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ORIGINAL ARTICLE

Epidemiology/Genetics

Six-year changes in N-terminal pro-brain natriuretic peptide and changes in weight and risk of obesity

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Abstract

Objective: The aim of this study was to study the prospective association between N-terminal pro-brain natriuretic peptide (NT-proBNP) and changes in weight and obesity risk in a community-based population.

Methods: Data from 9,681 participants from the Atherosclerosis Risk in Communities Study were analyzed at two time points 6 years apart. Among people without obesity at baseline, multivariable logistic regression models were used to examine the association between baseline levels of NT-proBNP and incident obesity. A multivariable linear regression model was used to examine the association between changes in NT-proBNP (visit 2 serum and visit 4 plasma samples) and changes in weight.

Results: The prevalence of obesity increased from 28% to 35% in the 6-year follow-up period. Compared with individuals in the highest NT-proBNP quartile, those in the lowest were more likely to have obesity at baseline (odds ratio 1.25; 95% CI: 1.08-1.45) and, among people who did not have obesity at baseline, were more likely to develop obesity at follow-up (odds ratio 1.35; 95% CI: 1.07-1.69). Changes in NT-proBNP were inversely associated with weight change.

Conclusions: In this prospective study, lower levels of NT-proBNP were associated with higher risk of obesity, and changes in NT-proBNP were inversely associated with changes in weight. This suggests that natriuretic peptides or their pathways may be potential targets in the treatment of obesity.

INTRODUCTION

Natriuretic peptides (NPs) are biochemical markers of cardiac function, which correlate with the severity of heart failure (HF) and also strongly predict future HF development (1). The main stimulus for NP release is distension of cardiac myocytes, which can occur in situations of increased ventricular wall stress caused by processes such as hypertension and volume overload (2). These hormones have well-established protective cardiovascular effects. Neprilysin inhibitors (Entresto; Novartis Pharmaceuticals Corp., East Hanover, New Jersey) are widely used in the treatment of congestive HF, promoting vasodilation, natriuresis, and decreased renin and aldosterone secretion (3). The action of NPs, however, is not restricted to the heart–kidney axis. They also may play a role in metabolic pathways and the development of insulin resistance. In adipose tissue, NPs are known to stimulate lipolysis, mitochondrial biogenesis, and browning of adipocytes (4).

Cross-sectional studies have demonstrated that diabetes and obesity are inversely associated with lower levels of B-type NP (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP). Wang et al. (5) found that, among 3,389 participants of the Framingham Heart Study offspring cohort without HF, BMI was inversely associated with NP levels. Compared with those with normal BMI, men and women with obesity had 40% and 38% lower plasma BNP levels, respectively. In the setting of HF, NT-proBNP is widely used to aid diagnosis, stratify cardiovascular risk, and monitor therapy effect. This inverse association of BMI with NP levels is also present in those with HF, and BMI-specific cutoff points for HF diagnosis and prediction have been proposed in the literature (6-8). Possible explanations for the low NP levels in obesity are impaired synthesis and release from the cardiomyocytes or, less likely, increased clearance by NP receptor-C (9-12).

A growing number of studies have suggested that NPs are not only associated with but may also protect against metabolic diseases. Transgenic mice overexpressing BNP were protected against diet-induced obesity and insulin resistance, despite being fed a high-fat diet (13). Preclinical studies have also shown that BNP treatment in obese mice improves glucose tolerance and insulin sensitivity (14,15). Similar observations have been seen in human studies. In a subsample of 3,019 participants from the Jackson Heart Study, a cohort of African American adults from Mississippi, BNP levels had a U-shape association with the incidence of metabolic syndrome (16). The Atherosclerosis Risk in Communities (ARIC) study also demonstrated that NT-proBNP levels were inversely associated with diabetes risk, even after multivariable adjustments (17). Likewise, the Women's Health Study (18), the Cardiovascular Health Study (19), and the Multi-Ethnic Study of Atherosclerosis (20) have additionally provided support for an inverse association between NP levels and incident diabetes. However, longitudinal data regarding the direct association of changes in NP levels with weight change and risk of obesity (independent of changes in other cardiometabolic risk markers) are limited.

Study Importance

What is already known?

► Cross-sectional studies have demonstrated that obesity is associated with lower levels of N-terminal pro-brain natriuretic peptide (NT-proBNP). Longitudinal data evaluating the association between natriuretic peptides (NPs) and weight change are scarce.

What does this study add?

► Lower levels of NT-proBNP were associated with higher risk of obesity, and changes in NT-proBNP were inversely associated with changes in weight.

How might these results change the direction of research or the focus of clinical practice?

