

NH₂-Terminal Pro–Brain Natriuretic Peptide and Risk of Diabetes

Mariana Lazo,^{1,2} J. Hunter Young,¹ Frederick L. Brancati,^{1,2†} Josef Coresh,² Seamus Whelton,² Chiadi E. Ndumele,² Ron Hoogeveen,³ Christie M. Ballantyne,³ and Elizabeth Selvin^{1,2}

Brain natriuretic peptide (BNP) has an established role in cardiovascular disease (CVD). However, recent animal studies suggest direct metabolic effects of BNP. To determine the association of BNP with the risk of diabetes, we conducted a prospective analysis of participants from the Atherosclerosis Risk in Communities (ARIC) study. We included 7,822 men and women without history of diabetes, CVD, or reduced kidney function at baseline. At baseline, NH₂-terminal (NT)-proBNP, a cleavage product of BNP, was inversely associated with adiposity, fasting glucose, insulin, and cholesterol but positively associated with blood pressure and C-reactive protein levels. During a median follow-up of 12 years, 1,740 participants reported a new diagnosis of diabetes or medication use for diabetes. Baseline quartiles of NT-proBNP were inversely associated with diabetes risk, even after multivariable adjustment including fasting glucose. The adjusted HRs for diabetes were 1.0 (reference), 0.84 (95% CI 0.74–0.96), 0.79 (95% CI 0.68–0.90), and 0.75 (95% CI 0.64–0.87) for the 1st, 2nd, 3rd, and 4th quartiles of baseline NT-proBNP, respectively (*P* for trend <0.001). This inverse association was robust across sex, race, and obesity subgroups. Our results extend animal studies and support a direct and important metabolic role of BNP in humans. *Diabetes* 62:3189–3193, 2013

Brain natriuretic peptide (BNP), one of the three natriuretic peptides released by the heart in response to hemodynamic stress, has an established role in cardiovascular (vasodilation) and renal (natriuresis) physiology, in which it confers protection against fluid overload and hypertension (1). It is widely accepted that BNP is closely associated with left ventricular mass and accurately detects heart failure (2). In the general population, elevated levels of BNP are associated with an increased risk of mortality and cardiovascular disease (CVD), especially heart failure (3,4).

More recently, it has been postulated that the effects of natriuretic peptides extend beyond the cardiovascular system and that they may play a role in metabolic regulation, lipolysis, and the development of insulin resistance (5–7). Receptors for natriuretic peptides have been found in cells of tissues other than the classical cardiovascular and renal

systems, including adipose tissue (8). In an experiment conducted by Miyashita et al. (6), BNP transgenic mice and wild-type controls were exposed to a high-fat and isocaloric diet; compared with the control mice, the BNP transgenic mice exhibited less weight gain, less ectopic fat accumulation, and less insulin resistance. Further experiments shed some light into some potential mechanisms involved in the protection of these transgenic mice: increased oxygen utilization, increased mitochondrial content in skeletal muscle, and increased gene expression of genes involved in fat oxidation and energy expenditure (peroxisome proliferator-activated receptor- γ coactivator [PGC]-1 α). Another animal study, by Bordicchia et al. (9), extended these findings by demonstrating that treating mice with BNP show increased energy expenditure and increased thermogenic activation in brown and white adipose tissue. All together, these studies suggest that BNP exert direct effects on mitochondrial and adipose tissue that can lead to increased glucose utilization and a decrease in adiposity.

Cross-sectional studies have shown low levels of BNP among persons who are overweight or obese (10–13) and, in some studies, lower BNP among adults with diabetes or the metabolic syndrome (11,12). To our knowledge, the independent association between BNP levels and risk of diabetes has been addressed by two small studies in Europe, with inconsistent results (14,15).

The objective of this study was to determine the independent association between BNP levels and risk of diabetes in a community-based population without diabetes or CVD at baseline. We hypothesized that elevated levels of NH₂-terminal (NT)-proBNP, a stable cleavage product of BNP, would be associated with decreased risk of diabetes.

