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Long-term pattern of brain natriuretic peptide and N-terminal pro brain natriuretic peptide and its determinants in the general population: contribution of age, gender, and cardiac and extra-cardiac factors

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Aims The natriuretic peptides BNP and NT-proBNP are potent cardiac markers, but knowledge of long-term changes is sparse. We thus quantified determinants of change in BNP and NT-proBNP in a study of south German residents (KORA).

Methods and results A total of 1005 men and women (age 25–74 years, mean 48 years) underwent physical examination and echocardiography at baseline and at follow-up after 10 years. The current analysis comprised 877 subjects with dual measurements of BNP and NT-proBNP. Both markers increased in both sexes ($P < 0.001$) during the 10-year follow-up, and higher levels in women persisted across time (P for sex difference <0.001). Among baseline covariates, predictors for 10-year change of NT-proBNP, BNP, or both were age, sex, diabetes status, and heart rate (multivariable regression analysis, each $P < 0.05$). However, changes of covariates over the 10-year follow-up were much stronger determinants. Specifically, incident myocardial infarction, new beta-blocker medication, and increased cardiac parameters (left atrial diameter, LV end-diastolic diameter, and LV mass index) were associated with increasing BNP, NT-proBNP, or both, whereas increased heart rate, haematocrit, and body mass index (BMI) were associated with decreasing BNP and NT-proBNP (all $P < 0.05$).

Conclusion Next to ageing and sex, a variety of changes in covariates reflecting the sequelae of cardiac remodelling as well as myocardial infarction and diabetes influence long-term changes of BNP and NT-proBNP. Of note, diabetes and increased BMI exert opposite effects. For interpretation of individual marker concentrations, a host of covariates needs to be considered, especially in subjects without prevalent or incident cardiac disease.

Keywords 10-year-follow-up • Hypertension • Natriuretic peptides • Echocardiography • LV hypertrophy • Heart failure

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Introduction

The natriuretic peptides BNP and NT-proBNP are robust biochemical markers which have shown benefit in emergency medicine and primary care when acute or chronic heart failure is suspected in dyspnoeic patients.[1] As the cardiac markers BNP and NT-proBNP are constantly gaining importance, they are increasingly also assessed outside the emergency department, such as in patients at increased risk for cardiovascular conditions. Population-based studies have shown that in such a setting, measures of cardiac structure and function as well as age and gender strongly influence marker concentrations.[2–5]

Since these associations have been derived from cross-sectional studies, only little is known regarding the temporal change of these biomarkers. Further, there is currently no information available regarding to what extent the cardiac and extra-cardiac covariates determine temporal changes of these biomarkers over time. Such analyses require a longitudinal study with repeated measurements of the cardiac biomarkers and of a set of potential determinants including cardiac and extra-cardiac parameters.

It was therefore our aim to assess temporal changes of BNP and NT-proBNP during ageing as well as the determinants of these changes. We hypothesized that both cardiac biomarkers would increase significantly during the ageing process and that cardiac parameters as well as extra-cardiac parameters would influence their temporal concentrations. To address this aim, repeated measurements of BNP and NT-proBNP after a 10-year follow-up were assessed in a large, population-based cohort with additional extensive phenotyping, including repeated echocardiography at baseline and follow-up.

Methods

Study cohort

Participants were from KORA (Cooperative Research in the Region of Augsburg), which is the successor of the German part of the international World Health Organization MONICA collaborative[6] and was designed to investigate the cardiovascular risk of the general population.[7] The baseline exam was conducted in 1994–1995 (KORA third survey, S3) on residents aged 25–74 years of the region of Augsburg, Germany. Participants from the baseline exam that displayed echocardiographic tracings with sufficient quality for quantitative measurements were eligible for an echocardiographic investigation at the follow-up exam (KORA F3), conducted in 2004–2005. From 1248 eligible individuals, 1005 participated in the follow-up (net response 80.5%).[8] On both exams, all participants underwent an extensive interview. Body height and weight were measured in light clothing. Resting blood pressure was measured three times under strictly standardized conditions at the right arm after subjects remained in a sitting position for a minimum of 30 min, using a random zero sphygmomanometer (Hawksley-Gelmann, Lancing, UK; zero range 0–60 mmHg), and the mean of the second and third measurement was used for these analyses. Arterial hypertension was defined as systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg or current intake of antihypertensive medication. Diabetes mellitus was defined as a self-reported history of type 2 diabetes and ascertained through medical records from general practitioners. The glomerular filtration rate (GFR) was estimated from serum creatinine using the Cockroft–Gault formula.[9] For calculation of parameters which require height as a variable [body mass index (BMI) and LV mass index (LVMI)], height from the baseline survey was used for both baseline and follow-up calculations.