► NPs or their pathways may be potential targets in the treatment of obesity. Nevertheless, interventional studies are needed to examine the therapeutic potential of NPs.

We hypothesized that lower baseline levels and decreases in NT-proBNP over time would be independently associated with increases in weight and a higher risk of obesity in the community-based population of the ARIC study.

METHODS

Study population

The ARIC study is an ongoing prospective cohort study designed to investigate the etiology of atherosclerosis and its clinical outcomes in 15,792 middle-aged adults. Participants were recruited from four communities in the United States (Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland). Participants were enrolled from 1987 to 1989 and they underwent clinical examinations approximately every 3 years thereafter for three more visits (1990 to 1992, 1993 to 1995, and 1996 to 1998). Subsequent visits also occurred in 2011 to 2013, 2016 to 2017, and 2018 to 2019. In this analysis, we used data on NT-proBNP available from visits 2 (1990 to 1992) and 4 (1996 to 1998). More information about data collection has been published elsewhere (21).

A total of 11,449 participants attended both visits. We excluded participants with race/ethnicity other than Black or White (n = 31) and Black individuals from the Minneapolis and Washington County centers (n = 38); those with missing data for variables of interest (n = 745); and those missing NT-proBNP levels (n = 954). The final sample size was composed of 9,681 adults. For the analyses

examining the incidence of obesity, individuals with obesity at baseline were excluded (n = 2,741).

The ARIC study has been approved by the Institutional Review Boards (IRBs) at all participating institutions: University of North Carolina at Chapel Hill IRB, Wake Forest University IRB, Johns Hopkins University IRB, University of Minnesota IRB, and University of Mississippi Medical Center IRB. Written informed consent was obtained from all study participants. All methods were carried out in accordance with the relevant guidelines and regulations for human subject research, in accordance with the Declaration of Helsinki (21).

Measurements

All covariates were assessed at baseline following standard protocols. BMI was calculated from measured weight and height at both visits, and obesity was defined as BMI ≥30 kg/m^2. Diabetes was defined as fasting (≥8 hours) blood glucose ≥126 mg/dL, nonfasting blood glucose ≥200 mg/dL, self-reported physician-diagnosed diabetes or "sugar in blood," or use of medication for diabetes in the past 2 weeks. Hypertension was defined as mean systolic blood pressure (BP) ≥140 mmHg, mean diastolic BP ≥90 mmHg, or use of medication for high BP in the past 2 weeks. Atherosclerotic cardiovascular disease was defined as history of coronary heart disease and/or stroke.

Assays of NT-proBNP levels were conducted in serum (visit 2) and plasma (visit 4) samples that had been stored at −70°C. Measurements were made using a sandwich immunoassay method on a Roche Elecsys 2010 analyzer (Roche Diagnostics, Indianapolis, Indiana) at visit 2 and an electrochemiluminescence immunoassay on an automated Roche Cobas e411 analyzer at visit 4. The lower detection limit for both assays was 5 pg/mL, and participants with unmeasurable levels were assigned a value of 2.5 pg/mL. NT-proBNP, glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, triglycerides, and high-sensitivity C-reactive protein were recalibrated based on published equations to minimize any systematic differences across study visits (22).

Statistical analyses

We compared the characteristics of the study participants by quartiles of NT-proBNP at baseline. *P* values for linear trends across NT-proBNP quartiles were obtained by assigning the median NT-proBNP value in each quartile and modeling this ordinal variable continuously. We used multivariable logistic regression models to estimate the association of NT-proBNP quartiles with prevalence of obesity at baseline. Among those who did not have obesity at baseline, we examined the risk of developing obesity at 6 years according to baseline quartiles of NT-proBNP. Two adjustment models were used: Model 1 included age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, HF, and atherosclerotic cardiovascular disease (coronary heart disease or stroke); Model 2 included the variables in Model 1 plus total cholesterol, HDL cholesterol, and use of lipid-lowering medication. We analyzed the associations of baseline deciles of NT-proBNP with 6-year change in weight. The reference category for change in NT-proBNP was the one with values crossing zero. We also used linear regression to evaluate weight change as a linear spline, which was regressed on log-transformed change in NT-proBNP (knots located at deciles of change in log-NT-proBNP). We conducted sensitivity analyses excluding patients with HF prior to visit 4. We also conducted a sensitivity analysis using BMI (weight in kilograms/height in meters squared) as a continuous dependent variable in a linear regression model. All statistical analyses were performed using Stata software version 15.1 (StataCorp LLC, College Station, Texas), and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline data

