The handle http://hdl.handle.net/1887/25009 holds various files of this Leiden University dissertation.

**Author:** Sabayan, Behnam  
**Title:** Cardiovascular and hemodynamic contribution to brain aging  
**Issue Date:** 2014-04-02
Serum NT-proBNP, Blood Pressure and Cognitive Function

Manuscript based on this chapter has been submitted as:
Summary

Hypertension in middle age is a risk factor for dementia, whereas in old age cognitive impairment is associated with lower blood pressures. Heart failure may play a role in this reversal of associations. In this chapter, we studied the relation between N-terminal pro-brain natriuretic peptide (NT-proBNP) levels, a marker of heart failure, blood pressure, and cognitive function over time in the oldest old. In the Leiden 85-plus Study, we measured NT-proBNP levels at baseline and annually global cognitive function (MMSE) and blood pressure (BP) in 560 subjects aged 85 years at baseline, who were followed for 5 years. Subjects in the highest tertile of NT-proBNP levels scored 1.8 points lower on the MMSE than subjects in the lowest tertile (p=0.004), and had a 0.7 point stronger decline in MMSE score per year (p=0.006). Subjects in the category highest tertile of NT-proBNP and the lowest tertile of systolic BP had a 3.7 point lower MMSE score at baseline (p<0.001) and a 0.6 point additional annual decline in MMSE score (p=0.040) compared to subjects in any other category. In the oldest old high NT-proBNP levels are associated with lower MMSE scores and with stronger declines in MMSE score. The combination of high NT-proBNP levels and low systolic BP is most detrimental for global cognitive function. Possibly, a failing pump function of the heart results in lower brain perfusion with resultant brain dysfunction.
Introduction

Cardiovascular diseases, such as myocardial infarction, generalized atherosclerosis, and stroke have been associated with increased risk of dementia and with steeper declines in cognitive function. Hypertension on the contrary seems to be a risk factor for dementia only when present in middle age, whereas most studies show that dementia and cognitive decline in the oldest old associate with lower blood pressures. In the oldest old blood pressures decrease over time, and stronger declines are related to the presence of dementia and cognitive decline. One possible explanation for the decline in blood pressure in the oldest old might be the presence of (subclinical) congestive heart failure, with a failing pump function resulting in lower blood pressures.

Congestive heart failure has been associated with cognitive impairment in several studies. In two hospital-based studies, patients with heart failure had an increased risk of cognitive impairment, and with increasing severity of heart failure patients had worse cognitive performance. Moreover, another study showed that lower left ventricular ejection fractions in elderly patients with heart failure associated with reduced verbal memory function. A commonly used serum marker of heart failure is the N-terminal pro-brain natriuretic peptide (NT-proBNP), the inactive fragment of the proBNP hormone. NT-proBNP has proven to be a quantitative marker of acute heart failure, with high sensitivity and reasonable specificity, and is also a useful tool to monitor (treatment of) heart failure. Several cross-sectional studies have shown that higher NT-proBNP levels associate with lower cognitive function, and one follow-up study showed that higher NT-proBNP levels at baseline associated with worse cognitive function five to eight years later. The relation between NT-proBNP levels, blood pressure, and cognitive function over time in the oldest old, has not been studied yet.

Here, we studied the association between NT-proBNP levels, blood pressure and cognitive function over time in the Leiden 85-plus Study, a population based follow-up study amongst subjects aged 85 years at baseline. We hypothesize that high NT-proBNP levels, and low systolic blood pressure associate with worse cognitive function.

Materials and Methods

Participants
Between September 1, 1997, and September 1, 1999, a total of 705 inhabitants of the community of Leiden, the Netherlands, reached the age of 85 years. Among these 85-year-old persons, we initiated a follow up study to investigate determinants of successful aging. There were no selection criteria on health or demographic characteristics. Fourteen inhabitants died before they could be enrolled. The response rate was 87%; a total of 599 subjects (397 women and 202 men) participated. Of the 599 participants in the cohort, 38 refused to provide a blood sample, and NT-proBNP measurement failed in one participant, yielding a total number of 560 participants for the present study. Participants were visited within one month after their 85th birthday at their home for face-to-face interviews and neuropsychological testing. They were revisited annually until age 90 years. The Medical Ethical Committee of the Leiden University Medical Centre approved the study, and informed consent was obtained from all participants.

