Increase in N-terminal pro-brain natriuretic peptide levels, renal function and cardiac disease in the oldest old

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Abstract

Background: the impact of renal function and its changes and the occurrence of cardiovascular events on changes in N-terminal pro-brain natriuretic peptide levels (NT-proBNP) is unknown in very old age.

Objective: to assess whether increase in NT-proBNP levels over time is still associated with cardiac disease and mortality in very old age, independent of renal function.

Methods: changes in NT-proBNP levels between age 85 and 90 years and their associations with incident cardiac disease, (cardiovascular) mortality and renal function were assessed in 252 nonagenarian participants from a population-based sample of the Leiden 85-plus Study.

Results: median NT-proBNP increase over 5 years was 154 pg/ml (inter-quartile range: 29–549), while in the same period estimated glomerular filtration rate (eGFR) decreased by 5.8 ml/min/1.73 m² (standard deviation 7.5). Participants with increasing NT-proBNP levels more frequently developed heart failure and atrial fibrillation (odds ratio 2.79, 95% confidence interval (CI) 1.11–7.02 and 2.63, 95% CI 1.02–6.79, respectively, adjusted for eGFR at age 85 and change in eGFR) between age 85 and 90 years. Increasing NT-proBNP levels between age 85 and 90 years were associated with an increased cardiovascular mortality risk after age 90 years compared with not-increasing NT-proBNP levels (hazard ratio 1.62, 95% CI 1.04–2.51, adjusted for eGFR at age 90 years and change in eGFR).

Conclusion: in the oldest old, increase in NT-proBNP is associated with incident heart failure and atrial fibrillation and risk for cardiovascular mortality, independent of decreasing renal function.

Keywords: ageing (aged 80 and over), NT-proBNP, renal function, heart failure, cardiovascular disease, older people

Introduction

Brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are the two fragments of the prohormone proBNP, which is released by ventricular myocytes in reaction to ventricular wall stress and hypoxia [1–3] and by the atrial myocytes in reaction to highly frequent atrial myocyte contraction in atrial fibrillation [4]. Thus, natriuretic peptide levels, especially NT-proBNP levels, are diagnostic blood-based biomarkers for heart failure, but also prognostic markers for incident cardiovascular morbidity and mortality in middle-aged [5–7] and older persons [8–11].

Few studies are available on the course of the NT-proBNP levels over time, their association with cardiovascular risk and the underlying conditions related to changes in NT-proBNP in older age, although not in the oldest old [12, 13]. One prospective, observational cohort study of cardiovascular disease in older people (mean age 73 years) found that NT-proBNP levels frequently change over time, reflecting a dynamic change in subsequent cardiovascular risk concordant with the direction of change of NT-proBNP [13]. Moreover, a community-based study of subjects aged 70 years and over found that not only single NT-proBNP levels, but also their changes over time, are predictive of all-cause and cardiovascular mortality [12]. Changes in NT-proBNP levels were associated with cardiovascular risk indicators such as male gender, ischaemic electrocardiogram (ECG) changes,
renal dysfunction and lower left ventricle ejection fraction, together with intercurrent cardiovascular events [12].

NT-proBNP levels increase with age, even in the absence of heart failure or cardiovascular disease [14]. NT-proBNP is mainly cleared through renal excretion [15]. Impaired renal function, which is common in old age and is a strong predictor for cardiovascular disease as well, is associated with higher levels of NT-proBNP [16]. Therefore, declining renal function could, at least in part, underlie the increase in NT-proBNP over time. There are currently no studies available that address this hypothesis in the oldest old. It has been suggested that, besides symptoms, signs and patients’ history, decline in renal function should also be considered when interpreting NT-proBNP values in old age [16, 17].