Mean age at baseline (1990 to 1992) was 57 years, 56% were women, and 78% were White. The prevalence of obesity was 28%. NT-proBNP levels were almost 12% lower in participants with obesity compared with those without obesity at baseline (77.0 ± 135.3 pg/mL in people with obesity and 87.1 ± 439.5 pg/mL in people without obesity). The prevalence of coronary heart disease generally increased with increasing quartiles of NT-proBNP levels at baseline, whereas the prevalence of diabetes as well as the levels of BMI, glucose, triglycerides, total cholesterol, and estimated glomerular filtration rate decreased (Table 1, *p*-for-trend < 0.0001). Individuals in the lowest quartile of NT-proBNP levels at baseline were less likely to have hypertension, HF, and coronary heart disease compared with those in the highest quartile (Table 1).

Outcomes

Obesity

In cross-sectional analyses, individuals in the lowest quartile of NT-proBNP (≤27.2 pg/mL) were more likely to have obesity at baseline than those in the highest quartile (odds ratio [OR] 1.37, 95% CI: 1.18-1.58; Model 1; Table 2). After additional adjustment for lipids (Model 2), the association was slightly attenuated but remained significant and strong (OR 1.25, 95% CI: 1.08-1.45). Results were similar in a sensitivity analysis using BMI as a continuous dependent variable in a linear regression model (Supporting Information Table S1).

During the 6-year follow-up period, the overall prevalence of obesity increased from 28% to 35%. The risk of developing obesity during the 6-year period was highest among individuals in the lowest quartile of NT-proBNP in both models (Table 3).

TABLE 1 Characteristics of ARIC participants according to NT-proBNP quartiles at baseline (visit 2, 1990 to 1992), *n* = 9,681

	Q1 (≤27.17 pg/mL)	Q2 (27.19-50.79 pg/mL)	Q3 (50.81-90.58 pg/mL)	Q4 (≥90.63 pg/mL)	*p* value for trend
N	2,422	2,419	2,421	2,419	
Age, y	55.0 (5.3)	56.3 (5.4)	57.2 (5.7)	58.3 (5.7)	<0.0001
Female (%)	838 (34.6%)	1,270 (52.5%)	1,611 (66.5%)	1,727 (71.4%)	<0.0001
Race (%)					
White	1,644 (67.9%)	1,908 (78.9%)	2,004 (82.8%)	2,029 (83.9%)	<0.0001
Black	778 (32.1%)	511 (21.1%)	417 (17.2%)	390 (16.1%)	<0.0001
Current smokers (%)	474 (19.6%)	431 (17.8%)	466 (19.2%)	492 (20.3%)	0.164
Hypertension (%)	727 (30.0%)	709 (29.3%)	755 (31.2%)	1,003 (41.5%)	<0.0001
Diabetes (%)	393 (16.2%)	320 (13.2%)	274 (11.3%)	258 (10.7%)	<0.0001
History of coronary heart disease or stroke (%)	62 (2.6%)	87 (3.6%)	124 (5.1%)	289 (11.9%)	
Prevalent heart failure (%)	74 (3.1%)	88 (3.6%)	72 (3.0%)	140 (5.8%)	<0.0001
Use of medication for hypertension, diabetes, or lipid lowering (%)	779 (32.2%)	762 (31.5%)	784 (32.4%)	1,061 (43.9%)	<0.0001
Weight, kg	84.1 ± 15.3	80.6 ± 16.0	76.7 ± 16.8	75.6 ± 17.1	<0.0001
BMI, kg/m^2	28.7 ± 4.9	28.2 ± 5.0	27.5 ± 5.5	27.3 ± 5.5	<0.0001
Obesity (BMI ≥30 kg/m^2) (%)	781 (32.2%)	716 (29.6%)	622 (25.7%)	622 (25.7%)	<0.0001
Waist circumference, cm	100.3 ± 12.4	98.8 ± 13.3	96.1 ± 14.6	95.4 ± 15.2	<0.0001
Glucose, mg/dL	102.1 (94.4-112.6)	99.2 (92.5-107.8)	97.3 (90.6-104.9)	96.3 (90.6-104.9)	<0.0001
Glycated hemoglobin, %-point	5.5 (5.2-5.9)	5.4 (5.2-5.8)	5.4 (5.2-5.7)	5.4 (5.2-5.7)	<0.0001
Triglycerides, mg/dL	126.1 (90.5-178.8)	117.9 (85.5-166.7)	112.9 (82.4-160.6)	111.8 (82.4-156.5)	<0.0001
HDL cholesterol, mg/dL	20.1 (17.9-23.0)	20.9 (17.9-23.8)	21.6 (18.7-26.0)	22.3 (18.7-26.7)	<0.0001
Total cholesterol, mg/dL	204.7 (180.8-231.5)	203.7 (179.8-228.5)	202.7 (180.8-227.5)	201.7 (178.8-227.5)	0.005
CRP, mg/L	2.0 (1.0-4.0)	2.1 (1.0-4.4)	2.3 (1.1-4.9)	2.6 (1.2-5.7)	<0.0001
eGFR, mL/min/1.73 m^2	99.1 (91.3-107.6)	97.7 (89.5-105.3)	96.9 (89.0-104.8)	95.6 (86.1-103.3)	<0.0001

Data given as numbers (%), means ± SD, or medians (interquartile range).

