# Epidemiology

# Association of Plasma Natriuretic Peptide Levels With Metabolic Risk Factors in Ambulatory Individuals

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***Background***—Experimental studies suggest that the natriuretic peptides influence lipid and fatty acid metabolism. Although it has been shown that obese individuals have reduced natriuretic peptide levels, conflicting data exist on the relation of natriuretic peptide levels to other metabolic risk factors.

***Methods and Results***—We examined the association of plasma levels of B-type natriuretic peptide and N-terminal pro-atrial natriuretic peptide with metabolic risk factors, the metabolic syndrome, and insulin resistance in 3333 Framingham study participants free of heart failure (mean age, 58 years; 54% women). Regression analyses were performed, with adjustment for clinical and echocardiographic variables. Plasma natriuretic peptide levels were inversely associated with all components of the metabolic syndrome except for elevated blood pressure. Adjusted natriuretic peptide levels were lower in persons with the metabolic syndrome compared with those without the metabolic syndrome: In men, B-type natriuretic peptide was 24% lower ($P<0.001$) and N-terminal pro-atrial natriuretic peptide was 16% lower ($P<0.001$); in women, B-type natriuretic peptide was 29% lower ($P<0.001$) and N-terminal pro-atrial natriuretic peptide was 18% lower ($P<0.001$). Individuals with insulin resistance, as indicated by an elevated homeostasis model assessment (HOMA-IR) index, had lower levels of B-type natriuretic peptide ($P=0.009$ in men, $P<0.001$ in women) and N-terminal pro-atrial natriuretic peptide ($P<0.001$ in men, $P=0.001$ in women).

***Conclusions***—Having several metabolic risk factors is associated with low circulating natriuretic peptide levels, even after adjustment for body mass index. These findings raise the possibility that reduced natriuretic peptide activity is a manifestation of the metabolic syndrome, which may have important clinical and pathophysiological implications. (***Circulation*. 2007;115:1345-1353.**)

**Key Words:** atrial natriuretic factor ■ epidemiology ■ natriuretic peptides ■ risk factors

Obesity is associated with reduced levels of natriuretic peptides, cardiac hormones that play critical roles in ventricular remodeling, salt and water homeostasis, and the regulation of vascular tone.[1] It has been hypothesized that a reduced natriuretic peptide response, called a natriuretic handicap, contributes to the increased susceptibility of obese individuals to fluid retention, hypertension, and heart failure.[2]

## Clinical Perspective p 1353

Obesity is frequently accompanied by glucose intolerance, hyperlipidemia, and hypertension,[3] traits that may reflect underlying insulin resistance.[4] This clustering has been called the metabolic syndrome. Although the clinical utility of this designation is controversial,[5] there is widespread agreement that it describes a subgroup of individuals with a high risk of cardiovascular disease.[4] Despite the well-documented associ-

ation between natriuretic peptide levels and obesity,[1,6] data on relations with other metabolic risk factors are mixed. Recently, Olsen and colleagues[7] reported an inverse association between N-terminal pro-B-type natriuretic peptide levels and plasma lipids, glucose, and insulin, although the prevalence of metabolic risk factors in that sample was relatively low. Other studies have not found an association between plasma natriuretic peptide levels and hyperlipidemia[8] or hyperglycemia.[9]

Thus, we sought to elucidate the relations between plasma natriuretic peptide levels and metabolic risk factors and the metabolic syndrome in a large, well-characterized community-based cohort. We hypothesized that plasma natriuretic peptide levels would be lower in the presence of the metabolic syndrome or its components, even after accounting for differences in body mass index.

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# Methods

## Participants and Clinical Evaluation

The Framingham Offspring Study was initiated in 1971 with the recruitment of 5124 offspring and spouses of offspring of the original Framingham Heart Study participants.[10] The 3532 participants who attended the sixth offspring examination (1995–1998) were eligible for the present investigation. Participants were excluded for the following reasons in hierarchical fashion: unavailable natriuretic peptide levels (n=80), renal insufficiency (creatinine >2.0 mg/dL; n=21), a history of heart failure (n=89), and missing covariates (n=9). After these exclusions, 3333 subjects (94% of attendees) remained eligible.

All participants underwent routine physical examination (with medical history), laboratory assessment of cardiovascular disease risk factors, and standardized echocardiographic examination. Systolic and diastolic blood pressure values were the means of 2 physician-obtained measurements on the left arm of the seated participant. Diabetes was defined by either a history of fasting glucose ≥126 mg/dL or the use of insulin or hypoglycemic medications. Impaired fasting glucose was defined as a fasting glucose ≥100 and <126 mg/dL.[11]

## Metabolic Syndrome Definition

We used the National Cholesterol Education Panel Adult Treatment Panel definition of the metabolic syndrome[12] with the modifications recently recommended by the American Heart Association and National Heart, Lung, and Blood Institute.[3] Thus, persons were defined as having the metabolic syndrome if they satisfied ≥3 of the following 5 criteria: (1) elevated waist circumference (≥102 cm in men, ≥88 cm in women); (2) fasting triglycerides ≥150 mg/dL or use of fibrates or nicotinic acid; (3) reduced high-density lipoprotein (HDL; <40 mg/dL in men, <50 mg/dL in women); (4) systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or use of antihypertensive medications; and (5) fasting glucose ≥100 mg/dL or use of hypoglycemic medications.

