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Cardiac Natriuretic Peptides, Obesity, and Insulin Resistance: Evidence from Two Community-Based Studies

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Background: The natriuretic peptides play an important role in salt homeostasis and blood pressure regulation. It has been suggested that obesity promotes a relative natriuretic peptide deficiency, but this has been a variable finding in prior studies and the cause is unknown.

Aim: The aim of this study was to examine the association between obesity and natriuretic peptide levels and evaluate the role of hyperinsulinemia and testosterone as mediators of this interaction.

Methods: We studied 7770 individuals from the Framingham Heart Study (n = 3833, 54% women) and the Malmö Diet and Cancer study (n = 3918, 60% women). We examined the relation of plasma N-terminal pro-B-type natriuretic peptide levels (N-BNP) with obesity, insulin resistance, and various metabolic subtypes.

Results: Obesity was associated with 6–20% lower levels of N-BNP ($P < 0.001$ in Framingham, $P = 0.001$ in Malmö), whereas insulin resistance was associated with 10–30% lower levels of N-BNP ($P < 0.001$ in both cohorts). Individuals with obesity who were insulin sensitive had only modest reductions in N-BNP compared with nonobese, insulin-sensitive individuals. On the other hand, individuals who were nonobese but insulin resistant had 26% lower N-BNP in Framingham ($P < 0.001$) and 10% lower N-BNP in Malmö ($P < 0.001$), compared with nonobese and insulin-sensitive individuals. Adjustment for serum-free testosterone did not alter these associations.

Conclusions: In both nonobese and obese individuals, insulin resistance is associated with lower natriuretic peptide levels. The relative natriuretic peptide deficiency seen in obesity could be partly attributable to insulin resistance, and could be one mechanism by which insulin resistance promotes hypertension. (*J Clin Endocrinol Metab* 96: 0000–0000, 2011)

The natriuretic peptides (NP) are secreted from cardiomyocytes in response to cardiac wall stress (1) and play an important role in the regulation of blood pressure, intravascular volume, and cardiac remodeling (1, 2). Genetically engineered mice with a deficiency in atrial natriuretic peptide, B-type natriuretic peptide (BNP), or the natriuretic peptide receptor are prone to hypertension, left ventricular hypertrophy, and premature death (2–5). Similarly, common genetic variants associated with decreased NP levels in humans are associated with higher blood pressure (6).

Obesity may also predispose to relative NP deficiency. Several studies have reported that obese individuals have lower circulating NP levels than lean individuals (7–14), and it has been hypothesized that NP deficiency contributes to the susceptibility of obese individuals to hypertension (15). Nonetheless, not all studies have shown an inverse relationship between body mass index (BMI) and NP levels (16–18), and if such a link does exist, there are few data regarding potential mediators. Although adipose tissue expresses NP clearance receptors, levels of N-terminal pro-BNP (N-BNP), which is not cleared by this receptor, are lower in obesity, arguing against enhanced clearance being the sole cause. Testosterone may play a role because testosterone levels vary with body size and body composition as well as insulin sensitivity in men and women, and experimental data indicate that androgens may inhibit NP synthesis (19, 20). Another proposed contributor is insulin resistance because obesity is strongly associated with hyperinsulinemia, and insulin may reduce NP (21).

We therefore examined the relations of obesity with NP in two large, community-based cohorts, comprising more than 7700 individuals. We sought to confirm the association between obesity and reduced NP and to assess the role of two potential mediators: hyperinsulinemia and testosterone.

Subjects and Methods

Study samples

The Framingham Heart Study (FHS) is a community-based study that was established in 1948 (22). Subsequent generations of participants were enrolled in 1971 (Framingham Offspring Study) (23) and in 2002 (Third Generation Study) (24). Third Generation participants who attended the first examination of this cohort were eligible for this investigation. Of the 4095 attendees, participants were excluded if they had missing measures of N-BNP (n = 13), BMI (n = 4), or hypertension medications (n = 2), or had prevalent cardiovascular disease (n = 28), atrial fibrillation (n = 17), glomerular filtration rate <60 ml/min per 1.73 m^2, or diabetes (n = 112). Participants were also excluded if they were not fasting (n = 49) or had missing measures of testosterone (n = 20). Individuals with prevalent diabetes were excluded from the present analysis due to the variability of insulin resistance measures in individuals with diabetes and/or taking medications to treat diabetes. After exclusions, 3833 participants (94%) were eligible for analysis.

