)	369 (13.7)	177 (25.7)	<0.001
History of vascular disease, n (%)	630 (34.7)	1246 (46.2)	393 (57.0)	<0.001
Current smoker, n (%)	536 (29.5)	667 (24.7)	175 (25.4)	0.001
Body mass index (kg/m$^{2)}$, mean (SD)	27.22 (4.02)	26.69 (4.21)	26.17 (4.20)	<0.001
Total cholesterol (mmol/L), mean (SD)	5.68 (0.90)	5.68 (0.91)	5.70 (0.93)	0.461
Systolic blood pressure (mmHg), mean (SD)#	152.60 (20.25)	155.11 (21.75)	158.75 (23.50)	<0.001
Diastolic blood pressure (mmHg), mean (SD)#	84.02 (10.95)	83.73 (11.33)	83.38 (12.01)	0.158
Pulse pressure (mmHg), mean (SD)	68.58 (0.42)	71.38 (0.35)	75.37 (0.68)	<0.001
Mean Arterial Pressure (mmHg), mean (SD)	106.88 (0.30)	107.53 (0.25)	108.51 (0.49)	0.001
Systolic blood pressure trend (mmHg), mean (SD)	-0.97 (7.94)	-1.49 (9.60)	-2.88 (12.44)	<0.001
Diastolic blood pressure trend (mmHg), mean (SD)	-1.25 (4.70)	-1.52 (5.25)	-1.93 (7.03)	0.001
Blood pressure lowering medication, n (%)				
Diuretics	650 (35.8)	1067 (39.5)	269 (39.0)	<0.001
Loop	153 (8.4)	327 (12.1)	107 (15.5)	<0.001
Other	497 (27.3)	740 (27.4)	162 (23.5)	
Calcium channel blockers	459 (25.2)	692 (25.6)	151 (21.9)	0.125
Beta blockers	241 (13.3)	831 (30.8)	273 (39.6)	<0.001
Ace-inhibitors	279 (15.3)	421 (15.6)	134 (19.4)	0.031
eGFR, mean (SD)	62.77 (13.79)	59.64 (14.48)	55.54 (14.99)	<0.001

*Probability values were calculated using log-transformed NT-proBNP levels for continuous variables and chi-squared tests for categorical variables. #Defined as the regression coefficient per year. Abbreviations: ACE=angiotensin-converting enzyme; eGFR=estimated glomerular filtration rate; NT-proBNP=N-terminal pro-brain natriuretic peptide; SD=standard deviation ; TIA=transient ischemic attack.

Table 2 shows the association of NT-proBNP levels with cognitive function at baseline. In the minimally adjusted model, participants with higher NT-proBNP levels had worse performance on the Stroop test (p=0.003) and the Letter-Digit Coding test (p<0.001). The same trend was observed for immediate and delayed Picture-Word Learning tests, showing that participants with higher NT-proBNP levels had worse performance, albeit these associations were not significant (p-value=0.060 and p=0.066 respectively). When further adjusting for prevalent cardiovascular diseases or risk factors at baseline, the estimates of the difference in cognitive function between the groups remained essentially the same. The association of NT-proBNP levels with the Stroop test and Letter-Digit Coding test in the fully adjusted model remained significant (p-value=0.003 and p<0.001 respectively), whereas for immediate and delayed Picture-Word Learning tests the associations were not significant (p-value=0.091 and p=0.062 respectively). Data on the association of NT-proBNP with cognitive function from crude models did not materially differ from minimally and fully adjusted models (data not shown).

Table 3 and Figure 1 show the association of NT-proBNP levels with changes in cognitive function during a mean follow-up period of 3.2 years. Participants with higher NT-proBNP

Table 2. Association of NT-proBNP with baseline cognitive function

Cognitive tests (mean, SE)	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Stroop, seconds				
Minimally adjusted model	64.37 (1.46)	64.15 (1.42)	67.40 (1.63)	0.003
Fully adjusted model	66.23 (1.56)	66.09 (1.53)	69.30 (1.72)	0.003
LDCT, digits coded				
Minimally adjusted model	23.94 (0.41)	23.54 (0.40)	23.02 (0.46)	<0.001
Fully adjusted model	23.33 (0.44)	22.88 (0.43)	22.31 (0.48)	<0.001
PLTi, pictures remembered				
Minimally adjusted model	9.58 (0.11)	9.52 (0.11)	9.44 (0.12)	0.060
Fully adjusted model	9.49 (0.12)	9.44 (0.12)	9.37 (0.13)	0.091
PLTd, pictures remembered				
Minimally adjusted model	10.43 (0.16)	10.40 (0.15)	10.29 (0.17)	0.066
Fully adjusted model	10.22 (0.17)	10.19 (0.16)	10.08 (0.18)	0.062