**Plasma levels of NT-proBNP**

Non-fasted blood samples were taken at the first visit early in the morning. Blood samples were kept frozen at -80°C. In 2011 citrated plasma levels of NT-proBNP were measured in one batch using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-170 automated immunoanalyser.

**Blood pressure**

Annually, blood pressure was measured, using a mercury sphygmomanometer, in seated position. During each home visit two blood pressure measurements were done, the first after at least five minutes of rest and no vigorous exercise in the preceding thirty minutes, the second after approximately 90 minutes at the end of the visit. The systolic value was measured at Korotkoff sound 1, and the diastolic value was measured at Korotkoff sound 5. For each year, the mean value of the two measurements was calculated and used in further analyses. Mean arterial pressure was calculated as \( \frac{1}{3} \) (systolic blood pressure) + \( \frac{2}{3} \) (diastolic blood pressure).

**Global cognitive function**

At age 85 years and then annually, global cognitive function was assessed in participants using the Mini-Mental State Examination (MMSE). The MMSE examines five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. Possible scores on the MMSE range from 0 to
30 points, with lower scores indicating worse global cognitive functioning.

**Other covariates**

The level of education of each participant was determined by the number of years a subject went to school. Information was obtained at the first visit using a questionnaire. Low education was defined by six or less than six years of schooling, whereas high education was defined by seven or more years of schooling. The burden of vascular disease at baseline was determined by the number of cardiovascular and cerebrovascular pathologies (myocardial infarction, angina pectoris or myocardial ischemia, claudicatio intermittens, arterial surgery, stroke, and transient ischemic attack). Information on use of antihypertensive medication was obtained from pharmacist records, or from a questionnaire, filled out by the treating physician for institutionalized participants. Participants were classified as having diabetes when they met at least one of the following criteria: (a) history of type 2 diabetes obtained from the general practitioner or the subject’s treating physician; (b) use of antidiabetic medication, based on information obtained from the subject’s pharmacist; or (c) nonfasting glucose of 11.1 mmol/L or higher. Information on smoking was obtained from questionnaires, which were filled out by each participant at baseline. BMI was calculated by dividing the weight in kilograms by the square of length in meters ($\text{kg/m}^2$). Creatine clearance was estimated with the Cockroft-Gault formula. Prevalence of atrial fibrillation was determined by automated Minnesota Coding (Minnesota Code 8-3-1) of ECGs, which were recorded on a Siemens Sicard 440 (Erlangen, Germany), and were transmitted to the ECG Core Laboratory in Glasgow Royal Infirmary.

**Statistical analyses**

Characteristics of the study participants are reported as mean (standard deviation) for continuous variables and number (percentages) for categorical variables in tertiles of NT-proBNP levels. The associations of both NT-proBNP levels and systolic blood pressure with MMSE score at baseline and during follow up were analyzed using two different methods. First, linear mixed models were used for graphically representing the associations. Linear mixed models use all available data during follow-up and account for repeated measurements, thereby handling missing data more appropriately than traditional models. For more accurate analyses using all available data, but without imputation methods for missing data, the associations of NT-proBNP levels and systolic blood pressure with MMSE score were analyzed using linear regression analysis. In these analy-
ses baseline associations were tested and for the longitudinal associations regression coefficients of change in MMSE score per year were calculated per subject, yielding new outcome variables used as the determinant. In the primary analyses categorical NT-proBNP levels and systolic blood pressure were the independent variable, whereby NT-proBNP levels and systolic blood pressure were divided in tertiles. For continuous analyses log-transformed NT-proBNP levels were used. In a multivariate model all analyses were corrected for level of education, use of antihypertensives, smoking status, prevalence of diabetes, body mass index, renal function, prevalence of atrial fibrillation, and, finally, the number of cardiovascular and cerebrovascular pathologies at baseline. In a final analysis a new variable consisting of four categories, using combinations of the lowest and highest tertile of NT-proBNP levels and the lowest and highest tertile of systolic blood pressure, was used as an independent variable with MMSE scores as the determinant. All calculations were performed using SPSS software (version 20.0.1, SPSS Inc, Chicago, Ill).
Results

Table 1 shows baseline characteristics of all 560 study participants in tertiles of NT-proBNP levels. Compared to subjects in the lowest tertiles, subjects in the highest tertile of NT-proBNP had a lower educational level, had lower blood pressures, had a lower body mass index, and a lower renal function, were more likely to use antihypertensives, and to have a history of smoking, and had a higher prevalence of cardiovascular pathologies and atrial fibrillation.