The Malmö Diet and Cancer study (MDC) is a population-based study that enrolled 28,449 individuals between 1991 and 1996. The MDC-Cardiovascular Arm comprised a group of 6103 individuals selected randomly from the parent MDC study and who underwent extensive cardiovascular evaluation (25). A total of 5400 of these individuals had plasma collected, of whom 5067 had complete values regarding risk factors (26). Participants were excluded if they had missing measures of N-BNP (n = 934), fasting serum insulin (n = 787) or BMI (n = 7) or had prevalent cardiovascular disease (n = 155), atrial fibrillation (n = 58), glomerular filtration rate less than 60 ml/min per 1.73 m^2 (n = 611), or diabetes (n = 486). After these exclusions, which overlapped to a certain extent, a total of 3918 participants (77%) were eligible for analysis.

Clinical assessment

FHS participants underwent a medical history, standardized physical examination, and laboratory assessment. Height, weight, and waist circumference were measured with the subject standing. Blood pressure was obtained as the mean of two measurements after the subject had been sitting for at least 5 min. MDC participants underwent a standardized medical history with physical examination and laboratory assessment. Blood pressure was obtained after 10 min of rest in the supine position. We calculated BMI as weight in kilograms divided by the square of the height in meters. Obesity was defined as a BMI of 30 kg/m^2 or greater. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater or use of antihypertensive medications. Antihypertensive medication use was defined as the use of angiotensin-receptor blockers, β-blockers, calcium channel blockers, diuretics, or other agents used to lower blood pressure. Diabetes in FHS was defined as a fasting glucose of 126 mg/dl or greater (7.0 mmol/liter) or use of medications for diabetes. Diabetes in MDC was defined as self-report of a physician diagnosis or use of diabetes medication or fasting glucose of 126 mg/dl or greater (7.0 mmol/liter). Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) (27). Participants were considered to have insulin resistance if they had a HOMA-IR measurement in the top quartile (28) of the distribution of HOMA-IR among a healthy sample of individuals identified as free of diabetes in each cohort (FHS and MDC separately). All participants provided written informed consent, and the Institutional Review Board of Boston Medical Center and the Ethical Committee at Lund University (Lund, Sweden) approved the study.

Laboratory assays

In the FHS, venous blood samples were obtained in the morning after an overnight fast and frozen at −80 C. Plasma N-BNP was determined using the commercially available Elecsys proBNP immunoassay (Roche Diagnostics, Indianapolis, IN) on an Elecsys 1010 analyzer using established methods (29). The mean intraassay coefficient of variation was 2.7%. Plasma insulin was measured using an ELISA (Linco Diagnostics, St. Louis, MO); the assay had negligible cross-reactivity with other insulin-related molecules and a mean intraassay coefficient of

variation of 2.7%. Free testosterone was calculated using the law of mass action equation (30, 31) from serum total testosterone measured by liquid chromatography-tandem mass spectrometry, and SHBG concentrations measured by immunofluorometric assay (DELFIA-Wallac, Inc., Turku, Finland).

In MDC, fasting blood samples were obtained and frozen at −80 C immediately after collection. N-BNP levels were determined using the Dimension RxL automated N-BNP method (Siemens Diagnostics, Nurnberg, Germany). The mean intraassay coefficient of variation was 2.7%. Serum insulin was measured using a RIA at the Department of Clinical Chemistry, Malmö University Hospital; the assay had a mean intraassay coefficient of variation of 5%.

Statistical analysis

Continuous variables with skewed distributions, including N-BNP, were logarithmically transformed. Multivariable linear regression was performed to examine the relation of N-BNP (dependent variable) with age, systolic blood pressure, antihypertensive medication use (which is known to influence N-BNP levels), and combinations of the following variables: obesity, insulin resistance, and free testosterone (with testosterone available in FHS only). Both sex-pooled and sex-specific analyses were performed for each cohort (FHS and MDC). In additional analyses, participants were categorized into metabolic subtypes: 1) nonobese and insulin sensitive; 2) obese and insulin sensitive; 3) nonobese and insulin resistant; and 4) obese and insulin resistant. Regression analyses were repeated using generalized linear models to accommodate metabolic subtype, using the nonobese, insulin-sensitive category as the referent. In secondary analyses, regression was repeated with continuous BMI and HOMA-IR. We also repeated the main analyses including estimated glomerular filtration rate as an additional covariate and in the subset of individuals with prevalent hypertension. In FHS, the main analyses were also repeated with additional adjustment for SHBG and after excluding individuals with prevalent thyroid disease as determined by self-report (n = 196).