ARIC, Atherosclerosis Risk in Communities; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartiles of NT-proBNP.

TABLE 2 Odds ratios (95% CI) of prevalent obesity (BMI ≥ 30 kg/m^2) at baseline according to quartiles of NT-proBNP at baseline, *n* = 9,681

	NT-proBNP categories (pg/mL)			
	Q1 (≤27.17)	Q2 (27.19-50.79)	Q3 (50.81-90.58)	Q4 (≥90.63)
Model 1	1.37 (1.18-1.58)*	1.26 (1.10-1.45)*	1.05 (0.91-1.21)	1 (reference)
Model 2	1.25 (1.08-1.45)*	1.17 (1.02-1.35)*	1.03 (0.89-1.18)	1 (reference)

Model 1: Adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, and atherosclerotic cardiovascular disease (coronary heart disease or stroke). Model 2: Model 1 plus total cholesterol, HDL cholesterol, and lipid-lowering medication.

NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartiles of NT-proBNP.

*$p < 0.05$.

Change in weight

We found an inverse association between change in weight and change in NT-proBNP level (Figure 1). Participants who had an increase in NT-proBNP between the two visits greater than or equal to the 90th percentile of change in NT-proBNP (≥126.2 pg/mL) decreased their weight by an average of ~1.3 kg (mean weight change −1.33 kg; 95% CI: −1.86 to −0.80). Statistically significant decreases in weight were observed when NT-proBNP levels increased by more than 59.1 pg/mL in the 6-year follow-up (Figure 2A). Decreases in NT-proBNP levels of more than 22.3 pg/mL over the same period were associated with statistically significant increases in weight

TABLE 3 Odds ratios (95% CI) of incident obesity (BMI ≥ 30 kg/m^2) at the 6-year follow-up visit (visit 4, 1996 to 1998) among participants who did not have obesity at baseline (visit 2, 1990 to 1992), *n* = 6,940

	NT-proBNP categories (pg/mL)				
	Q1 (≤27.17)	Q2 (27.19- 50.79)	Q3 (50.81-90.58)	Q4 (≥90.63)	*p* value for trend
Model 1	1.51 (1.21-1.89)*	1.49 (1.21-1.83)*	1.09 (0.89-1.35)	1 (reference)	<0.0001
Model 2	1.35 (1.07-1.69)*	1.37 (1.11-1.69)*	1.06 (0.85-1.30)	1 (reference)	0.003

Model 1: Adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, atherosclerotic cardiovascular disease (coronary heart disease or stroke). Model 2: Model 1 plus total cholesterol, HDL cholesterol, and lipid-lowering medication.
NT-proBNP, N-terminal pro-brain natriuretic peptide; Q, quartiles of NT-proBNP.
*$p < 0.05$.