Table 1. Baseline characteristics of study population.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Low (n=186)</th>
<th>Middle (n=187)</th>
<th>High (n=187)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>62 (33%)</td>
<td>54 (29%)</td>
<td>71 (38%)</td>
<td>0.176c</td>
</tr>
<tr>
<td>Low education (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>115 (62%)</td>
<td>112 (60%)</td>
<td>134 (72%)</td>
<td>0.030c</td>
</tr>
<tr>
<td>SBP, mmHg (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>156.8 (17.6)</td>
<td>155.9 (18.1)</td>
<td>152.9 (20.0)</td>
<td>0.045d</td>
</tr>
<tr>
<td>DBP, mmHg (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>79.0 (9.0)</td>
<td>77.2 (9.4)</td>
<td>74.1 (9.6)</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>MAP, mmHg (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>104.9 (10.5)</td>
<td>103.4 (11.0)</td>
<td>100.4 (11.4)</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>Body mass index, kg/m&lt;sup&gt;2&lt;/sup&gt; (SD)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>28.1 (4.2)</td>
<td>27.4 (4.9)</td>
<td>26.1 (4.0)</td>
<td>&lt;0.001d</td>
</tr>
<tr>
<td>Use of antihypertensives (%)</td>
<td>66 (36%)</td>
<td>87 (45%)</td>
<td>96 (51%)</td>
<td>0.007c</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>30 (16%)</td>
<td>24 (13%)</td>
<td>35 (19%)</td>
<td>0.307c</td>
</tr>
<tr>
<td>Former smoking (%)</td>
<td>90 (49%)</td>
<td>76 (42%)</td>
<td>99 (54%)</td>
<td>0.048c</td>
</tr>
<tr>
<td>Prevalence of DM type II (%)</td>
<td>30 (16%)</td>
<td>27 (14%)</td>
<td>35 (19%)</td>
<td>0.531c</td>
</tr>
<tr>
<td>Prevalence CVD (%)</td>
<td>49 (27%)</td>
<td>65 (36%)</td>
<td>111 (62%)</td>
<td>&lt;0.001c</td>
</tr>
<tr>
<td>Prevalence of atrial fibrillation (%)</td>
<td>3 (2%)</td>
<td>4 (2%)</td>
<td>49 (27%)</td>
<td>&lt;0.001c</td>
</tr>
</tbody>
</table>

<sup>a</sup> Level of education was dichotomized by six years of schooling

<sup>b</sup> Normally distributed continuous data are presented as means with standard deviations

<sup>c</sup> Statistical significance of the difference in number of subjects per tertile, using Chi<sup>2</sup> testing

<sup>d</sup> Statistical significance of the trend over the tertiles, using linear regression analysis

Abbreviations: SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, PP: pulse pressure

Figure 1a graphically shows the association between NT-proBNP levels and MMSE scores from age 85 to 90 years. At age 85 years, subjects in the highest tertile of NT-proBNP had a 1.8 point lower MMSE score than subjects in the lowest tertile (p=0.002). Moreover, during the five year follow-up, subjects in the highest tertile of NT-proBNP had a 0.24 point steeper decline in MMSE score per year compared to subjects in the lowest tertile (p=0.008). There was also an
association between systolic blood pressure and MMSE score (figure 1b). Subjects in the lowest tertile of systolic blood pressure had a 2.8 point lower MMSE score at age 85 years than subjects in the highest tertile (p<0.001). They also had a 0.39 point steeper decline in MMSE score per year compared to subjects in the highest tertile of systolic blood pressure (p<0.001).

When analyzing these associations with NT-proBNP levels and systolic blood pressure as continuous variables similar associations were found. An increase in log-transformed NT-proBNP levels associated both with lower MMSE scores as baseline (difference in MMSE score at age 85 years per 1 ln-NT-proBNP increase: -0.57, 95% CI, -0.98 to -0.16, p=0.007) and with stronger declines in MMSE score from age 85 to 90 years (additional annual change in MMSE score from age 85 to 90 years per 1 ln-NT-proBNP increase: -0.08, 95% CI, -0.15 to -0.02, p=0.012). An increase in systolic blood pressure associated with higher MMSE scores at baseline (difference in MMSE score at age 85 years per 10 mmHg increase in systolic blood pressure: +0.68, 95% CI, 0.43 to 0.93, p<0.001) and with weaker declines in MMSE score from age 85 to 90 years (additional annual change in MMSE score from age 85 to 90 years per 10 mmHg increase in systolic blood pressure: 0.08, 95% CI, 0.01 to 0.04, p<0.001).

