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Relation of Plasma Total and High-Molecular-Weight Adiponectin to New-Onset Heart Failure in Adults ≥ 65 Years of Age (From the Cardiovascular Health Study)

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Abstract

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Conflicts of interest/Disclosures

None.

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Adiponectin exhibits cardioprotective properties in experimental studies, but elevated levels have been linked to increased mortality in older adults and patients with chronic heart failure (HF). The adipokine's association with new-onset HF remains less well defined. We investigated the associations of total and HMW adiponectin with incident HF (n=780) and, in a subset, echocardiographic parameters in a community-based cohort of adults 65 and older. Total and high molecular weight (HMW) adiponectin were measured in 3,228 subjects without prevalent HF or CVD. The relationships of total and HMW adiponectin with HF were nonlinear, with significant associations observed only above their medians (12.4 and 6.2 mg/L, respectively). After adjustment for potential confounders, the hazard ratios (HR) per standard deviation (SD) increment in total adiponectin were 0.93 (95% confidence interval [CI]=0.72–1.21) below the median and 1.25 (95% CI=1.14–1.38) above it. There was a suggestion of effect modification by body mass index (BMI), whereby the association appeared strongest among participants with lower BMIs. Consistent with the HF findings, higher adiponectin tended to be associated with left ventricular systolic dysfunction and left atrial enlargement. Results were similar for HMW adiponectin. In conclusion, total and HMW adiponectin showed comparable relationships with incident HF in this older cohort, with a threshold effect of increasing risk occurring at their median concentrations. High levels of adiponectin may mark or mediate age-related processes that lead to HF in older adults.

Keywords

Adiponectin; Aging; Heart Failure

Obesity and diabetes are foremost risk factors for heart failure (HF),¹ which has drawn attention to the adipocyte-derived hormone adiponectin as a potential pathophysiological mediator.² Adiponectin exhibits insulin-sensitizing and anti-atherogenic properties, and the ability to counter ischemia-reperfusion injury, apoptosis, and hypertrophic signaling in cardiomyocytes.² Clinical studies in healthy, middle-aged adults have reported inverse associations of adiponectin with left ventricular (LV) mass^{3,4} and diastolic function,⁵ suggesting that the adipokine could offer protection against HF. Among patients with established HF, however, higher adiponectin concentrations portend increased mortality.⁶ This positive association is influenced by natriuretic peptides, which can directly stimulate adiponectin secretion,⁷ and by the weight loss that characterizes HF-associated cachexia, such that higher adiponectin levels in this setting may reflect underlying HF severity. This may account for the relationship observed for higher adiponectin levels with worse LV systolic function in older, higher-risk adults, which was attenuated by adjustment for natriuretic peptides.⁸ Still, the association between adiponectin and incident HF is not well defined. Whereas 2 modest-size population-based studies^{9,10} reported null associations for total adiponectin and new-onset HF, a larger investigation suggested a J-shaped association in men.¹¹ Moreover, no prospective study to date has examined this relationship for the reportedly more bioactive HMW adiponectin.² We therefore investigated the associations of total and HMW adiponectin with new-onset HF in a large older cohort, and also explored the adipokine's relationship to LV structure and function in a subset with available echocardiograms.

Methods

The Cardiovascular Health Study (CHS) is a prospective survey of risk factors for cardiovascular disease (CVD) in community-living U.S. adults aged 65.^{12,13} An original cohort of 5,201 individuals was enrolled in 1989–90. A second cohort of 687 African-Americans was recruited in 1992–93. All subjects underwent health evaluations per standardized protocols.^{12,13}

Of the 5,553 subjects who participated in the 1992–93 examination (hereafter “baseline”), 4,715 had samples available for adiponectin measurement. For the current analyses, subjects with prevalent HF, atrial fibrillation or CVD were excluded (n=1,444). These conditions were ascertained through questionnaires, review of medical records or adjudication of interim events. Another 43 subjects were excluded for missing laboratory measures assayed after baseline that were not part of the initial study-wide imputation, leaving 3,228 eligible participants.