Echocardiography

Echocardiographic measurements have been described elsewhere in detail.[8] M-mode measurements included LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), septal wall thickness (SWT), posterior wall thickness (PWT), and left atrial (LA) diameter, and were assessed according to the guidelines of the American Society of Echocardiography.[10] The LV mass was calculated according to Devereux and Reichek.[11] The echocardiographic investigations at baseline and follow-up were carried out with different equipment, reflecting technological progress. These systematic differences were accounted for by computing a correction factor for follow-up applying a mixed model as described previously.[8]

Natriuretic peptide measurements

Blood was drawn at rest, and samples were chilled, centrifuged, and the plasma was stored at −80°C until measurement. BNP was measured by standard radioimmunoassay from 100 μL of non-extracted plasma samples with a commercially available RIA-kit (Shionogi, Osaka, Japan). NT-proBNP was measured with a clinically approved assay on a large laboratory analyser (elecsys®-proBNP, Roche Diagnostics).

Statistical methods

Among the 1005 subjects with both baseline (BL) and follow-up (FU) echocardiographic measurements, 877 participants had values available of BNP at BL and FU or NT-proBNP at BL and FU, which comprised the analysed sample. BNP and NT-proBNP were log-normally transformed to yield approximate normality. BNP values below the lower detection limit of 2 pg/mL were set to 2 pg/mL. NT-proBNP did not have values below the detection limit, but nine extreme NT-proBNP values, i.e. > 1800 pg/mL which was the exp(mean + 3 SDs on a log scale), which we set to 1800 pg/mL.

The change in BNP or NT-proBNP values of FU compared with BL was defined as the difference on the log scale (here only for BNP as an example)

$$change\_in\_\log(BNP) = \log(BNP\_FU) - \log(BNP\_BL) = \log\left(\frac{BNP\_FU}{BNP\_BL}\right)$$

Thus, exp(change) can be viewed as the quotient of FU BNP to BL BNP on the original scale, which can also be interpreted as the factor by which BNP_FU has increased compared with BNP_BL.

Generally, we evaluated a list of covariates [BMI, hypertension, hypertension or beta-blocker medication, systolic or diastolic blood pressure, heart rate, LA diameter, LVEDD, LV mass, fractional shortening, septum, myocardial infarction (MI), diabetes mellitus, GFR, creatinine, and haematocrit] for their association with BNP or NT-proBNP or the BNP or NT-proBNP change after the 10-year follow-up, all via linear regression analyses and all adjusted for age and sex. We applied three types of analyses: we evaluated (i) the association of the covariates at BL with BNP at BL and the association of the covariates at FU with BNP at FU (cross-sectional analyses); (ii) the association of the covariates at BL with the change of BNP (ΔBNP as described above) after the 10-year follow-up (longitudinal analyses with covariates at BL); and (iii) the association of the change of covariates during the 10-year-follow-up (Δcovariates) with change of BNP (ΔBNP) during the 10-year follow-up (longitudinal analyses with

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change of covariates). All analyses were also performed for NT-proBNP. We built a multiple regression model by those covariates that show $P < 0.05$ in simple models (each covariate at a time) and then excluding covariates that were no longer nominally significant ($P < 0.05$) in either BNP or NT-proBNP. Thus, we ensured that the models for BNP or NT-proBNP contained exactly the same covariates for comparability.

Results

Participant characteristics

The characteristics of the participants are depicted in *Table 1*. At baseline, median age in both sexes was 48 years. During the 10-year follow-up, BMI increased by ~ 1 kg/m^2 in both sexes. Systolic and diastolic blood pressure, prevalence of hypertension, and antihypertensive medication including beta-blocker therapy increased markedly. Heart rate decreased slightly. Whereas the prevalence of myocardial infarction in men was very low at baseline and absent in women, it increased markedly after 10 years in both sexes. Likewise, the initially low prevalence of diabetes increased markedly. Creatinine increased and estimated GFR decreased. Regarding cardiac structure and function, a mild increase of LA and septal wall thickness and LV mass was observed, and systolic function also tended to increase.