We hypothesised that an increase in NT-proBNP level still reflects cardiac morbidity and risk for cardiovascular mortality in old age, independent of decreasing renal function. Therefore, we assessed whether (i) increase of NT-proBNP levels over 5 years is associated with incident cardiovascular disease during these 5 years; (ii) whether this association is independent of the renal function and (iii) whether persons with an increase in NT-proBNP levels over 5 years have a higher mortality risk after these 5 years. Our analyses were performed in a population-based cohort of nonagenarians of the Leiden 85-plus Study, where NT-proBNP levels and estimated glomerular filtration rate (eGFR) levels were available at both 85 and 90 years of age.

NT-proBNP
Non-fasting blood samples were drawn before 11 AM. Plasma samples were stored at −80°C. Serum levels of NT-proBNP were measured for all participants at age 85 and 90 years using the NT-proBNP assay of Roche Diagnostics (Mannheim, Germany) on a Roche Modular E-17 automated immunoanalyzer. Predefined change patterns were used to analyse the change in NT-proBNP levels from 85 to 90 years. These change patterns were defined considering the biological variability of NT-proBNP in healthy populations and were based on change patterns used in previous studies [12, 20]: (i) increasing: change in NT-proBNP levels greater than or equal to +100% (i.e. NT-proBNP level at least doubled) or (ii) not-increasing: change in NT-proBNP levels less than +100%.

Renal function
Plasma creatinine concentrations were measured according to the Jaffe method using a fully automated Hitachi 747 analyzer (Hitachi, Tokyo, Japan). Creatinine clearances were estimated using the Cockcroft–Gault formula [21].

Incident cardiovascular events
Incident cardiovascular events were recorded between the age of 85 and 90 years. Each participant’s general practitioner (or, if applicable, nursing home physician) was interviewed annually about the participant’s medical history. ECGs were recorded yearly. Incident atrial fibrillation was defined as the appearance of Minnesota Code 8-3-1 on the ECG. Incident myocardial infarction was defined by newly diagnosed myocardial infarction according to the general practitioner and incident myocardial infarction on the ECG. Information about incident stroke and heart failure was collected from the general practitioner.

Mortality
All participants were followed for mortality from age 90 years onwards. Dates of death were obtained from municipality records, with censoring date 31 December 2011 (until age 97–99 years). Specific data on cause of death were obtained from Statistics Netherlands, where all national death certificates are coded according to the International Classification of Diseases and Related Disorders, 10th revision (ICD-10) [22]. Causes of death were divided into two groups: cardiovascular mortality (ICD codes 100-199) and non-cardiovascular mortality (all other ICD codes).

Statistical analysis
Summary characteristics are reported as mean with standard deviation (SD) or median with inter-quartile range (IQR) for continuous variables and as numbers with percentage (%) for categorical variables. Relations between the two groups of
NT-proBNP change and various clinical characteristics were explored using χ² tests and independent t-test as appropriate.

Differences in incident events that occurred between age 85 and 90 years between the two groups of NT-proBNP change were analysed using logistic regression analysis. We performed our analysis in three steps. First, crude analyses were performed. Second, we added eGFR at age 85 years. Third, change in eGFR between age 85 and 90 years was added. For incident atrial fibrillation and heart failure, subjects with a history of this event at age 85 years were excluded in this analysis.

For mortality after age 90 years, time to event curves were constructed with the Kaplan–Meier method, adjusted for competing risks. Hazard ratios (HR) and corresponding 95% confidence intervals (CIs) were calculated with Cox proportional-hazard models. We performed our analyses in four steps. First, crude analyses were performed. Second, we added eGFR at age 85 years. Third, the change in eGFR between age 85 and 90 years was added. Furthermore, in a fully adjusted model, we also added sex, smoking, total cholesterol and high-density lipoprotein cholesterol, systolic blood pressure, hypertension, body mass index, plasma creatinine, history of diabetes, myocardial infarction, stroke, atrial fibrillation and heart failure and the use of antihypertensive medication, loop diuretics and/or digoxin. All participants were 90 years of age, so no adjustment for age was made.