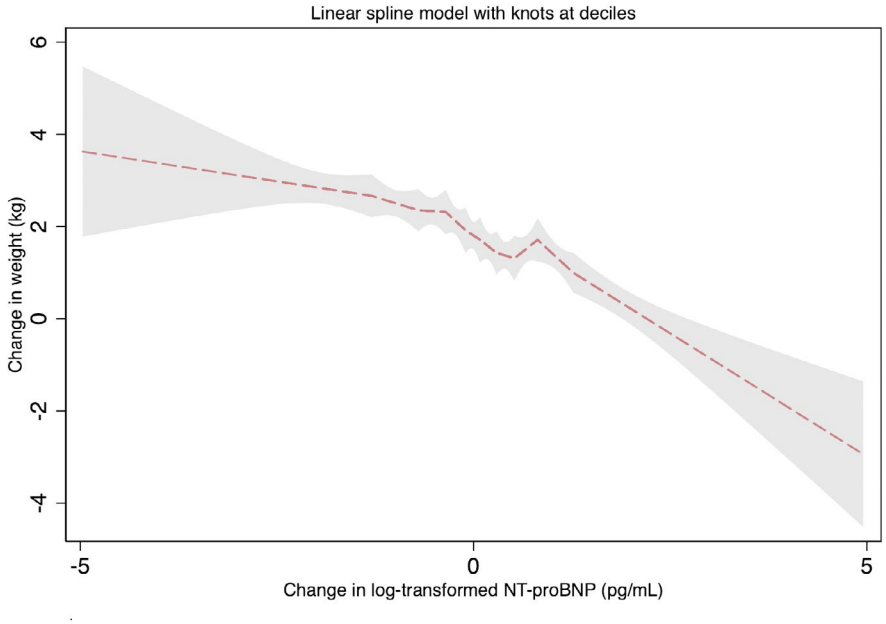

FIGURE 1 Adjusted 6-year change in log-transformed NT-proBNP with change in weight (β coefficient, 95% CI) in the ARIC study (1990-1992 to 1996-1998). The association between weight change as a linear spline with log-transformed change in NT-proBNP. The dashed line is the β coefficient, and the shaded region is the 95% CI. Knots are located at deciles of change in log NT-proBNP. This model is adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, atherosclerotic cardiovascular disease (coronary heart disease or stroke), total cholesterol, high-density lipoprotein cholesterol, and lipid-lowering medication. We found an inverse association between change in weight and change in NT-proBNP level. [Color figure can be viewed at wileyonlinelibrary.com]

(decrease in NT-proBNP −22.3 to −42.3 pg/mL, mean weight change 0.55 kg; 95% CI: 0.03 to 1.07; decrease in NT-proBNP <−42.3 pg/mL, mean weight change 0.60 kg; 95% CI: 0.09 to 1.12). Results were similar in a sensitivity analysis excluding participants with HF (Figure 2B).

DISCUSSION

In this prospective cohort of 9,681 adults, we found that lower NT-proBNP levels at baseline were associated with an increased risk of obesity, and changes in NT-proBNP levels over a 6-year follow-up period were inversely associated with changes in weight. This relationship was not driven by incident HF, which is known to directly affect NT-proBNP levels. Consistent with other cross-sectional studies, individuals with obesity also had lower levels of NT-proBNP compared with individuals without obesity. To our knowledge, this is the first study to show the prospective association of baseline levels and changes in NT-proBNP with the incidence of obesity and changes in weight over time.

NPs and obesity

Several mechanisms have been proposed to explain the inverse relation between NPs and obesity. In the adipose tissue, BNP has a lipolytic effect via stimulation of guanylyl cyclase-A and guanylyl cyclase-B. Activation of these receptors induces a rise in cyclic guanosine monophosphate levels and subsequent activation of cyclic guanosine monophosphate–dependent protein kinase 1 (cGK1),