Association of covariates with natriuretic peptides in cross-sectional analysis

In the cross-sectional association analyses, when considering each covariate one at a time (Supplementary material, *Table S1*), age showed by far the strongest association with BNP and NT-proBNP in both exams, closely followed by gender. Increases in BNP, NT-proBNP, or both were further observed with: hypertension, antihypertensive medication, beta-blocker intake, increased systolic blood pressure, prevalent MI, and prevalent diabetes. Increased cardiac parameters (LA diameter, LVEDD, and LVMI) were associated with increased marker values, and an inverse association was found with BMI, LV function (fractional shortening), GFR, haematocrit, and heart rate. Hypertension, hypertension medication, and prevalent diabetes did not remain in the multiple regression model accounting for all significant covariates ($P < 0.05$, Supplementary material, *Table S2*).

Contribution of age and sex to natriuretic peptides during the 10-year follow-up

The increase of both markers after 10 years, shown in *Figure 1*, was similar in both men and women, and the higher levels for women persisted over time. The increase in marker concentrations across age is shown in *Figure 2*.

Predictors of temporal changes of natriuretic peptides in longitudinal analyses

When analysing the association of the baseline covariates with change in BNP (Δ BNP) or NT-proBNP (Δ NT-proBNP) during the 10-year follow-up, we found only age, sex, heart rate, and prevalent diabetes as statistically independent predictors (*Table 2*). LA diameter was also significantly associated with change in BNP when analysed separately, but lost significance in the multiple regression model (Supplementary material, *Table 3*).

When analysing the association of the temporal changes of the covariates (Δcovariate) with change in BNP (Δ BNP) or NT-proBNP (Δ NT-proBNP), the strongest predictors in the multiple regression model were age, change in haematocrit, and onset of beta-blocker medication, followed by change in BMI and incident MI. Further independent predictors were change in heart rate and cardiac parameters (LA diameter, LVEDD, and LVMI) as well as prevalent diabetes (*Table 3*). When analysed separately, new onset of hypertension medication and change in GFR were also associated with change in BNP (Δ BNP) or NT-proBNP (Δ NT-proBNP), but lost significance in the multiple regression model (Supplementary material, *Table 4*).

Interestingly, persons whose BMI increased during the 10-year follow-up showed a smaller increase in BNP or NT-proBNP over time than those with stable BMI. To visualize these results, *Figure 3A* depicts the change of BNP (left) and NT-proBNP (right) comparing subjects without an increase in BMI with those with a 5 kg/m^2 increase in BMI for a modelled man, 60 years old at baseline, with all other covariates in the multiple regression model (as in *Table 3*) assumed to be zero. *Figure 3B–F* illustrates the corresponding changes of BNP (left) and NT-proBNP (right) modulated by other covariate changes.

Discussion

In a large, population-based cohort with repeat echocardiography and measurement of BNP and NT-proBNP at baseline and follow-up after 10 years, we identified determinants of temporal change in these important biomarkers. Among baseline covariates, we found age, sex, heart rate, and prevalent diabetes to determine the 10-year change in BNP or NT-proBNP. In addition, changes in BMI, haematocrit, cardiac size and geometry, as well as incident MI and new onset of beta-blocker medication were predictors of long-term changes in BNP and NT-proBNP.

Contribution of ageing

The current study demonstrates age-associated increases of BNP and NT-proBNP, which are particularly steep above 70 years of age (see *Figure 2*). The brain type natriuretic peptides have nevertheless been suggested for the exclusion of heart failure also in elderly patients.[12] Whereas an age dependency has already been shown in cross-sectional studies,[13,14] the current study confirms this finding in a long-term longitudinal study design. Furthermore, it is of particular interest that these age-dependent changes are statistically independent from cardiac structural changes and other covariates. Previously, age-dependent increases have been thought to reflect the intrinsic sequelae of arterial hypertension, cardiac hypertrophy, and renal deterioration. Our current data further support the investigation of age-adjusted cut-off points also in clinical cohorts and through continuous rather than discrete algorithms. Three discrete age-adjusted cut-off points for the detection of LV dysfunction in the population have recently been suggested for NT-proBNP.[14]

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Table 1 Descriptive statistics for participant characteristics at baseline and follow-up