RESEARCH DESIGN AND METHODS

The Atherosclerosis Risk in Communities (ARIC) study is an ongoing community-based, predominantly biracial cohort of 15,792 middle-aged adults from four U.S. communities: Forsyth County, North Carolina; Jackson, Mississippi; Minneapolis, Minnesota; and Washington County, Maryland (16). The first examination of participants took place from 1987 to 1989, with three follow-up visits taking place, each approximately 3 years apart, and a fifth visit currently taking place (2011–2013). The fourth visit (during 1996–1998) was attended by 11,656 and is the baseline for the current study. We excluded participants with race/ethnicity other than black or white (*n* = 31); persons with a history of diabetes (*n* = 1,362), coronary heart disease, or heart failure (*n* = 1,120); persons with reduced kidney function (estimated glomerular filtration rate <60 mL/min/1.73 m²) (*n* = 623); and persons with missing data (*n* = 555) or without an 8 h fasting sample (*n* = 143). The final sample size was 7,822 adults.

All participants signed written informed consent. The institutional review boards at each clinical site approved the study.

Measurement of NT-proBNP. NT-proBNP was measured in plasma samples collected from participants during visit 4 and stored at –70°C using an electrochemiluminescent immunoassay on an automated Cobas e411 analyzer (Roche Diagnostics) with a lower limit of detection \leq 5 pg/mL and coefficient of variation 3.5–4.7%. Studies have demonstrated that NT-proBNP is a good and more stable marker of BNP, with long-term stability (17).

From the ¹Division of General Internal Medicine, Department of Medicine, Johns Hopkins School of Medicine, Johns Hopkins University, Baltimore, Maryland; the ²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland; and the ³Section of Atherosclerosis and Vascular Medicine, Department of Medicine, Baylor College of Medicine, Houston, Texas.

Corresponding author: Mariana Lazo, mlazoel1@jhmi.edu.

Received 24 March 2013 and accepted 29 May 2013.

DOI: 10.2337/db13-0478

This article contains Supplementary Data online at <http://diabetes.diabetesjournals.org/lookup/suppl/doi:10.2337/db13-0478/-DC1>.

†Deceased.

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

Assessment of diabetes. Incident diabetes was defined as a self-reported physician diagnosis of diabetes or use of medications for diabetes identified during the annual telephone calls to all participants beginning after visit 4 (1996–1998) with follow-up through April 2011.

Other measurements. Smoking history, alcohol consumption (never, former, and current drinker and usual ethanol intake [g/week] among current drinkers), medical history, medication use, and family history of diabetes were assessed during a home interview and according to a published protocol (18). We defined history of CVD as self-reported myocardial infarction or stroke before visit 1 or silent myocardial infarction (diagnosed by electrocardiographic changes), adjudicated myocardial infarction, or revascularization (at or before visit 4) and adjudicated hospitalization for congestive heart failure (at or before visit 4). Using standardized methods, height, weight, waist circumference, and blood pressure were measured. Fasting blood samples were obtained, and using standard methods the following assays were performed: serum glucose, insulin, cholesterol (total, LDL, and HDL cholesterol), triglycerides, creatinine, high-sensitivity (hs)-C-reactive protein (hs-CRP), plasma lactate, and hematoctrit (19). Cardiac troponin T (cTnT) was measured using a novel high-sensitivity assay, Elecsys Troponin T (Roche Diagnostics, Indianapolis, IN) with a lower limit of detection of 3.0 ng/L.

Statistical methods. Baseline levels of NT-proBNP were categorized into quartiles. Baseline characteristics of the study population were summarized across quartiles of NT-proBNP. Participants with NT-proBNP below the limit of detection ($n = 248$ [3.2%]) were assigned a value of 2.5 pg/mL. We used the Kaplan-Meier method to show the differences in the overall risk (cumulative incidence) of diabetes by baseline quartiles of NT-proBNP. Adjusted hazard ratios (HRs) and CIs were estimated using Cox proportional hazards model.

We implemented four core models. Model 1 included age, race/center, sex, and education. Model 2 included all variables in model 1 plus BMI (linear spline with a knot at 30 kg/m²). Model 3 included all variables in model 2 plus height (in meters) squared, systolic and diastolic blood pressure, and hs-CRP. Model 4 included all variables in model 3 plus fasting glucose and family history of diabetes. We tested for interactions with race, sex, and obesity status.

