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Longitudinal associations between adiponectin and cardiac structure differ by hypertensive status: Coronary Artery Risk Development in Young Adults

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Abstract

Objective—We studied the longitudinal association between adiponectin and cardiac structure and function 10 years later stratified by hypertension status.

Methods—Multicenter longitudinal study of black and white men and women that began in 1985–1986, when participants were 18–30 years old. Adiponectin was measured at year 15(2000–2001). Echocardiograms were completed at year 25(2010–2011). Participants were stratified by the presence of hypertension. Risk factor-adjusted echocardiographic variables were compared across adiponectin quintiles. Linear and quadratic regression models were also derived for risk factor-adjusted echocardiographic variables.

Results—Relative to the lowest quintile of adiponectin, participants from the highest quintile had a 6% lower LV mass index (LVMI) among normotensives, and an 8% higher LVMI among hypertensives. Among normotensive participants, regression analysis demonstrated a linear inverse relationship between adiponectin and LV mass, LVMI, posterior wall thickness (PWT) and ventricular septal thickness (VST) (all $p < 0.05$). Among hypertensive participants, regression analysis demonstrated a U-shaped relationship between adiponectin and LV mass, LVMI, PWT and VST ($p < 0.005$ for all quadratic terms).

Conclusions—Among normotensive participants, higher adiponectin may be a useful marker of less adverse future cardiac structure. Further study is required to see if adiponectin receptor agonists may provide a benefit among these individuals. Among hypertensive participants, further study is required to assess the prognostic and therapeutic use of adiponectin.

Keywords

Adiponectin; Adipokine; Remodeling; Left Ventricular Mass

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Background

Adiponectin is a protein mainly produced by adipose tissue, though cardiac myocytes also produce adiponectin [1, 2]. Adiponectin concentrations are inversely correlated with BMI [1]. Adiponectin benefits the heart in several ways: it directly increases coronary blood flow, increases VEGF production leading to increased coronary angiogenesis, and protects against reactive oxygen species, angiotensin II induced fibrosis and TNF-alpha induced apoptosis of myocytes [3–8]. Some earlier studies have also shown individuals with low adiponectin have increased risk of hypertension, though this finding is not consistent across all studies [9–11]. However, some earlier studies showed that higher adiponectin was associated with higher coronary artery calcium and serum markers of oxidative stress, as well as more heart failure and mortality in patients with ischemic heart disease [12, 13].

Several earlier studies showed higher adiponectin was cross-sectionally associated with lower LV ejection fraction (LVEF) and LV mass [14–17]. Cross-sectional analysis from the Jackson Heart Study showed a difference in the association between adiponectin and LV mass between normotensive versus hypertensive participants [15]. However, earlier studies have not examined the association between adiponectin and cardiac structure several years after adiponectin was measured, as well as clearly described the difference in these associations after stratification by hypertension status. The goal of this study was to examine the association between serum adiponectin and multiple measures of LV structure and function 10 years after adiponectin was measured in the young bi-ethnic cohort available in The Coronary Artery Risk Development in Young Adults (CARDIA) study. Based on previous reports from the Jackson Heart Study, we stratified participants by hypertension status and assessed for the presence of linear as well as quadratic relationships [15].

Methods

Study Population

The Coronary Artery Risk Development in Young Adults (CARDIA) study began in 1985–1986. 5115 Caucasian and African American men and women who were initially 18 to 30 years of age were recruited at clinical centers in Chicago IL, Birmingham AL, Oakland CA and Minneapolis MN. Informed consent was obtained from each participant. The study was approved annually by the Institutional Review Boards of the participating centers. Echocardiograms were completed for the participants at year 25 (2010–2011). The CARDIA study is currently ongoing. The current analysis includes CARDIA participants who had all of the following measurements (See also Figure 1): adiponectin measured at study year 15, all adjustment covariables measured at study year 15, a full set of echocardiographic variables at study year 25 and hypertensive status recorded at Year 25.

Measurements

Details of CARDIA measurements have been reported previously [18]. Briefly, height and weight were measured in light clothing and without shoes at each visit. After resting five minutes, participants had blood pressure measured three times using a random zero sphygmomanometer and the last two values were averaged. Alcohol and tobacco use were

assessed by self-report using a standardized questionnaire. Diabetes status was determined by fasting glucose ≥ 126 mg/dl or by diabetic medication usage. Lipids were also assayed from blood samples.

