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## ADIPONECTIN IS INDEPENDENTLY ASSOCIATED WITH NT-ProBNP: THE MULTI-ETHNIC STUDY OF ATHEROSCLEROSIS

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### Abstract

**Background and Aims**—To investigate the associations between selected adipokines and the N-terminal prohormone of B-type natriuretic peptide (NT-proBNP).

**Methods and Results**—1489 individuals enrolled in the Multi-Ethnic Study of Atherosclerosis were evaluated at 4 clinic visits about every 2 years. The evaluation included fasting venous blood, which was analyzed for NT-proBNP (at visits 1 and 3) and the adipokines adiponectin and leptin (at visits 2 and 3). The mean age was  $64.8 \pm 9.6$  years and 48% were female. After multivariable adjustment, a 1-SD increment in adiponectin was associated with a 14 pg/ml higher NT-proBNP level ( $p < 0.01$ ), while, compared to the 1<sup>st</sup> quartile of adiponectin, the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> quartiles had 28, 45 and 67% higher NT-proBNP levels ( $p < 0.01$  for all). For changes in NT-proBNP over the follow-up period, and after multivariable adjustment including baseline NT-proBNP, a 1-SD increment in adiponectin was associated with a 25 pg/ml absolute increase in NT-proBNP ( $p < 0.01$ ), while those in the 2<sup>nd</sup>, 3<sup>rd</sup> and 4<sup>th</sup> quartiles of adiponectin were associated with increases of 5, 28 and 65 pg/ml ( $p = 0.74, 0.09$  and  $< 0.01$ , respectively). There was a significant interaction between adiponectin and sex for visit 3 NT-proBNP ( $p$ -interaction  $< 0.01$ ), with significantly stronger associations in men. Leptin was not associated with NT-proBNP.

**Conclusion**—Higher adiponectin, but not leptin, is significantly associated with higher levels of NT-proBNP, as well as with greater longitudinal increases in NT-proBNP. The associations were stronger in men.

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## INTRODUCTION

Obese individuals often have higher levels of sympathetic nervous system activity[1], which results in activation of the renin-angiotensinogen-aldosterone system (RAAS) and renal tubular resorption of sodium.[2] Despite elevations in blood pressure due to these effects, and in the presence of excess adiposity, sodium resorption continues and extracellular volume expands.[3] The increased wall stress on the ventricle results in the release of the prohormone pro B-type natriuretic peptide (proBNP) from the myocardium, which is ultimately converted to the active hormone [BNP], and the inactive N-terminal fragment (NT-proBNP).[4] As volume overload is a typical finding in patients with heart failure, BNP and/or NT-proBNP have become standard screening tests for this condition.[6, 7, 8]

Adipokines are cytokines released from adipose tissue that have diverse physiologic effects. For example, leptin is a satiety hormone that increases with obesity, while adiponectin levels correlate inversely with fat mass and has been associated with lower CVD risk. Both are secreted by adipocytes.[9] We have previously shown that higher levels of leptin are associated with smaller left ventricular mass and volume, as well as a significantly lower odds for left ventricular hypertrophy[10], but higher levels of blood pressure and odds for prevalent hypertension. In this same study, higher levels of total adiponectin were associated with higher stroke volume and cardiac output. Given the linkages between excess adiposity and volume overload, and volume status to BNP, we conducted a study to test the hypothesis of significant associations between NT-proBNP and both adiponectin and leptin.

## METHODS

### Participants

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of African-, Chinese- and Hispanic-Americans, as well as non-Hispanic Whites. Details about the study design have been published.[11] In brief, between July 2000 and August 2002, 6,814 men and women who were 45 to 84 years old and free of clinically apparent cardiovascular disease (CVD) were recruited from 6 United States communities. Individuals with a history of physician-diagnosed heart attack, angina, heart failure, stroke or transient ischemic attack, or having undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement or pacemaker placement) were excluded from participation. Enrolled participants returned for follow-up clinic examinations on 3 subsequent visits at approximately 18-month intervals. All participants provided written informed consent and the institutional review boards (IRB) at the participating Universities approved the study.