Anthropometry was assessed in standard fashion.¹⁴ Hypertension was defined by blood pressure ≥ 140 mm Hg systolic or ≥ 90 diastolic or by self-report and anti-hypertensive treatment. Diabetes was defined by fasting glucose ≥ 126 mg/dl or hypoglycemic therapy. Subclinical CVD was based on carotid ultrasound, ankle-brachial index, ECG, and Rose angina questionnaire.^{15,16} Blood samples were collected after a 12-hour overnight fast, and laboratory testing performed as reported.¹⁷ Homeostasis model assessment of insulin resistance (HOMA-IR) and cystatin C-based estimated glomerular filtration rate (eGFR) were calculated using standard methods.^{18,19} Total and HMW adiponectin were measured by ELISA (Millipore, Billerica, MA) on stored EDTA-plasma; inter-assay analytical CV's were 6.9% and 11.1%, respectively.

Two-dimensional and Doppler echocardiograms were obtained in 1994–95 following standardized protocols.²⁰ LV mass was indexed to sex, height and weight, and anteroposterior left atrial (LA) diameter to sex and height only, based on regression equations derived in a healthy subset of the cohort (BMI < 30 kg/m² and absence of hypertension, diabetes, clinical and subclinical CVD, and cardiovascular medications) using previously described methods.²¹ The corresponding indices, LV mass/(e^{4.47+0.1[male]} × height^{-0.64} × weight^{0.72}) and LA diameter/(e^{-0.16+0.05[male]} × height^{0.28}), were then multiplied by 100 to yield percent predicted LV mass and LA diameter. LV hypertrophy and LA enlargement were defined as percent predicted values $>95^{\text{th}}$ ile, or $>144\%$ and 126% , respectively. LV ejection fraction was classified as normal vs. reduced (vs. $<55\%$). Diastolic function was assessed by the transmitral E/A ratio (<0.7 , $0.7\text{--}1.5$, >1.5).²⁰

Semi-annual contacts were used to survey for potential clinical events.²² All potential incident events were confirmed through review of subjects' medical records. Both diagnosis and treatment were used to determine the presence of HF. The CHS cardiovascular events committee also reviewed symptoms, signs and chest X-ray findings of HF in order to classify all events.^{20,22}

Cross-sectional associations of adiponectin with covariates were evaluated by Pearson correlations or Student's t test. Missing data on baseline covariates (n=273) were handled by carry-forward of previous values or multiple imputation. Associations of total and HMW adiponectin with incident HF were evaluated with Cox models (with the proportional hazards assumption verified by Schoenfeld residuals), while those with echocardiographic measures (after excluding interim HF cases) were assessed with logistic regression. The functional forms of these associations were evaluated with penalized cubic splines. Based on visual inspection of the cubic spline plots, and previous data,²³ continuous associations of total and HMW adiponectin with HF were modeled using linear splines with knots at their median concentrations.

To determine the independent associations of total and HMW adiponectin with outcome, we fit models to adjust for aggregate potential confounding. Models were initially adjusted for age, sex and race. Thereafter, we considered an array of covariates previously linked to adiponectin levels, arriving at a parsimonious model that additionally included income, systolic and diastolic blood pressure, body mass index (BMI), angiotensin-converting-

enzyme (ACE) inhibitors, current smoking, alcohol use, self-reported health status, and eGFR. We also adjusted for confounding by N-terminal pro-brain natriuretic peptide (NT-proBNP) in the subset with available measurements (n=2,500). For incident HF, exploratory analyses evaluated the influence of putative mediators, consisting of subclinical CVD, diabetes, lipids, and C-reactive protein (CRP). We also examined the impact of adjusting for interim CHD as a time-varying covariate. Assessment for interaction with key covariates entailed inclusion of cross-product terms.

All analyses were performed with STATA, version 11.0 (College Station, TX), or R version 2.13.0 (<http://www.r-project.org>).

Results

Eligible participants had a mean age of 74 ± 5 years and 63.5% were women. Table 1 displays the associations of total adiponectin with baseline covariates. Adiponectin was positively correlated with age, HDL, and NT-proBNP, but negatively correlated with BMI, waist-hip ratio, diastolic blood pressure, HOMA-IR, LDL, triglycerides, physical activity and CRP. In turn, total and HMW were highly positively correlated. Furthermore, total adiponectin levels were higher in women, non-blacks, alcohol drinkers, and participants with prior weight loss or LA enlargement. Concentrations were instead lower in subjects with more modest incomes, with hypertension, diabetes, or subclinical CVD, or receiving anti-hypertensive therapy.

