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Plasma NT-proBNP as predictor of change in functional status, cardiovascular morbidity and mortality in the oldest old: the Leiden 85-plus study

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Abstract In the aging society, it is important to identify very old persons at high risk of functional decline, cardiovascular disease and mortality. However, traditional risk markers lose their predictive value with age. We investigated whether plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels predict change in functional status, cardiovascular morbidity and mortality in very old age. Here we present an observational prospective cohort study (Leiden 85-plus Study, 1997–2004) in a population-based sample of 560 individuals aged 85 years with a 5-year complete follow-up for functional status, cardiovascular morbidity and cause-specific mortality. Median NT-proBNP for men was 351 pg/ml (cutoff values for low-medium tertiles 201 pg/ml and medium-high tertiles 649 pg/ml) and, for women, 297 pg/ml (cutoffs 204 and 519 pg/ml, respectively). During the 5-year follow-up, participants with high NT-proBNP had an accelerated cognitive decline and increase of activities of daily living (ADL) disability over time (all at $p<0.01$) and an increased risk of incident heart failure [hazard ratio (HR) 3.3 (95 % confidence interval (CI) 1.8–6.1)], atrial fibrillation [HR 4.1 (2.0–8.7)], myocardial infarction [HR 2.1 (1.2–3.7)], stroke [HR 3.4 (1.9–6.3)], cardiovascular mortality [HR 5.5 (3.1–10)], non-cardiovascular mortality [HR 2.0 (1.4–3.0)] and all-cause mortality [HR 2.9 (2.1–4.0)], independent of other known risk markers. All results remained similar after exclusion of participants with heart failure at baseline. In very old age, high-NT-proBNP levels predict accelerated cognitive and functional decline, as well as cardiovascular morbidity and mortality. Results suggest that NT-proBNP can help clinicians to identify very old people at high risk of functional impairment and incident cardiovascular morbidity.

Keywords Aged 80 years and over · Pro-brain natriuretic peptide · Activities of daily living · Cognition · Cardiovascular disease · Cardiovascular morbidity · Cardiovascular mortality · Prediction · Prevention

Abbreviations

ADL	Activities of daily living
AF	Atrial fibrillation
AUC	Area under the curve
BNP	B-type natriuretic peptide
CI	Confidence interval
CRP	C-reactive protein
CVD	Cardiovascular disease
GDS	Geriatric Depression Scale
HCY	Homocysteine
HF	Heart failure
HR	Hazard ratio

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ICD	International Classification of Diseases
MDRD	Estimated GFR (eGFR) using the Modification of Diet in Renal Disease formula
MI	Myocardial infarction
MMSE	Mini-Mental State Examination
NRI	Net reclassification improvement
NT-proBNP	N-terminal pro-B-type natriuretic peptide
SE	Standard error
TIA	Transient ischemic attack

Background

In very old age, cardiovascular disease is an important cause of disability, morbidity and mortality (Laslett et al. 2012; Murray et al. 2012). In recent decades, research into new risk markers for cardiovascular disease (Kavousi et al. 2012; Kistorp et al. 2005; Zethelius et al. 2008; Melander et al. 2009; Wang et al. 2006; Pikula et al. 2012) has shown that N-terminal pro-B-type natriuretic peptide (NT-proBNP) is not only a marker of heart failure but also a promising risk marker for the development of cardiovascular disease and mortality, both in primary and secondary preventions (Nadir et al. 2012; Welsh et al. 2013; Campbell 2008; Di Angelantonio et al. 2009; Olsen et al. 2007; Wannamethee et al. 2011; Marz et al. 2007) However, data in older populations are scarce (Ueda et al. 2003; Vaes et al. 2009a; Valle et al. 2005) and have sometimes been reported exclusively for secondary prevention (van Peet et al. 2013a). As traditional risk markers gradually lose their predictive value with age (Uthoff et al. 2010; de Ruijter et al. 2009; van Peet et al. 2013b), NT-proBNP may become an increasingly important risk marker for cardiovascular disease and mortality in older age groups (Ueda et al. 2003; Vaes et al. 2009a, b; Valle et al. 2005). Since, in old age, preservation of functioning and independency, and not morbidity and mortality per se, has become growingly important, associations of new risk markers with (changes in) functional status and cognitive decline are also of paramount interest. Few associations of NT-proBNP with cognitive function and functional decline have so far been observed (Feinkohl et al. 2012; Daniels et al. 2011; Kerola et al. 2010; Hiltunen et al. 2013), and in very old age, the predictive value of NT-proBNP with regard to changes in activities of daily living (ADL) functioning and cognition over time is still unknown.

NT-proBNP is a polypeptide belonging to the natriuretic peptide family. The main source of synthesis and secretion is the ventricular myocardium, initiated by ventricular wall stress caused by pressure and/or volume overload (Weber and Hamm 2006). NT-proBNP is highly elevated in heart failure patients (Maisel and Daniels 2012; Vaes et al. 2009b; Groenning et al. 2004). Levels of NT-proBNP are also increased in acute coronary syndrome, stable angina pectoris, pulmonary embolism, atrial fibrillation, left ventricular hypertrophy, chronic obstructive pulmonary disease, and renal dysfunction (Weber and Hamm 2006; DeFilippi et al. 2008). In the elderly, including the presumed 'healthy' elderly, plasma levels of NT-proBNP are generally elevated (Alehagen et al. 2007; Rutten and Hoes 2008). Alterations in cardiac structure or function, such as age-related myocardial fibrosis and subtle diastolic dysfunction not detectable by current techniques, as well as reduced renal clearance, have been suggested to be involved (Weber and Hamm 2006; DeFilippi et al. 2008). These subtle cardiac changes, although not leading to overt clinical disease, might already influence functional status (Suwa and Ito 2009; Ueda et al. 2003) and predispose for incident cardiovascular disease and functional deterioration. However, possible associations with the development of cognitive and functional impairment in very old age have not yet been studied.