After at least 8 hours of fasting, blood samples were collected from seated participants. Samples were then centrifuged, aliquoted and frozen at -70°C within 90 minutes of collection. Radioimmunoassay (Linco Research) was used to measure adiponectin using a polyclonal antibody raised in a rabbit and purified recombinant adiponectin with an effective range of 0.2 to 40 mg/L [19]. At adiponectin concentrations of 3 mg/L and 15 mg/L, intra-assay coefficients of variation were respectively 1.8% and 6.2%, and inter-assay coefficients of variation were respectively 6.9% and 9.3% [20].

The year 25 standardized echocardiographic protocol has been described extensively in the past and follows recommendations by the American Society of Echocardiography [18, 21]. Briefly, chamber sizes were determined by 2D echocardiogram from apical four chamber views and dimensions were determined by 2D guided M-mode echocardiogram from parasternal short axis views. Images were read at a central laboratory at Johns Hopkins University. Inter-reader, intra-reader and intra-participant coefficients of variation for LV mass were $<8\%$ [18]. Echocardiographic variables analyzed were LV mass, LV mass index (LVMI), posterior wall thickness in diastole (PWT), ventricular septal thickness in diastole (VST), LV diastolic dimension (LVDD) and LVEF. LV mass was calculated by the Devereux formula [22]. LVMI was defined as $\text{LV mass}/\text{height}^{1.7}$ because indexing to 1.7 rather than 2.7 has been shown to be a better marker of cardiovascular risk in obese populations, and thus more representative of the population we studied [23].

Statistical Analysis

Participants were classified into quintiles of adiponectin concentration. Risk factor adjusted echocardiographic variables were compared across quintiles of adiponectin concentration stratified by year 25 hypertension status. Hypertension was defined as blood pressure $\geq 140/90$ or use of an antihypertensive medication. Also, a sensitivity analysis was done with participants stratified by never versus ever hypertensive over the 25 year followup available in CARDIA.

Separate from the quintile analysis, adiponectin concentrations were skewed, so they were $\log_2$ transformed to approximate a normal distribution. A 1 unit increase in $\log_2$ adiponectin represents a doubling of the adiponectin level. Adiponectin ranged from 1.0–64.0 mg/L within the sample studied, so a doubling of adiponectin concentration was well within the physiologic range, and thus clinically relevant. Two regression models, one assuming linear and the second assuming quadratic or U-shaped relationships between year 15 $\log_2$ adiponectin and year 25 echocardiographic variables were assessed separately for normotensive and hypertensive participants. Both models were risk factor-adjusted (age, race, gender, BMI, diabetes, LDL, HDL, alcohol and tobacco use) with model 1 containing only a linear term for $\log_2$ adiponectin and model 2 containing both a linear and quadratic term. A similar regression analysis was completed among participants stratified by never versus ever hypertensive over the 25 year followup available in CARDIA. Interaction of hypertension status with $\log_2$ adiponectin was assessed by pooling the data for normotensive

and hypertensive participants, introducing an indicator variable for hypertensive status into the model, and including in the model the products of the indicator variable with the linear and quadratic adiponectin terms. Separately, effect modification by ethnicity was examined by including interaction terms between $\log_2$ adiponectin and ethnicity, as well as for $\log_2$ adiponectin² and ethnicity.

A generalized additive model, implemented with the “mgcv” package in R.3.3.3 (R foundation for statistical computing), was used to model and illustrate the nonlinear relation of LVMI with $\log_2$ adiponectin by hypertension status group and adjusting for risk factors.

Results

Median adiponectin was 9.6 mg/L (IQR 6–14). Table 1 displays the baseline demographic and clinical characteristics stratified by year 25 hypertensive status. The normotensive sub-cohort had a mean age of 40 ± 4 years, mean BMI of 27 ± 6 kg/m², mean year 25 LVMI of 64 ± 16 , and 65% were white and 44% were male. The hypertensive sub-cohort had a mean age of 41 ± 4 years, mean BMI of 31 ± 7 kg/m², mean LVMI of 77 ± 23 , and 35% were white and 43% were male. Relative to the normotensive cohort, the hypertensive cohort included participants who were heavier, had a worse lipid profile and were more likely to smoke and to have diabetes. Similarly, the hypertensive cohort had increased year 25 LV mass and dimensions relative to the normotensive cohort. An interaction between the linear and quadratic adiponectin terms and hypertension status was present in the linear regression model pooling the normotensive and hypertensive data for LVMI ($p=0.02$ for linear term and $p=0.004$ for quadratic term).