During a median follow-up of 11.7 years, 780 incident HF events occurred. Adjusted cubic splines analyses demonstrated that the association of total adiponectin with incident HF was non-linear ($p=0.012$), with a suggestion of a similar non-linear relationship for HMW adiponectin ($p=0.12$) (Figure 1). The relationships were such that, below median levels of total adiponectin (12.4 mg/L) and HMW adiponectin (6.2 mg/L), there were no significant associations with incident HF at various levels of adjustment for potential confounders, including NT-proBNP (Table 2, models 1–3). Above their median concentrations, however, total and HMW adiponectin exhibited significant direct associations with new-onset HF. After extensive adjustment for confounders (model 2), for every SD increment in total adiponectin ($SD=7.9$ mg/L) or HMW adiponectin ($SD=5.9$ mg/L), HF risk increased by about one-quarter. This was attenuated slightly by additional adjustment for NT-proBNP (model 3).

Further adjustment for putative metabolic and inflammatory mediators (model 4), however, led to higher risk estimates in the lower range of concentrations for total and HMW adiponectin (Table 2). This was characterized by a tendency toward an increased risk of HF with rising concentrations, making the association of either measure with HF more linear across its distribution. No meaningful change in risk estimates occurred at the upper range of concentrations. Findings were unchanged after additional adjustment for subclinical CVD or HOMA-IR.

We observed no significant interaction by age, sex, race, diabetes or health status ($p>0.12$). There was a suggestion of effect modification by BMI for total ($p=0.010$) and HMW adiponectin ($p=0.057$), however, whereby the direct association with HF observed for adiponectin levels greater than their medians appeared strongest among participants with lower BMI. For instance, stratifying participants by WHO categories of BMI, those with $BMI < 25$ kg/m² showed a significant relationship for total adiponectin above its median concentration (adjusted HR per SD [model 2] = 1.37 [95% CI=1.21–1.55]), but this was inapparent among participants in higher BMI strata ($BMI=25$ – 29.9 kg/m², adjusted HR=1.13 [95% CI=0.95–1.34]; $BMI \geq 30$ kg/m², adjusted HR=0.91 [95% CI=0.64–1.32]).

This interaction persisted after exclusion of participants with BMI<18.5 kg/m² or those with fair or poor health status.

There was no evidence of a differential effect of adiponectin on systolic vs. diastolic HF in the subset of 356 participants in whom HF type could be ascertained. Furthermore, the overall findings were not meaningfully altered following adjustment for incident CHD (n=113), nor were they materially different after exclusion of elevated NT-proBNP or antecedent weight loss.

Unlike the associations with incident HF, there was no evidence of a non-linear relationship between adiponectin measures and echocardiographic parameters (p>0.09). There were no significant associations between total adiponectin and LV hypertrophy (adjusted [model 2] odds ratio [OR]=1.04 per SD increase, 95% CI=0.88–1.23) or high (>1.5) transmitral E/A as compared to normal (0.7–1.5) (adjusted OR=1.11 per SD, 95% CI=0.88–1.40). Total adiponectin did show a significant inverse association with low (<0.7) transmitral E/A compared to normal (adjusted OR=0.88 per SD, 95% CI=0.78–0.99), as well as borderline direct associations with LA enlargement (adjusted OR=1.13 per SD, 95% CI=0.99–1.32, p=0.097) and reduced LV systolic function (adjusted OR=1.23 per SD, 95% CI=1.00–1.51, p=0.054), but these were abolished by adjustment for NT-proBNP. To mirror the approach taken with incident HF, corresponding findings stratified by the median concentration of total adiponectin are presented in Table 3, which suggest that such associations occurred predominantly above the median. Findings were similar for HMW adiponectin. There was no interaction with BMI in these associations.

Discussion

To our knowledge, this study is the largest to date to investigate the association of total and HMW adiponectin with incident HF in older men and women. Our analyses in community-dwelling elders show that the associations of total and HMW adiponectin with HF were similar and characterized by a threshold effect, whereby higher concentrations above, but not below, the median conferred significantly increased risks of this outcome. These increased risks of HF in the higher range of adiponectin levels persisted after adjustment for potential confounders, including NT-proBNP, and remained largely unchanged after excluding participants with elevated baseline NT-proBNP levels or antecedent weight loss.

Consistent with the direct association with incident HF, higher adiponectin levels tended to be associated with reduced LV systolic function and increased LA diameter in the subset of participants who completed echocardiograms 2 years later, although no departure from linearity was detected. Higher adiponectin was also associated with a decreased prevalence of low transmitral E/A ratio, with no difference in high transmitral E/A ratio, as compared to E/A values in the intermediate range, the significance of which is less clear given the limited accuracy of this measure in isolation for the assessment of LV diastolic function.²⁴ Unlike the findings for incident HF, however, these associations were abolished after adjustment for NT-proBNP.