For sensitivity analysis, see Supplementary data, Appendix S2, available in Age and Ageing online.

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

### Results

#### Study population

Change in NT-proBNP and eGFR levels was available for 252 nonagenarian participants, 67 (26.6%) men and 185 (73.4%) women. Median NT-proBNP increase over 5 years was 154 pg/ml (IQR 29–549). Participants were divided into two groups based on the NT-proBNP change pattern (increasing levels, n = 119 and not-increasing levels, n = 133). Renal function decreased between the age of 85 and 90 years, with a mean eGFR decrease of 5.6 ml/min/1.73 m² over 5 years (SD 7.5). Table 1 shows the relations between the two change patterns of NT-proBNP and various clinical characteristics. History of hypertension and lower eGFR at age 85 years were associated with an increasing NT-proBNP level over time (P = 0.025 and P = 0.023, respectively). Participants with atrial fibrillation on the baseline ECG (n = 17) had higher median levels of NT-proBNP at age 85 years compared with those without atrial fibrillation on the baseline ECG (1,228.4 pg/ml [751.1–1,673.8] and 225.8 pg/ml [1,071.4–1,362.1]).

#### Characteristics at age 85 and 90 years dependent on NT-proBNP change pattern (85–90 years) (n = 252)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (n = 252)</th>
<th>NT-proBNP change pattern (85–90 years)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increasing (n = 119)</td>
<td>Not-increasing (n = 133)</td>
<td></td>
</tr>
<tr>
<td>Men (%)</td>
<td>67 (26.6)</td>
<td>38 (31.9)</td>
<td>29 (21.8)</td>
</tr>
<tr>
<td>Characteristics at age 85</td>
<td></td>
<td></td>
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<tr>
<td>Smoking (%)</td>
<td></td>
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</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>157.9 (17.3)</td>
<td>158.7 (18.0)</td>
<td>157.2 (16.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>78.5 (8.6)</td>
<td>78.4 (9.0)</td>
<td>78.6 (8.1)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>152 (60.3)</td>
<td>81 (68.1)</td>
<td>71 (54.2)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>34 (13.5)</td>
<td>24 (20.2)</td>
<td>10 (7.6)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4 (4.5)</td>
<td>27.2 (4.4)</td>
<td>27.6 (4.5)</td>
</tr>
<tr>
<td>History of myocardial infarction (clinical or on ECG) (%)</td>
<td>26 (10.3)</td>
<td>15 (12.6)</td>
<td>11 (8.3)</td>
</tr>
<tr>
<td>History of heart failure (%)</td>
<td>21 (8.3)</td>
<td>13 (10.9)</td>
<td>8 (6.0)</td>
</tr>
<tr>
<td>History of arrhythmia (%)</td>
<td>41 (16.3)</td>
<td>18 (15.1)</td>
<td>23 (17.3)</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>15 (6.0)</td>
<td>5 (4.2)</td>
<td>10 (7.5)</td>
</tr>
<tr>
<td>Atrial fibrillation on ECG (%)</td>
<td>17 (6.7)</td>
<td>3 (2.5)</td>
<td>14 (10.5)</td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>239.1 (141.1–429.3)</td>
<td>208.0 (115.7–362.7)</td>
<td>270.2 (153.3–524.4)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)</td>
<td>46.7 (10.5)</td>
<td>45.1 (9.7)</td>
<td>48.1 (11.0)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.8 (1.0)</td>
<td>5.8 (1.0)</td>
<td>5.9 (1.0)</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mmol/l)</td>
<td>1.4 (0.4)</td>
<td>1.3 (0.4)</td>
<td>1.4 (0.4)</td>
</tr>
<tr>
<td>C-reactive protein (mg/l)</td>
<td>3.0 (1.0–5.0)</td>
<td>3.0 (1.0–5.0)</td>
<td>3.0 (2.0–6.0)</td>
</tr>
<tr>
<td>Characteristics at age 90 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (pg/ml)</td>
<td>430.5 (230.7–1,136.8)</td>
<td>762.4 (368.6–2,216.0)</td>
<td>287.4 (177.7–543.7)</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate (ml/min/1.73 m²)</td>
<td>40.7 (11.7)</td>
<td>38.3 (11.9)</td>
<td>42.9 (11.9)</td>
</tr>
<tr>
<td>Change in NT-proBNP (pg/ml) (between 85 and 90 years)</td>
<td>153.6 (28.9–548.8)</td>
<td>518.5 (228.6–1,753.4)</td>
<td>32.5 (56.6–124.2)</td>
</tr>
<tr>
<td>Change in estimated glomerular filtration rate (ml/min/1.73 m²) (between 85 and 90 years)</td>
<td>−5.6 (7.5)</td>
<td>−6.7 (8.4)</td>
<td>−5.0 (6.6)</td>
</tr>
</tbody>
</table>