Table 2 displays the echocardiographic variables stratified by adiponectin quintile. Relative to the lowest quintile of adiponectin, normotensive participants from the highest adiponectin quintile had a lower risk factor adjusted LV mass (–7%), LVMI (–6%), PWT (–4%) and VST (–7%) (all $p \leq 0.05$). Similarly, among participants who were never hypertensive during the 25 year follow-up available in CARDIA (Supplemental Table 1), relative to the lowest quintile of adiponectin, participants from the highest quintile had a lower risk factor adjusted LV mass (–7%), LVMI (–9%), PWT (–4%) and VST (–8%) (all $p \leq 0.005$).

In contrast, relative to the lowest quintile of adiponectin, hypertensive participants from the highest quintile had a higher risk factor adjusted LV mass (9%) and LVMI (8%) (both $p \leq 0.05$). Also, mean LV mass for the highest adiponectin quintile was 45g (30%) higher for hypertensive participants versus normotensive participants. Similarly, among participants who were hypertensive at any examination throughout the 25 year follow-up available in CARDIA (Supplemental Table 1), relative to the lowest quintile of adiponectin, participants from the highest quintile had a higher risk factor adjusted LV mass (9%), LVMI (9%) and LVDD (3%) (all $p \leq 0.005$).

Table 3 displays the regression analysis for the echocardiographic variables stratified by hypertensive status. Similar to the quintile analysis, among normotensive participants, higher adiponectin was associated with lower LV mass, LVMI, PWT and VST in the linear model. Figure 2 displays the linear relationship between LVMI and $\log_2$ adiponectin among

normotensive participants. In contrast, only the quadratic model for VST was significant for normotensive participants. As a result, there appears to be a linear inverse relationship between adiponectin and LV mass, LVMI and PWT (all $p < 0.05$) among normotensive participants. Supplemental table 2 shows a similar linear inverse relationship among participants who were never hypertensive during the 25 years of CARDIA followup. Among normotensive participants, no significant interactions between adiponectin and ethnicity were present for any of the echocardiographic variables significant in the initial regression analysis other than VST. After stratification by race, the relationship between adiponectin and VST appeared to be U-shaped in normotensive whites and inverse linear for normotensive blacks.

In contrast, among hypertensive participants, table 3 shows quadratic models better describe the association between adiponectin and echocardiographic parameters because four of the six echocardiographic parameters had significant quadratic terms. Also, the quintile analysis showed no significant difference in LVDD between the lowest and highest adiponectin quintile, and as a result, this finding of a linear association for LVDD may be spurious. Figure 2 displays this U-shaped relationship between LVMI and $\log_2$ adiponectin among hypertensive participants. As a result, there appears to be a U-shaped relationship between very low and very high adiponectin with higher LV mass, LVMI, PWT and VST (all $p < 0.005$) among hypertensive participants. Supplemental table 2 shows a similar U-shaped relationship among participants who were hypertensive at any point during the 25 years of CARDIA followup. Among hypertensive participants, no significant interactions between adiponectin and ethnicity were present for any of the echocardiographic variables. In order to further explore causes for this U-shaped relationship, supplemental table 3 displays demographic and clinical characteristics of the hypertensive cohort stratified by adiponectin quintile. None of these variables, other than increased use of tobacco and alcohol among participants with higher adiponectin, appear to explain the association between higher adiponectin and higher LVMI among hypertensive participants. Supplemental table 4 displays the full quadratic models, including linear terms, for both normotensive and hypertensive participants.

Discussion

Principal Findings

Among normotensive participants, higher adiponectin was linearly associated with lower risk- factor adjusted LV mass, LVMI, PWT and VST 10 years later. In contrast, among hypertensive participants, there was a U-shaped relationship between adiponectin and risk factor-adjusted LV mass, LVMI, PWT and VST 10 years later.

Earlier studies did not report these differences between normotensive and hypertensive individuals, perhaps because most earlier studies did not stratify participants by hypertension status. Also, earlier studies examined only the cross-sectional association between adiponectin and cardiac structure and function, while we assessed the longitudinal association between adiponectin and LV structure 10 years later.

Results Relative to Earlier Studies

An earlier study using ECG as the means of detecting LV hypertrophy showed higher adiponectin was associated with less left ventricular hypertrophy in both normotensive and hypertensive participants [17]. However, our study used echocardiogram, which is a more sensitive measure of left ventricular hypertrophy than ECG [24].

An analysis from the Jackson Heart study showed that among normotensive participants, higher adiponectin was associated with lower LVMI, but there was no significant association between adiponectin and LVMI among hypertensive participants as a whole [15]. CARDIA includes both blacks and whites, while the Jackson Heart Study only includes blacks. Earlier analysis from the Dallas Heart Study showed that blacks have higher LV mass than whites even after adjustment for age, gender and systolic blood pressure [25]. As a result, ethnic differences in the populations studied may explain the discrepancy with the current study. Nevertheless, we showed the lack of an interaction between adiponectin and ethnicity for LVMI.