## Natriuretic Peptide Measurements

Plasma N-terminal pro-atrial natriuretic peptide (N-ANP) and B-type natriuretic peptide (BNP) levels were measured at the sixth examination cycle using highly sensitive, noncompetitive immunoradiometric assays (Shionogi, Osaka, Japan).[13] Fasting subjects underwent phlebotomy in a supine position, typically between 8 and 9 AM. Samples were transferred immediately to chilled tubes containing EDTA and centrifuged, and the plasma was frozen at −70°C. The lower limits of the working range were 94 pmol/L for N-ANP and 4 pg/mL for BNP. The average interassay coefficients of variation were 12.7% for N-ANP and 12.2% for BNP.

## Assessment of Insulin Resistance

Fasting insulin levels, measured in plasma as total immunoreactive insulin, were routinely assessed during the fifth examination (1991–1994). Insulin resistance was assessed from fasting insulin and glucose levels using the previously validated homeostasis model assessment (HOMA-IR): HOMA-IR equals fasting glucose (mmol/L) times fasting insulin ($\mu$U/mL) divided by 22.5.[14] A priori, we defined an HOMA-IR value exceeding the 75th percentile as indicating insulin resistance.[15]

## Echocardiography

All participants underwent M-mode and 2-dimensional echocardiography with Doppler color flow imaging at the sixth examination cycle. Echocardiograms were read by a technician or cardiologist (experienced in echocardiography) blinded to clinical and laboratory information. Cardiac dimensions were measured from M-mode recordings using the leading edge technique, in accordance with American Society of Echocardiography guidelines.[16] Measurements were averaged over at least 3 cardiac cycles. Left ventricular systolic dysfunction was defined as an endocardial fractional shortening <0.29 or an ejection fraction <0.50 by visual assessment of left ventricular wall motion in multiple 2-dimensional views. Left ventricular mass was calculated with the American Society of Echocardiography formula.[17]

## Statistical Analyses

We used natural logarithmic (log) transformations of peptide levels because N-ANP and BNP followed approximately lognormal distributions. Furthermore, to accommodate left censoring by the lower detection limit (LDL) of the natriuretic peptide assays (2% and 31% of values censored for N-ANP and BNP, respectively), Tobit regression models for left-censored data were used (SAS LIFEREG procedure, SAS Institute Inc, Cary, NC).[18] Tobit regression assumes that a latent variable, $Y^*$, is linearly related to predictors X as $Y^*=X\beta+E$, where E has a normal distribution, but the observed data are $Y=\max(Y^*, LDL)$; the maximum likelihood method is used to estimate parameters. Sex-specific multivariable Tobit regressions were performed to relate log N-ANP and log BNP to metabolic variables that included body mass index, total cholesterol, HDL cholesterol, systolic blood pressure, diastolic blood pressure, hypertension therapy, fasting glucose, and use of diabetes medication. These models also included age, prior myocardial infarction, atrial fibrillation, serum creatinine, cigarette smoking, echocardiographic left atrial size, echocardiographic left ventricular mass, and presence of left ventricular systolic dysfunction. We adjusted for echocardiographic variables to assess whether influences on natriuretic peptide levels were attributable to intermediary changes in cardiac structure or function.

Next, multivariable Tobit regression analyses were used to relate plasma natriuretic peptide levels to individual binary components of the metabolic syndrome. A separate analysis was performed to relate plasma natriuretic peptide levels to the metabolic syndrome (ie, having ≥3 components). These models were adjusted for clinical characteristics not part of the metabolic syndrome definition and for echocardiographic features. We performed analyses with and without adjustment for body mass index. In secondary analyses, the association of plasma natriuretic peptide levels with insulin resistance (using HOMA-IR) was examined.

Because the components of the metabolic syndrome tend to cluster, we assessed for potential multicollinearity of the predictor variables in the multivariable regression models. For each variable, we calculated tolerance ($1-R^2$ for regression of the selected variable on other variables in the model) and variance inflation factors (1/tolerance). All of the variance inflation factors were <2, suggesting that multicollinearity was not a problem.

Continuous predictor variables were standardized (mean, 0; SD, 1). Percent changes were estimated for latent (underlying) variables with back-transformation. Percent change and the lower and upper confidence intervals were estimated from the following equations: $100[\exp(\beta)-1]$, $100[\exp(\beta-1.96\times SE)-1]$, and $100[\exp(\beta+1.96\times SE)-1]$, where $\beta$ represents the $\beta$-coefficient from the multivariable Cox regression. Cox-Snell $R^2$ statistics were estimated with the following equation: $1-\exp\{2[\log L(M)-\log L(0)]/n\}$, where L(0) is null likelihood and L(M) is multivariable-model likelihood. All analyses were performed with the SAS system (release 6.12, SAS Institute Inc). A 2-sided value of $P<0.05$ was considered statistically significant.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

# Results

Characteristics of the study sample (n=3333) are shown in Table 1. Mean N-ANP levels were 353 pmol/L (SD, 261 pmol/L) in men and 402 pmol/L (SD, 229 pmol/L) in women. Mean BNP levels were 14.2 pg/mL (SD, 20.7 pg/mL) in men and 16.4 pg/mL (SD, 20.8 pg/mL) in women. Seven hundred men (45%) and 669 women (38%) met criteria for the metabolic syndrome.