Three prior population-based studies have evaluated the relationship between total adiponectin and incident HF. Two of these studies^{9,10} did not find significant associations, but they had limited power to characterize the relationship. A third reported a J-shaped relationship with incident HF in middle-aged men,¹¹ but the association lost significance after adjustment for BMI, whose role is more fitting as a potential confounder than as a mediator.

By contrast, in hospitalized patients with advanced HF, higher adiponectin has been documented to predict mortality⁶, a finding replicated in the CHS cohort for community-

dwelling elders.²³ Discrepancies have likewise been observed in studies correlating echocardiographic measures of cardiac structure and function, wherein healthy younger populations exhibit inverse associations between total adiponectin and LV hypertrophy,^{3,4} whereas older, higher-risk cohorts show a positive relationship between adipokine levels and reduced LV systolic function.⁸ Such contrasting associations were also noted in a community-based study of African-Americans, in whom adiponectin's relationship with LV mass was inverse in the absence of hypertension and insulin resistance, but direct otherwise.²⁵

Our findings regarding incident HF conform to the overall pattern of opposite associations observed with other adverse outcomes in healthy, middle-aged cohorts versus older populations or those with prevalent CVD.²⁶ Although the basis for this paradox remains incompletely defined, the positive associations of adiponectin with adverse outcomes despite the adipokine's beneficial experimental properties^{2,27} are perhaps best understood in the context of established HF. In this setting, three fundamental processes contribute to a rise in adiponectin levels that is proportional to the severity of the underlying HF. First is the increase in circulating natriuretic peptides, produced by the myocardium in response to elevated cardiac strain, which directly stimulate adipocyte secretion of adiponectin.⁷ The second, occurring in advanced HF, is the development of "cardiac cachexia," in which loss of weight and, with it, adipose mass, lead to a corresponding increase in circulating adiponectin levels.⁶ The third is impaired kidney function from decreased cardiac output, which raises adiponectin levels through reduced excretion.²⁸ Hence, in the setting of advanced HF, these different factors drive adiponectin levels higher, and such elevations may serve as a strong marker of overall HF-associated risk.

Furthermore, the finding that adiponectin promotes opsonization of apoptotic bodies for macrophage disposal has led to the notion that the adipokine serves an important housekeeping role.²⁷ Such a role in clearance of apoptotic cells would suggest that, for older adults, higher concentrations in the upper range may reflect reactive increases in adiponectin whose beneficial endocrine actions might no longer be operative (i.e., functional adiponectin resistance)²⁹ or are otherwise eclipsed by the heightened risks associated with underlying disease processes.

No U-shaped association emerged for incident HF as it did for CVD or mortality in this cohort.²³ Yet adjustment for metabolic and inflammatory intermediates appeared to unmask a direct association with incident HF. The latter finding suggests that any favorable effects on HF of adiponectin increases in the lower range of concentrations may be offset by associations with deleterious underlying processes that remain to be delineated.

Turning to the suggestion of effect modification by BMI uncovered herein, the true validity of the nominally significant interaction for total, but not for HMW adiponectin, is uncertain in the setting of multiple testing, and will require independent confirmation. Still, aging-associated weight loss and sarcopenia are strong markers of aging-related decline that are linked to higher adiponectin levels.^{16,30} If confirmed, an interaction whereby the adiponectin-associated risk of HF occurs predominantly at lower BMI could signal that reactive increases in adiponectin levels in response to unmeasured factors reflecting the homeostatic stress of declining weight are themselves potential contributors to such risk.

Among our study's limitations, echocardiographic data were only available in a subset, and current state-of-the-art measurements of LA size or LV diastolic function were not performed, which restricts the information obtainable from our analyses of echocardiographic measures. Similarly, NT-proBNP was available only for a subgroup, although there is no evidence that participants with and without such measurements differed

systematically from each other. We were also unable to study meaningful associations with systolic versus diastolic HF separately, because such data were unavailable in over half of incident HF cases. Additionally, this prospective observational study is only able to detect associations, but insights into causal mechanisms will require serial measurements of adiponectin to establish temporal relationships, along with molecular and genetic approaches to disentangle the contributing pathways.

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Figure 1. Relationship of adiponectin and incident HF - Spline regression graphs depict the associations of continuous levels of total adiponectin (right panel) and HMW adiponectin (left panel) with incident HF, after adjustment for covariates in model 2, Table 2. The 95% CI are presented in light gray.