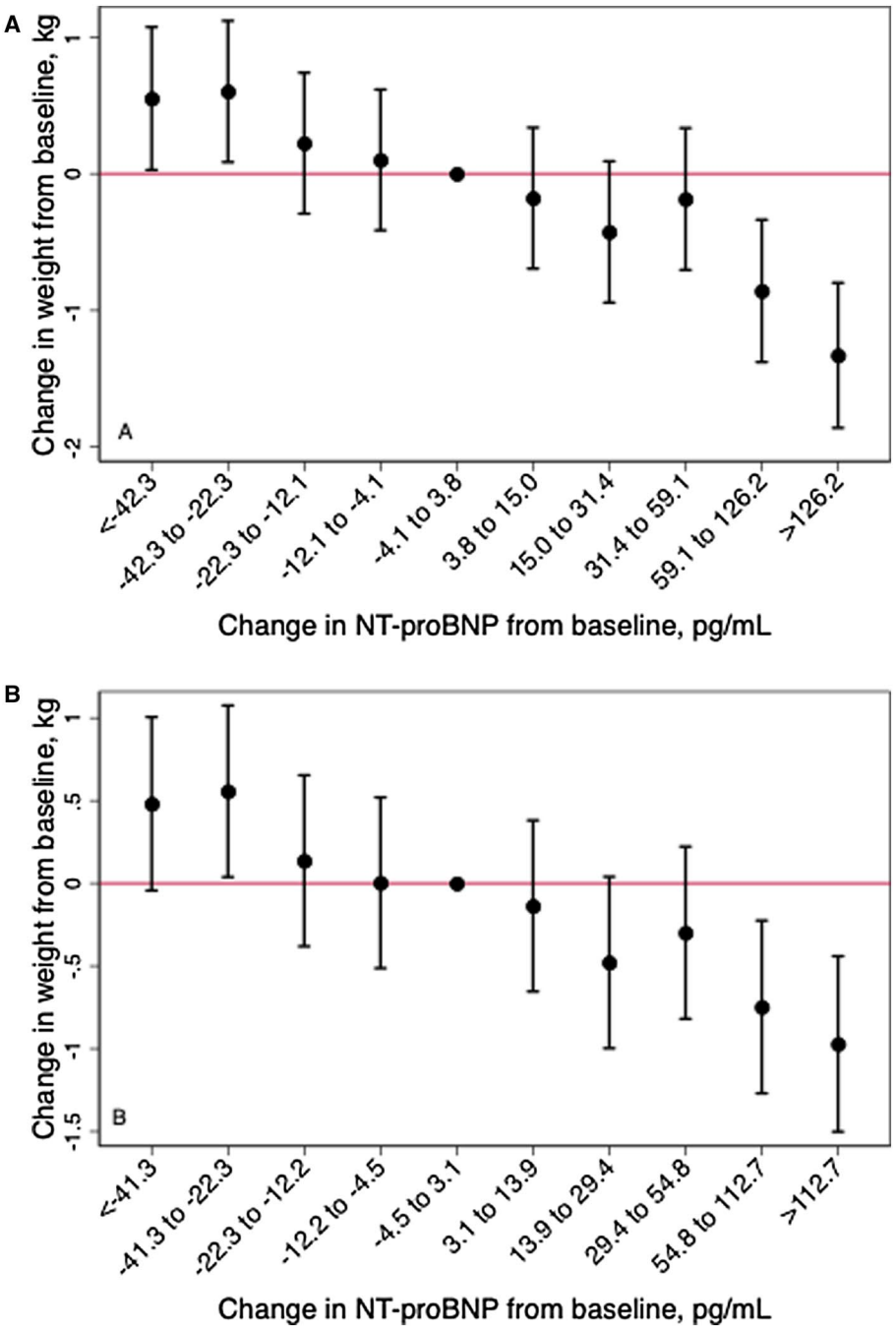

FIGURE 2 Change in weight by deciles of change in NT-proBNP (A) over the 6-year follow-up period and (B) after exclusion of participants with heart failure occurring at or prior to visit 4, the ARIC study (1990-1992 to 1996-1998). Adjusted for age, sex, race-center, smoking status, estimated glomerular filtration rate, hypertension, diabetes, heart failure, atherosclerotic cardiovascular disease (coronary heart disease or stroke), total cholesterol, high-density lipoprotein cholesterol, and lipid-lowering medication. Statistically significant decreases in weight were observed when NT-proBNP levels increased by more than (A) 59.1 pg/mL and (B) 54.8 pg/mL in the 6-y follow-up. Decreases in NT-proBNP levels of more than 22.3 pg/mL over the same period were associated with statistically significant increases in weight (panel A). [Color figure can be viewed at wileyonlinelibrary.com]

which in turn modify the lipid droplet surface to facilitate lipolysis (3). The existence of this pathway is supported by *in vitro* studies on isolated human fat cells (13,23-25). Notably, the impact of NPs on adipose tissue may be altered in individuals with obesity or insulin resistance, with attenuation or loss of the protective lipolytic effect of NPs (26,27).

NPs and hormones

NPs are also linked with modulated expression of numerous hormones and they may indirectly influence food intake. In a randomized controlled trial with 10 healthy men, acute intravenous infusion of BNP decreased circulating ghrelin concentrations, an important

hormone that stimulates appetite (28). Participants reported decreased hunger and increased feelings of satiety, demonstrating an induced anorexic effect of BNP infusion. However, this study evaluated only the acute effect of infusion with BNP, and changes in other variables affected by NPs (for example, insulin) could be responsible for the decrease in ghrelin. In contrast, adiponectin, which is responsible for the regulation of various metabolic pathways, has a positive association with NT-proBNP levels. Higher levels of adiponectin are associated with decreased BMI and lower risk of metabolic syndrome and diabetes. Fully understanding the link between NPs and the endocrine system is essential to interpret the interplay of these peptides with obesity.

Directionality of the relationship between NPs and adiposity

Low NP levels have also been proposed to be a consequence of obesity (5). Several mechanisms have been suggested, such as reduced synthesis and release from the heart. Substances released by the adipose tissue could be involved in suppressing production of NPs by the myocytes. Higher glycosylation of proBNP, seen in individuals with obesity, leads to impaired conversion of this molecule and, consequently, to lower plasma concentrations of BNP and NT-proBNP. Individuals with obesity also appear to have increased expression of neprilysin, an endopeptidase that degrades NPs. Taking into account these investigations along with our findings, it is possible to assume that the relationship between NPs and adiposity is bidirectional, with each factor influencing the levels of the other. Previous work has demonstrated inverse associations of NT-proBNP with the development of metabolic syndrome (18,29) and diabetes (30). Although this study does not directly address metabolic syndrome and diabetes, it is likely that an increases in weight and thus lower levels of NPs contribute to a greater likelihood of these metabolic abnormalities.