We conducted sensitivity analyses excluding 1) persons with elevated hs-cTnT (defined as levels >99th percentile value [14 ng/L] in a healthy sub-population ages 20–70 years [19]) or 2) participants with impaired fasting glucose or undiagnosed diabetes (fasting glucose ≥ 100 mg/dL) at baseline. We also conducted competing risk regression analyses to examine the possible effect of competing mortality on our results (20).

To characterize the shape of the association of NT-proBNP with incident diabetes in our adjusted Cox regression model, we implemented a piecewise linear spline model, with knots at the 33rd and 66th percentiles. In this model, we truncated the data at percentile 99th, and the HR at the 10th percentile of NT-proBNP was used as the reference.

RESULTS

Baseline characteristics of the study population are shown in Table 1. Participants in the lowest quartile of NT-proBNP at baseline were younger; less likely to be white, female, or current smokers; and were more likely to have an adverse lipid profile, higher BMI and waist circumference, and higher levels of fasting glucose, insulin, and

TABLE 1
Characteristics of the study population* according to quartiles of NT-proBNP at baseline

	Quartile 1 (<31 pg/mL)	Quartile 2 (31.1–61.8 pg/mL)	Quartile 3 (61.9–114.4 pg/mL)	Quartile 4 (>114.4 pg/mL)	P for linear trend†
<i>n</i>	1,953	1,952	1,957	1,960	
Age (years)	60.4 (5.0)	61.6 (5.3)	62.7 (5.4)	64.0 (5.7)	<0.001
Female, %	38.8	56.2	67.8	73.5	<0.001
White, %	67.5	79.8	83.8	87.2	<0.001
Current smoker, %	13.8	15.4	13.0	16.3	0.006
LDL cholesterol (mg/dL)	128.5 (34.4)	125.9 (32.8)	121.6 (31.3)	118.2 (32.3)	<0.001
HDL cholesterol (mg/dL)	47.5 (14.6)	50.5 (15.9)	53.9 (17.0)	55.4 (17.7)	<0.001
Triglycerides >150 mg/dL, %	32.7	32.6	27.7	29.4	0.001
BMI (kg/m ²)	29.3 (5.0)	28.6 (5.5)	28.1 (5.5)	27.6 (5.7)	<0.001
>30 kg/m ² , %	37.6	32.3	29.7	27.4	<0.001
≤20 kg/m ² , %	0.6	1.7	2.8	4.6	<0.001
Weight (kg)	177.8 (31.3)	169.8 (35.7)	163.6 (33.1)	160.6 (35.3)	<0.001
Height (m)	1.70 (0.09)	1.68 (0.09)	1.66 (0.09)	1.65 (0.08)	<0.001
Waist (cm)	96.7 (11.4)	95.0 (13.0)	93.5 (13.3)	92.8 (13.9)	<0.001
High waist circumference‡	62.7	64.5	63.5	61.8	0.42
Waist-to-hip ratio	0.96 (0.06)	0.94 (0.07)	0.93 (0.08)	0.92 (0.08)	<0.001
Fasting glucose (mg/dL)	101 (95–109)	99 (94–107)	97 (92–104)	96 (90–103)	<0.001
Family history of diabetes, %	22.1	23.8	21.9	19.7	0.02
Impaired fasting glucose, %§	50.5	39.8	35.3	31.7	<0.001
Insulin (ng/mL)					<0.001
Median	11.8	10.1	9.1	8.6	
IQR	(8.4–16.6)	(7.1–14.5)	(6.4–13)	(5.8–12.1)	
Lactate (mg/dL)					<0.001
Median	6.8	6.4	6.3	6.1	
IQR	(5.5–8.7)	(5.2–8.3)	(5.1–7.9)	(5–7.8)	
C-reactive protein (mg/L)					<0.001
Median	2.0	2.1	2.2	2.6	
IQR	(0.95–4.42)	(0.98–4.77)	(1.0–5.0)	(1.1–5.8)	
Hypertension, %	24.6	22.5	26.6	32.7	<0.001
SBP (mmHg)	122.3 (15.3)	123.9 (16.8)	126.9 (18.9)	131.3 (20.6)	<0.001
DBP (mmHg)	72.4 (9.4)	71.3 (9.4)	70.8 (10.1)	71.0 (10.9)	<0.001
Elevated hs-cTnT, %	4.1	3.8	5.1	6.8	<0.001
Hematocrit (%)	41.7 (3.3)	40.6 (3.2)	39.6 (3.3)	38.8 (3.4)	<0.001

Data are means (SD) unless otherwise indicated. DBP, diastolic blood pressure; IQR, interquartile range; SBP, systolic blood pressure. * $n = 7,822$ participants of the ARIC study without a history of diabetes, coronary heart disease, congestive heart failure, or kidney disease. †Linear test using quartile numbers. ‡Waist circumference >102 or 88 cm for men and women, respectively. §Fasting plasma glucose 100–125 mg/dL. ||Among noncurrent smokers.