Table 1

Associations of Total Adiponectin with Baseline Covariates

Covariate	Correlation Coefficient or Geometric Mean (95% Confidence Interval) in mg/L	p
Age (years)	0.20	<0.001
Sex		<0.001
Female	14.1 (13.8–14.4)	
Male	9.9 (9.6–10.2)	
Race-ethnicity		<0.001
Non-black	13.1 (12.8–13.3)	
Black	9.4 (8.9–9.8)	
Income <\$16,000		0.009
Yes	12.0 (11.6–12.4)	
No	12.6 (12.3–12.9)	
Body mass index (kg/m ²)	−0.33	<0.001
Waist-hip ratio	−0.36	<0.001
Hypertension		<0.001
Yes	11.7 (11.4–12.1)	
No	12.8 (12.5–13.1)	
Systolic blood pressure (mm Hg)	0.01	0.700
Diastolic blood pressure (mm Hg)	−0.06	0.001
Diabetes mellitus		<0.001
Yes	8.7 (8.2–9.2)	
No	13.0 (12.8–13.2)	
Homeostasis model assessment of insulin resistance [*]	−0.17	<0.001
Low-density lipoprotein (mg/dL)	−0.03	0.049
High-density lipoprotein (mg/dL)	0.48	<0.001
Triglycerides [†] (mg/dL)	−0.32	<0.001
Current smoker		0.081
Yes	11.8 (11.2–12.5)	
No	12.5 (12.2–12.7)	
7 alcoholic drinks/week		<0.001
Yes	13.4 (12.8–14.1)	
No	12.2 (12.0–12.5)	
Physical activity (kcal/week) ^b	−0.04	0.028
Lipid-lowering medication		0.004
Yes	11.3 (10.5–12.0)	
No	12.5 (12.2–12.7)	
Use of any anti-hypertensive medication		<0.001
Yes	11.6 (11.2–11.9)	

Covariate	Correlation Coefficient or Geometric Mean (95% Confidence Interval) in mg/L	p
No	12.9 (12.6–13.2)	
Beta-blocker use		<0.001
Yes	10.3 (9.7–10.9)	
No	12.6 (12.4–12.8)	
Angiotensin-converting-enzyme inhibitor use		<0.001
Yes	10.8 (10.2–11.5)	
No	12.5 (12.3–12.8)	
Weight loss >10 lbs in previous 3 years [‡]		<0.001
Yes	14.8 (13.8–15.9)	
No	12.8 (12.5–13.0)	
Fair/Poor Health Status		0.990
Yes	12.4 (11.8–13.0)	
No	12.4 (12.2–12.6)	
Serum albumin (mg/dL)	−0.03	0.053
Estimated glomerular filtration rate (mL/min/1.73 m ²)	0.01	0.530
C-reactive protein (mg/L)	−0.08	<0.001
N-terminal pro-brain natriuretic peptide (pg/mL)	0.17	<0.001
High-molecular-weight adiponectin (mg/L)	0.93	<0.001
Subclinical cardiovascular disease		<0.001
Yes	12.1 (11.8–12.4)	
No	12.9 (12.6–13.3)	
Left ventricular hypertrophy		0.34
Yes	12.0 (11.2–12.8)	
No	12.4 (12.1–12.7)	
Reduced left ventricular systolic function		0.73
Yes	12.1 (11.1–13.2)	
No	12.3 (12.1–12.6)	
Left ventricular diastolic function (transmitral E/A)		0.14
<0.7	12.6 (11.3–14.1)	
0.7–1.5	12.3 (12.0–12.5)	
>1.5	11.7 (11.2–12.2)	
Dilated left atrial diameter		<0.001
Yes	14.4 (13.3–15.7)	
No	12.0 (11.8–12.3)	

* In subjects not receiving hypoglycemic medication (n=3,012).

[†] Log-transformed variable.

[‡] Available for original cohort only (n=2,815).