At clinic exams 2 and 3, a random subsample of 1,970 participants (approximately . at each visit) enrolled in an ancillary study on body composition, inflammation and cardiovascular disease. [12] This included measurements for adiponectin and leptin from stored blood collected at those visits.

## Data Collection

At all clinic examinations, standardized questionnaires were used to obtain sociodemographic and health history information. Cigarette smoking was defined as current, former, or never. Height and weight were measured with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist and hip circumferences were measured using a standard flexible tape measure. Resting blood pressure was measured 3 times in seated participants with a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon, Tampa, FL), with the second and third readings being averaged and used in the analysis. Hypertension (HTN) was defined as systolic blood pressure  $\geq 140$  mm Hg, diastolic blood pressure  $\geq 90$  mm Hg, or current use of antihypertensive medication.

At the baseline clinic visit, MRI exams of the heart were performed using scanners with 1.5-Tesla magnets to determine specific measures of cardiac structure and function. [13] Imaging consisted of fast gradient echo cine LV images using a phased-array surface coil with time resolution of  $<50$  milliseconds and the following scan protocol: 6 mm slice thickness, 400 mm field of view,  $256 \times 128$  matrix,  $20^\circ$  flip angle, echo time (TE) = 3 – 5 msec and repetition time (TR) = 8 – 10 msec. Imaging data were read using MASS software version 4.2 (Medis, Leiden, the Netherlands) by technologists trained in the MESA protocol but without knowledge of risk factor information.

## Laboratory

At all clinic examinations, total and high density lipoprotein (HDL) cholesterol, triglycerides, and glucose levels were measured from blood samples obtained after a 12-hour fast. Fasting blood was also assayed for measures of systemic inflammation (C-reactive protein [CRP], fibrinogen, interleukin-6) and insulin concentration. Dyslipidemia was defined as a total-cholesterol/HDL-cholesterol ratio  $> 5.0$  or if the participant used medication to reduce cholesterol. Diabetes was defined as fasting glucose  $\geq 126$  mg/dL or use of hypoglycemic medication.

The core lab at the University of California San Diego analyzed stored blood samples obtained at clinic visits 1 and 3 for NT-proBNP using a highly sensitive and specific Elecsys electrochemiluminescence immunoassay (Roche Diagnostics Corporation, Indianapolis, IN). Samples from visits 2 or 3 were analyzed for leptin and total adiponectin using Bio-Rad Luminesx flow cytometry (Millipore, Billerica, MA) at the Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, VT).

## Statistical Analysis

The primary exposure variables were leptin and total adiponectin obtained at visits 2 or 3, while the primary outcome variable was NT-proBNP measured at visit 3. We also examined the associations with the change in NT-proBNP from visit 1 to visit 3. All covariate data (e.g. age, BMI, blood pressure, etc.) was used from values obtained at visit 3.

Among the 1,970 potential participants who had measurements of leptin and total adiponectin, and after accounting for missing covariate data and exclusion of those with

incident heart failure and acute myocardial infarction after visit 1, there were 1,489 individuals who had NT-proBNP measured at visit 3 and 1,452 who had NT-proBNP measured at visits 1 and 3 that could be used for analyses using the change in this biomarker. To reduce skewness, it was necessary to log transform visit 3 NT-proBNP. The change in NT-proBNP from visit 1 to 3 was normally distributed.

Differences in the cohort characteristics by quartile of NT-proBNP were tested for statistical significance using ANCOVA ( $P > F$  for ANCOVA) adjusting for age, sex and race. To determine the linear association between the adipokines and NT-proBNP, we utilized multivariable linear regression and the continuous and categorical (in quartiles) forms of leptin and total adiponectin. Then, to determine if there were significant associations with a relevant clinical cut-point for NT-proBNP (i.e.  $> 70$  pg/mL [14, 15]), we conducted multivariable logistic regression analyses using both the continuous and categorical forms of leptin and total adiponectin. For all regression analyses, the initial model 1 was adjusted for age, sex and race. Models were subsequently adjusted for additional covariates to include visit 1 NT-proBNP (in the analyses utilizing the change in this variable from visit 1 to visit 3). Of note, we compared the associations with adjustment for height and the waist to hip ratio versus adjustment for BMI. In the latter case, the changes in the effect sizes after the adjustment were smaller (i.e. likely accounted for less confounding). As such, we elected to use height and the waist to hip ratio (WHR) in the final models.