Data represent mean (standard error) score of each cognitive function test. Minimally adjusted model: adjusted for age, sex, country, education (age on leaving school), ApoE genotype, treatment group, test version for LDCT and PLT. Fully adjusted model: minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, and estimated gloermular filtration rate. *Probability values were calculated using the continuous value of log-transformed NT-proBNP levels. Abbreviations: LDCT=Letter-Digit Coding Test; NT-proBNP=N-terminal pro-brain natriuretic peptide; test; PLTd=Picture-Word Learning test, delayed; PLTi=Picture-Word Learning test, immediate.

levels had a steeper cognitive decline on the Stroop test, Letter-Digit Coding test and immediate and delayed Picture-Word Learning tests (all p-values≤0.001). Again, further adjustments for prevalent cardiovascular diseases or risk factors at baseline did not appreciably alter the observed associations (all p-values≤0.001). The association of NT-proBNP levels with cognitive decline from crude models did not materially differ from adjusted models (data not shown).

To further explore the influence of cardiovascular diseases and risk factors, we performed additional analyses in which we stratified for history of various cardiovascular diseases and risk factors, and tested for interaction. Figure 2 shows the association of NT-proBNP levels with cognitive decline, stratified by history of cardiovascular diseases and risk factors. There was no significant difference in change in cognitive function during follow-up between participants with and without cardiovascular diseases or risk factors, except on the Letter-Digit Coding test for participants with a history of stroke and/or transient ischemic attack (TIA) and myocardial infarction. Participants with previous stroke and/or TIA had a less steep decline on Letter-Digit Coding test (p for interaction=0.003), while participants with previous myocardial infarction had a steeper decline on Letter-Digit Coding test (p

Table 3. Association of NT-proBNP with cognitive decline during follow-up

Cognitive tests (mean annual change, SE)	NT-proBNP			
	Low N=1818 <100 ng/L	Middle N=2698 100-450 ng/L	High N=689 ≥450 ng/L	P-value*
Stroop, seconds				
Minimally adjusted model	0.46 (0.11)	0.71 (0.09)	1.04 (0.26)	0.001
Fully adjusted model	0.47 (0.11)	0.72 (0.09)	1.04 (0.26)	0.001
LDCT, digits coded				
Minimally adjusted model	-0.32 (0.02)	-0.36 (0.02)	-0.46 (0.04)	0.001
Fully adjusted model	-0.32 (0.02)	-0.35 (0.02)	-0.47 (0.04)	<0.001
PLTi, pictures remembered				
Minimally adjusted model	-0.00 (0.01)	-0.03 (0.01)	-0.05 (0.02)	<0.001
Fully adjusted model	0.00 (0.01)	-0.02 (0.01)	-0.04 (0.02)	<0.001
PLTd, pictures remembered				
Minimally adjusted model	-0.05 (0.01)	-0.06 (0.01)	-0.10 (0.03)	0.001
Fully adjusted model	-0.03 (0.01)	-0.05 (0.01)	-0.10 (0.03)	0.001

Data represent mean annual change (standard error) in each cognitive function test. Minimally adjusted model: adjusted for age, sex, country, education (age on leaving school), ApoE genotype, treatment group, test version for LDCT and PLT.Fully adjusted model: minimally adjusted model + adjustments for history of cerebrovascular and cardiovascular disease, history of hypertension, history of diabetes mellitus, current smoking, baseline systolic and diastolic blood pressure, HDL and LDL cholesterol, triglycerides, body mass index, and estimated glomerular filtration rate. *Probability values were calculated using the interaction term of time and log-transformed NT-proBNP levels.Abbreviations: LDCT=Letter-Digit Coding test; NT-proBNP=N-terminal pro-brain natriuretic peptide; PLTd, Picture-Word Learning test, delayed; PLTi=Picture-Word Learning test, immediate

for interaction=0.008). However, no such differences were observed for participants with previous stroke and/or TIA or myocardial infarction on any of the other cognitive tests.