Categorical data are presented as frequencies (%); continuous data as mean (SD) or median (IQR). Missings, n = 0–6.

1History of hypertension and/or systolic blood pressure >160 mmHg and/or antihypertensive medication.
2History of diabetes and/or glucose >11.0 and/or diabetic drugs.
3History of myocardial infarction and heart failure and the use of antihypertensive medication.
[134.5–391.1], respectively, \(P < 0.001\). However, participants with an increasing NT-proBNP level less often had atrial fibrillation on the ECG at age 85 years (\(P = 0.011\)).

Incident cardiovascular events

Between age of 85 and 90 years, a total of 23 participants (9.1%) had an incident myocardial infarction. A total of 26 participants (11.1%) had incident atrial fibrillation, 11 participants (4.4%) experienced an incident stroke and 25 (10.9%) developed incident heart failure. Table 2 shows that increasing NT-proBNP was associated with incident atrial fibrillation (HR 3.11, 95% CI 1.25–7.70) and newly developed heart failure (HR 2.77, 95% CI 1.14–6.71), but not with incident myocardial infarction or stroke. The adjustment for eGFR at age 85 years and the change in eGFR between age 85 and 90 years did not alter the observed associations. The sensitivity and specificity of increasing NT-proBNP in identifying participants with atrial fibrillation were 73 and 53%, respectively, with a positive predictive value of 16.4% and a negative predictive value of 94.1%. For the identification of participants with heart failure, sensitivity of increasing NT-proBNP was 68% and specificity 57%, with a positive predictive value of 16.0% and a negative predictive value of 93.5%.

Mortality

Time to death from age 90 years onwards by NT-proBNP change pattern is shown in Figure 1. Participants with an increasing NT-proBNP level over 5 years had a 1.6-fold increased all-cause mortality risk compared with those with a not-increasing NT-proBNP level when adjusted for eGFR at age 90 years and change in eGFR between age 85 and 90 years (HR 1.57, 95% CI 1.20–2.05) (Figure 1a). Increasing NT-proBNP level over 5 years was associated with an increased cardiovascular mortality risk (HR 1.62, 95% CI 1.04–2.51) (Figure 1b) and non-cardiovascular mortality risk (Figure 1c). The same trend was seen for the fully adjusted model (Supplementary data, Table S1 and Appendix S3, available in Age and Ageing online).