**TABLE 1.    Characteristics of the Study Sample**

| | Men (n=1549) | Women (n=1784) |
|---|---|---|
| Age, y | 58±10 | 58±10 |
| Body mass index, kg/m$^2$ | 28.5±4.4 | 27.3±5.7 |
| Diabetes mellitus, % | 13 | 9 |
| Fasting glucose, mg/dL | 107±26 | 100±26 |
| Impaired fasting glucose, % | 40 | 24 |
| On diabetes medication, % | 6 | 4 |
| Systolic blood pressure, mm Hg | 129±17 | 127±20 |
| Diastolic blood pressure, mm Hg | 77±9 | 74±9 |
| On antihypertensive therapy, % | 30 | 25 |
| Hypertension, % | 44 | 38 |
| Total cholesterol, mg/dL | 199±41 | 212±38 |
| HDL cholesterol, mg/dL | 43±12 | 58±16 |
| Triglycerides, mg/dL | 148±167 | 133±83 |
| Metabolic syndrome, % | 45 | 38 |
| Smoking, % | 15 | 16 |
| Serum creatinine, mg/dL | 1.2±0.2 | 1.1±0.2 |
| Left atrial size, cm | 4.2±0.5 | 3.8±0.5 |
| Left ventricular systolic dysfunction, % | 8 | 2 |
| Left ventricular mass, g | 192±43 | 140±30 |
| Prior myocardial infarction, % | 7 | 2 |
| Atrial fibrillation, % | 2 | 1 |

Values are mean±SD when appropriate.

## Natriuretic Peptides and Metabolic Risk Factors

Results of multivariable regression models relating plasma N-ANP and BNP with metabolic risk factors are shown in Table 2. In all models, a negative association was observed between plasma natriuretic peptide levels and body mass index ($P=0.02$ to $<0.001$) as previously described. Additionally, natriuretic peptide levels were inversely associated with diastolic blood pressure ($P=0.002$ to $<0.001$), total choles-

terol ($P<0.001$), and in women, fasting glucose ($P=0.004$ to $<0.001$). In men, the inverse association with fasting glucose was significant for plasma N-ANP ($P<0.001$) but not plasma BNP ($P=0.18$). Plasma N-ANP also was negatively associated with use of diabetic medications in women ($P=0.003$) but not in men. The interaction between gender and use of diabetic medications had borderline significance in models for N-ANP ($P=0.049$). Natriuretic peptide levels were positively associated with systolic blood pressure ($P<0.001$) and HDL cholesterol ($P=0.04$ to $<0.001$) in all models.

The above findings were similar in models excluding individuals on antihypertensive therapy or individuals with left ventricular systolic dysfunction (data not shown). Additionally, in multivariable models substituting pulse pressure for systolic and diastolic blood pressures, a positive association was observed between pulse pressure and both N-ANP (men, 6% increment per 1-SD increase in pulse pressure [$P<0.001$]; women, 4% increment [$P=0.002$]) and BNP (men, 21% increment per 1-SD increase in pulse pressure [$P<0.001$]; women, 12% increment [$P<0.001$]).

## Natriuretic Peptides and Components of the Metabolic Syndrome

Results of models relating plasma natriuretic peptide levels to individual dichotomous components of the metabolic syndrome are shown in Table 3. Four components of the metabolic syndrome—elevated waist circumference, elevated triglycerides, reduced HDL, and elevated fasting glucose—were associated with lower plasma N-ANP levels in models adjusting for all metabolic syndrome components, other clinical characteristics, and echocardiographic variables. The elevated blood pressure criterion was associated with higher plasma N-ANP in women but not in men; however, the interaction between gender and elevated blood pressure did not attain statistical significance ($P=0.21$). Similar findings were obtained for plasma BNP, except for weaker relations to elevated waist circumference in men and reduced HDL in women.

**TABLE 2.    Multivariable Association of Plasma Natriuretic Peptides With Metabolic Variables**

| | N-ANP* | | | | BNP† | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Metabolic Variable | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P |
| Body mass index | −6.7 (−9.6−−3.7) | <0.001 | −7.5 (−10.1−−4.9) | <0.001 | −8.7 (−15.3−−1.6) | 0.02 | −11.2 (−16.7−−5.4) | <0.001 |
| Systolic blood pressure | 7.9 (4.2−11.7) | <0.001 | 5.8 (2.4−9.3) | <0.001 | 26.2 (16.4−36.8) | <0.001 | 14.9 (6.8−23.6) | <0.001 |
| Diastolic blood pressure | −8.0 (−11.0−−4.9) | <0.001 | −7.1 (−9.7−−4.5) | <0.001 | −18.3 (−24.4−−11.6) | <0.001 | −9.5 (−15.1−−3.5) | 0.002 |
| Hypertension therapy | 14.9 (8.2−21.9) | <0.001 | 11.9 (5.8−18.4) | <0.001 | 21.0 (5.2−39.0) | 0.007 | 2.4 (−9.8−16.3) | 0.71 |
| Total cholesterol | −7.6 (−10.2−−5.0) | <0.001 | −8.9 (−11.0−−6.8) | <0.001 | −15.8 (−21.6−−9.6) | <0.001 | −16.4 (−20.6−−12.0) | <0.001 |
| HDL cholesterol | 6.6 (3.8−9.5) | <0.001 | 5.7 (3.2−8.1) | <0.001 | 14.3 (7.4−21.7) | <0.001 | 5.5 (0.1−11.2) | 0.04 |
| Fasting glucose | −7.0 (−9.9−−4.0) | <0.001 | −4.2 (−6.9−−1.4) | 0.004 | −5.1 (−12.1−2.4) | 0.18 | −12.2 (−18.1−−6.0) | <0.001 |
| Diabetes medication | −3.5 (−15.5−10.2) | 0.60 | −19.6 (−30.4−−7.1) | 0.003 | −25.1 (−45.6−2.9) | 0.07 | 14.6 (−17.5−59.3) | 0.42 |