Furthermore, we performed additional sensitivity analyses to investigate whether the association between NT-proBNP levels and cognitive function and decline could be affected by 1) participants taking pravastatin treatment during follow-up (n=2,588); 2) participants with incident stroke and/or TIA during follow-up (n=355); 3) participants with incident myocardial infarction during follow-up (n=339); 4) participants with incident atrial fibrillation during follow-up (n=421); 5) participants with vascular events, including coronary heart disease death, nonfatal myocardial infarction, nonfatal and fatal stroke and/or TIA during follow-up (n=648); 6) participants with NT-proBNP levels of ≥ 450 ng/L; and 7) participants taking loop diuretics (n=588), beta blockers (n=1,345) or ace-inhibitors (n=834) at baseline. Exclusion of these participants did not essentially change our results (data available on request).

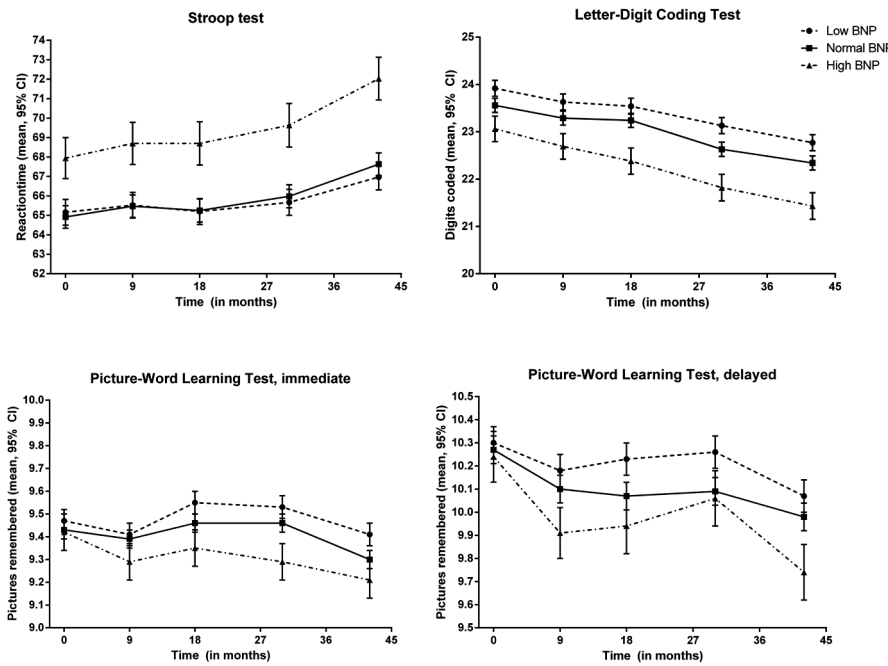

Figure 1. Association of NT-proBNP with cognitive decline during follow-up
Data represent mean score (95% confidence interval) of each cognitive test during follow-up, in each group of NT-proBNP. Because the time-point of the measurement at the end of the study varied between 36 and 48 months, the mean of these time points (42 months) is reported. Probability values were calculated using the interaction term of time and log-transformed NT-proBNP levels. Adjustments were made for age, sex, country, education, ApoE genotype, treatment group and test version where appropriate.