Variable	Baseline (n = 877)				Follow-up (n = 877)			
	Men		Women		Men		Women	
	Mean ± SD[a]	n	Mean ± SD[a]	n	Mean ± SD[a]	n	Mean ± SD[a]	n
Age (years)	48.4 ± 12.9	424	48.1 ± 12.1	453	58.4 ± 12.9	424	58.1 ± 12.1	453
BMI (kg/m^2)	26.8 ± 3.0	424	26.0 ± 4.3	449	27.6 ± 3.5	422	27.0 ± 4.7	452
HT	41.5%	424	33.1%	453	58.4%	421	48.0%	452
HT med.	14.6%	424	15.2%	453	32.5%	422	34.7%	453
BB med.	7.1%	424	7.1%	453	21.8%	422	21.9%	453
SBP (mmHg)	129.7 ± 18.2	424	120.7 ± 19.5	453	136.5 ± 19.7	422	127.7 ± 21.5	452
DBP (mmHg)	83.5 ± 11.6	424	79.3 ± 10.8	453	84.8 ± 11.0	422	80.8 ± 10.7	452
HR (b.p.m.)	72.6 ± 10.4	423	74.4 ± 10.1	453	68.0 ± 11.1	422	71.1 ± 10.1	452
LA diameter (cm)	3.9 ± 0.4	417	3.5 ± 0.5	444	4.0 ± 0.5	418	3.6 ± 0.5	445
Septum (mm)	9.9 ± 1.9	424	9.0 ± 1.9	453	10.5 ± 1.8	385	9.1 ± 1.7	418
LVEDD (mm)	51.1 ± 4.3	424	46.9 ± 4.2	453	51.3 ± 4.6	385	47.0 ± 4.1	417
LVMI (g/m^2)	92.6 ± 19.9	424	79.4 ± 19.0	449	100.2 ± 22.8	383	81.9 ± 18.2	417
FS (%)	35.2 ± 5.5	423	35.9 ± 5.9	453	39.6 ± 6.3	308	41.0 ± 6.6	339
Prevalent MI	1.4%	419	0.0%	451	3.8%	419	1.6%	451
Prevalent DM	3.1%	421	1.3%	449	8.1%	421	4.9%	449
GFR (mL/min)	127.9 ± 29.0	422	114.8 ± 33.5	447	98.4 ± 26.4	422	88.6 ± 26.5	453
HCT (%)	44.3 ± 2.6	420	39.8 ± 2.9	442	44.4 ± 3.0	424	40.6 ± 2.9	453
BNP (pg/mL)[b]	5.1 (2.0, 10.8)	424	9.0 (4.6, 15.3)	452	6.2 (2.0, 19.4)	424	11.3 (2.0, 27.5)	453
NT-proBNP (pg/mL)[b]	35.8 (21.4, 63.8)	421	61.7 (40.6, 104.0)	451	46.6 (27.1, 111.8)	424	85.4 (45.9, 148.5)	453

BB med., beta-blocker medication; BMI, body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FS, fractional shortening; GFR, glomerular filtration rate; HCT, haematocrit; HR, heart rate; HT, hypertension, HT med., hypertension medication; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; MI, myocardial infarction; SBP, systolic blood pressure.

[a]Unless indicated otherwise.

[b]Median (lower quartile, upper quartile); P-value tested on a log scale.