CI indicates confidence interval. Tobit analyses were conducted on log-transformed N-ANP and BNP and adjusted for the variables above plus age, prior myocardial infarction, atrial fibrillation, serum creatinine, cigarette smoking, left atrial diameter, left ventricular mass, and presence of left ventricular systolic dysfunction. Percent changes were estimated for latent (underlying) variables with back-transformation as described in Methods. Percent changes are per 1-SD increment in continuous variables or for the presence vs absence of dichotomous variables.

*$R^2$ for men, 0.43; for women, 0.31.

†$R^2$ for men, 0.32; for women, 0.19.

**TABLE 3.  Plasma Natriuretic Peptides and Individual Components of the Metabolic Syndrome**

| | N-ANP | | | | BNP | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Component | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P |
| Large waist circumference | −6.0 (−11.1−−0.6) | 0.03 | −12.8 (−17.2−−8.2) | <0.001 | −5.1 (−16.7−8.1) | 0.43 | −18.7 (−27.3−−9.1) | <0.001 |
| Elevated triglycerides | −16.6 (−21.4−−11.4) | <0.001 | −11.9 (−16.5−−7.0) | <0.001 | −21.9 (−32.2−−10.0) | <0.001 | −29.7 (−37.5−−20.8) | <0.001 |
| Reduced HDL | −5.4 (−10.7−0.2) | 0.06 | −8.0 (−12.7−−3.0) | 0.002 | −15.8 (−26.5−−3.6) | 0.01 | 0.87 (−10.1−13.2) | 0.88 |
| Elevated fasting glucose | −6.5 (−11.4−−1.4) | 0.01 | −10.4 (−15.0−−5.4) | <0.001 | −11.4 (−21.8−0.5) | 0.06 | −18.8 (−27.8−−8.7) | <0.001 |
| Elevated blood pressure | 1.6 (−4.1−7.6) | 0.59 | 5.4 (0.1−10.9) | 0.04 | 4.0 (−9.2−19.2) | 0.57 | 14.3 (2.2−27.8) | 0.02 |

Components of the metabolic syndrome are defined in the text. Tobit analyses were conducted on log-transformed ANP and BNP and are adjusted for all of the variables above plus age, prior myocardial infarction, atrial fibrillation, left atrial diameter, left ventricular mass, and presence of left ventricular systolic dysfunction. Percent changes were estimated for latent (underlying) variables with back-transformation as described in Methods.

Table 4 displays results of multivariable regressions relating plasma natriuretic peptide levels to presence of the metabolic syndrome, defined as having ≥3 of the components. Plasma BNP levels were 24% lower in men ($P<0.001$) and 29% lower in women ($P<0.001$) with the metabolic syndrome after adjustment for age, prior myocardial infarction, atrial fibrillation, and echocardiographic characteristics. The inverse relation between plasma BNP and the metabolic syndrome remained significant after further adjustment for body mass index ($P=0.006$ for men, $P<0.001$ women). Similarly, plasma N-ANP was 16% lower in men ($P<0.001$) and 18% lower in women ($P<0.001$) with the metabolic syndrome after adjustment for clinical and echocardiographic characteristics. These relations remained significant with further adjustment for body mass index ($P<0.001$ for men and women). Plasma natriuretic peptide levels also were associated with the number of metabolic syndrome criteria met (Table 4). Figures 1 and 2 depict multivariable-adjusted mean plasma natriuretic peptide levels according to the number of metabolic syndrome criteria.

### Natriuretic Peptides and Insulin Measures

In individuals not treated with insulin, HOMA-IR values in the top quartile were associated with lower plasma natriuretic peptide levels after adjustment for age, body mass index, prior myocardial infarction, atrial fibrillation, and echocardiographic measures. Plasma BNP levels were 18% lower in men ($P=0.009$) and 23% lower in women ($P<0.001$) with high HOMA-IR compared with all other participants. Similarly, plasma N-ANP levels were 13% lower in men ($P<0.001$) and 10% lower in women ($P=0.001$) with high HOMA-IR. Similar findings were obtained in analyses that included individuals taking insulin, with such individuals classified in the top quartile of HOMA-IR.