When using linear regression analyses for analyzing the association between tertiles of NT-proBNP levels and MMSE scores at baseline and during follow-up, similar results were found as in the linear mixed models analyses (table 2). Subjects in the highest tertile of NT-proBNP had lower MMSE scores at age 85 years and had stronger declines in MMSE score from age 85 to 90 years. Also for the baseline association between systolic blood pressure and MMSE score similar results were found, with the lowest MMSE scores at age 85 years in subjects in the lowest tertile of systolic blood pressure. However, subjects in the lowest tertile of systolic blood pressure did not have a significant stronger decline in MMSE score from age 85 to 90 years compared to subjects in the highest tertile. In continuous multivariate analyses, with further correction for possible confounders, similar associations were found. After correction for sex, education, smoking, prevalence of diabetes mellitus and atrial fibrillation, use of antihypertensives, BMI, and renal function, higher ln-NT-proBNP levels associated with lower MMSE scores at age 85 years (difference in MMSE score at age 85 years per 1 ln-NT-proBNP increase: -0.49, 95% CI, -0.94 to -0.04, p=0.032), and with stronger declines in MMSE score from age 85 to 90 years (change in MMSE score from age 85 to 90 years: -0.19, 95% CI, -0.37 to -0.02, p=0.030). With further correction for the prevalence of cardiovascular pathologies the association was no longer significant for the baseline analysis (p=0.131), but stayed for the longitudinal analysis (p=0.043). In the multivariate analyses there was a strong association between systolic blood pressure and MMSE score at baseline (difference in MMSE score at age 85 years per 10 mmHg increase in systolic blood
Figure 1. NT-proBNP and systolic blood pressure were divided in tertiles, based on the medians. Data points represent estimates and their standard errors, calculated using linear mixed models, with adjustment for sex and level of education. Number of subjects and range of values per tertile: low NT-proBNP, n=186, 20.8-200.9 pg/ml; high NT-proBNP, n=187, 552.9-28,362.7 pg/ml; low systolic blood pressure, n=186, 110.0-146.5 mmHg; high systolic blood pressure, n=193, 162.0-215.0 mmHg.
pressure: +0.49, 95% CI, 0.24 to 0.75, p<0.001), but not with MMSE score from age 85 to 90 years (change in MMSE score from age 85 to 90 years per 10 mmHg increase in systolic blood pressure: +0.08, 95% CI, -0.02 to 0.18, p=0.138).

### Table 2. MMSE score at age 85 years and change in MMSE score from age 85 to 90 years dependent on tertiles of NT-proBNP and tertiles of systolic blood pressure.

<table>
<thead>
<tr>
<th>Tertiles of the determinant</th>
<th>Low</th>
<th>Middle</th>
<th>High</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NT-proBNP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>25.8 (0.4)</td>
<td>24.6 (0.4)</td>
<td>24.0 (0.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>-0.9 (0.2)</td>
<td>-1.0 (0.2)</td>
<td>-1.6 (0.2)</td>
<td>0.006</td>
</tr>
<tr>
<td><strong>SBP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>23.1 (0.4)</td>
<td>25.3 (0.4)</td>
<td>25.9 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>-1.4 (0.2)</td>
<td>-1.0 (0.2)</td>
<td>-1.1 (0.2)</td>
<td>0.139</td>
</tr>
</tbody>
</table>

Tertiles of NT-proBNP and tertiles of systolic blood pressure were created on the median. Estimates with their standard errors were calculated, with correction for sex and level of education. P-values represent the statistical significance of the trend over the tertiles of NT-proBNP and tertiles of systolic blood pressure (SBP), calculated using linear regression analysis, with adjustment for sex and level of education. Number of subjects per tertile NT-proBNP: lowest, n=186; medium, n=187; highest, n=187. Number of subjects per tertile systolic blood pressure: lowest, n=186; medium, n=181; highest, n=193.