Study limitations

Our study has some limitations. We had only one measure of NT-proBNP at each visit, and this peptide is known to vary within individuals over short periods of time, similar to other neurohormones (31). We did not have measures of BNP; however, NT-proBNP and BNP are secreted in equimolar amounts after cleavage of proBNP, and previous studies have shown that their levels are closely correlated (32). Nevertheless, the biological variation of NT-proBNP is much less than that of BNP (33). We also did not have information on lean and fat body mass, which could be useful because some studies have suggested that the percentage of body fat mass may be more closely associated with BNP levels than BMI (34). It is also possible that differences in other factors which were not evaluated in this analysis could influence the associations of NPs with weight change. Because of the observational nature of the study, we cannot exclude the possibility of residual confounding.

Study strengths

Nonetheless, our study has important strengths. We used data from the ARIC study, a prospective cohort that has followed a biracial community-based sample since 1987 using standardized and rigorous data collection methods. Our large sample and availability of serial measurements of multiple cardiometabolic markers allowed us to investigate, over a 6-year follow-up period, the relationship between NPs and weight. We were able to show the prospective association of baseline levels and changes in NT-proBNP with incident obesity controlling for other risk factors.

CONCLUSION

In conclusion, we found inverse associations of baseline and longitudinal NT-proBNP levels with weight change and incidence of obesity. Our results suggest that NPs or their pathways may be potential targets in the treatment of obesity. However, the molecular networks involving the natriuretic system are complex, and additional research, especially interventional studies, is needed to address the clinical relevance of our findings.O

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

MSdS, ML, and ES designed the study and drafted the manuscript. MSdS and NRD conducted the analyses. MSdS, ML, NRD, OT, BDS, CMB, CN, and ES provided data interpretation and meaningful contributions to the revision of the manuscript. MSdS and ES are the guarantors of this work and, as such, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Nakagawa Y, Nishikimi T, Kuwahara K. Atrial and brain natriuretic peptides: hormones secreted from the heart. *Peptides*. 2019;111:18-25.
2. Gruden G, Landi A, Bruno G. Natriuretic peptides, heart, and adipose tissue: new findings and future developments for diabetes research. *Diabetes Care*. 2014;37:2899-2908.