### Discussion

The principal finding of this study is that reduced plasma natriuretic peptide levels were associated with the metabolic syndrome and its individual components, even after adjustment for body mass index. The validity of this finding is supported by the use of multivariable analyses with a wide

**TABLE 4.  Plasma Natriuretic Peptides and the Metabolic Syndrome***

| | Log N-ANP | | | | Log BNP | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| Model | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P | Change, % (95% CI) | P |
| Adjusted for age, prior myocardial infarction, atrial fibrillation, and echocardiography | | | | | | | | |
| Metabolic syndrome (Y/N) | −15.6 (−20.1−−10.9) | <0.001 | −17.5 (−21.7−−13.2) | <0.001 | −24.4 (−33.5−−14.2) | <0.001 | −28.6 (−36.2−−20.1) | <0.001 |
| By metabolic syndrome features, n | | | | | | | | |
| 0 | Referent | | Referent | | Referent | | Referent | |
| 1 | −5.6 (−14.5−4.3) | 0.26 | −11.1 (−17.2−−4.4) | 0.001 | −18.1 (−35.2−3.5) | 0.09 | −9.5 (−22.6−5.8) | 0.21 |
| 2 | −12.2 (−20.2−−3.3) | 0.008 | −19.2 (−25.1−−12.9) | <0.001 | −16.6 (−33.4−4.3) | 0.11 | −25.3 (−36.7−−11.9) | <0.001 |
| 3+ | −22.4 (−29.3−−14.9) | <0.001 | −28.0 (−33.1−−22.5) | <0.001 | −35.4 (−48.0−−19.9) | <0.001 | −39.4 (−48.4−−28.7) | <0.001 |
| Adjusted for above plus body mass index | | | | | | | | |
| Metabolic syndrome (Y/N) | −10.6 (−15.7−−5.1) | <0.001 | −11.8 (−16.6−−6.8) | <0.001 | −17.6 (−28.2−−5.4) | 0.006 | −21.4 (−30.4−−11.3) | <0.001 |
| By metabolic syndrome features, n | | | | | | | | |
| 0 | Referent | | Referent | | Referent | | Referent | |
| 1 | −3.9 (−12.9−6.2) | 0.44 | −8.5 (−14.9−−1.7) | 0.02 | −16.0 (−33.5−6.1) | 0.14 | −5.8 (−19.5−10.3) | 0.46 |
| 2 | −8.3 (−16.8−1.1) | 0.08 | −14.5 (−20.9−−7.5) | <0.001 | −10.7 (−28.9−12.1) | 0.33 | −18.8 (−31.6−−3.7) | 0.02 |
| 3+ | −15.8 (−23.7−−7.1) | <0.001 | −21.3 (−27.4−−14.6) | <0.001 | −26.7 (−41.8−−7.7) | 0.008 | −31.0 (−42.3−−17.4) | <0.001 |

CI indicates confidence interval. Tobit analyses were conducted on log N-ANP and BNP and adjusted for the variables listed. Percent changes were estimated for latent (underlying) variables with back-transformation as described in the Methods.