Analyses were performed in Framingham using SAS version 9.1.3 (SAS Institute, Cary, NC) and in Malmo using SPSS version 16.0 (SPSS). A two-tailed $P < 0.05$ was considered statistically significant.

Results

Characteristics of the study participants are listed in Table 1. The mean age was 40 yr in FHS and 57 yr in MDC. The prevalence of obesity was 22% in FHS and 12% in MDC. In the FHS and MDC samples, the frequency of HOMA-IR greater than 2.6 was 4.8 and 12.5%, respectively; the frequency of HOMA-IR greater than 3.0 was 2.9 and 8.5%, respectively. Base-

TABLE 1. Sample characteristics

	FHS		MDC	
	Men (n = 1771)	**Women (n = 2062)**	**Men (n = 1572)**	**Women (n = 2346)**
Age (yr)	39.9 ± 8.7	39.9 ± 8.8	56.8 ± 5.9	56.6 ± 5.8
BMI (kg/m²)	27.8 ± 4.5	25.8 ± 5.8	25.9 ± 3.3	25.5 ± 4.0
Obesity (BMI ≥30 kg/m²), n (%)	435 (25)	402 (20)	152 (10)	301 (13)
SBP (mm Hg)	120 ± 12	113 ± 14	142 ± 18	139 ± 19
DBP (mm Hg)	78 ± 9	73 ± 9	88 ± 9	85 ± 9
Hypertension, n (%)	349 (20)	230 (11)	1018 (65)	1350 (58)
Antihypertensive medication use, n (%)	149 (8)	132 (6)	189 (12)	326 (14)
Total to HDL cholesterol ratio	4.4 ± 1.5	3.2 ± 1.0	5.2 ± 1.4	4.3 ± 1.3
Fasting glucose (mg/dl)	96.3 ± 8.0	90.2 ± 7.9	5.0 ± 0.4	4.8 ± 0.4
Fasting insulin (mU/liter)	5.0 ± 3.5	4.4 ± 3.1	7.9 ± 5.2	7.0 ± 5.7
HOMA-IR	1.2 ± 0.9	1.0 ± 0.8	1.8 ± 1.2	1.5 ± 1.3
Total testosterone (ng/dl)	653.0 ± 233.8	27.5 ± 16.8	NA	NA
Free testosterone (pg/ml)	128.0 ± 49.3	2.5 ± 1.9	NA	NA
SHBG (nmol/liter)	40.5 ± 20.2	111.1 ± 77.4	NA	NA
Metabolic subtype				
Nonobese and insulin sensitive, n (%)[a]	1162 (66)	1434 (70)	1125 (72)	1644 (70)
Obese and insulin sensitive, n (%)	209 (12)	171 (8)	49 (3)	114 (5)
Nonobese and insulin resistant, n (%)	174 (10)	226 (11)	295 (19)	401 (17)
Obese and insulin resistant, n (%)	226 (13)	231 (11)	103 (7)	187 (8)
N-BNP (ng/liter), median (Q1, Q3)	16.1 (8.0, 28.4)	43.2 (25.8, 72.7)	44.0 (24.0, 81.0)	70.0 (42.0, 122.0)
N-BNP by metabolic subtype (ng/liter), median (Q1, Q3)				
Nonobese and insulin sensitive	17.2 (9.1, 29.9)	47.7 (28.4, 75.3)	45.0 (25.1, 83.0)	73.0 (43.9, 128.7)
Obese and insulin sensitive	16.4 (8.8, 27.2)	46.8 (23.8, 77.3)	41.9 (15.5, 84, 5)	80.6 (50.8, 128.3)
Nonobese and insulin resistant	11.4 (5.4, 22.6)	33.5 (22.3, 55.1)	41.0 (23.0, 78.1)	58.7 (37.0, 99, 2)
Obese and insulin resistant	13.2 (6.1, 25.0)	31.0 (15.8, 57.0)	41.7 (22.0, 76.0)	66.0 (39.0, 107.4)

Values are displayed as means (±SD) or frequency in percent, unless otherwise indicated. SBP, Systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; NA, not available.