Downloaded from http://diabetesjournals.org/ at 189/57/2046/3189.pdf by guest on 07 October 2024

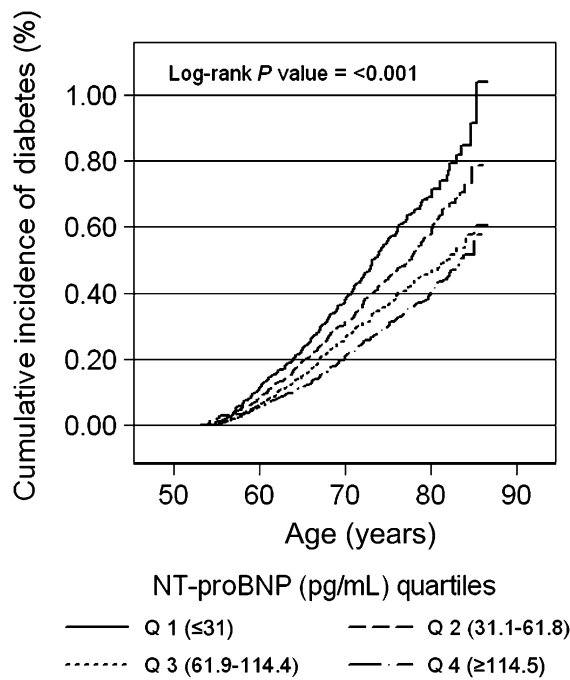


FIG. 1. Cumulative incidence (%) of diagnosed diabetes by quartiles (Q) of NT-proBNP at baseline.

lactate compared with participants in the highest quartile of NT-proBNP. In contrast, participants in the lowest quartile of NT-proBNP had lower levels of hs-CRP and systolic blood pressure and lower prevalence of hypertension and lower prevalence of elevated troponin compared with participants in the upper quartile.

During a median follow-up for 12 years, there were 1,740 new cases of self-reported diabetes among the 7,822 persons in the study population at baseline. The cumulative incidence of diabetes by quartile of baseline NT-proBNP is shown in Fig. 1. The unadjusted incidence rates are shown in Supplementary Table 1.

Persons in the lowest quartile of NT-proBNP had a significantly higher risk of diabetes compared with persons in the upper quartiles, even after multivariable adjustment (Table 2). In model 1, the adjusted HRs of diabetes were 1.0 (reference), 0.88 (95% CI 0.77–0.99), 0.76 (95% CI 0.66–0.87), and 0.67 (95% CI 0.58–0.78) for the 1st, 2nd, 3rd, and 4th quartile, respectively (P value for trend < 0.001). After additional adjustment for BMI and cardiovascular risk factors, the associations were attenuated but remained statistically significant. The risk

of diabetes remained significantly lower in all three upper quartiles compared with the first quartile of NT-proBNP even after further adjustment for baseline fasting glucose (model 4).

Consistent with the results from the models of NT-proBNP in quartiles, our spline model showed a threshold effect with the steepest and significant decline in diabetes risk at the NT-proBNP levels 14.7–24.9 pg/mL (P value = 0.02), with a shallower and nonsignificant slope at higher levels of NT-proBNP. Indeed, the slope was strongly significant (P value > 0.05) (Fig. 2).

We did not observe any significant interactions by sex, race or obesity (Table 3).