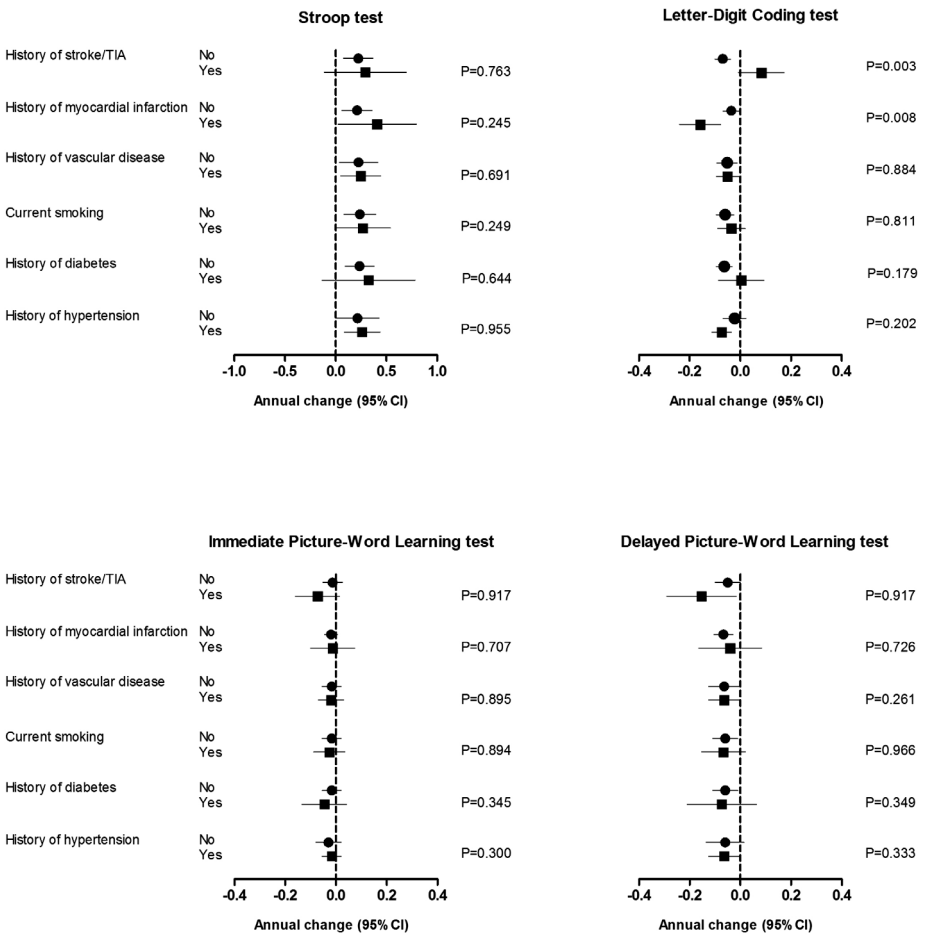

Figure 2. Association of NT-proBNP with cognitive decline during follow-up, stratified by cardiovascular diseases and risk factors

Data represent mean annual change (95% confidence interval) per 1 ng/L increase in log-transformed NT-proBNP for each cognitive test, stratified by cardiovascular diseases. Probability values were calculated using the interaction term of cardiovascular disease and log-transformed NT-proBNP level and represent the statistical difference in annual change in cognitive function between participants with and without cardiovascular disease or risk factors. Adjusted for age, sex, country, education, ApoE genotype, treatment group and test version where appropriate. Abbreviation: TIA=transient ischemic attack.

Discussion

In this prospective cohort study including over 5,000 men and women with mean age of 75 years, we showed that participants with higher NT-proBNP levels had worse cognitive

function and steeper cognitive decline during a mean period of 3.2 years. These associations were independent of cardiovascular diseases and risk factors.

Our findings are in line with previous cross-sectional studies, showing that higher NT-proBNP levels were associated with worse memory and with lower global and executive cognitive function.(1-4) Only few longitudinal studies with limited number of participants investigated the association between NT-proBNP and cognition during follow-up. They showed that higher NT-proBNP levels are associated with a steeper decline in Mini-Mental State Examination (MMSE) scores and a higher incidence of dementia during a mean follow-up period of 5 years.(5, 6) To our knowledge, this is the first study reporting on the association of NT-proBNP and cognitive function and decline, using an extended standardized test battery over a mean follow-up period of 3.2 years, in a large cohort of older adults with pre-existing cardiovascular disease or risk factors thereof.

Brain natriuretic peptide (BNP) and the biologically inactive N-terminal pro-brain natriuretic peptide are secreted by the ventricles of the heart in response to excessive stretching of cardiomyocytes.(24) BNP has favorable physiological properties, including increased natriuresis and diuresis, relaxation of vascular smooth muscle cells and inhibition of the renin-angiotensin-aldosterone-axis, eventually causing a reduction in blood pressure and ventricular preload.(24) Our results showed that higher NT-proBNP levels were associated with higher systolic blood pressure. Initially, higher systolic blood pressure might increase the ventricular stress of cardiomyocytes and therefore causes an increased release of NT-proBNP. In case of chronic ventricular stress, this might further proceed to reduced cardiac function and heart failure. Subsequently, cardiac output will be reduced and blood pressure will be lower.(9)