In this study on individuals aged 85 years with a 5-year complete follow-up, we investigated cross-sectional and longitudinal associations of plasma NT-proBNP with cognitive function, ADL disability, well-being, depressive symptoms, cardiovascular disease and cause-specific mortality.

Methods

Study population

The Leiden 85-plus Study is an observational, prospective population-based study of inhabitants of the city of Leiden, the Netherlands. Between September 1997 and September 1999, all inhabitants of Leiden, born between 1912 and 1914, were asked to participate from their 85th birthday onwards. There were no exclusion criteria. From the 705 people who were eligible, 92 refused participation and 14 died before enrollment. A total of 599 (87 %) people gave informed consent and

were enrolled. At baseline and yearly up to the age of 90, the participants were visited at their place of residence to take questionnaires, functional tests, and blood samples and to record an ECG. At baseline, medical history was obtained from the participant's general practitioner or nursing home physician, and between age 85 and 90 incident events were obtained yearly.

The Medical Ethics Committee of the Leiden University Medical Center approved the study, and all participants provided informed consent.

NT-proBNP

Plasma level of NT-proBNP was determined with a chemiluminescent enzyme immunoassay (CLEIA) procedure (Roche, Switzerland) and was carried out on a PATHFAST (Mitsubishi Chemical Medience Corp., Tokyo, Japan). For the assay, 50 μl citrate-plasma was mixed with 30 μl phosphate-buffered saline, and 50 μl of the mixture was used. The final results were corrected for this dilution (* 8/5) and the dilution in the citrate tube (* 10/9). Detection range was 15–30,000 pg/ml and the coefficient of variation was <5 %.

Outcomes

Functional status

At baseline and annually during the 5-year follow-up, cognitive function was assessed by the Mini-Mental State Examination (MMSE), with scores ranging from 0 to 30 points (optimal) (Tombaugh and McIntyre 1992). Disability was assessed with the activities of daily living (ADL) items from the Groningen Activity Restriction Scale with scores ranging from 9 (optimal) to 36 points. At baseline, we dichotomized the answers into a score of 0 ('cannot' or 'only with help from others') or 1 ('yes, fully independently', with or without difficulty). Disability in ADL was considered present when a participant responded 'cannot' or 'only with help from others' on at least one ADL item. Subjective well-being was tested with a visual analogue scale (Cantril) in those with MMSE of >18 points, scores ranging from 0 to 10 (optimal) (Cantril 1965). At baseline, poor well-being was considered present if Cantril was <7 points. Depressive symptoms were also measured in participants with MMSE of >18 points using the 15-item Geriatric Depression Scale (GDS-15), with scores ranging from 0 (optimal) to 15 points (de Craen et al. 2003). At baseline, depression was considered present with a GDS score of ≥5.

Cardiovascular disease

The general practitioner or nursing home physician of each participant was interviewed about the patient's medical history, using standardized questionnaires, including questions on present and past cardiovascular morbidities, at baseline and annually up to age of 90 years. Specific cardiac diagnoses at baseline were defined as the presence of a medical history of heart failure, atrial fibrillation, angina, myocardial infarction (MI), transient ischemic attack, stroke, intermittent claudication or surgery for arterial disease, or as the presence of atrial fibrillation (Minnesota Code 8-3-1) or a prior MI (Minnesota Code 1–1 or 1–2, excluding 1-2-8) on the ECG. ECGs were recorded yearly. Incident heart failure was defined by newly diagnosed heart failure according to the primary care physician. Incident atrial fibrillation was defined as the appearance of Minnesota Code 8-3-1 on the ECG. Annually, incident fatal and non-fatal MIs were gathered using clinical data from the primary care physician, ECGs and death registration forms. Incident MI on the ECG was defined as the appearance of Minnesota Code 1–1 or 1–2, or Minnesota Code 1–3 in combination with the first appearance of Minnesota Code 5-x in the same myocardial area (Macfarlane and Latif 1996). All incident MIs on the ECG were visually confirmed by an expert in electrocardiophysiology. A fatal incident MI was categorized by cause of death codes I21-I23 (ICD-10). Information on incident stroke was collected annually from the primary care physician. A fatal incident stroke was categorized by cause of death codes I61-I69 (ICD-10).

Mortality

All participants were followed for mortality until the age of 90 years. Dates and cause of death were obtained from civic and national registries. Causes of death were divided into cardiovascular causes (ICD-10 codes I00-I99) and non-cardiovascular causes (all other ICD-10 codes). Assignment of cause of death was done blinded for baseline and follow-up study data.

Combined endpoint

The combined endpoint consisted of the 5-year incidence of cardiovascular events (MI and stroke) and cardiovascular mortality.

Other characteristics

Medication use

Pharmacists provided detailed information on all medication used by the participants. These included blood-pressure-lowering drugs (β-blockers, ACE inhibitors, diuretics and calcium channel blockers), anticoagulants/aspirin, and lipid-lowering drugs.

Traditional risk markers

Blood pressure was measured on two occasions with a mean interval of 2 weeks. The mean of the measured systolic values was used for the analyses. Serum concentrations of total cholesterol and high-density lipoprotein were analysed on fully automated computerized analysers (Hitachi 747 and 911, Hitachi, Tokyo, Japan). Diabetes mellitus was considered present when listed in the medical records of the participant's physician, when non-fasting glucose concentrations were ≥11.0 mmol/l, or when a participant was taking antidiabetic medication according to pharmacists' records. All participants were interviewed about past and present smoking habits and were considered as smokers if they were current smokers of cigarettes, cigars or pipes.

Possible confounding factors in relation to NT-proBNP

Body mass index (BMI) at age of 85 years was assessed by measuring height and weight. Modification of Diet in Renal Disease (MDRD) was calculated as follows: MDRD (ml/min/1.73 m^2) = 186 × (serum creatinine (μmol/l) / 88.4)$^{-1,154}$ × age (in years)$^{-0,203}$ × 0.742 (for females).