Multiplicative interactions between each adipokine and sex, race, BMI group and chronic kidney disease status (separately) for both visit 3 NT-proBNP and the change in this variable were assessed. A two-tailed  $p$ -value  $< 0.05$  was considered statistically significant and all statistical analyses were conducted using STATA (Version 13; StataCorp, College Station, TX).

## RESULTS

The mean age of the cohort was  $64.8 \pm 9.6$  years and 48% were female (Table 1). Forty-two percent were non-Hispanic White, 26% Hispanic/Latino, 18% African American and 14% Chinese American. The mean BMI and waist circumference values were  $28.1 \pm 5.2$  kg/m<sup>2</sup> and  $98 \pm 14$  cm, respectively, and 30% had a BMI greater than 30 kg/m<sup>2</sup>. Forty-seven percent of the participants were hypertensive, 40% were dyslipidemic, 14% had diabetes mellitus, 14% were classified with chronic kidney disease (i.e. eGFR  $< 60$ ) and 6% had a positive family history of premature myocardial infarction. Forty-seven percent were never smokers, 43% were former smokers and 10% were current smokers. Mean/median (standard deviation) values for total adiponectin, leptin and NT-proBNP were 20.6/17.3 (13.1)  $\mu$ g/ml, 20.3/13.1 (21.8) ng/ml and 123/67 (215) pg/mL, respectively.

Higher quartiles of NT-proBNP were significantly associated with increasing age and a higher proportion of women ( $p < 0.01$  for both) (Table 2). After adjustment for age, sex and race, significant differences by quartile of NT-proBNP were found for total and LDL-cholesterol, systolic blood pressure, pulse pressure, diagnosis of hypertension, urine albumin, eGFR, left ventricular mass and total adiponectin ( $p < 0.05$  for all). The differences for left ventricular ejection fraction were not statistically significantly different ( $p = 0.06$ ).

NT-proBNP levels were significantly higher among women (81 vs. 52 pg/mL;  $p < 0.01$ ), while Non-Hispanic Whites had the highest levels of NT-proBNP (78 pg/mL), followed by Hispanic/Latino (62 pg/mL), Chinese (53 pg/mL) and African Americans (52 pg/mL). Although there was a trend toward lower NT-proBNP levels with higher BMI, the difference was not statistically significant ( $p = 0.17$ ): BMI 18.5 – 25 [ $n = 431$ ]: 69 pg/mL, 25 – 30 [ $n = 588$ ]: 65 pg/mL, 30 – 40 [ $n = 393$ ]: 59 pg/mL, > 40 [ $n = 40$ ]: 67 pg/mL) while adiponectin was different by BMI group ( $p < 0.01$ ): 18.5 – 25: 25  $\mu\text{g/mL}$ , 25 – 30: 20  $\mu\text{g/mL}$ , 30 – 40: 18  $\mu\text{g/mL}$ , > 40: 15  $\mu\text{g/mL}$ ). NT-pro BNP did increase significantly across quartiles of total adiponectin ( $p < 0.01$ ): Q1: 50 pg/mL, Q2: 59 pg/mL, Q3: 69 pg/mL, Q4: 87 pg/mL;  $p < 0.01$ ), but decreased modestly across quartiles of leptin ( $p = 0.40$ ): Q1: 70 pg/mL, Q2: 65 pg/mL, Q3: 64 pg/mL, Q4: 60 pg/mL;  $p = 0.40$ ).