Table 2

Relations of Adiponectin with Incident Heart Failure

Hazard Ratio per Standard Deviation* Increase (95% Confidence Interval), p		
	<Median	Median
Total Adiponectin (Median=12.4 mg/L)		
Model 1 [†]	0.83 (0.64–1.07), 0.14	1.15 (1.04–1.26), 0.005
Model 2 [‡]	0.93 (0.72–1.21), 0.61	1.25 (1.14–1.38), <0.001
Model 3 [§]	0.97 (0.72–1.30), 0.84	1.18 (1.05–1.32), 0.004
Model 4 [\]	1.23 (0.94–1.61), 0.14	1.33 (1.21–1.48), <0.001
High-Molecular-Weight Adiponectin (Median=6.2 mg/L)		
Model 1 [†]	0.82 (0.62–1.09), 0.17	1.15 (1.05–1.25), 0.002
Model 2 [‡]	0.97 (0.73–1.29), 0.83	1.23 (1.13–1.34), <0.001
Model 3 [§]	0.95 (0.69–1.30), 0.73	1.16 (1.05–1.29), 0.005
Model 4 [\]	1.29 (0.96–1.75), 0.09	1.30 (1.19–1.42), <0.001

* Total adiponectin, standard deviation=7.9 mg/L; High-molecular weight adiponectin, standard deviation=5.9 mg/L.

[†] Adjusted for age, race, and gender.

[‡] Adjusted for age, race, gender, income, body mass index, systolic blood pressure, diastolic blood pressure, angiotensin-converting-enzyme inhibitors, current smoking, alcohol, health status, and estimated glomerular filtration rate.

[§] Adjusted for covariates in [‡]plus N-terminal pro-brain type natriuretic peptide (in subset with available measures n= 2,500).

[\] Adjusted for covariates in [‡]plus diabetes, low-density lipoprotein, high-density lipoprotein, triglycerides and C-reactive protein.

Table 3

Association between Total Adiponectin and Echocardiographic Parameters

n		Odds Ratio per Standard Deviation * Increase (95% Confidence Interval), p Value	
		<Median (12.4 mg/L)	Median (12.4 mg/L)
Left Ventricular Hypertrophy			
Model 1 [†]	1943	0.98 (0.59–1.63), 0.940	0.99 (0.79–1.23), 0.920
Model 2 [‡]	1943	1.01 (0.60–1.68), 0.978	1.02 (0.82–1.28), 0.858
Model 3 [§]	1504	0.90 (0.50–1.62), 0.723	0.95 (0.74–1.22), 0.691
Transmitral E/A Ratio <0.7 (vs. E/A Ratio 0.7–1.5)			
Model 1 [†]	2539	1.11 (0.80–1.55), 0.520	0.80 (0.68–0.93), 0.005
Model 2 [‡]	2539	1.13 (0.80–1.61), 0.486	0.82 (0.69–0.96), 0.014
Model 3 [§]	1975	0.93 (0.62–1.39), 0.727	0.88 (0.74–1.06), 0.173
E/A Ratio >1.5 (vs E/A Ratio 0.7–1.5)			
Model 1 [†]	1990	2.65 (1.07–6.52), 0.034	1.01 (0.72–1.41), 0.960
Model 2 [‡]	1990	2.11 (0.83–5.34), 0.117	0.96 (0.69–1.34), 0.799
Model 3 [§]	1550	1.79 (0.61–5.26), 0.291	0.86 (0.53–1.40), 0.543
Reduced Left Ventricular Ejection Fraction (<55%)			
Model 1 [†]	2564	0.89 (0.49–1.62), 0.695	1.19 (0.93–1.52), 0.158
Model 2 [‡]	2564	1.01 (0.56–1.84), 0.964	1.26 (0.97–1.64), 0.081
Model 3 [§]	1982	0.96 (0.48–1.94), 0.914	0.99 (0.73–1.34), 0.936
Left Atrial Enlargement			
Model 1 [†]	2633	0.98 (0.54–1.79), 0.954	1.39 (1.15–1.68), 0.001
Model 2 [‡]	2633	0.77 (0.41–1.45), 0.426	1.27 (1.04–1.55), 0.017
Model 3 [§]	2033	0.78 (0.37–1.62), 0.500	1.21 (0.97–1.51), 0.092

* Total adiponectin, standard deviation=7.9 mg/L

[†] Adjusted for age, race, and gender[‡] Adjusted for age, race, gender, income, body mass index, systolic blood pressure, diastolic blood pressure, angiotensin-converting-enzyme inhibitors, current smoking, alcohol use, health status, and estimated glomerular filtration rate. Risk estimates did not change materially when height and weight replaced body mass index.[§] Adjusted for age, race, gender, income, body mass index, systolic blood pressure, diastolic blood pressure, angiotensin-converting-enzyme inhibitors, current smoking, alcohol use, health status, estimated glomerular filtration rate and N-terminal pro-brain type natriuretic peptide. Risk estimates did not change materially when height and weight replaced body mass index.