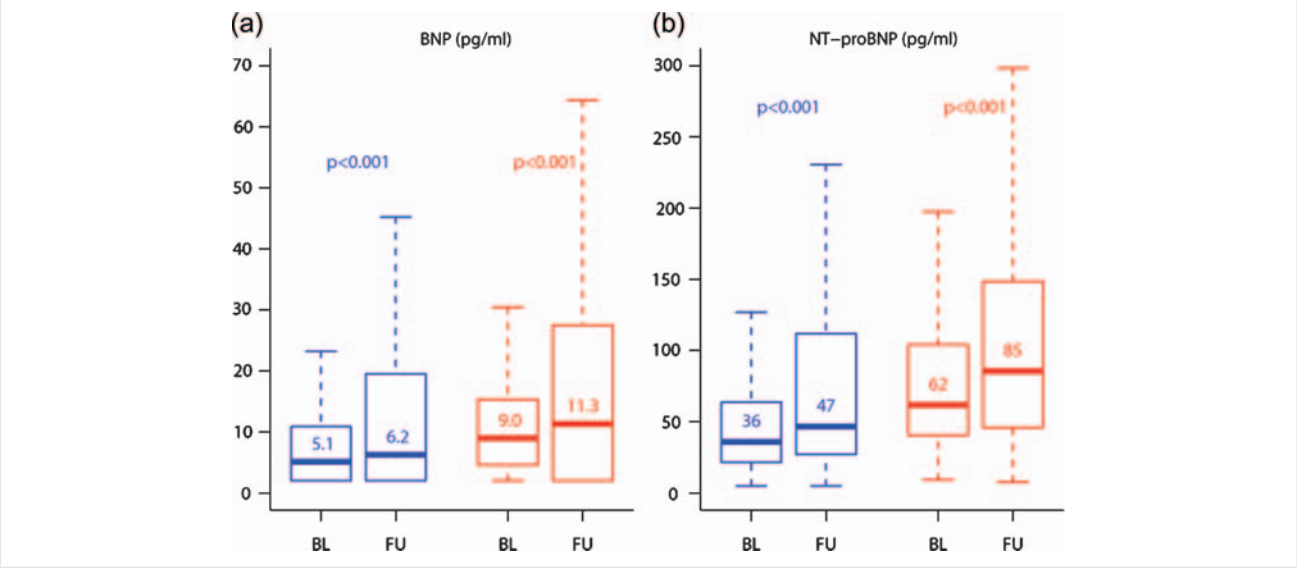

Figure 1 Influence by sex: shown are natriuretic peptide concentrations of male (blue) and female (red) participants at baseline (BL) and follow-up (FU) for (*a*) BNP and (*b*) NT-proBNP.

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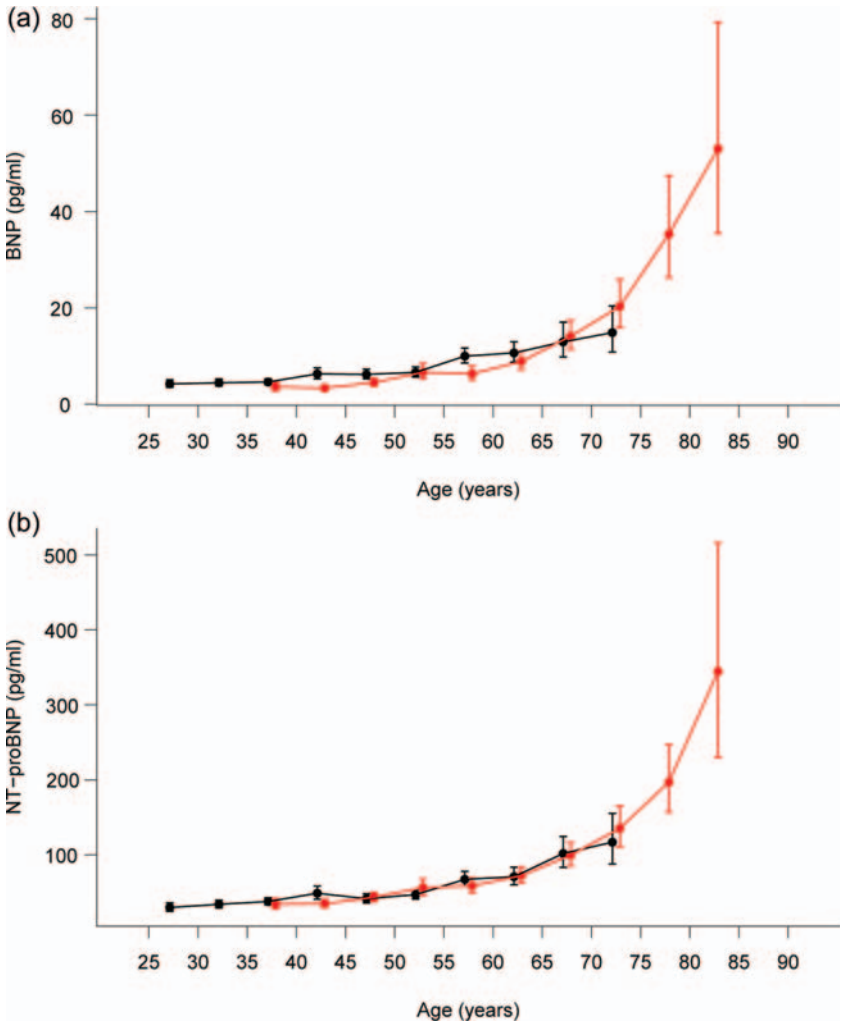

Figure 2 Influence of age: shown are median natriuretic peptide concentrations by 5-year age groups at baseline (black) and at the 10-year follow-up (red) for (*a*) BNP and (*b*) NT-proBNP.