### Total Adiponectin

In multivariable linear regression models adjusted for age, sex and race/ethnicity, a 1-standard deviation (SD) increment in total adiponectin was associated with a 21 pg/ml higher visit 3 NT-proBNP concentration ( $p < 0.01$ ), which decreased minimally to 21 pg/ml ( $p < 0.01$ ) with additional adjustment for height, visceral and subcutaneous fat areas, dyslipidemia, diabetes, smoking, hypertension, eGFR, leptin, aldosterone and plasma renin activity (Table 3). The association was further attenuated, but remained statistically significant, with adjustment for left ventricular mass and ejection fraction (14 pg/ml,  $p < 0.01$ ). When total adiponectin was categorized into quartiles (Q1: < 11.8, Q2: 11.8 – 17.5, Q3: 17.5 – 26.3, Q4: > 26.3), and after full adjustment with all of the variables listed above, quartiles 2, 3 and 4 were associated with 15, 42 and 58% higher NT-proBNP concentrations respectively, compared to the first quartile.

After adjustment for age, sex and race/ethnicity, a 1- SD increment in total adiponectin was associated with an increase of 17 pg/ml in NT-proBNP from visit 1 to visit 3 ( $p < 0.01$ ) (Table 3). This association was accentuated (20 pg/ml,  $p < 0.01$ ) with additional adjustment for height, visceral and subcutaneous fat areas, dyslipidemia, diabetes, smoking, hypertension, eGFR, leptin, aldosterone, renin, left ventricular mass and left ventricular ejection fraction. The association was accentuated even more (24 pg/ml,  $p < 0.01$ ) when the baseline (visit 1) NT-proBNP level was added to the model. Moreover, compared to the 1<sup>st</sup> quartile, and in models that included all of the covariates listed above, the 3<sup>rd</sup> and 4<sup>th</sup> quartiles of total adiponectin were associated with 19 ( $p = 0.27$ ) and 43 pg/ml ( $p = 0.03$ ) higher increases in NT-proBNP from visit 1 to visit 3, while the increase among those in the 2<sup>nd</sup> quartile was not significantly different ( $-5$  pg/ml,  $p = 0.74$ ).

We then conducted multivariable logistic regression analyses to test the association between total adiponectin and the odds for having an NT-proBNP level greater than 70 pg/ml at visit 3. After adjustment for age, sex and race, a 1-SD increment in total adiponectin was associated with 56% higher odds of an NT-proBNP greater than this cut-point. The magnitude of the association was not materially changed with adjustment for all of the covariates used in the previous analyses. When total adiponectin was categorized into quartiles, and after adjustment for age, sex and race, the 3<sup>rd</sup> quartile was associated with over twice the odds (Odds Ratio: 2.21,  $p < 0.01$ ) for an elevated NT-proBNP, while those in

the 4<sup>th</sup> quartile had nearly 3-times the odds (2.93,  $p < 0.01$ ), compared to those in the 1<sup>st</sup> quartile (Figure 1). Those in the 2<sup>nd</sup> quartile did not have significantly different odds for an elevated NT-proBNP (1.36,  $p = 0.08$ ). Further adjustments accentuated the magnitudes of these associations.

The test for effect modification between total adiponectin and sex for NT-proBNP at visit 3 was significant ( $p < 0.01$ ). As such, we conducted analyses stratified by sex and found that the associations were significantly stronger among men such that, in the fully adjusted model, a 1-SD increment of total adiponectin was associated with a 25 pg/ml higher NT-proBNP level in men ( $p < 0.01$ ) and a 10 pg/ml higher in women ( $p < 0.01$ ). No other significant interactions were found.

### Leptin

Leptin (as a continuous or categorical [quartiles] variable) was not associated with NT-proBNP (data not shown).

## DISCUSSION

In this study of a relatively large, multi-ethnic population-based cohort from multiple sites across the United States, higher adiponectin concentrations were significantly associated with higher NT-proBNP levels independent of relevant covariates. The associations were significant for not only cross-sectional associations, but also for absolute changes in NT-proBNP over approximately 5 years. Moreover, a total adiponectin level above the median was associated with at least twice the odds for having an NT-proBNP value greater than 70 pg/ml. At the same time, there were no significant associations between leptin and NT-proBNP in analyses using cross-sectional or longitudinal data. These findings indicate a complex relationship between selected cytokines released from adipose tissue and NT-proBNP.