Finally, to test for the combined effect of NT-proBNP levels and systolic blood pressure on MMSE scores, a new variable was created, consisting of combinations of the lowest and highest tertiles of NT-proBNP levels and systolic blood pressure. Figure 2 shows that subjects in the category ‘high NT-proBNP & low systolic blood pressure’ had the lowest MMSE score at baseline and had the strongest decline in MMSE score from age 85 to 90 years. Compared to the other three categories, subjects in the category ‘high NT-proBNP & low systolic blood pressure’ had a 3.7 point lower MMSE score at age 85 years (95% CI, 2.1 to 5.3, p<0.001), and a 0.49 point annual additional decline in MMSE score from age 85 to 90 years (95% CI, 0.24 to 0.75, p<0.001). When using diastolic blood pressure, mean arterial pressure, and pulse pressure in the models, similar associations were found at baseline (all p≤0.001) and during follow up for pulse pressure (p<0.001), but not for diastolic blood pressure (p=0.580) and mean arterial pressure (p=0.089).

When analyzing the associations between NT-proBNP levels, systolic blood pressure and MMSE scores with linear regression analysis instead of linear mixed models, similar results were found for baseline associations, and results
Figure 2. MMSE score from age 85 to 90 years dependent on categories of tertiles of NT-proBNP and tertiles of systolic blood pressure. Categories of NT-proBNP and systolic blood pressure were created by making tertiles, based on the medians, and using the highest and the lowest tertile of each parameter. Data points represent estimates, calculated using linear mixed models, with adjustment for sex and level of education.

were less outspoken for the longitudinal associations. When comparing the category ‘high NT-proBNP & low systolic blood pressure’ with the other three categories the difference in MMSE score at age 85 years was 3.7 points (95% CI, 2.1 to 5.3, *p* < 0.001), and the additional annual decline in MMSE score from age 85 to 90 years was 0.6 points (95% CI, 0.0 to 1.3, *p* = 0.040).

**Discussion**

The main finding of our study is that higher NT-proBNP levels are associated with worse global cognitive function at baseline and with stronger cognitive decline during follow-up in the oldest old. Moreover, lower systolic blood pressures associated with worse global cognitive function at baseline, but not clearly with stronger cognitive decline during follow-up. When combining NT-proBNP levels and systolic blood pressures in a new variable, subjects with both high NT-proBNP levels and low systolic blood pressures had the worst global cognitive
Our finding of higher NT-proBNP levels associating with worse cognitive function is in accordance with previous studies. In the Rancho Bernardo Study, a population-based study amongst 950 subjects with a mean age of 77 years, subjects with high NT-proBNP levels had worse cognitive test scores compared to subjects with low NT-proBNP levels. A recently published study amongst elderly patients with type 2 diabetes also showed that higher NT-proBNP levels associated with lower cognitive function. However, these studies reported on cross-sectional associations and lack follow up data. In the Hoorn Study, higher NT-proBNP levels at baseline associated with worse cognitive performance, which was measured after a follow up period of five to eight years. There was no information on cognitive performance at baseline, and therefore conclusions on cognitive decline could not be drawn from these results. The only study reporting on prospective associations was performed in 464 subjects aged 75 years and over. In this study, high NT-proBNP levels associated with both higher declines in MMSE score, measured at baseline and after five years of follow up, and with an increased risk of dementia. Information on blood pressure was not reported. Only one study has shown the absence of an association between NT-proBNP levels and cognitive function, despite the clear association between high NT-proBNP levels and vascular disease in the population of elderly patients with mental illness.

NT-proBNP has emerged as an important biomarker of cardiac function and is commonly used in clinical practice for the evaluation of congestive heart failure. NT-proBNP is the biologically inactive N-terminal fragment of the prohormone proBNP, which is evenly split into the active BNP and NT-proBNP. ProBNP is secreted predominantly by cardiac myocytes of the ventricles in response to stretching and distension of the cardiac wall and has a natriuretic and diuretic effect. An experimental study amongst healthy male volunteers showed that infusion of low-dose BNP resulted in natriuresis and the inhibition of plasma renin activity. Moreover, in animals, sustained infusion of natriuretic peptides resulted in a lower blood pressure. Additionally, genetic variation in the natriuretic peptide precursor B gene was shown to associate with both lower NT-proBNP levels and higher blood pressures. These findings might explain the observed association between high NT-proBNP levels and lower blood pressures in our study. However, this contradicts with results from previously published studies, in which high NT-proBNP levels associated with higher blood pressures, albeit in younger populations. An explanation for these opposing results might be that initially, as a consequence of hypertension, higher filling pressures of the ventricles result in an increased release of NT-proBNP. However, with longer standing hypertension ventricular enlargement and dysfunction may develop. This leads to heart failure with lower car-
diac output and persisting NT-proBNP release with increased natriuresis and diuresis, subsequently resulting in lower blood pressures.