Data analysis

In line with the literature (Di Angelantonio et al. 2009), participants were ranked into tertiles (low, middle and high NT-proBNP) based on plasma NT-proBNP level at baseline, and sex. Odds ratios (ORs) with corresponding 95 % confidence intervals (CIs) were calculated for the presence of functional impairment, cardiovascular risk markers and cardiovascular disease at baseline, using binary logistic regression analysis with the low-NT-proBNP group as reference group.

We used linear mixed models to assess the association of NT-proBNP with cognitive function (MMSE), ADL disability, well-being, and depression over time. The low-, middle- and high-NT-proBNP groups were plotted using Kaplan-Meier curves for all-cause mortality during the 5-year follow-up. Cumulative incidences of cardiovascular mortality were calculated and plotted, accounting for the competing risk of non-cardiovascular mortality, using the two-step process described by Satagopan et al. (Satagopan et al. 2004; Verduijn et al. 2011). For comparison, we used the log rank test. Hazard ratios (HR) were calculated (with corresponding 95 % CIs), for 5-year cardiovascular morbidity (heart failure, atrial fibrillation, fatal and non-fatal MI, fatal and non-fatal stroke) and cause-specific mortality for the NT-proBNP groups, using a Cox proportional hazards model. The *p* value for trend was calculated with the NT-proBNP groups as a covariate.

Next, we constructed prediction models for the combined endpoint of cardiovascular events and cardiovascular mortality, with (1) only the traditional risk markers (reference model; sex, blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, history of diabetes, current smoking) and with (2) the traditional risk markers plus (log-transformed) NT-proBNP. We computed for each participant the linear predictor score (X-β), representing their individual predicted risk of the combined endpoint cardiovascular events and cardiovascular mortality, using Cox proportional hazards models, all adjusted for sex. For this combined endpoint, C-statistics and receiver operating characteristic (ROC) curves with *p* values and 95 % confidence intervals were calculated (1) of the model with the traditional risk markers (reference model) and (2) of the model with the traditional risk markers plus (log-transformed) NT-proBNP. We also calculated the category-less net reclassification improvement (NRI) regarding the combined endpoint, comparing the model including (log-transformed) NT-proBNP to the reference model (Pencina et al. 2010; Pencina et al. 2011).

Sensitivity analyses

First, we excluded participants with heart failure at baseline and repeated the analyses with linear mixed

models for functional parameters, and Cox regression for incident cardiovascular morbidity and mortality. Second, we repeated our analyses with linear mixed models adjusted for traditional risk markers (sex, systolic blood pressure (BP), total cholesterol, HDL cholesterol, history of diabetes mellitus and current smoking) and possible other known confounders (BMI, MDRD, medication for hypertension), as well as adjusted for the presence of cardiovascular disease or of cerebrovascular disease, respectively. Third, we calculated Odds ratios (ORs) with corresponding 95 % confidence intervals for the presence of functional impairment, adjusted for the presence of cardiovascular disease at baseline and adjusted for cardiovascular disease plus low income (net monthly income of ≤750€) at baseline. Fourth, we calculated HRs for incident cardiovascular morbidity and mortality, adjusted for (a) traditional risk markers, (b) traditional risk markers plus possible other known confounders, and (c) all these plus prevalent cardiovascular disease. Fifth, we repeated the fully adjusted analyses with log-transformed continuous NT-proBNP.

Data analysis was performed using SPSS 20 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

NT-proBNP was determined in 560 of the 599 participants. Missing NT-proBNP values were completely at random. Sociodemographic, functional and clinical characteristics are described in Table 1. The majority of participants were living independently, without severe cognitive impairment and subjectively well. Prevalence of cardiovascular morbidity was high. Median NT-proBNP for men was 351 pg/ml (cutoff values for low-medium tertiles 201 pg/ml and medium-high tertiles 649 pg/ml) and, for women, 297 pg/ml (cutoffs 204 and 519 pg/ml, respectively).

Baseline associations of plasma NT-proBNP levels with functional and cardiovascular characteristics

Table 2 shows the cross-sectional associations of low, middle and high plasma NT-proBNP with functional status and cardiovascular characteristics. Higher levels of NT-proBNP were associated with cognitive impairment [$OR_{high\ vs\ low}$ 2.2 (95 % CI 1.2–3.8)], ADL disability [$OR_{high\ vs\ low}$ 2.4 (1.5–3.8)] and all specific cardiac diagnoses at baseline. The relation of NT-proBNP with atrial fibrillation [$OR_{high\ vs\ low}$ 22 (6.6–72)] was even stronger than its relation with heart failure [$OR_{high\ vs\ low}$ 4.9 (2.4–10)].

Table 1 Baseline characteristics of participants from the Leiden 85-plus Study

	n=560
Sociodemographic characteristics	
Women	372 (66 %)
Net monthly income >750€	271 (49 %)
Post primary school education	195 (35 %)
Non-institutionalized living	458 (82 %)
Functional status	
Cognitive impairment (MMSE≤18)	90 (16 %)
Dependent in daily living[a]	147 (26 %)
Poor well-being (Cantril <7)[b] (*n*=463)	108 (23 %)
Depression (GDS-15≥5)[b] (*n*=466)	73 (16 %)
Cardiovascular characteristics	
Cardiovascular morbidity present	305 (55 %)
Atrial fibrillation	56 (10 %)
Angina	106 (19 %)
Myocardial infarction	91 (16 %)
Heart failure	70 (13 %)
Transient ischemic attack	72 (13 %)
Stroke	56 (10 %)
Intermittent claudication	34 (6 %)
Surgery for arterial disease	37 (7 %)
Medication use	
Blood-pressure-lowering drugs[c]	319 (57 %)
Anticoagulants[d]	157 (28 %)
Lipid-lowering drugs	6 (1 %)
Traditional risk factors	
Hypertension[e]	324 (58 %)
Systolic BP (mmHg)	155 (143–166)
Total cholesterol (mmol/l)	5.7 (4.9–6.4)
HDL cholesterol (mmol/l)	1.3 (1.0–1.6)
Diabetes[f]	90 (16 %)
Smoking[g]	89 (16 %)
NT-proBNP (pg/ml)	
Men	351 (157–1,023)
Women	297 (153–729)