Table 2 Longitudinal investigation: association of baseline covariates with change of brain natriuretic peptide or N-terminal pro brain natriuretic peptide during follow-up in a multiple regression model

Covariate	Change in BNP		Change in NT-proBNP	
	Factor by which BNP changes[a]	*P*-value[b]	Factor by which NT-proBNP changes[a]	*P*-value[b]
Sex (female)	0.937	0.35	0.880	**0.01**
Age (years)	1.030	**<0.001**	1.018	**<0.001**
HR (b.p.m.)	1.008	**0.02**	1.005	**0.04**
Prevalent DM	1.610	**0.04**	1.715	**0.002**

Results from a multiple regression model with change of BNP or change of NT-proBNP as outcome on the log scale including age and sex and those covariates that showed $P < 0.05$ when each was tested one at a time (Supplementary mterial, *Table S3*) for BNP or NT-proBNP (to ensure that the same covariates are used for both).
DM, diabetes mellitus; HR, heart rate.
[a]Factor by which BNP or NT-proBNP at follow-up has changed relative to BNP or NT-proBNP at baseline per unit change in the covariate.
[b]Bold indicates significance to 5%.

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Table 3 Longitudinal investigation: association of changes in covariates with change of brain natriuretic peptide or N-terminal brain natriuretic peptide during follow-up in a multiple regression model

Covariate	Change in BNP		Change in NT-proBNP	
	Factor by which BNP changes[a]	*P*-value[b]	Factor by which NT-proBNP changes[a]	*P*-value[b]
Sex (female)	1.011	0.87	0.959	0.42
Age (years)	1.021	**<0.001**	1.012	**<0.001**
ΔBMI (kg/m^2)	0.941	**<0.001**	0.965	**0.007**
New BB med.	1.498	**<0.001**	1.327	**<0.001**
ΔHR (b.p.m.)	0.989	**0.001**	0.997	0.20
ΔLA diameter (cm)	1.225	**0.03**	1.222	**0.003**
ΔLVEDD (mm)	1.020	**0.04**	1.007	0.33
ΔLVMI (g/m^2)	1.004	0.07	1.004	**0.005**
Incident MI	2.105	**0.004**	1.769	**0.002**
Prevalent DM	1.239	0.37	1.419	**0.04**
ΔHCT (%)	0.951	**<0.001**	0.955	**<0.001**

Results from a multiple regression model with change of BNP or change of NT-proBNP as outcome on the log scale including age and sex and those covariates that showed $P < 0.05$ when each was tested one at a time (Supplementary material, *Table S4*) for BNP or NT-proBNP (to ensure that the same covariates are used for both).
BB med., beta-blocker medication; BMI, body mass index; DM, diabetes mellitus; HCT, haematocrit; HR, heart rate; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; MI, myocardial infarction.
[a]Factor by which BNP or NT-proBNP at follow-up has changed relative to BNP or NT-proBNP at baseline per unit change in Δcovariate (with Δcovariate being the difference between the follow-up value and the baseline value of the covariate).
[b]Bold indicates significance to 5%.

Contribution of sex

Our data extend previous knowledge[3,4] by showing that the age-related increase in men and women is similar and the higher levels in women persist during ageing. As for age, our data underscore the need to investigate sex-specific cut-off points of BNP and NT-proBNP levels for diagnostic purposes in clinical cohorts.

Contribution of cardiac remodelling and myocardial infarction

Longitudinal changes of BNP and NT-proBNP were significantly correlated with changes in cardiac structural parameters. Specifically, changes in BNP and NT-proBNP were significantly correlated with changes in LA diameter, and BNP also with changes in LVEDD, and NT-proBNP with changes in LVMI. Although not statistically significant, a change in LV function had at least a strong relative effect (see Supplementary material, *Table S4*), and the lack of statistical significance is probably due to the narrow range of LV function and the low prevalence of impaired LV function in the general population. Together, both BNP and NT-proBNP are therefore sensitive indicators of atrial and ventricular remodelling during follow-up, which is consistent with experimental studies.[15,16] Atrial and/or ventricular hypertrophy are therefore very likely reasons for increased BNP or NT-proBNP in the absence of prevalent cardiac disease. It is also of note that BNP and NT-proBNP are sensitive enough to indicate cardiac remodelling within a range of plasma concentrations which are considered normal.

In addition, incident MI was strongly associated with changes of BNP and NT-proBNP, a finding which is consistent with the abrupt changes in cardiac structure and function such as LV dilatation and LV dysfunction, which often occur after MI and may also eventually lead to heart failure.