In sensitivity analyses, excluding 438 ARIC participants with undiagnosed diabetes or impaired fasting glucose at baseline, the results were very similar or even strengthened, with HRs for diabetes of 1.0 (reference), 0.88 (95% CI 0.76–1.02), 0.80 (95% CI 0.69–0.94), and 0.71 (95% CI 0.60–0.84) for those in the 1st, 2nd, 3rd, and 4th quartile, respectively. Similarly, after exclusion of 386 participants with elevated hs-cTnT, the results were not appreciably altered (Supplementary Table 2). Finally, with use of competing risk models the inverse association of NT-proBNP with diabetes was strengthened. After accounting for competing mortality in model 4 was accounted for, the HRs (95% CIs) for diabetes in the 1st, 2nd, 3rd, and 4th quartile were 1.0 (reference), 0.81 (0.71–0.93), 0.67 (0.57–0.79), and 0.61 (0.52–0.72), respectively.

DISCUSSION

Our findings show that in a community-based population without diabetes, CVD (coronary heart disease or congestive heart failure), or reduced renal function at baseline, higher levels of NT-proBNP were associated with a significantly decreased risk of diabetes, even after adjustment for traditional risk factors and fasting glucose. Our results were consistent across race, sex, and BMI categories. Furthermore, the association remained significant after exclusion of people with impaired fasting glucose at baseline. These results are consistent with limited animal and in vivo studies that suggest circulating levels of BNP levels are metabolically active.

The mechanisms by which BNP and related peptides may influence adipose and glucose metabolism are not well understood. Studies conducted thus far have demonstrated direct effects of BNP on muscle and adipose tissue that could, at least in part, influence the development of insulin resistance. Miyashita et al. (6) showed that BNP transgenic mice with overexpression of BNP had decreased risk of obesity and insulin resistance after

TABLE 2
Adjusted HRs (95% CI) of incident diagnosed diabetes by quartiles of NT-proBNP at baseline

	Quartile 1 (< 31 pg/mL)	Quartile 2 (31.1–61.8 pg/mL)	Quartile 3 (61.9–114.4 pg/mL)	Quartile 4 (> 114.4 pg/mL)	P for linear trend*
n	1,953	1,952	1,957	1,960	
Model 1†	1.0 (Reference)	0.88 (0.77–0.99)¶	0.76 (0.66–0.87)¶	0.67 (0.58–0.78)¶	< 0.001
Model 2‡	1.0 (Reference)	0.92 (0.81–1.04)	0.83 (0.72–0.95)¶	0.76 (0.66–0.88)¶	< 0.001
Model 3§	1.0 (Reference)	0.88 (0.78–1.00)¶	0.76 (0.67–0.88)¶	0.65 (0.56–0.76)¶	< 0.001
Model 4	1.0 (Reference)	0.84 (0.74–0.96)¶	0.79 (0.68–0.90)¶	0.75 (0.64–0.87)¶	< 0.001

*Linear test using quartile numbers. †Model 1: age, sex, race/ARIC center, education. ‡Model 2: model 1 plus BMI (linear spline with a knot at 30 kg/m²). §Model 3: model 2 plus height² plus systolic blood pressure, diastolic blood pressure, smoking, LDL and HDL cholesterol, and hs-CRP. ||Model 4: model 3 plus fasting glucose and family history of diabetes. ¶Statistically significant, $P < 0.05$.

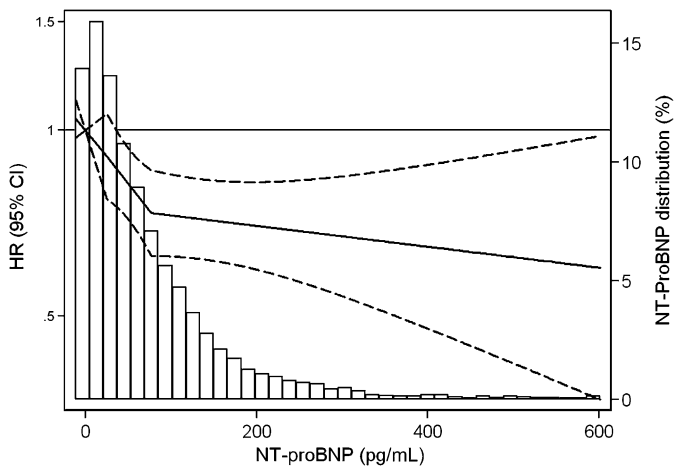


FIG. 2. Adjusted* HR (95% CI) of incident diagnosed diabetes by baseline NT-proBNP level overlaid on the distribution (frequency histogram) of NT-proBNP in the study population. HRs are presented using a logarithmic scale. Linear spline centered at 14.7 (10th percentile), with knots at the 33rd and 66th percentiles (24.9 and 76.2, respectively), after excluding values ≥ 99 percentile (NT-proBNP ≥ 611 pg/mL). *Adjusted for weight, height, age, race/center, sex, systolic blood pressure, diastolic blood pressure, smoking, LDL cholesterol, HDL cholesterol, C-reactive protein, fasting glucose, and family history of diabetes.