Since low NT-proBNP levels reliably exclude heart failure and high NT-proBNP levels are related to heart failure, our results may suggest that heart failure associates with worse cognitive function and with stronger cognitive decline in the oldest old. The relation between cognitive function and heart failure, irrespective of NT-proBNP levels, has been reviewed before. The authors conclude that there is a strong cross-sectional association between heart failure and cognitive impairment, but that there are very few longitudinal data available. Possible pathophysiological mechanisms explaining for the association between heart failure and cognitive impairment may be found in direct and indirect pathways. An indirect pathway may be the presence of common risk factors that associate with both heart failure and cognitive impairment. Hypertension at midlife for instance is a risk factor for late-life cognitive impairment, but is also a well-known risk factor for heart failure up to old age. Similar common risk factors are a history of smoking and prevalence of atherosclerotic disease, which all associate with both an increased risk of heart failure and an increased risk of cognitive impairment. Specifically the latter one may explain the found associations for a substantial part, because correction for the prevalence of cardiovascular pathologies in the multivariate model diminished the cross-sectional association between NT-proBNP levels and MMSE scores at age 85 years. However, these indirect pathways may only explain part of the observed association between NT-proBNP levels and cognitive function in our study, since correction for all these risk factors in our analyses did not materially change the longitudinal results. Another likely pathophysiological explanation might be found in the direct effect of heart failure on cerebral perfusion. Heart failure is characterized by a decreased cardiac pump function, with resultant lower cardiac output. This eventually may result in cerebral hypoperfusion with concomitant decreased cerebral function. In an older population of patients with heart failure, ejection fractions below 30% were indeed associated with worse memory function compared to ejection fractions over 30%. In further support of this possible pathophysiological mechanism we showed in a recently performed meta-analysis that both patients with Alzheimer’s disease and patients with vascular dementia have lower cerebral blood flow velocities than age-matched controls. Other explanatory factors that associate with both NT-proBNP levels and cognitive function, such as atrial fibrillation and renal function, are less likely to play a substantial role, since correction for these variables did not materially change the associations.

In cross-sectional analyses low systolic blood pressure associated with worse global cognitive function. However, results from the longitudinal analyses are less clear. When using linear mixed models low systolic blood pressure associ-
ated with stronger declines in MMSE score. This could however not be replicated when using linear regression analyses, using regression coefficients of change in MMSE scores over the years as outcome variable. A possible explanation may be found in the handling of missing values. Linear mixed models uses imputation techniques for missing values of MMSE scores, whereas the regression coefficients of change in MMSE score are created using available data points only, without imputation of missing values. Likely, the imputation of missing values in the linear mixed models gave a slight overestimation of the effect observed when using linear regression analysis. Worst global cognitive function and strongest cognitive decline was observed in subjects who had both high NT-proBNP levels and low systolic blood pressures, as opposed to all other subjects. This suggests that only the combination of the two is detrimental. A possible explanation for this finding might be that high NT-proBNP levels reflect a different pathomechanism in the group of subjects with low blood pressure compared to the group with high blood pressure. In subjects with low blood pressure high NT-proBNP levels may be the result of longer existing heart failure, which results in cardiac dysfunction, lower cardiac output and low blood pressure. This then eventually may result in cerebral hypoperfusion. In subjects with high blood pressure high NT-proBNP levels may be the result of cardiac stress caused by the hypertension, which does not necessarily have a direct negative impact on cerebral function. In other words, the latter group may reflect subjects with better cardiac function, and possibly better general health than the former group. This reasoning corresponds with previous findings, in which lower diastolic blood pressure in old age was shown to associate with increased mortality risk\textsuperscript{41}. In the Leiden 85-plus Study we previously showed that in the oldest old declines in blood pressure during follow up associate with increased mortality risk\textsuperscript{6,42}. Within the context of this reasoning low blood pressure and possibly high NT-proBNP levels in old age could also be a marker of underlying disease, such as general wasting, explaining for these findings.

A limitation of our study is that information on cardiac output, and cerebral perfusion is not available. Echocardiography was only performed in a convenience sample of 90 year olds, and unfortunately not at baseline. With additional information of these two parameters the possible pathophysiological mechanisms could have been further elucidated. Another limitation of our study is that these results cannot be extrapolated to younger populations, since the study was performed in the oldest old only.

In conclusion, high NT-proBNP levels in the oldest old associate with worse global cognitive function and with stronger cognitive decline. The combination of high NT-proBNP levels and low systolic blood pressure is specifically detrimental for cognitive function.
References