Based on previous findings linking BNP to left ventricular structure and function[16], and the results we have published that showed significant associations between leptin and left ventricular mass, volume and hypertrophy[10], we hypothesized that leptin would be inversely associated with NT-proBNP levels. The results of the current study do not support this supposition. Rather, adiponectin was strongly and robustly associated with NT-proBNP levels, which has been demonstrated previously in patients after acute coronary syndromes. [17] The logical next question is, why the difference in the associations for adiponectin and leptin with NT-proBNP?

Both of these hormones appear to be important in glucose regulation by increasing insulin sensitivity. In this regard, tumor necrosis factor - alpha (TNF- $\alpha$ ) has been shown to decrease insulin sensitivity and leptin secretion[18], while adiponectin decreases both the production and activity of TNF- $\alpha$ . [19] Despite these differences, both adiponectin and leptin increase fatty acid oxidation and thermogenesis.[20] From this, it is not readily apparent why adiponectin is significantly associated with NT-proBNP and leptin is not.

We further explored this question by examining several published relationships of adiponectin and NT-proBNP with common anatomic or physiologic characteristics. First, adiponectin is inversely associated with measures of diastolic dysfunction, but not ejection fraction (i.e. systolic dysfunction).[21] Since diastolic dysfunction is related to higher ventricular wall stress, and NT-proBNP would rise correspondingly to the latter, diastolic dysfunction would predict lower levels of adiponectin but higher levels of NT-proBNP. Notably, previous studies have shown associations between adiponectin and incident CVD are no longer significant after adjustment for NT-proBNP suggesting a complex relationship between these variables.[22] Second, adiponectin is inversely associated with insulin resistance, waist circumference and triglycerides.[20, 23–25] However, using existing data in the MESA, none of the correlations between NT-proBNP and waist circumference and the waist to hip ratio, as well as fasting triglycerides, insulin and glucose were significant ( $r = -0.03, -0.02, -0.01, -0.05$  and  $0.01$ , respectively). Similarly, NT-proBNP is lower among those who are obese[26], which, in some circumstances, may be due to treatment with antihypertensive agents.[27] In the analysis for this report, we tested for effect modification of NT-proBNP by BMI category, which was not significant. Also, our findings were persistent after adjustment for blood pressure medications. Third, higher adiponectin is inversely associated with aldosterone[28] and, as mentioned above, NT-proBNP influences the RAAS system resulting in sodium natriuresis to reduce fluid volume. As an increase in aldosterone would increase fluid volume, and thereby NT-proBNP, and adiponectin is inversely associated with aldosterone, it does not appear that this RAAS hormone could explain the positive association between adiponectin and NT-proBNP. Moreover, from our data, NT-proBNP was not correlated with aldosterone ( $r = 0.01$ ).

Given that adiponectin is secreted predominately by visceral fat and leptin by subcutaneous fat, physiologic differences between these fat depots may provide insight into the association between adiponectin and NT-proBNP.[9] In this regard, TNF- $\alpha$  is released from visceral adipose tissue and results in decreased expression of adiponectin.[29] As higher levels of obesity are associated with lower NT-proBNP levels, it seems plausible that visceral adipose tissue may be the common link. Indeed, there is some evidence for a strong correlation between visceral fat and higher NTproBNP. [30] This hypothesis requires further investigation.

As can be surmised from the discussion provided above, the physiology between adiponectin and NT-proBNP is quite complex. In some ways, the available data suggests that the association could be inverse. On the other hand, nonconcomitant studies suggest that visceral adipose tissue may be the common factor that links these two biomarkers physiologically. Given the burgeoning nature of both obesity and heart failure, we believe further study of this complex relationship is indicated.

Strengths of this study include a relatively large, well-characterized, multi-ethnic cohort from across the United States that is free of clinical CVD and both valid and reproducible measures of two different adipokines. Limitations include few subjects at the highest levels of obesity and a pseudo longitudinal study design whereby the adipokine measures were collected during the follow-up period, which may limit inferences on causality. Additionally, it may be possible that there is residual confounding.