Contribution of diabetes and body composition

Diabetes and changes in BMI were important extra-cardiac parameters that were associated with changes in BNP and NT-proBNP. Regarding diabetes, we observed that prevalent diabetes at baseline was associated with increases of BNP and NT-proBNP during follow-up, whereas incident diabetes mellitus during the follow-up was not. We therefore conclude that it takes long-standing diabetes to induce the mechanisms that increase BNP and NT-proBNP. The effect with diabetes was quite pronounced and in a similar range to the effect of a 10 mm increase in LA diameter. Of note, diabetes-associated changes were statistically independent from cardiac remodelling, renal deterioration, and ageing. Whether there is an independent effect of diabetes has been controversial so far. In this respect, Beer *et al.* have shown that NT-proBNP is higher in subjects with diabetes and vascular complications than in diabetics without vascular complications.[17] Van den Hurk *et al.* have shown that BNP was associated with LV diastolic function in diabetics.[18] Also, Bertoni *et al.* have shown that NT-proBNP increased significantly more in diabetics with relevant weight loss during 1 year as compared with diabetics without weight loss.[19] Our current data extend these findings and suggest that diabetes, like ageing, affects marker concentrations independently from and in addition to cardiac remodelling and renal deterioration.

The levels of BNP and NT-proBNP increased less over time in subjects whose BMI increased. Whereas the above-mentioned

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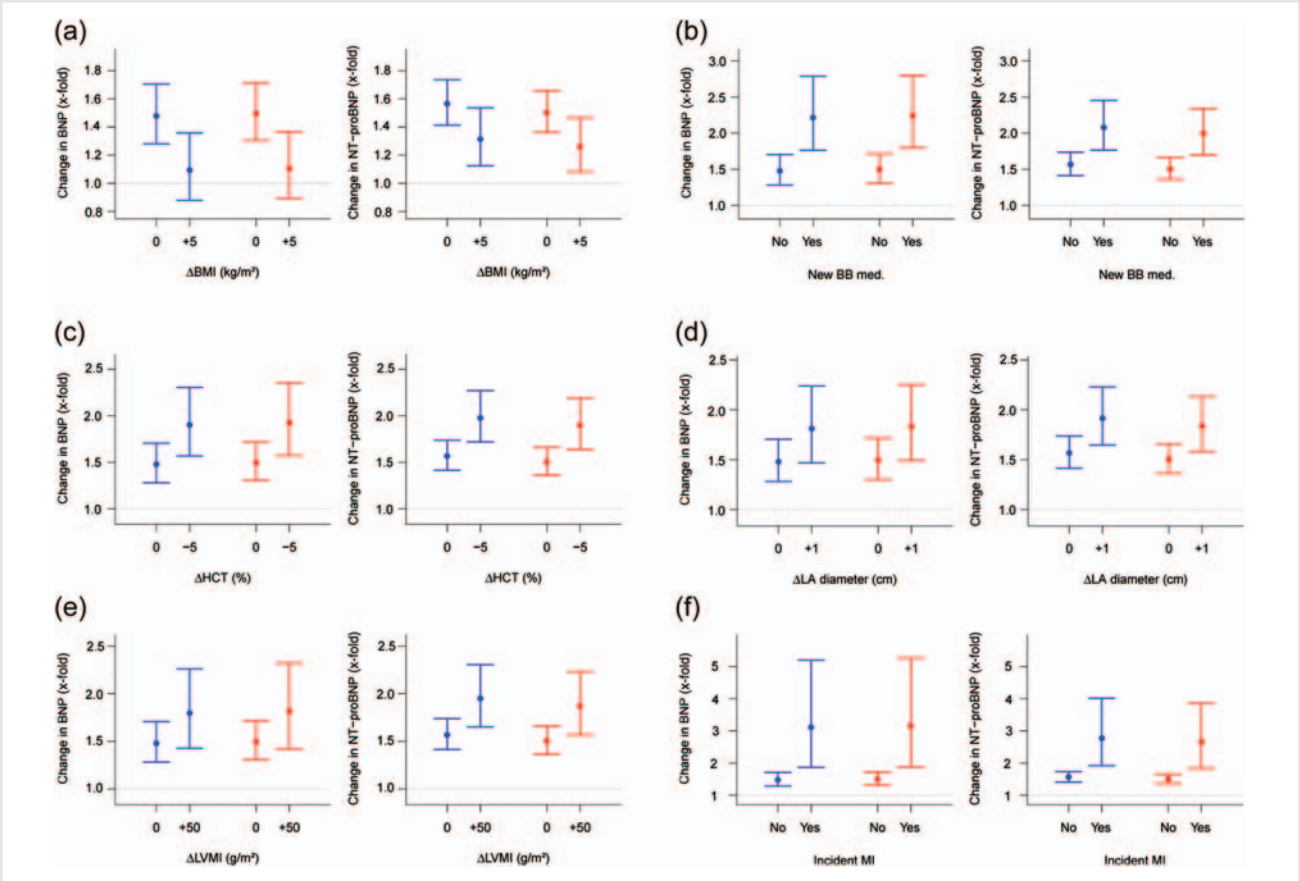