Different explanations can be proposed for the observed association of NT-proBNP with cognitive decline. First, NT-proBNP and cognitive decline are highly likely to reflect underlying cardiovascular damage and therefore stem from common causes. Previous studies have shown that NT-proBNP levels have a prognostic value for the occurrence of cardiovascular events, such as myocardial infarction, atrial fibrillation, coronary heart disease, unstable angina, stroke and transient ischemic attack.(12, 15, 25, 26) This has also been demonstrated in subjects with elevated NT-proBNP levels, but without clinical heart failure.(27) Furthermore, NT-proBNP levels provide predictive information for use of risk stratification in nonfatal cardiac events, stroke and mortality in range of populations including diabetes.(26, 28-30) These cardiovascular and metabolic diseases are closely linked to

cognitive dysfunction and dementia.(18, 19) This is in line with the finding that high NT-proBNP levels are associated with an increased prevalence of cardiovascular diseases and risk factors in the population under study. However, when adjusting and stratifying our analyses for cardiovascular diseases and risk factors, our results did not appreciably alter. Furthermore, excluding participants with incident myocardial infarction, stroke and/or TIA showed the same results. Nevertheless, we cannot rule out the possibility that unmeasured cardiovascular risk factors resulted in both increased NT-proBNP and cognitive decline. Second, impaired cardiac function may activate the renin-angiotensin system which in turn has been associated with cognitive decline.(31) In line with this evidence, observational studies have suggested that subjects receiving angiotensin receptor blockers may have a lower risk of developing dementia.(32, 33) Since only a small number of participants used angiotensin receptor blockers in the population under study (n<100), we could not further investigate this issue. Third, since natriuretic peptides have first been identified in porcine brain extract, one could hypothesize that NT-proBNP could have a direct effect in the brain. Although there is evidence that natriuretic peptides have receptors on endothelial cells, it is, to our knowledge, unknown whether NT-proBNP alters cerebral autoregulation.(7, 34) A fourth explanation might be that high NT-proBNP levels in subjects without advanced stages of heart failure indicate a suboptimal left ventricular functioning with subsequent decreased cardiac output and cerebral hypoperfusion.(9, 16) Cerebral hypoperfusion, which impairs the delivery of oxygen and nutrients to the brain, has been associated with cognitive dysfunction and dementia.(7-9) Although this explanation seems plausible, there is a need for interventional studies investigating the influence of improvement in cardiac function with its subsequent influence on cerebral perfusion, and eventually the prevention of cognitive decline in old age.

The present study found that participants with previous stroke and/or TIA had a less steep decline on Letter-Digit Coding test, which is unexpected and not in line with previous literature. Nevertheless, no differences were observed for participants with previous stroke and/or TIA on the Stroop test, immediate Picture-Word Learning test and delayed Picture Word Learning test. Furthermore, as there was no significant association between NT-proBNP levels and history of stroke and/or TIA, we could not explain this association from a biologically perspective. Therefore, we believe that the most likely explanation for this finding is chance.

Major strengths of this study include the large sample size of over 5000 older participants and the repeated use of an extended standardized cognitive test battery to assess cognitive

function over a mean follow-up period of 3.2 years. Furthermore, in contrast to previous studies, participants with NYHA functional class III/IV were excluded, which gave us the opportunity to investigate NT-proBNP in relation with cognitive function and decline in participants without advanced stages of clinical heart failure. However, a limitation of the study is that there was no information on the incidence of dementia during follow-up, nor was there information on cardiac functioning or NYHA class I or II. We might therefore have included participants with (beginning stages of) clinical heart failure, without ever being diagnosed with this condition. However, excluding participants with NT-proBNP levels of $\geq$ 450 ng/L showed essentially the same results. As high NT-proBNP levels have been recognized as predictor of heart failure, this finding further suggests an association between NT-proBNP and cognitive decline.(35) Furthermore, our study population consisted of older participants at risk of cardiovascular diseases with relatively preserved cognitive function (MMSE $\geq$ 24 points), which might limit extrapolation of our findings to a general population of older subjects.

In conclusion, higher NT-proBNP levels associate with worse cognitive function and steeper cognitive decline in older adults, independent of cardiovascular diseases and risks. Further studies to unravel the underlying mechanisms are warranted.

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