In conclusion, total adiponectin, and not leptin, is significantly and independently associated with NT-proBNP among a multi-ethnic cohort that had no clinical evidence of cardiovascular disease at baseline. Moreover, the associations appear to be stronger in men, but not by race/ethnic group. These findings suggest a potentially important, albeit potentially paradoxical, relationship between adiponectin and NT-proBNP.

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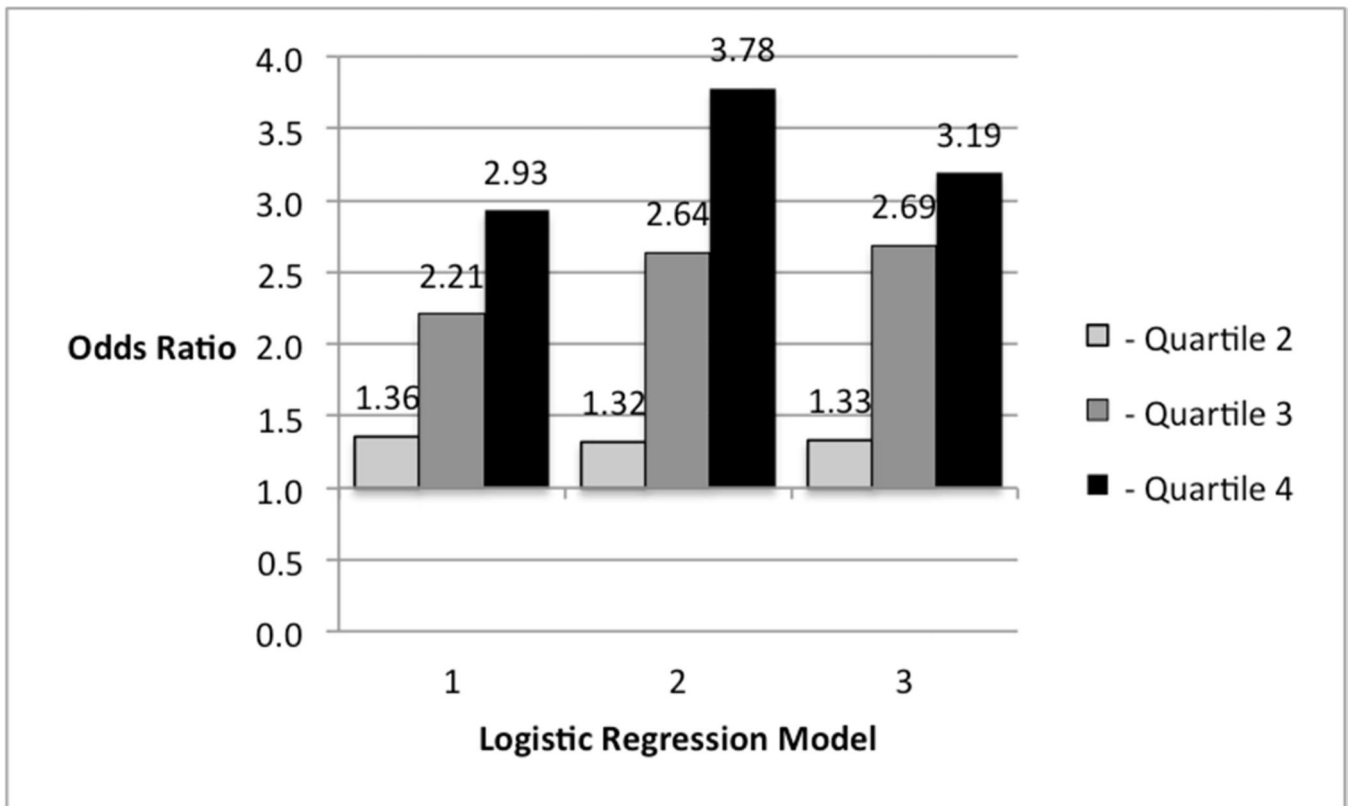
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**HIGHLIGHTS**

1. We examined the cross-sectional and longitudinal associations between two adipokines (adiponectin and leptin) and NT-pro BNP.
2. Higher adiponectin was found to be associated with higher NT-pro BNP, larger increases in NT-pro BNP over 5 years and a higher odds of having an NT-pro BNP greater than 70 pg/mL.
3. The association between adiponectin and NT-pro BNP was significantly larger in men.
4. Leptin was not associated with NT-pro BNP.