[a] Insulin resistance is defined as having HOMA-IR in the upper quartile of the specific derivation sample.

TABLE 2. Association of N-BNP with obesity and insulin resistance

	FHS		MDC	
	Regression coefficient (SE)[a]	*P* value	Regression coefficient (SE)[a]	*P* value
Individual predictors (in separate models)				
Obesity	−0.200 (0.033)	<0.001	−0.062 (0.019)	0.001
Insulin resistance	−0.322 (0.033)	<0.001	−0.101 (0.014)	<0.001
Joint predictors (both in same model)				
Obesity	−0.093 (0.036)	0.009	−0.026 (0.020)	0.19
Insulin resistance	−0.288 (0.035)	<0.001	−0.095 (0.015)	<0.001
Metabolic subtypes (in same model)				
Nonobese and insulin sensitive	Referent		Referent	
Obese and insulin sensitive	−0.104 (0.045)	0.02	−0.047 (0.029)	0.11
Nonobese and insulin resistant	−0.299 (0.044)	<0.001	−0.102 (0.016)	<0.001
Obese and insulin resistant	−0.374 (0.043)	<0.001	−0.110 (0.024)	<0.001

[a] Values represent the change in log N-BNP (dependent variable) per presence (*vs.* absence or referent) of the variable shown. For example, obesity was associated with an $e^{-0.202} = 0.82$, *e.g.* 18% reduction in N-BNP. Each model is adjusted for age, sex, systolic blood pressure, and antihypertensive therapy.

line characteristics of individuals according to metabolic subtype are shown in Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org.

Obesity, insulin resistance, and NP

Obesity was associated with lower levels of N-BNP in both FHS ($P < 0.001$) and MDC ($P = 0.001$) after adjustment for age, sex, and blood pressure (Table 2). Obese individuals had approximately 18 and 6% lower adjusted N-BNP levels in FHS and MDC, respectively, compared with nonobese individuals.

Insulin resistance also was associated with lower N-BNP levels in both cohorts (FHS, $P < 0.001$; MDC, $P < 0.001$). In models that included obesity and insulin resistance together, both covariates were significantly associated with N-BNP levels in FHS ($P = 0.009$ for obesity, and $P < 0.001$ for insulin resistance), whereas only insulin resistance was significantly associated with N-BNP levels in MDC ($P = 0.19$ for obesity, $P < 0.001$ for insulin resistance).

In models accounting for metabolic subtype, we observed decreased levels of N-BNP in both the nonobese, insulin-resistant group and the obese, insulin-resistant group ($P < 0.001$ in both FHS and MDC), compared with the reference group (Table 2). Being obese and insulin resistant was associated with 31% lower levels of N-BNP in the FHS cohort and 10% lower levels of N-BNP in MDC. Being nonobese and insulin resistant was associated with 26% lower levels of N-BNP in FHS and 10% lower levels of N-BNP in MDC. Levels of N-BNP in the obese, insulin-sensitive group were only 10% lower than those in the reference group in FHS ($P = 0.02$) and not significantly different from those in the reference group in MDC ($P = 0.11$).

Results from sex-specific analyses were similar to those from sex-pooled analyses (Table 3). Results from the main analyses were unchanged in models that included additional adjustment for estimated glomerular filtration rate and in analyses of individuals with prevalent hypertension (data not shown). Results from the FHS sample were also unchanged when analyses were repeated in the subset of individuals without a self-reported history of thyroid disease (data not shown).

Obesity, androgens, and NP

Table 4 shows results of analyses in FHS that incorporated serum-free testosterone measurements. The associations of N-BNP with obesity, insulin resistance, and metabolic subtype were not altered by adjustment for free testosterone. The results were also similar when models were repeated in men and women separately (adjusting for testosterone), and in models using total testosterone rather than free testosterone or adjusting for SHBG separately.

Discussion

In summary, our findings confirm that obesity and insulin resistance are associated with lower circulating NP levels, even after adjusting for other factors known to be associated with NP. Our data also suggest that the reduction in NP in obese individuals could be largely mediated by insulin resistance because the obesity relationship was attenuated with adjustment for HOMA-IR in two different epidemiological cohorts. These findings highlight the influence of metabolic factors, particularly insulin resistance, on the cardiac NP system and suggest a potential mechanism for susceptibility to hypertension-related disorders in individuals with insulin resistance (32–34).