3. Moro C, Lafontan M. Natriuretic peptides and cGMP signaling control of energy homeostasis. *Am J Physiol Heart Circ Physiol*. 2013;304:H358-H368.
4. Collins S. A heart–adipose tissue connection in the regulation of energy metabolism. *Nat Rev Endocrinol*. 2014;10:157-163.
5. Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation*. 2004;109:594-600.
6. Daniels LB, Clopton P, Bhalla V, et al. How obesity affects the cut-points for B-type natriuretic peptide in the diagnosis of acute heart failure: Results from the Breathing Not Properly Multinational Study. *Am Heart J*. 2006;151:999-1005.
7. Christenson RH, Azzazy HME, Duh S-H, Maynard S, Seliger SL, deFilippi CR. Impact of increased body mass index on accuracy of b-type natriuretic peptide (BNP) and N-terminal proBNP for diagnosis of decompensated heart failure and prediction of all-cause mortality. *Clin Chem*. 2010;56:633-641.
8. Ndumele CE, Matsushita K, Sang Y, et al. N-Terminal pro-brain natriuretic peptide and heart failure risk among individuals with and without obesity: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*. 2016;133:631-638.
9. Bayes-Genis A, DeFilippi C, Januzzi JL Jr. Understanding amino-terminal pro-B-type natriuretic peptide in obesity. *Am J Cardiol*. 2008;101(3A):S89-S94.
10. Clerico A, Fontana M, Vittorini S, Emdin M. The search for a pathophysiological link between gender, cardiac endocrine function, body mass regulation and cardiac mortality: proposal for a working hypothesis. *Clin Chim Acta*. 2009;405:1-7.
11. Morabito D, Vallotton MB, Lang U. Obesity is associated with impaired ventricular protein kinase C-MAP kinase signaling and altered ANP mRNA Expression in the heart of adult Zucker rats. *J Investig Med*. 2001;49:310-318.
12. Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides. *Circulation*. 2005;112:2163-2168.
13. Miyashita K, Itoh H, Tsujimoto H, et al. Natriuretic peptides/cGMP/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes*. 2009;58:2880-2892.
14. Plante E, Menaouar A, Danalache BA, Broderick TL, Jankowski M, Gutkowska J. Treatment with brain natriuretic peptide prevents the development of cardiac dysfunction in obese diabetic db/db mice. *Diabetologia*. 2014;57:1257-1267.
15. Coué M, Badin P-M, Vila IK, et al. Defective natriuretic peptide receptor signaling in skeletal muscle links obesity to type 2 diabetes. *Diabetes*. 2015;64:4033-4045.
16. Musani SK, Vasan RS, Bidulescu A, et al. Aldosterone, C-reactive protein, and plasma B-type natriuretic peptide are associated with the development of metabolic syndrome and longitudinal changes in metabolic syndrome components: findings from the Jackson Heart Study. *Diabetes Care*. 2013;36:3084-3092.
17. Lazo M, Young JH, Brancati FL, et al. NH2-terminal pro-brain natriuretic peptide and risk of diabetes. *Diabetes*. 2013;62:3189-3193.
18. Everett BM, Cook NR, Chasman DI, et al. Prospective evaluation of B-type natriuretic peptide concentrations and the risk of type 2 diabetes in women. *Clin Chem*. 2013;59:557-565.
19. Brutsaert EF, Biggs ML, Delaney JA, et al. Longitudinal assessment of N-terminal pro-B-type natriuretic peptide and risk of diabetes in older adults: the cardiovascular health study. *Metabolism*. 2016;65:1489-1497.
20. Sanchez OA, Duprez DA, Bahrami H, et al. Changes in N-terminal pro-B-type natriuretic peptide and incidence of diabetes: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Metab*. 2015;41:378-386.
21. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. *Am J Epidemiol*. 1989;129:687-702.
22. Parrinello CM, Grams ME, Couper D, et al. Recalibration of blood analytes over 25 years in the atherosclerosis risk in communities study: impact of recalibration on chronic kidney disease prevalence and incidence. *Clin Chem*. 2015;61:938-947.
23. SengenÈS C, Berlan M, De Glisezinski I, Lafontan MAX, Galitzky J. Natriuretic peptides: a new lipolytic pathway in human adipocytes. *FASEB J*. 2000;14:1345-1351.
24. Bordicchia M, Liu D, Amri E-Z, et al. Cardiac natriuretic peptides act via p38 MAPK to induce the brown fat thermogenic program in mouse and human adipocytes. *J Clin Invest*. 2012;122:1022-1036.
25. Birkenfeld AL, Boschmann M, Moro C, et al. Lipid mobilization with physiological atrial natriuretic peptide concentrations in humans. *J Clin Endocrinol Metab*. 2005;90:3622-3628.
26. Santhekadur PK, Kumar DP, Seneshaw M, Mirshahi F, Sanyal AJ. The multifaceted role of natriuretic peptides in metabolic syndrome. *Biomed Pharmacother*. 2017;92:826-835.
27. Moro C. Targeting cardiac natriuretic peptides in the therapy of diabetes and obesity. *Expert Opin Ther Targets*. 2016;20:1445-1452.
28. Vila G, Grimm G, Resl M, et al. B-type natriuretic peptide modulates ghrelin, hunger, and satiety in healthy men. *Diabetes*. 2012;61:2592-2596.
29. Bruno G, Barutta F, Landi A, et al. Levels of N-terminal pro brain natriuretic peptide are enhanced in people with the uncomplicated metabolic syndrome: a case-cohort analysis of the population-based Casale Monferrato study. *Diabetes Metab Res Rev*. 2015;31:360-367.
30. Magnusson M, Jujic A, Hedblad B, et al. Low plasma level of atrial natriuretic peptide predicts development of diabetes: the prospective Malmo Diet and Cancer study. *J Clin Endocrinol Metab* 2012;97:638-645.
31. Apple FS, Panteghini M, Ravkilde J, et al. Quality specifications for B-type natriuretic peptide assays. *Clin Chem*. 2020;51:486-493.
32. de Lemos JA, McGuire DK, Drazner MH. B-type natriuretic peptide in cardiovascular disease. *Lancet*. 2003;362:316-322.
33. Wu AHB, Smith A, Wieczorek S, et al. Biological variation for N-terminal pro- and B-type natriuretic peptides and implications for therapeutic monitoring of patients with congestive heart failure. *Am J Cardiol*. 2003;92:628-631.
34. Huang F-Y, Wang H, Huang B-T, et al. The influence of body composition on the N-terminal pro-B-type natriuretic peptide level and its prognostic performance in patients with acute coronary syndrome: a cohort study. *Cardiovasc Diabetol*. 2016;15:58. doi:10.1186/s12933-016-0370-0

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

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