receiving a high-fat diet and increased muscle mitochondrial content and fat oxidation. The authors suggest that the cellular effects of BNP emulate the effects observed through catecholamines and include binding to the natriuretic peptide receptor (NPR)-A in adipocytes, activation of the cGMP cascade, and downstream activation of cGMP-dependent protein kinase and p38MAPK, which results in increased mitochondrial biogenesis and uncoupled respiration. More recently, Bordicchia et al. demonstrated in a series of animal and in vivo experiments that natriuretic peptides (BNP and atrial natriuretic peptide [ANP]) activate “brown adipose tissue-like” mechanisms involved with thermogenesis but in white adipose tissue (9,21). In an experimental study in humans, Heinisch et al. (5) intravenously administered BNP or placebo to 20 healthy volunteers and performed an intravenous glucose tolerance test. Their results showed that after infusion of

BNP, there were reduced levels of circulating glucose but no effect on insulin secretion or sensitivity.

To our knowledge, little work has been done examining the interrelationship between cardiovascular and non-cardiovascular effects of BNP as they pertain to the etiology or development of insulin resistance. In our study, participants in the lowest quartile of NT-proBNP had higher levels of lactate compared with participants in the highest quartile of NT-proBNP, suggesting that blood flow and oxygen delivery may play into the development of insulin resistance. Future studies should be conducted to test this hypothesis.

Most previous epidemiological studies of NT-proBNP and diabetes were cross-sectional and focused on potential mechanisms for the “natriuretic handicap,” which refers to the reduced levels of BNP seen in people with obesity, which in turn could lead to an increased susceptibility for hypertension and heart failure (10,22). It has been postulated that there is increased clearance of BNP by the NPR-C in adipose tissue. However, recent studies have shown that NT-proBNP is cleared by kidney elimination and not by binding to the clearance receptor (NPR-C) (8). Nonetheless, our results were consistent after excluding persons with reduced kidney function and among persons with normal BMI.

To our knowledge, data examining the prospective association between natriuretic peptides and diabetes risk in humans are limited. In Sweden, using data from the Malmo Diet and Cancer study, investigators examined the association between ANP and NT-proBNP and incident diabetes in a sample of 1,828 adults (301 cases of diabetes). The authors found a significant and inverse association between ANP and the risk of diabetes and an inverse but not statistically significant association between NT-proBNP and diabetes risk (odds ratio 0.95 [95% CI 0.84–1.08] comparing the 4th quartile of NT-proBNP to the 1st quartile) (14). In a study using data from the FINRISK97 study ($n = 7,827$) with 417 cases of incident diabetes, there was a significant inverse association between BNP and diabetes (23). In a case-cohort study with 440 case and 740 control subjects drawn from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk Study, there was a significant inverse association between NT-proBNP and diabetes risk (HR 0.82 [95% CI 0.69–0.97] per 1-SD increase in NT-proBNP) (15). Finally, Pfister et al. (15) combined the results of the EPIC-Norfolk Study with

TABLE 3
Adjusted* HRs (95% CI) of incident diagnosed diabetes by quartiles of NT-proBNP at baseline in population subgroups