Table 1 (continued)

	n=560
Possible NT-proBNP influencing factors	
BMI >25 kg/m^2	374 (69 %)
MDRD (ml/min)	59 (50–68)

Data presented as *n* (%) for categorical variables and median (IQR) for continuous variables

MMSE Mini-Mental State Examination, *GDS* Geriatric Depression Scale, *BP* blood pressure, *HDL* high-density lipoprotein, *MDRD* Modification of Diet in Renal Disease, *BMI* body mass index

[a] Dependent on ≥1 activity of daily living

[b] Assessed only in participants with MMSE >18

[c] Use of ß-blockers, ACE inhibitors, diuretics or calcium channel blockers as reported by the participants' pharmacists

[d] Anticoagulants or aspirin

[e] RR ≥160 systolic at baseline or a history of hypertension

[f] History of diabetes, antidiabetic medication use or non-fasting glucose ≥11 mmol/l

[g] Current smoker of cigarettes, pipe or cigars

Functional status over time

Figure 1 and Table 3 present the associations of NT-proBNP with cognitive impairment, ADL disability, general well-being and depressive symptoms over time. Compared to participants with low NT-proBNP, participants with high NT-proBNP not only had a lower MMSE and higher ADL disability score at baseline but also showed an accelerated annual decrease in MMSE score (−0.23 points per year, $p<0.01$) and accelerated increase in ADL disability score (0.49 points per year, $p<0.001$). NT-proBNP was not associated with well-being. Depressive symptoms increased over time in participants in the high tertile of NT-proBNP but were not significantly different from participants in the low tertile.

Risks of cardiovascular morbidity and mortality

Table 4 presents absolute numbers of events and HRs for incident atrial fibrillation, MI, stroke, cardiovascular and all-cause mortality, all dependent on tertiles of plasma NT-proBNP at baseline. Compared to that in the low-NT-proBNP group, the HR for heart failure in the group with high NT-proBNP was 3.3 (95 % CI 1.8–6.1), for atrial fibrillation 4.1 (95 % CI 2.0–8.7), for MI 2.1 (95 % CI 1.2–3.7), for stroke 3.4 (95 % CI 1.9–6.3), for cardiovascular mortality 5.5 (95 % CI 3.1–10), for non-cardiovascular mortality 2.0 (95 % CI 1.4–3.0), and for all-cause mortality 2.9 (95 % CI 2.1–4.0).

Figure 2 presents the cumulative incidence of 5-year cardiovascular mortality, adjusted for the competing risk of non-cardiovascular mortality, and Kaplan-Meier curves for all-cause mortality for gender-specific tertiles of NT-proBNP (log rank all at $p<0.001$).

We estimated C-statistics and created ROC curves for the traditional risk markers (reference model) and for the traditional risk markers plus NT-proBNP, with the combined endpoint of 5-year cardiovascular events (MI and stroke) and cardiovascular mortality as predicted outcome (Fig. 3). The combination of traditional risk markers had a C-statistic of 0.577 (0.525–0.628). Addition of NT-proBNP increased the C-statistic to 0.673 (0.624–0.721), with a p value for Δ C-statistic of <0.001. This means that the model including NT-proBNP better separates those who will develop the combined endpoint from those who will not.

The category-less net reclassification improvement (NRI) with addition of NT-proBNP to the traditional risk markers was 45 % ($p<0.001$), indicating that nearly half of the participants were correctly reclassified, when NT-proBNP was added to the model with the traditional risk markers.

Sensitivity analyses

After exclusion of participants with prevalent heart failure at baseline, the association of NT-proBNP with cognition (MMSE) and ADL disability over time and HR for incident cardiovascular disease and mortality remained similar (data not shown). The association of NT-proBNP with cognition and ADL disability over time remained similar and significant after adjustment for all traditional risk markers (sex, systolic BP, total cholesterol, HDL cholesterol, history of diabetes mellitus and current smoking) and for traditional risk markers plus BMI, MDRD and medication for hypertension, as well as after adjustment for all these plus the presence of cardiovascular or cerebrovascular disease at baseline, respectively (online supplementary Table 5). Cross-sectional associations of NT-proBNP with functional status did not materially change after adjustments for the presence of cardiovascular disease and for cardiovascular disease plus low income at baseline. After adjustment for all traditional risk markers, for traditional risk markers plus BMI, MDRD and medication for

Table 2 Association between plasma NT-proBNP and functional status and cardiovascular characteristics at baseline (n=560)