**FIGURE 1. ASSOCIATIONS BETWEEN QUARTILES OF TOTAL ADIPONECTIN AND A VISIT 3 NT-PROBNP VALUE > 70 pg/ml**

Referent Category = Quartile 1

Model 1: age, sex, race

Model 2: Model 1 + height, waist to hip ratio, dyslipidemia, diabetes, smoking, hypertension, eGFR, leptin, aldosterone and renin

Model 3: Model 2 + LV mass and LV ejection fraction

TABLE 1

## COHORT CHARACTERISTICS

Characteristic	Mean (SD)/Median or Frequency (%)
Visit 1 NT-pro BNP (pg/ml)	90.8 (128.5)/54.6
Visit 3 NT-pro BNP (pg/ml)	122.6 (214.9)/66.7
NT-pro BNP Difference (Visit 3 – Visit 1)	32.7 (11.6)/11.6
Visit 3 NT-pro BNP > 70 pg/ml	714 (48.0%)
Age (years)	64.8 (9.6)/65
Gender (male)	768 (51.6%)
Race	
-Non-Hispanic White	627 (42.1%)
-Chinese	210 (14.1%)
-African American	266 (17.9%)
-Hispanic	385 (25.9%)
Waist circumference (cm)	98.3 (14.1)/97
Hip circumference (cm)	104.3 (10.9)/102.6
BMI (kg/m <sup>2</sup> )	28.1 (5.2)/27.3
Waist to Hip Ratio	0.94 (0.07)/0.95
<b>Visceral Fat Area (cm<sup>2</sup>)</b>	<b>148 (69.2)/137</b>
<b>Subcutaneous Fat Area (cm<sup>2</sup>)</b>	<b>254 (117.7)/236</b>
Dyslipidemia (Y/N)	587 (40.2%)
Triglycerides (mg/dl)	135 (98)/116
Glucose (mg/dl)	98 (26)/91
Diabetes Mellitus	211 (14.2%)
Smoking	
-Current	151 (10.2%)
-Former	636 (43.1%)
-Never	689 (46.7%)
Systolic Blood Pressure (mmHg)	124 (20)/121
Diastolic Blood Pressure (mmHg)	70 (10)/70
Hypertension	697 (47.2%)
eGFR by CKD Epi (ml/min/1.73 m <sup>2</sup> )	79 (17)/79
Chronic Kidney Disease (eGFR < 60)	209 (14.1%)
Family History of Premature Myocardial Infarction	89 (6%)
Adiponectin (µg/ml)	21 (13)/17
Leptin (ng/ml)	20 (22)/13
Aldosterone (pg/ml)	151 (88)/131
Renin (ng/ml)	1.45 (3.3)/0.57
End-Diastolic LV Mass (grams)	147 (39)/141
LV Ejection Fraction (%)	69 (7)/70

N = 1,489 for visit 3 variables; N = 1,452 for change in NT-proBNP from visit 1 to visit 3

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**TABLE 2**  
**MEANS OF THE COHORT CHARACTERISTICS BY QUARTILE OF NT-proBNP**