	Quartile 1 (<31 pg/mL)	Quartile 2 (31.1–61.8 pg/mL)	Quartile 3 (61.9–114.4 pg/mL)	Quartile 4 (>114.4 pg/mL)	<i>P</i> for linear trend†	<i>P</i> for interaction
Race						
Black ($n = 1,598$)	1.0 (Reference)	0.89 (0.71–1.12)	0.80 (0.61–1.03)	0.71 (0.52–0.97)‡	0.02	0.87
White ($n = 6,224$)	1.0 (Reference)	0.81 (0.69–0.95)‡	0.78 (0.66–0.92)‡	0.75 (0.62–0.89)‡	0.002	
Sex						
Men ($n = 3,201$)	1.0 (Reference)	0.82 (0.68–0.99)‡	0.87 (0.71–1.09)	0.82 (0.63–1.06)	0.11	0.55
Women ($n = 4,621$)	1.0 (Reference)	0.84 (0.71–1.01)	0.72 (0.60–0.87)‡	0.69 (0.56–0.84)‡	<0.001	
Age (years)						
<62 ($n = 3,846$)	1.0 (Reference)	0.82 (0.69–0.98)‡	0.82 (0.67–0.99)‡	0.63 (0.49–0.79)‡	<0.001	0.28
≥ 62 ($n = 3,976$)	1.0 (Reference)	0.83 (0.68–1.00)‡	0.74 (0.60–0.91)‡	0.82 (0.66–1.01)	0.05	
Obesity (kg/m^2)						
<30 ($n = 5,340$)	1.0 (Reference)	0.94 (0.79–1.14)	0.82 (0.67–1.00)‡	0.80 (0.64–0.99)‡	0.02	0.52
≥ 30 ($n = 2,482$)	1.0 (Reference)	0.76 (0.63–0.91)‡	0.76 (0.63–0.92)‡	0.69 (0.56–0.86)‡	0.02	

*Adjusted for age, sex, race, ARIC center, education, BMI, height², systolic blood pressure, diastolic blood pressure, smoking, LDL and HDL cholesterol, hs-CRP, fasting glucose, and family history of diabetes. †Linear test using quartiles numbers. ‡ $P < 0.05$.

small case-control studies with genotype information and demonstrated that a common genetic variant (rs198389) within the genome region that encodes BNP was associated with a reduced risk of type 2 diabetes.

Our study has some limitations that should be considered in the interpretation of these results. We only had information on new cases of diabetes defined by self-reported diagnosis or diabetes medication use, which is a highly specific definition of diabetes but has relatively low sensitivity (24). We also had only single measurements of NT-proBNP at baseline, and it has been found that all natriuretic peptides have relatively high intraindividual variation (17). This introduces random error to the classification of participants and most likely biased the results toward the null. As with any observational study, the possibility of residual confounding cannot be completely eliminated. Although we had information on fasting glucose and the results were consistent after adjustment for it, we lacked information on oral glucose tolerance test, and therefore it is not possible to test whether NT-proBNP predicts diabetes independently of 2-h oral glucose tolerance test. Our study also has a number of important strengths including the prospective design, long-term follow-up (median of 12 years), large biracial community-based sample with a large number of cases of diabetes occurring during the follow-up ($N = 1,740$), and rigorous measurements of known risk factors for diabetes using standardized protocols.

In conclusion, our results suggest that persons with very low levels of BNP have a significantly higher risk of developing diabetes compared with persons with moderately high levels of NT-proBNP in a general population. These results provide additional evidence of a novel role for natriuretic peptides in metabolic disorders. Given the availability of recombinant human BNP (25,26), more studies are needed to determine their usefulness in prevention of the development of diabetes.

ACKNOWLEDGMENTS

The Atherosclerosis Risk in Communities study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C. F.L.B. and R.H. received grant support from the National Institutes of Health.

Roche Diagnostics provided reagents and loan of an instrument to conduct the NT-proBNP assays. F.L.B. and R.H. received grant support from Roche Diagnostics. No other potential conflicts of interest relevant to this article were reported.

Roche Diagnostics had no role in the study design, analysis, or presentation preparation.

M.L. developed the research question, analyzed the data, and wrote the manuscript. J.H.Y., F.L.B., J.C., S.W., and C.E.N. reviewed and edited the manuscript. R.H. and C.M.B. collected data and reviewed and edited the manuscript. E.S. refined the research question and study design, collected data, and reviewed and edited the manuscript. M.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Parts of this study were presented in abstract form at the 72nd Scientific Sessions of the American Diabetes Association, Philadelphia, Pennsylvania, 8–12 June 2012.

The authors thank the staff and participants of the ARIC study for their important contributions.