A



B
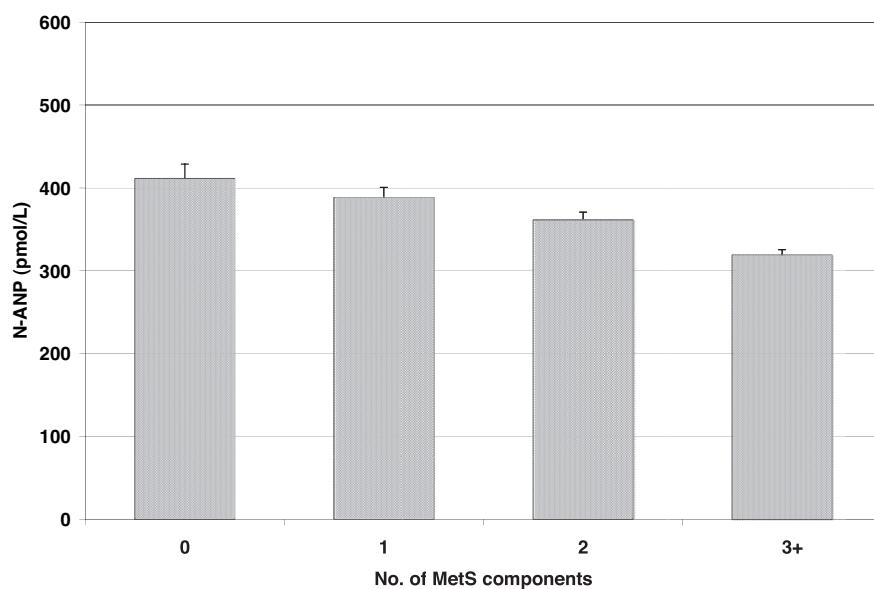


**Figure 1.** Adjusted mean levels of plasma N-ANP in men (A) and women (B) according to number of metabolic syndrome (MetS) criteria. Levels were obtained by back-transformation of log-N-ANP levels adjusted for age, prior myocardial infarction, atrial fibrillation, left atrial diameter, left ventricular mass, and presence of left ventricular systolic dysfunction. Bars indicate SE.
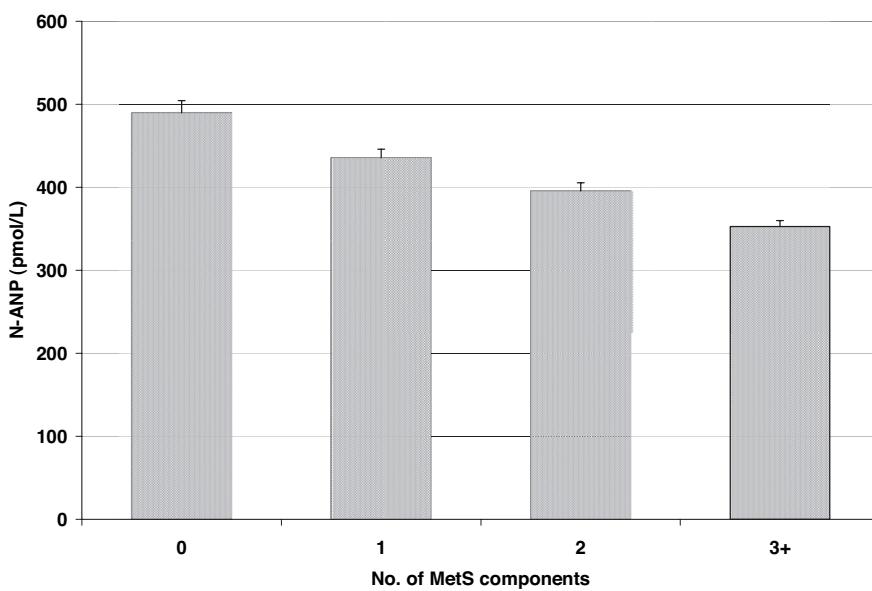
range of clinical and echocardiographic covariates; the inverse association of natriuretic peptide levels with an index of insulin resistance, HOMA-IR; and the general consistency of the results across both sexes and 2 peptides (N-ANP and BNP).

To the best of our knowledge, the present investigation is the largest to examine the association of plasma natriuretic peptide levels with metabolic risk factors for cardiovascular disease. Our findings suggest a close relation between lipid and glucose metabolism and the natriuretic peptide axis, a concept supported by prior experimental and physiological

observations.[19,20] These data also reinforce the premise that extracardiac factors may influence circulating natriuretic peptide levels, which may have important clinical and pathophysiological implications given the role of the natriuretic peptide axis in the endogenous response to hemodynamic and neurohormonal stress.

## Comparison With Prior Studies
An inverse association between plasma natriuretic peptide levels and obesity has previously been described in Framingham[1] and other cohorts.[6,21,22] Nonetheless, few studies have