Potential Mechanisms

Several mechanisms may contribute to how higher adiponectin is associated with lower LVMI and wall thickness among normotensive participants. An earlier study in mice showed that adiponectin decreased pressure overload induced left ventricular hypertrophy [8]. Adiponectin deficiency also leads to decreased activation of AMPK pathways, and thus less VEGF mediated angiogenesis; this may lead to increased compensatory concentric remodeling and fibrosis [8]. Adiponectin also inhibits reactive oxygen induced cardiomyocyte hypertrophy and protects against angiotensin-II induced fibrosis [3, 4]. Earlier studies also showed that low adiponectin levels are associated with endothelial and microvascular dysfunction, which may also contribute to the association between low adiponectin and higher LV mass seen in normotensive participants [26]. Also, adiponectin is inversely associated with BMI [1]. As a result, individuals in the higher adiponectin quintiles have lower BMI, which is also associated with lower LVMI [22].

The mechanism for the U-shaped association between adiponectin with LVMI and wall thickness among hypertensive participants likely differs from that in normotensive participants. Figure 2 shows that the lowest point of the U-shaped association seen in hypertensives occurs at $\log_2(\text{adiponectin}) \approx 2.5$, or where $\text{adiponectin} \approx 5.6$ ng/ml. Because median $\text{adiponectin} = 9.6$ ng/ml (IQR 6–14) in our sample, most hypertensive participants fall in the range of the association between higher adiponectin and higher LVMI. Higher tobacco use among hypertensive participants with higher adiponectin may partially explain the association between higher adiponectin and LVMI; we attempted to account for this by adjusting for tobacco use, but some residual confounding may exist [18]. An earlier study from CARDIA showed that although higher adiponectin was associated with increased coronary artery calcium, it was also associated with higher HDL and lower triglycerides and CRP, suggesting the higher adiponectin may be a compensatory response to underlying macrovascular disease [13]. Also, earlier animal studies showed that rats fed high salt diets developed hypertension and higher adiponectin levels. The elevated adiponectin levels persisted even after the treatment of the hypertension with direct vasodilators and

sympathetic blockade using hydralazine and clonidine. These elevated adiponectin levels only resolved when the renin-angiotensin system was blocked by telmisartan or eplerenone, suggesting that the renin-angiotensin system mediates elevated adiponectin levels seen in hypertensive individuals due to higher salt intake, rather than to the increased blood pressure itself [27]. This may explain our findings in hypertensive participants because these individuals often have increased salt intake relative to a normotensive population. The increased salt intake increases blood pressure and thus LVMI, but the salt intake also increases adiponectin levels in a compensatory response to the adverse effects of the increased salt.

Study Limitations and Future Research

One of the limitations of the current study was that we did not have repeated measures of adiponectin measured contemporaneously with repeated measures of echocardiographic variables and could not assess how change in adiponectin related to change in echocardiographic parameters. Also, we stratified participants by hypertension status at year 25 and did not account for duration of hypertension. However, the sensitivity analysis that stratified by ever-hypertensive versus never-hypertensive yielded similar results. Another limitation of this study was that this was an observational study, and as a result, we can only observe associations, rather than causation. Another limitation is that we were unable to adjust for the fact that several medications can affect adiponectin concentrations. For example, pravastatin increases serum adiponectin concentrations, while atorvastatin decreases serum adiponectin concentrations [28, 29]. Because adiponectin concentrations respond differently to medications even within the same class, we were unable to account for all the different medications that patients were currently on.

The current study showed that normotensive participants in the highest adiponectin quintile had a 6% lower risk factor adjusted LVMI relative to the lowest adiponectin quintile. Also, there was a 45g (30%) difference in risk factor adjusted LV mass between hypertensive versus normotensive participants in the highest adiponectin quintile. Earlier studies showed that higher LV mass is associated with worse clinical outcomes [30]. Future study, likely initially in animal models, is required to assess if adiponectin supplementation causes reverse remodeling and improvements in clinical endpoints such as mortality and the development of heart failure. If these beneficial effects of adiponectin supplementation are found in animal models, adiponectin receptor agonists may represent a potential therapeutic target for future drug development. However, we also showed that hypertensive participants in the highest adiponectin quintile had an 8% higher risk factor adjusted LVMI relative to the lowest adiponectin quintile. As a result, further study is required to determine if higher adiponectin causes the higher LVMI in hypertensive individuals or if the association between higher adiponectin and higher LVMI is merely a compensatory response to hypertension induced increase in LVMI. If higher adiponectin is merely a compensatory response to hypertension induced LV hypertrophy in hypertensive, adiponectin supplementation may be a potential therapeutic target for drug therapy as noted earlier. However, if higher adiponectin is a direct cause of pathologic LV hypertrophy in hypertensive individuals, the use of adiponectin receptor agonists for therapeutic purposes becomes less clear.