	NT-proBNP[a]						
	Low (ref) (n=185) n (%)	OR	Middle (n=188) n (%)	OR	High (n=187) n (%)	OR	p Trend
Functional status							
Cognitive impairment (MMSE ≤18)	22 (12)	1	26 (14)	1.2 (0.65–2.2)	42 (23)	2.2 (1.2–3.8)	0.005
Dependent in daily living[b]	35 (19)	1	46 (25)	1.4 (0.85–2.3)	66 (36)	2.4 (1.5–3.8)	<0.001
Poor well-being[c] (Cantril <7) (n=463)	38 (24)	1	33 (21)	0.84 (0.50–1.4)	37 (26)	1.1 (0.68–1.9)	0.64
Depression[c] (GDS-15≥5) (n=466)	29 (18)	1	23 (14	0.76(0.42–1.4)	21 (15)	0.79 (0.43–1.5)	0.43
Cardiovascular characteristics							
Cardiovascular morbidity	72 (39)	1	84 (45)	1.3 (0.84–1.9)	149 (80)	6.2 (3.9–9.8)	<0.001
Atrial fibrillation	3 (2)	1	4 (2)	1.3 (0.29–6.0)	49 (26)	22 (6.6–71)	<0.001
Angina	22 (12)	1	27 (15)	1.3 (0.69–2.3)	57 (31)	3.3 (1.9–5.7)	<0.001
Myocardial infarction	16 (9)	1	27 (14)	1.8 (0.92–3.4)	48 (26)	3.6 (2.0–6.7)	<0.001
Heart failure	10 (5)	1	19 (10)	2.0 (0.89–4.4)	41 (22)	4.9 (2.4–10)	<0.001
Transient ischemic attack	17 (9)	1	25 (13)	1.5 (0.78–2.9)	30 (16)	1.9 (0.99–3.5)	0.054
Stroke	14 (8)	1	17 (9)	1.2 (0.57–2.5)	25 (13)	1.9 (0.94–3.7)	0.069
Intermittent claudication	6 (3)	1	10 (5)	1.7 (0.60–4.7)	18 (10)	3.2 (1.2–8.3)	0.011
Surgery for arterial disease	7 (4)	1	9 (5)	1.3 (0.64–3.5)	21 (11)	3.2 (1.3–7.7)	0.005
Medication use							
Blood-pressure-lowering drugs[d]	92 (50)	1	101 (54)	1.2 (0.77–1.7)	126 (67)	2.0 (1.3–3.1)	0.001
Anticoagulants[e]	33 (18)	1	48 (56)	1.6 (0.96–2.6)	76 (41)	3.2 (2.0–5.1)	<0.001
Traditional risk factors							
Hypertension[f]	100 (55)	1	78 (42)	1.2 (0.78–1.8)	114 (61)	1.3 (0.86–2.0)	0.22
Cholesterol ≥5 mmol/l	149 (81)	1	133 (71)	0.58 (0.36–0.94)	129 (69)	0.52 (0.32–0.85)	0.009
HDL <1 mmol/l	36 (20)	1	37 (20)	1.0 (0.61–1.7)	56 (30)	1.8 (1.1–2.8)	0.018
Diabetes mellitus[h]	30 (16)	1	25 (13)	0.79 (0.45–1.4)	35 (19)	1.2 (0.69–2.0)	0.52
Current smoking[g]	29 (16)	1	24 (13)	0.79 (0.44–1.4)	36 (19)	1.3 (0.75–1.2)	0.34
NT-proBNP influencing factors							
BMI >25 kg/m^2	147 (80)	1	122 (67)	0.51 (0.31–0.82)	105 (60)	0.36 (0.22–0.57)	<0.001
MDRD <60 ml/min	83 (45)	1	90 (50)	1.1 (0.75–1.7)	129 (70)	2.8 (1.8–4.2)	<0.001

Data are presented as odds ratios with corresponding 95 % confidence intervals; low tertile was used as reference category

NT-proBNP cutoff value between low and middle tertile: 201 pg/ml for men and 204 pg/ml for women; between middle and high tertile: 649 pg/ml for men and 519 pg/ml for women

anticoagulants or aspirin

OsR odds ratio, *MMSE* Mini-Mental State Examination, *GDS* Geriatric Depression Scale, *HDL* high-density lipoprotein, *MDRD* Modification of Diet in Renal Disease, *BMI* body mass index

[a] Gender-specific tertiles of NT-proBNP

[b] Dependent on ≥1 activity of daily living

[c] Assessed only in participants with MMSE of >18

[d] Use of ß-blockers, ACE inhibitors, diuretics or calcium channel blockers as reported by the participants' pharmacists

[e] RR ≥160 systolic at baseline or a history of hypertension

[f] History of hypertension according to GP or systolic BP ≥160 at baseline

[g] History of diabetes, antidiabetic medication use or non-fasting glucose ≥11 mmol/l

[h] Current smoker of cigarettes, pipe or cigars

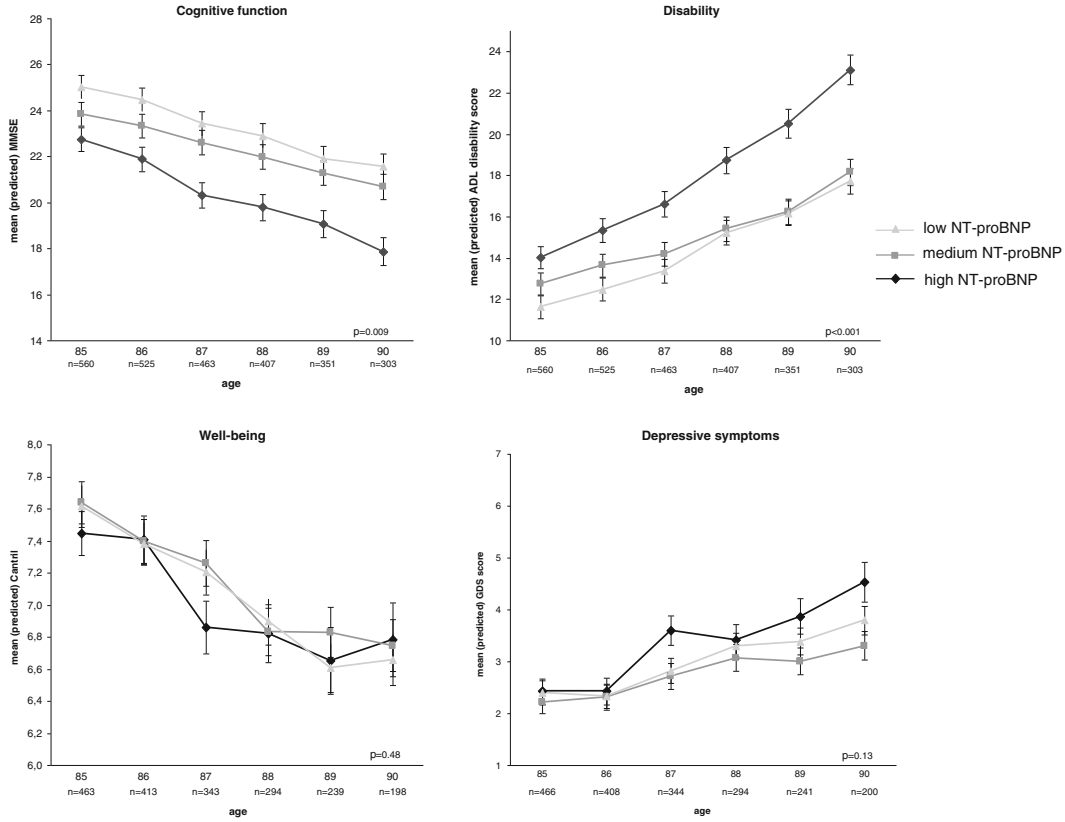

Fig. 1 Changes over time in cognitive function (MMSE, scores 0–30), disability (GARS, ADL scores 9–36), subjective wellbeing (Cantril, score 0–10) and depressive symptoms (GDS 15, scores 0–15) for gender-specific tertiles of NT-proBNP, as estimated from linear mixed models. Data are presented as means with standard errors; *p* is presented for additional annual change high versus low tertile