A



B
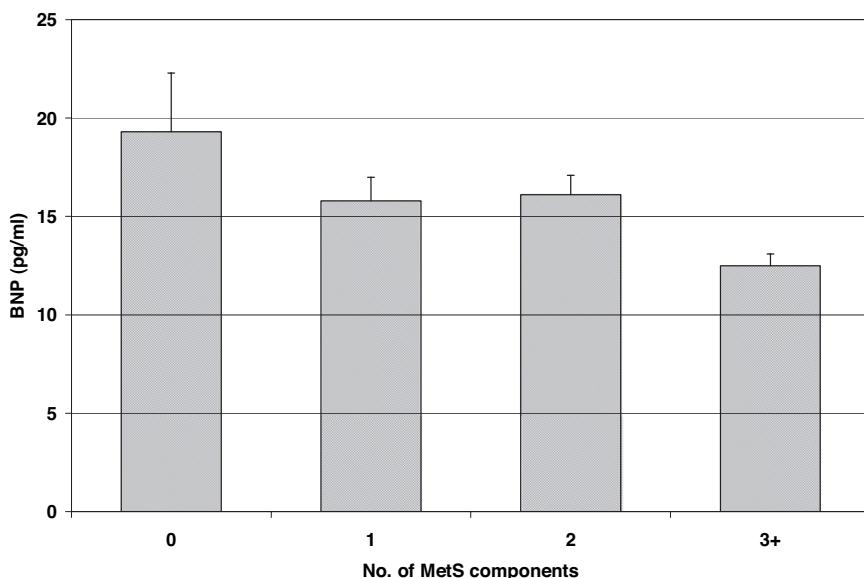


**Figure 2.** Adjusted mean levels of plasma BNP in men (A) and women (B) according to number of metabolic syndrome (MetS) criteria. Levels were obtained by back-transformation of log-BNP levels adjusted for age, prior myocardial infarction, atrial fibrillation, left atrial diameter, left ventricular mass, and presence of left ventricular systolic dysfunction. Bars indicate SE.
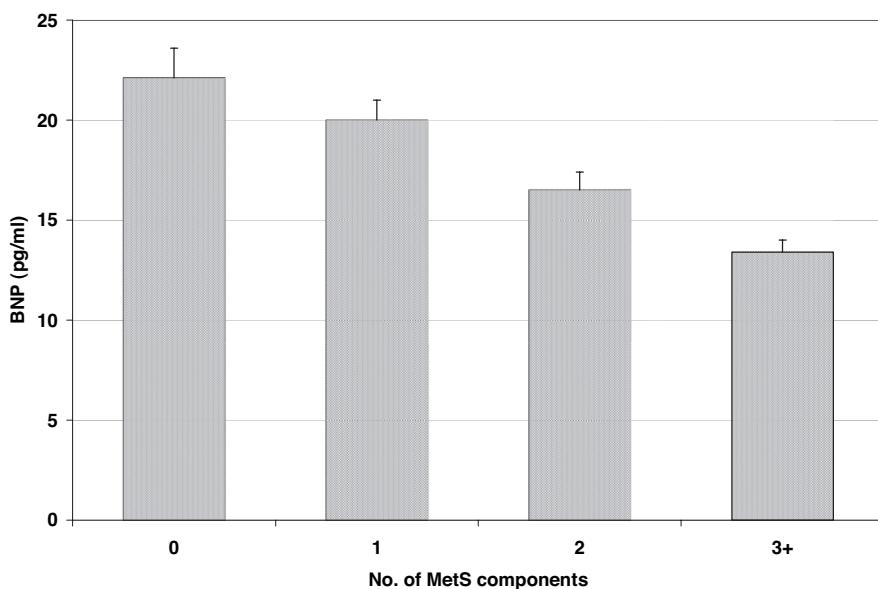
examined the relations of natriuretic peptide levels to other metabolic risk factors.[7,8] In smaller studies, inconsistent associations have been noted between plasma natriuretic peptides and glycemic status[9,23,24] or plasma lipids.[8] Olsen and colleagues[7] reported results of the only other large-scale investigation of plasma natriuretic peptide levels and metabolic risk factors. In their population-based Danish cohort, plasma N-terminal pro-BNP was inversely associated with serum total cholesterol, serum triglycerides, plasma glucose, and plasma insulin. The present investigation extends these findings to a larger cohort (by ≈50%), with substantially higher prevalences of the metabolic syndrome, diabetes, and obesity. Other differences between the Danish study and ours include the use of 2 peptides (N-ANP and BNP) in the present study, the ability to adjust for differences in renal function

with serum creatinine, and the use of clinical information ascertained over 2 decades rather than self-reported clinical data. These differences notwithstanding, the overall similarity in study findings provides convincing evidence of an association between the natriuretic peptide axis and metabolic traits.

## Potential Mechanisms
Our cross-sectional data cannot establish whether low natriuretic peptide levels precede or follow the development of metabolic risk factors. Nonetheless, several lines of experimental evidence suggest that low natriuretic peptide levels could predispose to insulin resistance. Reduced natriuretic peptide activity leads to greater activation of the renin-angiotensin system.[25] Activation of the renin-angiotensin system promotes the development of insulin resistance via multiple

mechanisms,[26] including inhibition of intracellular insulin signaling,[27] enhanced oxidative stress,[28] inflammation,[29] reduced adipocyte differentiation,[30,31] and decreased perfusion to the skeletal muscle and pancreas.[32,33]

The natriuretic peptides also may exert a direct influence on lipid and glucose metabolism. It has been reported that infusion of ANP elevates plasma insulin levels by $\approx$50%[34] and inhibits glucagon secretion.[35] The natriuretic peptides also have antiinflammatory properties, reducing the production of tumor necrosis factor-$\alpha$,[36] cyclooxygenase 2,[37] and monocyte chemoattractant protein-1.[38] An association between natriuretic peptides and levels of the insulin-sensitizing hormone adiponectin has been reported, with low levels of BNP associated with low levels of adiponectin despite adjustment for body mass index.[39] Natriuretic peptides also stimulate lipolysis and release of triacylglycerols from adipose tissue.[40] Reduced natriuretic peptide signaling could have detrimental effects via the promotion of lipid accumulation in adipose tissue and skeletal muscle. Finally, the second messenger for the natriuretic peptides, cGMP, plays a role in insulin-stimulated glucose transport.[41]

### Natriuretic Peptides and Blood Pressure

Low natriuretic peptide levels were associated with each component of the metabolic syndrome except hypertension. Elevated systolic blood pressure was associated with higher natriuretic peptide levels, which likely reflects the hemodynamic influence of blood pressure on natriuretic peptide synthesis. Systemic vascular resistance is a major determinant of left ventricular wall stress. Other studies have reported a positive association between plasma natriuretic peptide levels and systolic blood pressure, although most of these studies focused on individuals with essential hypertension.[42,43]

The observation that natriuretic peptide levels relate differently to systolic blood pressure than to other metabolic risk factors is in keeping with studies suggesting that blood pressure segregates separately from other components of the metabolic syndrome.[44,45] In the Insulin Resistance Atherosclerosis Study, Hanley and colleagues[45] used principal factor analysis to identify 2 "factors," or clusters of traits, that explained a significant proportion of phenotypic variability: a metabolic factor, consisting of body mass index, glycemic measures, triglycerides, and HDL, and a blood pressure factor, comprising systolic and diastolic blood pressure. HOMA-IR and fasting insulin correlated with the metabolic factor but not with the blood pressure factor. Studies from other cohorts, including Framingham,[44] have reported similar findings. These data suggest that blood pressure may share different pathophysiological determinants from other metabolic traits, which have a closer association with insulin resistance, and may help to explain the different relations with the natriuretic peptides.