The present study is one of the largest investigations of clinical correlates of circulating NP levels in an ambula-

TABLE 3. Association of N-BNP with obesity and insulin resistance in men and women

	Men		Women	
	Regression coefficient (SE)[a]	P value	Regression coefficient (SE)[a]	P value
FHS				
Individual predictors (in separate models)				
Obesity	−0.121 (0.048)	0.01	−0.285 (0.050)	<0.001
Insulin resistance	−0.308 (0.049)	<0.001	−0.373 (0.043)	<0.001
Joint predictors (both in same model)				
Obesity	−0.014 (0.051)	0.78	−0.161 (0.049)	<0.001
Insulin resistance	−0.303 (0.053)	<0.001	−0.318 (0.046)	<0.001
Metabolic subtypes (in same model)				
Nonobese and insulin sensitive	Referent		Referent	
Obese and insulin sensitive	−0.097 (0.064)	0.13	−0.130 (0.063)	0.04
Nonobese and insulin resistant	−0.400 (0.069)	<0.001	−0.294 (0.056)	<0.001
Obese and insulin resistant	−0.264 (0.063)	<0.001	−0.496 (0.058)	<0.001
MDC				
Individual predictors (in separate models)				
Obesity	−0.083 (0.035)	0.02	−0.043 (0.022)	0.05
Insulin resistance	−0.100 (0.024)	<0.001	0.112 (0.017)	<0.001
Joint predictors (both in same model)				
Obesity	−0.043 (0.036)	0.24	−0.000 (0.023)	0.99
Insulin resistance	−0.092 (0.025)	<0.001	0.112 (0.018)	<0.001
Metabolic subtypes (in same model)				
Nonobese and insulin sensitive	Referent		Referent	
Obese and insulin sensitive	−0.095 (0.059)	0.11	0.017 (0.034)	0.62
Nonobese and insulin resistant	−0.102 (0.027)	<0.001	−0.106 (0.020)	<0.001
Obese and insulin resistant	−0.114 (0.042)	0.007	−0.121 (0.028)	<0.001

[a] Values represent the change in log N-BNP (dependent variable) per presence (*vs.* absence or referent) of the variable shown. Each model is adjusted for age, systolic blood pressure, and antihypertensive therapy.

tory population. The sample size enabled us to study N-BNP in individuals discordant for obesity and insulin resistance status. The validity of our results is supported by the consistency of the findings across two different epidemiological cohorts, the strong statistical associations, and the ability to adjust for multiple potential confounders.

TABLE 4. Association of N-BNP with obesity and insulin resistance, accounting for serum testosterone

	FHS	
	Regression coefficient (SE)[a]	P value
Individual predictors (in separate models)		
Obesity	−0.178 (0.033)	<0.001
Insulin resistance	−0.312 (0.033)	<0.001
Joint predictors (in same model)		
Obesity	−0.072 (0.035)	0.04
Insulin resistance	−0.286 (0.035)	<0.001
Metabolic subtypes (in same model)		
Nonobese and insulin sensitive	Referent	
Obese and insulin sensitive	−0.078 (0.045)	0.08
Nonobese and insulin resistant	−0.293 (0.044)	<0.001
Obese and insulin resistant	−0.354 (0.043)	<0.001

[a] Values represent the change in log N-BNP (dependent variable) per presence (*vs.* absence or referent) of the variable shown. Each model is adjusted for age, sex, systolic blood pressure, antihypertensive therapy, and serum-free testosterone.

Furthermore, the focus on ambulatory individuals without cardiovascular disease minimizes the risk of confounding by hemodynamic stress or acute illness, both of which may alter NP levels.

Several prior studies have reported an association of NP levels with obesity (7, 8, 35) or insulin resistance (35–37). Using the data from an older Framingham cohort (mean age 58 yr), we previously reported that mature BNP levels were lower in individuals with the metabolic syndrome (37). However, the separate contributions of obesity and insulin resistance have been difficult to distinguish in prior work because these characteristics often coexist, and very large studies are needed to separate the two. The present investigation was explicitly designed to compare the associations of obesity and insulin resistance with NP and to validate these findings across different community-based cohorts.