Figures 3 Temporal change by risk factors: shown are x-fold changes of BNP (left) and NT-proBNP (right) during the 10-year follow-up for a modelled male (blue) or female (red) person, 60 years old at baseline, and assuming no changes in any of the other covariates in the multiple regression model (as in *Table 3*) comparing persons (*a*) without and with a 5 kg/m^2 increase of body mass index during follow-up; (*b*) without and with beta-blocker (BB) therapy initiated during follow-up; (*c*) without and with a 5% decrease of haematocrit (HCT) during follow-up; (*d*) without and with a 10 mm increase in left atrial (LA) diameter during follow-up; (*e*) without and with a 50 g/m^2 increase in left ventricular mass index (LVMI) during follow-up; and (*f*) without and with incident myocardial infarction (MI) during during follow-up.

increases in marker concentrations secondary to diabetes are consistent with elevated cardiovascular stress, the contrasting effects of increased BMI clearly complicate the interpretation and clinical application of BNP and NT-proBNP for diabetic and/or obese individuals. Our data from the general population are thus in line with findings from clinical studies, which have suggested lower cut-off points for heart failure diagnosis in obese subjects.[20,21]

Contribution of beta-blockade

The current data demonstrated that initiation of beta-blocker therapy during follow-up was associated with an increase of BNP and NT-proBNP. In contrast, beta-blocker therapy continuously administered during the full observation period was not associated with altered BNP or NT-proBNP. Of note, such an effect was not observed for other antihypertensive medications. The current data confirm our initial report, which has already shown that beta-blocker therapy is associated with higher BNP independently from blood pressure, age, and cardiac structure and function,[22] and extend this finding to NT-proBNP and to longitudinal data. The underlying mechanism is likely to be due to interactions and cross-talk between the sympathetic nervous system and the natriuretic peptide system, which includes activation of the natriuretic peptides through the alpha-receptor, suppression of natriuretic peptides through the beta-receptor, and activation of the natriuretic peptide clearance receptor through beta-receptors. Additional increases may be caused by reduction of contractility and increases in LV end-diastolic pressure and diameter. Interestingly, an increase in natriuretic peptides has also been reported after initiation of beta-blockade in patients with heart failure.[23,24]

Contribution of haematocrit and renal function

Our data provide evidence that a decrease in haematocrit during long-term follow-up is associated with a greater increase in BNP and NT-proBNP than a stable haematocrit. Our finding is in line with cross-sectional studies[25,26] which have reported an inverse association between haematocrit and the natriuretic peptides from cross-sectional studies.

Regarding renal function, we observed that BNP and NT-proBNP were significantly and independently associated with GFR upon cross-sectional analyses, which is in line with our own

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and other previous reports.[27–29] While a decrease in renal function was further associated with increased NT-proBNP upon longitudinal analysis when considering renal function as the sole covariate, it did not show statistical significance in the multiple adjusted linear regression.

Strengths and limitations

The current study has the strength of being based on the general population with 10-year follow-up with rigid standardization of all assessments also across time. The sample size is quite large and includes a large panel of different anthropometric, cardiac, and other measures, and enabled us to identify a host of independent determinants of temporal changes of BNP and NT-proBNP. As a limitation, we need to acknowledge that BNP and NT-proBNP were measured from frozen blood. However, this is standard practice in epidemiological studies. Further limitations are lack of detailed assessment of diastolic function and the rather small number of diabetics.

Conclusions

The current data provide a longitudinal assessment of temporal changes of BNP and NT-proBNP during long-term follow-up in the general population. They confirm that the sequelae of MI, cardiac remodelling, and diabetes influence BNP and NT-proBNP independently from sex and ageing. They further demonstrate that diabetes and increased BMI exert opposite effects on changes in marker concentrations. For the interpretation of individual test results in subjects without incident or prevalent cardiac disease, a host of anamnestic and anthropometric covariates needs to be considered.

Supplementary material

Supplementary material is available at *European Journal of Heart Failure* online.

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