hypertension (online supplementary Table 6), as well as after adjustment for all these plus prevalent cardiovascular disease (online supplementary Table 7), HRs remained similar, except for the risk of MI in the high-NT-proBNP group, that was lower in the fully adjusted model (HR 1.3 (95 % CI 0.68–2.6, $p=0.30$)). Fully adjusted HRs with log-transformed continuous NT-proBNP were similar (HRs ranging from 1.3 (1.04–1.6) for fatal and non-fatal MI to 1.9 (1.5–2.4) for cardiovascular mortality).

Discussion

The present study shows that, in a large population-based cohort of 85-year-old participants, higher levels of NT-proBNP are associated with the presence of cognitive impairment, ADL disability and cardiovascular, mainly specific cardiac, disease. Moreover, higher levels of NT-proBNP predict accelerated cognitive decline and disability over time, increased incidence of cardiovascular morbidity and increased cardiovascular and non-cardiovascular mortality, even after adjustment for other known risk markers and previous cardiovascular or cerebrovascular disease. These findings demonstrate that NT-proBNP can be used to identify very old persons at high risk of functional decline, cardiovascular morbidity and mortality, which is of pivotal importance in aging populations, where preservation of independency is vital. While traditional cardiovascular risk markers lose their predictive value with age, the present study shows that in very old age, NT-proBNP remains a strong prognostic indicator for the development of cardiovascular disease. The C-statistic (discrimination between

Table 3 Association between NT-proBNP at the age 85 years and (changes in) functional status in participants aged 85 through 90 years (n=560)

	Cross-sectional effect				Annual effect Reference group Low NT-proBNP		Additional annual effect			
	Middle[a]		High				Middle		High	
	B (SE)	p Value	B (SE)	p Value	B (SE)	p Value	B (SE)	p Value	B (SE)	p Value
MMSE	−1.2 (.68)	0.089	−2.3 (.68)	<0.001	−0.73 (.054)	<0.001	0.093 (.074)	0.21	−0.23 (.088)	0.009
ADL disability	1.2 (.71)	0.083	2.4 (.72)	0.001	1.2 (.084)	<0.001	−0.23 (.11)	0.041	0.49 (.14)	<0.001
Well-being[b]	0.003 (.17)	0.99	−0.15 (.18)	0.41	−0.22 (.025)	<0.001	0.021 (.035)	0.56	0.033 (.047)	0.48
Depressive symptoms[b]	−0.051 (.30)	0.86	0.077 (.32)	0.81	0.30 (.042)	<0.001	−0.071 (.059)	0.23	0.12 (.076)	0.13

Associations were assessed by linear mixed models

NT-proBNP cutoff value between low and middle tertile: 201 pg/ml for men and 204 pg/ml for women; between middle and high tertile: 649 pg/ml for men and 519 pg/ml for women

Scale: MMSE 0–30 points, ADL disability 9–36 points

MMSE Mini-Mental State Examination, *ADL* activities of daily living

[a] Gender specific tertiles of NT-proBNP

[b] Assessed only in participants with MMSE of >18

Table 4 Five-year risk of cardiovascular morbidity and mortality depending on plasma NT-proBNP level at age of 85 years (n=560)

	Number of events (%)	NT-proBNP[a]						p Trend
		Low (ref) (n=185)		Middle (n=188)		High (n=187)		
		n (%)	HR	n (%)	HR	n (%)	HR	
Heart failure (n=461)[b]	76 (14)	16(10)	1	26 (16)	1.8 (0.98-3.4)	34 (25)	3.3 (1.8-6.1)	<0.001
Atrial fibrillation (n=504)[c]	53 (10)	10 (6)	1	20 (11)	2.1 (1.0-4.6)	23 (17)	4.1 (2.0-8.7)	<0.001
Fatal and non-fatal MI	78 (14)	19 (10)	1	29 (16)	1.6 (0.90-2.9)	30 (16)	2.1 (1.2-3.7)	0.008
Fatal and non-fatal stroke	75 (13)	15 (8)	1	22 (12)	1.6 (0.81-3.0)	38 (20)	3.4 (1.9 -6.3)	<0.001
Cardiovascular mortality	100 (18)	14 (8)	1	29 (15)	2.2 (1.2-4.1)	57 (31)	5.5 (3.1-10)	<0.001
Non-CV mortality	158 (28)	46 (25)	1	26 (25)	1.1 (0.71-1.6)	66 (35)	2.0 (1.4-3.0)	<0.001
All-cause mortality	258 (46)	60 (32)	1	75 (40)	1.3 (0.95-1.9)	123 (66)	2.9 (2.1-4.0)	<0.001
Combined endpoint[d]	174 (31)	38 (21)	1	54 (29)	1.5 (0.99-1.3)	82 (44)	3.0 (2.0-4.4)	<0.001

Hazard ratios and corresponding 95 % confidence intervals were estimated by Cox proportional hazards models

NT-proBNP cutoff value between low and middle tertile: 201 pg/ml for men and 204 pg/ml for women; between middle and high tertile: 649 pg/ml for men and 519 pg/ml for women