Table 2. NT-proBNP change pattern and incident cardiovascular events

<table>
<thead>
<tr>
<th></th>
<th>Increasing (n = 119)</th>
<th>Not-increasing (n = 133)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction(^{be})</td>
<td>13 (10.9%)</td>
<td>10 (7.5%)</td>
<td>1.50 (0.63–3.55)</td>
</tr>
<tr>
<td>Atrial fibrillation on ECG(^{d})</td>
<td>19 (16.4%)</td>
<td>7 (5.9%)</td>
<td>3.11 (1.25–7.70)</td>
</tr>
<tr>
<td>Heart failure(^{c})</td>
<td>17 (16.0%)</td>
<td>8 (6.5%)</td>
<td>2.77 (1.14–6.71)</td>
</tr>
<tr>
<td>Stroke(^{c})</td>
<td>4 (3.4%)</td>
<td>7 (5.3%)</td>
<td>0.63 (0.18–2.23)</td>
</tr>
</tbody>
</table>

For incident heart failure and incident atrial fibrillation, subjects with a history of the relevant event were excluded in this analysis.

\(^{a}\)Model 2 adjusted for eGFR at age 85 years; Model 3 adjusted for eGFR at age 85 years and change in eGFR over 5 years.

\(^{b}\)Data from general practice (or, if applicable, nursing home physician) and ECG recordings.

\(^{c}\)Missing, \(n = 1\).

\(^{d}\)Excluded, \(n = 17\); missing, \(n = 1\).

\(^{e}\)Excluded, \(n = 21\); missing, \(n = 1\).

For the results from the sensitivity analysis, see Supplementary data, Appendix S2, available in Age and Ageing online.

Discussion

This study shows that in the oldest old an increase in NT-proBNP level, compared with a not-increasing NT-proBNP level, is predictive for an increased cardiovascular mortality risk, independent of (change in) renal function. An increase in NT-proBNP in this group is also associated with incident atrial fibrillation and newly developed heart failure, irrespective of the renal function. Thus, interpretation of NT-proBNP and NT-proBNP changes over time in the oldest old is challenging, as they do not only reflect parallel changes in renal function.

In line with the literature, we found a predictive value of increasing NT-proBNP levels for increased mortality risk. This has been reported earlier in two observational studies in an elderly population [12, 13]. As described previously, NT-proBNP levels were found to increase with advancing age [5, 12, 14, 23]. Present study investigates two possible biological pathways related to increasing NT-proBNP levels over time in old age: (i) decreasing renal function and (ii) cardiovascular pathology. There is some evidence in the literature suggesting that, in old age, decreasing renal function could, in part, underlie increasing NT-proBNP levels over time [16]. In an observational study among subjects aged 70 years [12], increasing NT-proBNP levels were associated with lower eGFR. In line with these findings, the present study found that, in the oldest old, lower eGFR is related to increase in NT-proBNP levels over time. However, in line with the second possible pathway, the present study found that incident atrial fibrillation is independently related to increasing NT-proBNP levels over time in the oldest old. This concords with a study by Patton et al. [24] that reported that NT-proBNP is a remarkable predictor of incident atrial fibrillation. In the present study, atrial fibrillation at baseline was inversely associated with increasing NT-proBNP levels. This is probably due to already higher baseline levels in participants with atrial fibrillation compared with those without
When the level of NT-proBNP is already high, this value is less likely to double (increase of ≥100%). It is known from literature that patients with atrial fibrillation have markedly higher levels of NT-proBNP [24, 25].

This study provides insight into the biology and clinical applicability of NT-proBNP in very old age. To our knowledge, our study is the first to evaluate the relation between increasing NT-proBNP levels and cardiac morbidity and mortality independent of the change in renal function in the oldest old. We show that an increase in NT-proBNP of at least 100% is driven by cardiac abnormalities causing increased wall stress or highly frequent atrial contraction, in the oldest old mainly heart failure and atrial fibrillation, and that this association is independent of renal function. Although a decline in renal function should still be considered when interpreting NT-proBNP values in old age, our results call for the awareness of physicians to consider the presence of (so far unrecognised) atrial fibrillation and/or heart failure when observing an increase in NT-proBNP in the oldest old. Future studies are needed to evaluate the appropriate time intervals for NT-proBNP testing, to evaluate the clinical thresholds for changes in NT-proBNP levels over time and to evaluate the use of NT-proBNP in risk assessment in the oldest old in clinical practice, as well as its cost-effectiveness.