The inverse correlation between natriuretic peptide levels and diastolic blood pressure may reflect the influence of pulse pressure[7] because increased pulse pressure (reduced arterial compliance) often is accompanied by lower diastolic blood pressure, particularly in older individuals. Like systolic blood pressure, arterial compliance is an important determinant of ventricular afterload.

### Study Limitations

Several limitations of the study deserve comment. First, our study was cross-sectional, so we cannot establish the temporal relations between low plasma natriuretic peptide and metabolic risk factors. Second, plasma BNP levels in healthy individuals are frequently below the assay detection limit. We used Tobit models to account for the left censoring of the BNP distribution. Misclassification of BNP levels above and below the detection limit would likely cause a conservative bias, which may have contributed to the weaker relations of metabolic factors with BNP levels in men, who have lower BNP levels than women.[13] The consistency of results across BNP and N-ANP supports the validity of our findings because left censoring does not significantly affect the distribution of N-ANP levels. Third, plasma insulin was measured $\approx$4 years before the natriuretic peptide measurements. Progression or regression in insulin sensitivity over time may have caused misclassification of insulin status in models using HOMA-IR, likely also causing a conservative bias. The results of plasma insulin assays were not provided to participants or their physicians, minimizing the possibility that differential treatment of individuals with insulin resistance biased our findings. All other clinical and echocardiographic data were obtained on the same day as the natriuretic peptide measurements. Fourth, the multivariable regression models explained only a moderate proportion of the total variance in natriuretic peptide levels. Other environmental and genetic[46] factors may contribute to the unexplained variation. Finally, it is important to acknowledge that our cohort was predominantly middle-aged to elderly and white; our findings may not be generalizable to younger individuals or those of nonwhite descent.

### Clinical Implications

The diagnostic and prognostic utility of plasma natriuretic peptide measurements has been demonstrated in a variety of settings. Interpretation of the results of any assay requires an understanding of the range of factors that may influence the biomarker, particularly those factors unrelated to the condition being tested for. Some studies have suggested the use of lower natriuretic peptide cut points for diagnosing heart failure in obese individuals.[22] Our data raise the possibility that other metabolic traits should be taken into account when plasma natriuretic peptide measurements are interpreted. Whether diagnostic thresholds should be altered in individuals with the metabolic syndrome is unknown and warrants investigation in prospective studies.

Additionally, the clinical consequences of reduced circulating natriuretic peptides in individuals with the metabolic syndrome are unknown. Because natriuretic peptides play an important role in the counterregulatory response to volume and pressure overload, it is possible that lower natriuretic peptide levels contribute to the susceptibility of individuals with the metabolic syndrome to hypertension and left ventricular hypertrophy.[4,47] In transgenic animal models, reductions in natriuretic peptide levels of lesser magnitude than those observed here are associated with salt-sensitive hypertension,[48] although the applicability of such data to human disease remains speculative.

In summary, metabolic risk factors and components of the metabolic syndrome were associated with low natriuretic peptide levels, even after adjustment for body mass index. The interrelations of the natriuretic peptide axis, neurohormonal activation, and insulin resistance may have important clinical and pathophysiological implications. More data are needed regarding the temporal relations of low natriuretic peptide levels and insulin resistance, the effect of endogenous versus exogenous natriuretic peptides on insulin signaling, and the impact of reduced natriuretic peptide activity on the risk of cardiovascular events in the metabolic syndrome.

## Sources of Funding

## Disclosures

None.

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## CLINICAL PERSPECTIVE

Obesity is associated with reduced levels of natriuretic peptides, which are cardiac hormones that play critical roles in ventricular remodeling, sodium homeostasis, and regulation of vascular tone. Conflicting data exist on the relation of natriuretic peptide levels to other metabolic risk factors, although experimental studies suggest that the natriuretic peptides influence lipid and glucose metabolism. In this large, community-based study, we found that plasma natriuretic peptide levels were inversely associated with all components of the metabolic syndrome except for blood pressure, even after adjusting for body mass index. Multivariable-adjusted natriuretic peptide levels were lower in persons with the metabolic syndrome compared with those without the metabolic syndrome: In men, B-type natriuretic peptide was 24% lower ($P<0.001$) and N-terminal pro-atrial natriuretic peptide was 16% lower ($P<0.001$); in women, B-type natriuretic peptide was 29% lower ($P<0.001$) and N-terminal pro-atrial natriuretic peptide was 18% lower ($P<0.001$). Individuals with insulin resistance, as indicated by an elevated homeostasis model assessment index, had lower levels of B-type natriuretic peptide ($P=0.009$ in men, $P<0.001$ in women) and N-terminal pro-atrial natriuretic peptide ($P<0.001$ in men, $P=0.001$ in women). These findings suggest a close relation between lipid and glucose metabolism and the natriuretic peptide axis and support the hypothesis that extracardiac factors may influence circulating natriuretic peptide levels. Clinically, it may be important to take metabolic traits into account when interpreting plasma natriuretic peptide concentrations obtained for diagnostic or prognostic purposes. The results also raise the possibility that lower natriuretic peptide levels contribute to the susceptibility of individuals with the metabolic syndrome to hypertension and left ventricular hypertrophy.