[a] Gender-specific tertiles of NT-proBNP

[b] Cases with prevalent heart failure at 85 years (n=70) were excluded, with 29 missing values; low tertile n=163, middle tertile n=160, high tertile n=138

[c] cases with prevalent atrial fibrillation at 85 years (n=56) were excluded; low tertile n=182, middle tertile n=184, high tertile n=138

[d] Combined endpoint: cardiovascular events (MI and stroke) and cardiovascular mortality

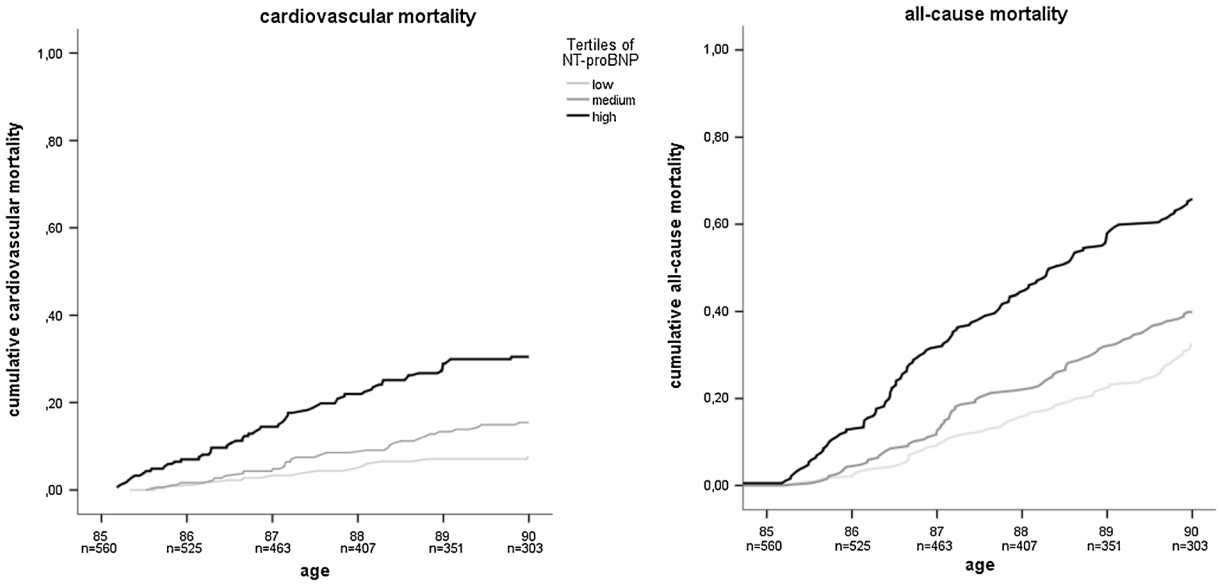

Fig. 2 Cumulative incidence of 5-year cardiovascular mortality, adjusted for the competing risk of non-cardiovascular mortality, and Kaplan-Meier curves for all-cause mortality for gender-specific tertiles of NT-proBNP (log rank all at $p<0.001$)

those who will develop the endpoint and those who will not) of the prediction model for a combined endpoint of cardiovascular events and mortality improved when NT-proBNP was added to the model with the traditional risk markers. Since improvement of general model performance is not easy to interpret, we also assessed the improvement in risk prediction on an individual level (reclassification). The net reclassification improvement showed that nearly half of all participants were correctly reclassified when NT-proBNP was added to the model.

In the knowledge that the treatment gap in primary and secondary preventions is still considerable (Garcia et al. 2013; Kumbhani et al. 2013; Koopman et al. 2013), optimizing blood pressure, cholesterol and anticoagulant treatment (in the secondary prevention

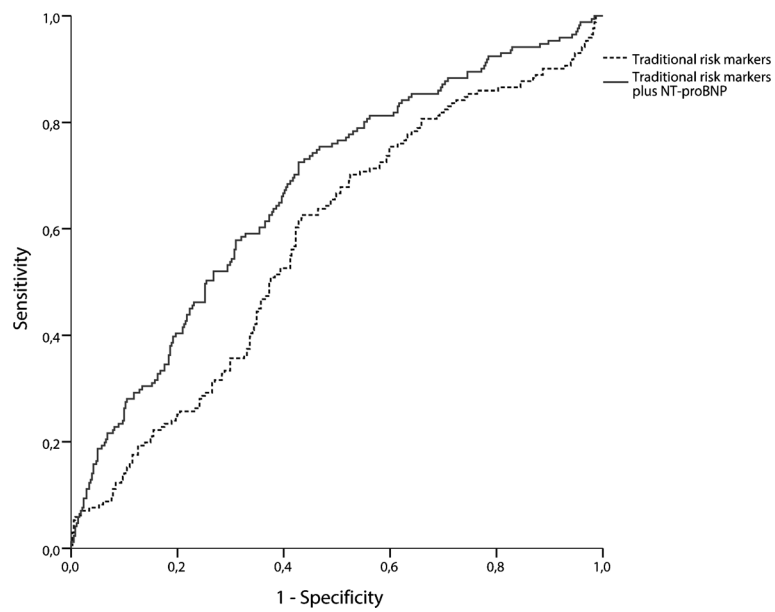

Fig. 3 ROC curves for a combined endpoint of cardiovascular events (MI and stroke) and cardiovascular mortality of a model with traditional risk markers (*dotted line*) and a model with traditional risk markers plus (log-transformed) NT-proBNP (*black line*); p value Δ <0.001, n=560

population) in those with a high NT-proBNP might improve prognosis (Perreault et al. 2012; Longstreth et al. 2013). Checking for symptoms and signs of discrete cardiac dysfunction (ECG, cardiac ultrasound) in patients with high-NT-proBNP levels might result in early diagnosis and treatment of subtle cardiac disease or atrial fibrillation and consequently prevent clinical heart disease and cerebrovascular events. Clinicians may thus use NT-proBNP for risk stratification in very old age and thereby select patients that might benefit most from proactive diagnostic, therapeutic and preventive interventions. On the other hand, low-NT-proBNP levels are associated with a favourable prognosis, and clinicians might use this information in their decisions about (not) starting or stopping medication in very old age.