This study has several strengths: a large group of oldest-old individuals who were recruited from the general population without exclusion criteria, complete long-term follow-up for cause-specific mortality and a low attrition rate. Nevertheless, this study has a number of limitations. We included a specific population in our cohort, namely participants with NT-proBNP measurements at both ages 85 and 90 years, a selection of strong survivors. There was a significant difference in almost all baseline characteristics between participants alive at age 90 years and those who died between ages 85 and 90 years (Supplementary data Table S2 and Appendix S4, available in *Age and Ageing* online). Participants alive at age 90 years and included in our analyses less frequently had a history of cardiovascular disease and had higher systolic and diastolic blood pressure and total cholesterol, all factors associated with better survival in very old age [26–28]. Persons with serious heart failure at age 85 were likely to have died before they could reach the age of 90 years and were therefore not included in our study. The selection of strong survivors has most likely led to an underestimation of the found association (odds ratios) between the increase in NT-proBNP and incident events. Second, the diagnosis of heart failure and myocardial infarction in the present study was based solely on the information from the participant’s general practitioner and electrocardiography, respectively. No echocardiography was available to confirm the diagnosis of heart failure. Misclassification may have played a role. However, this is a representation of routine clinical practice during the time the study was conducted. Still, our general population-based study is well suited to show the determinants associated with changes in NT-proBNP in the oldest old and therefore generalisable to the older population.

In conclusion, the present study shows that in the oldest old, an increase in NT-proBNP is associated with incident heart failure and atrial fibrillation, independent of changes in renal function. Also, this increase still reflects increased risk for (cardiovascular) mortality, independent of decreasing renal function.

![Figure 1](image-url)

*Figure 1. Cumulative mortality from age 90 years onwards in relation to the relative change in NT-proBNP levels (n = 252)* (a) all-cause mortality, (b) cardiovascular mortality and (c) non-cardiovascular mortality.
Key points

- An increase in NT-proBNP is associated with incident heart failure and atrial fibrillation, independent of renal function, in the oldest old.
- An increase in NT-proBNP reflects increased risk for (cardiovascular) mortality, independent of renal function, in the oldest old.
- NT-proBNP changes over time in the oldest old do not only reflect parallel changes in renal function.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in Age and Ageing online.

References

Determinants of 25-hydroxyvitamin D in older Irish adults

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Abstract

Background: vitamin D deficiency is prevalent in older adults living in Northern Europe and is influenced by several factors which may vary significantly with age.

Objective: we aimed to investigate the determinants of 25-hydroxyvitamin D [25(OH)D] in older Irish adults and in particular to examine the effect of supplement use and surrogate markers of sun exposure.

Methods: subjects were non-institutionalised community dwelling Irish adults aged over 60 years who were participants of a large cross-sectional study comprising three disease defined cohorts. Serum 25(OH)D was measured by liquid chromatography mass spectroscopy. Associations between 25(OH)D and potential confounders were explored in forward regression models in each cohort.

Results: the three cohorts comprised 1895, 1233 and 1316 participants (respective mean ages 70.1, 71.0 and 80.4 years). Statistical models explained between a fifth to a third of the variation in 25(OH)D. Supplement use and global solar radiation were positive predictors of 25(OH)D in all cohorts whereas the only universal negative predictor was body mass index. Supplement use was associated with a mean increase in 25(OH)D of between 21.4 and 35.4 nmol/l. The other main predictors varied by cohort but included sun holiday travel, enjoyment of sunshine when outside, use of vitamin D fortified milk, smoking, oily fish and egg consumption and physical frailty.

Conclusion: supplement use was the most important determinant of vitamin D status. Vitamin D fortified milk and spending time in the sun, even in the oldest old may also be useful strategies to improve 25(OH)D.

Keywords: vitamin D, older adults, supplements, older people