Studies of short-term hyperinsulinemia suggest that insulin may directly suppress NP secretion. Two small studies have found that NP levels decrease during acute euglycemic hyperinsulinemia in patients with congestive heart failure (21) and in healthy volunteers free of diabetes (38), although this finding has not been replicated by other investigators (39–42). The failure of insulin infusion to suppress NP levels in some studies may be explained by the use of water diuresis before insulin infusion (39, 41) or to

the increase in plasma volume or tonicity during the infusion, which could act to augment NP levels (40, 42). Two experimental studies have examined the direct effects of insulin on cardiac natriuretic peptide release with conflicting results. Sicard *et al.* (43) observed a decrease in atrial natriuretic factor in response to insulin in isolated neonatal porcine hearts. In contrast, Bai *et al.* (44) reported an increase in atrial natriuretic peptide secretion in response to insulin in a perfused beating atria model created from an isolated murine heart.

Interestingly, experimental and human genetic investigations suggest that NP deficiency may not just be a consequence of insulin resistance but may also promote it (45, 46). NP bind to adipocytes and induce lipolysis by a cGMP-mediated process (47), suppress activation of the renin-angiotensin system, and inhibit secretion of proinflammatory mediators, effects that may protect against insulin resistance (48, 49). *In vivo* and clinical studies support an insulin-sensitizing effect of NP. Transgenic mice that overexpress BNP are protected from obesity and insulin resistance, compared with wild-type mice (45). Furthermore, a genetic variant in the promoter of the proBNP gene leading to approximately 20% higher BNP levels has been associated with a 15% reduced risk of type 2 diabetes in humans (50, 51). Human intervention studies to assess the direct contribution of NP variation to metabolic risk have not been performed.

Obese, insulin-resistant individuals had 31% lower NP levels in FHS and 10% lower NP levels in MDC. The difference in the magnitude of association between cohorts could have been the result of chance or due to differences in the characteristics of the studies. Individuals in FHS were younger and more obese, whereas individuals in MDC were older and more likely to be hypertensive. A higher prevalence of nonmetabolic influences on NP levels in MDC could have attenuated observed relations with metabolic factors. Nonetheless, the reductions in NP were sizable and highly significant in both cohorts. Indeed, genetic variants leading to relatively small reductions in NP levels (10–15% across genotype categories) have been associated with hypertension susceptibility in humans, underscoring the potential pathophysiological significance of the changes observed (6).

There is increasing awareness that the cardiovascular and metabolic risk profile of obese individuals is variable (52, 53) and that some lean individuals possess metabolic traits that are associated with obesity (54). Obese, insulin-sensitive individuals have a favorable inflammatory profile (55). In contrast to nonobese, insulin-resistant individuals (56), obese, insulin-sensitive individuals may not be at elevated risk of cardiovascular disease (57, 58). In the present study, nonobese, insulin-resistant individuals had lower NP levels than obese, insulin-sensitive individuals. Because the NP have beneficial cardiovascular and metabolic effects, a relative NP deficiency could be one mechanism by which obese, insulin-resistant individuals are at increased cardiovascular risk. Conversely, the relative preservation of NP levels in obese individuals without insulin resistance could contribute to a more favorable risk profile. Because experimental and physiological studies suggest a possible bidirectional interplay between low NP and insulin resistance (59, 60), further prospective studies are warranted in humans.

Testosterone may be an important mediator of NP levels (19) and is also related to obesity (61) and insulin resistance (62). To determine whether testosterone levels influence the relation between obesity, insulin, and NP levels, we repeated our analyses in the FHS with free testosterone as an additional covariate in both sex-pooled and sex-specific multivariable models. The overall results were unchanged, suggesting that testosterone is not the primary mediator of the association between NP and metabolic subtypes.

There are several limitations of this study. These data are cross-sectional, limiting the ability to infer a causal relationship between either obesity or insulin resistance and NP levels. We did not measure other NP, including mature atrial natriuretic peptide or BNP. The longer half-life of N-BNP compared with other peptides in the family makes it well suited for studies in ambulatory individuals who have generally low resting levels. Furthermore, prior studies indicate a high correlation between N-BNP and other NP. Lastly, both cohorts were comprised predominantly of white individuals of European ancestry, and therefore, the results of this study may not be generalizable to other racial/ethnic groups.

In an analysis in two large, community-based cohorts, we observed robust associations between obesity, insulin resistance, and lower NP levels. Our findings suggest that the natriuretic handicap observed in obese individuals could be attributable in part to insulin resistance. Further studies are needed to elucidate the biological mechanisms underlying the close interaction between insulin and the NP axis.

Acknowledgments

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