Characteristic	VISIT 3 NT-proBNP				p-value
	Q1	Q2	Q3	Q4	
Age (years)	59.4	62.3	66.3	71.1	<0.01
Sex (male)	69.6	51.2	46.0	40.0	<0.01
Waist circumference (cm)*	97.7	97.0	96.6	95.9	0.45
Hip circumference (cm)*	103.5	102.7	102.6	102.5	0.60
BMI (kg/m <sup>2</sup> )*	28.0	27.5	27.4	27.2	0.19
Waist to Hip Ratio*	0.9	0.9	0.9	0.9	0.40
<b>Visceral Fat Area (cm<sup>2</sup>)*</b>	<b>147</b>	<b>144</b>	<b>149</b>	<b>140</b>	<b>0.25</b>
<b>Subcutaneous Fat Area (cm<sup>2</sup>)*</b>	<b>250</b>	<b>238</b>	<b>243</b>	<b>234</b>	<b>0.34</b>
Dyslipidemia (Y/N)*	38.9	36.3	37.7	36.7	0.90
Triglycerides (mg/dl)*	136.3	140.6	133.2	133.6	0.75
Glucose (mg/dl)*	97.0	100.5	97.4	97.2	0.22
Diabetes (Y/N)*	12.7	13.2	12.9	18.0	0.18
Ever Smoker*	50.1	46.8	52.5	50.7	0.46
Systolic Blood Pressure (mmHg)*	120.4	123.3	126.0	129.6	<0.01
Diastolic Blood Pressure (mmHg)*	68.9	68.9	69.5	69.7	0.71
Hypertension (Y/N)*	41.0	45.8	49.9	63.3	<0.01
eGFR by CKD Epi (ml/min/1.73 m <sup>2</sup> )*	79.3	79.5	78.9	76.2	0.03
CKD (eGFR < 60)*	15.3	16.4	17.7	21.6	0.12
Adiponectin (µg/ml)*	16.5	18.3	20.2	24.0	<0.01
Leptin (ng/ml)*	20.8	20.0	20.3	19.5	0.88
Aldosterone (pg/ml)*	152.6	142.2	153.6	150.4	0.32
Renin (ng/ml)*	1.6	1.4	1.0	1.1	0.11



Characteristic	VISIT 3 NT-proBNP				p-value
	Q1	Q2	Q3	Q4	
End-Diastolic LV Mass (g)*	139.3	139.8	142.8	152.9	<0.01
LV Ejection Fraction (%)*	70.1	70.2	69.9	68.6	0.06

Q1 = Quartile 1 (< 34.4 pg/ml), Q2 = Quartile 2 (34.4 – 66.7 pg/ml), Q3 = Quartile 3 (66.7 – 130.1 pg/ml), Q4 = Quartile 4 (> 130.1 pg/ml)

\* Adjusted for age, sex and race.

**TABLE 3**  
**MULTIVARIABLE LINEAR ASSOCIATIONS BETWEEN TOTAL ADIPONECTIN AND NT-proBNP**

Adipokine	OUTCOME: Visit 3 NT-Pro BNP (pg/ml)							
	Model 1		Model 2		Model 3*		Model 4**	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Adiponectin (1-SD)	21.16	<0.01	21.0	<0.01	14.0	<0.01		
Adiponectin Quartiles								
-Q2*	1.16	0.03	1.16	0.06	1.15	0.09		
-Q3*	1.40	<0.01	1.41	<0.01	1.42	<0.01		
-Q4*	1.74	<0.01	1.65	<0.01	1.58	<0.01		
Adipokine	OUTCOME: NT-Pro BNP Change from Visit 1 to Visit 3 (pg/ml)							
	Model 1		Model 2		Model 3		Model 4**	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
Adiponectin (1-SD)	16.9	<0.01	16.3	<0.01	19.8	<0.01	23.9	<0.01
Adiponectin Quartiles								
-Q2	-7.9	0.55	-15.0	0.35	-7.7	0.65	-5.0	0.77
-Q3	13.1	0.34	14.8	0.37	13.9	0.43	18.9	0.27
-Q4	34.4	0.02	27.6	0.13	31.9	0.11	43.0	0.03

1-SD = 1-standard deviation increment of total adiponectin (13.1 µg/ml), Parameter estimate is a percent (i.e. 1.16 = 16% higher than reference)

\*  $R^2$  (1-SD) = 0.36,  $R^2$  (Quartiles) = 0.37;

\*\*  $R^2$  = 0.09,  $R^2$  = 0.09

Model 1: age, sex and race

Model 2: Model 1 + height, visceral and subcutaneous fat areas, dyslipidemia, diabetes, smoking, hypertension, eGFR, leptin, aldosterone & renin

Model 3: Model 2 + left ventricular mass and left ventricular ejection fraction

Model 4: Model 3 + NT-proBNP (visit 1 value)