Comparison with literature

To our knowledge, this is the first report on positive associations between NT-proBNP and cognitive function and ADL disability over time in very old age. An earlier study showed a cross-sectional association of NT-proBNP with cognitive function in diabetic patients aged 60–74 years (Feinkohl et al. 2012) and in community-dwelling older adults (Daniels et al. 2011), whereas a Finnish study observed no association of BNP with the development of cognitive disorders in the oldest subgroup aged 83–96 years (Hiltunen et al. 2013). However, the present study with NT-proBNP not only showed a strong association with cognitive impairment at baseline but also an association with accelerated cognitive decline during the 5-year follow-up. Regarding ADL disability, one study in participants aged ≥80 years found a cross-sectional association of NT-proBNP with ADL disability (Ueda et al. 2003); however, to our knowledge, no association of NT-proBNP with accelerated ADL disability over time has yet been reported.

In the present study, as expected, plasma NT-proBNP at baseline was mainly associated with all cardiac diseases, particularly atrial fibrillation. That NT-proBNP that is also a strong predictor for incident atrial fibrillation was not earlier observed in very old populations but was in younger populations (Schnabel et al. 2010; Patton et al. 2009; Rienstra et al. 2012). During the 5-year follow-up, NT-proBNP also predicted the development of heart failure, in line with other studies in elderly populations (Valle et al. 2005; Rutten and Hoes 2008). In a meta-analysis of studies in younger populations, the relative risk for coronary heart disease and stroke was about twofold higher for the high versus low tertile of NT-proBNP (Di Angelantonio et al. 2009). In line with this observation, our study in a very old population shows a twofold increased risk for MI and an even higher (threefold) increased risk for stroke in subjects with high NT-proBNP. A relation of NT-proBNP and cardiovascular and non-cardiovascular mortality has earlier been reported in both older populations (Ueda et al. 2003; Wallen et al. 1997; Vaes et al. 2009a, b; Eggers et al. 2013; Beleigoli et al. 2013a) and younger populations (Di Angelantonio et al. 2009; Wang et al. 2004; Linssen et al. 2010). In the present study, including participants aged 85 years, we observed a twofold increased risk of non-cardiovascular mortality, as was shown before in nonagenarians (Vaes et al. 2009a). The exact mechanism is not yet clear. Maybe NT-proBNP can be seen as a general measure of decreased vitality. Also, subclinical cardiac dysfunction as reflected in high-NT-proBNP levels might for example in the case of pneumonia lead to a more unfavourable course, including death. We also observed a more than fivefold increased risk for cardiovascular mortality in participants with high NT-proBNP. All the above-stated risks for the development of cardiovascular disease and mortality were independent of other known risk markers, thereby highlighting the potency of NT-proBNP as a risk marker in very old age.

In contrast with our results, in a younger population (mean age 69 years) and with all-cause mortality as endpoint, Beleigoli et al. observed no improvement in discrimination and reclassification with addition of NT-proBNP to a model with traditional risk markers (Beleigoli et al. 2013b). This might be explained by the already good performance of their model with traditional risk markers only (C-statistic 0.78).

Strengths and limitations

The present study has several strengths. First, our population-based study had a high-participation rate and no exclusion criteria, allowing our conclusions to be generalized to the oldest old in the general population. Second, we studied multiple relevant outcomes for an aging population: functional status, cardiovascular morbidity and cause-specific mortality. Finally, NT-proBNP levels are easy to obtain in routine clinical practice and are often already available to the physician.

A limitation of this study is that, although all our endpoints were clinically validated, there was no central adjudication of cardiovascular events and cardiovascular morbidity. It could also be seen as a limitation that our prediction model was built in persons all aged 85 years. However, in fact, this increases the power of our study, since the probability for a change in C-statistic is now higher (because age is no longer in the model), and this enables our results to reflect the added value of NT-proBNP in subjects aged 85 years. Another limitation could be that we did not measure NT-proBNP repeatedly over time, which would have allowed us to examine participants with increasing, decreasing and stable NT-proBNP levels. Also, although we observed associations of NT-proBNP with functional impairment at baseline and over time, we do not know the exact cause or pathway of this relationship. Since we primarily performed a prediction study, future studies will have to provide more etiological insight in the possible mechanism(s) underlying these associations. Another limitation is that echocardiographic measurements or data on physical activity or cardiorespiratory fitness are not available. A final limitation is that the three NT-proBNP groups were composed according to rank number, and no predefined cutoff values were applied; this makes translation of our findings into clear-cut clinical thresholds more difficult.

Further investigation

We recommend further studies to affirm our findings especially with regard to NT-proBNP levels and functional decline and to further explore possible clinically relevant cutoff values. Also, intervention studies evaluating the use of NT-proBNP in risk assessment in (very) old age and monitoring subsequent cognitive, functional and cardiovascular outcomes may reveal whether addition of NT-proBNP in risk stratification actually improves prognostic accuracy. Studies investigating the etiology of the association of NT-proBNP with ADL functioning and cognitive impairment are tempting. Establishing whether this association is mediated by subclinical heart failure (and subsequent low blood pressure), diastolic dysfunction (Suwa and Ito 2009), intermittent atrial fibrillation (and subsequent (micro) thromboembolisms) (Kalantarian et al. 2013), incident cardiovascular disease, general atherosclerosis or yet another mechanism is mandatory. Thereafter, clear clinical implications of high-NT-proBNP levels can be formulated.

Conclusion

In very old age, NT-proBNP is a strong predictor of accelerated cognitive and functional decline as well as of cardiovascular morbidity (heart failure, atrial fibrillation, myocardial infarction and stroke) and mortality. High levels of NT-proBNP may help clinicians identify patients who will probably benefit most from proactive follow-up. Early detection and treatment of incident cardiovascular disease and optimizing (secondary) preventive measures might help preserve independency.

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