REFERENCES

- Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339:321–328
- Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008;358:2148–2159
- de Lemos JA, Lloyd-Jones DM. Multiple biomarker panels for cardiovascular risk assessment. *N Engl J Med* 2008;358:2172–2174
- Kragelund C, Grønning B, Køber L, Hildebrandt P, Steffensen R. N-terminal pro-B-type natriuretic peptide and long-term mortality in stable coronary heart disease. *N Engl J Med* 2005;352:666–675
- Heinisch BB, Vila G, Resl M, et al. B-type natriuretic peptide (BNP) affects the initial response to intravenous glucose: a randomised placebo-controlled cross-over study in healthy men. *Diabetologia* 2012;55:1400–1405
- Miyashita K, Itoh H, Tsujimoto H, et al. Natriuretic peptides/cGMP-dependent protein kinase cascades promote muscle mitochondrial biogenesis and prevent obesity. *Diabetes* 2009;58:2880–2892
- Wang TJ. The natriuretic peptides and fat metabolism. *N Engl J Med* 2012;367:377–378
- Sarzani R, Dessi-Fulgheri P, Paci VM, Espinosa E, Rappelli A. Expression of natriuretic peptide receptors in human adipose and other tissues. *J Endocrinol Invest* 1996;19:581–585
- Bordicchia M, Liu D, Amri EZ, 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
- Das SR, Drazner MH, Dries DL, et al. Impact of body mass and body composition on circulating levels of natriuretic peptides: results from the Dallas Heart Study. *Circulation* 2005;112:2163–2168
- Khan AM, Cheng S, Magnusson M, et al. Cardiac natriuretic peptides, obesity, and insulin resistance: evidence from two community-based studies. *J Clin Endocrinol Metab* 2011;96:3242–3249
- Wang TJ, Larson MG, Keyes MJ, Levy D, Benjamin EJ, Vasan RS. Association of plasma natriuretic peptide levels with metabolic risk factors in ambulatory individuals. *Circulation* 2007;115:1345–1353
- Wang TJ, Larson MG, Levy D, et al. Impact of obesity on plasma natriuretic peptide levels. *Circulation* 2004;109:594–600
- Magnusson M, Jujic A, Hedblad B, et al. Low plasma level of atrial natriuretic peptide predicts development of diabetes: the prospective Malmö Diet and Cancer study. *J Clin Endocrinol Metab* 2012;97:638–645
- Pfister R, Sharp S, Luben R, et al. Mendelian randomization study of B-type natriuretic peptide and type 2 diabetes: evidence of causal association from population studies. *PLoS Med* 2011;8:e1001112
- The ARIC investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol* 1989;129:687–702
- Apple FS, Panteghini M, Ravkilde J, et al.; Committee on Standardization of Markers of Cardiac Damage of the IFCC. Quality specifications for B-type natriuretic peptide assays. *Clin Chem* 2005;51:486–493
- ARIC Study protocol. *Manual 1: General Description and Study Management Visit 4*. Chapel Hill, ARIC, 1997 (Version 3.0)
- ARIC Study protocol. *Manual 7: Blood Collection and Processing*. Chapel Hill, ARIC, 1993 (Version 3.0)
- Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509
- Whittle AJ, Vidal-Puig A. NPs—heart hormones that regulate brown fat? *J Clin Invest* 2012;122:804–807
- Bayes-Genis A, DeFilippi C, Januzzi JL Jr. Understanding amino-terminal pro-B-type natriuretic peptide in obesity. *Am J Cardiol* 2008;101:89–94
- Salomaa V, Havulinna A, Saarela O, et al. Thirty-one novel biomarkers as predictors for clinically incident diabetes. *PLoS ONE* 2010;5:e10100
- Schneider AL, Pankow JS, Heiss G, Selvin E. Validity and reliability of self-reported diabetes in the atherosclerosis risk in communities study. *Am J Epidemiol* 2012;176:738–743
- Cataliotti A, Schirger JA, Martin FL, et al. Oral human natriuretic peptide activates cyclic guanosine 3',5'-monophosphate and decreases mean arterial pressure. *Circulation* 2005;112:836–840
- Rubattu S, Sciarretta S, Valenti V, Stanzione R, Volpe M. Natriuretic peptides: an update on bioactivity, potential therapeutic use, and implication in cardiovascular diseases. *Am J Hypertens* 2008;21:733–741