Conclusions

We demonstrated the novel finding of a linear inverse relationship between adiponectin with LVMi and wall thickness 10 years later among normotensive participants. In contrast, there was a U-shaped relationship between adiponectin with LVMi and wall thickness 10 years later among hypertensive participants. Among normotensive participants, adiponectin may be a useful marker of less adverse future cardiac structure. Further study is required to see if adiponectin receptor agonists may provide a benefit among these individuals by inducing reverse remodeling or decreasing mortality and the development of heart failure. Among hypertensive participants, further study is required to assess the prognostic and therapeutic use of adiponectin because the underlying relationship between adiponectin and LV structure remains less clear.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body mass index
LV	Left ventricular
LVEF	Left ventricular ejection fraction
CARDIA	The Coronary Artery Risk Development in Young Adults
LVMi	Left ventricular mass index
PWT	Posterior wall thickness in diastole
VST	Ventricular septal thickness in diastole
LVDD	Left ventricular diameter in diastole

References

1. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, et al. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochemical and biophysical research communications*. 1999; 257:79–83. [PubMed: 10092513]
2. Natarajan R, Salloum FN, Fisher BJ, Kukreja RC, Fowler AA 3rd. Hypoxia inducible factor-1 upregulates adiponectin in diabetic mouse hearts and attenuates post-ischemic injury. *Journal of cardiovascular pharmacology*. 2008; 51:178–87. [PubMed: 18287886]

3. Essick EE, Ouchi N, Wilson RM, Ohashi K, Ghobrial J, Shibata R, et al. Adiponectin mediates cardioprotection in oxidative stress-induced cardiac myocyte remodeling. *American journal of physiology Heart and circulatory physiology*. 2011; 301:H984–93. [PubMed: 21666115]
4. Fujita K, Maeda N, Sonoda M, Ohashi K, Hibuse T, Nishizawa H, et al. Adiponectin protects against angiotensin II-induced cardiac fibrosis through activation of PPAR- α . *Arteriosclerosis, thrombosis, and vascular biology*. 2008; 28:863–70.
5. Gonon AT, Widegren U, Bulhak A, Salehzadeh F, Persson J, Sjoquist PO, et al. Adiponectin protects against myocardial ischaemia-reperfusion injury via AMP-activated protein kinase, Akt, and nitric oxide. *Cardiovascular research*. 2008; 78:116–22. [PubMed: 18222959]
6. Grossini E, Prodam F, Walker GE, Sigaud L, Farruggio S, Bellofatto K, et al. Effect of monomeric adiponectin on cardiac function and perfusion in anesthetized pig. *The Journal of endocrinology*. 2014; 222:137–49. [PubMed: 24860147]
7. Kondo K, Shibata R, Unno K, Shimano M, Ishii M, Kito T, et al. Impact of a single intracoronary administration of adiponectin on myocardial ischemia/reperfusion injury in a pig model. *Circulation Cardiovascular interventions*. 2010; 3:166–73. [PubMed: 20332381]
8. Shimano M, Ouchi N, Shibata R, Ohashi K, Pimentel DR, Murohara T, et al. Adiponectin deficiency exacerbates cardiac dysfunction following pressure overload through disruption of an AMPK-dependent angiogenic response. *Journal of molecular and cellular cardiology*. 2010; 49:210–20. [PubMed: 20206634]
9. Chow WS, Cheung BM, Tso AW, Xu A, Wat NM, Fong CH, et al. Hypoadiponectinemia as a predictor for the development of hypertension: a 5-year prospective study. *Hypertension*. 2007; 49:1455–61. [PubMed: 17452504]
10. Kim DH, Kim C, Ding EL, Townsend MK, Lipsitz LA. Adiponectin levels and the risk of hypertension: a systematic review and meta-analysis. *Hypertension*. 2013; 62:27–32. [PubMed: 23716587]
11. Onat A, Aydin M, Can G, Koroglu B, Karagoz A, Altay S. High adiponectin levels fail to protect against the risk of hypertension and, in women, against coronary disease: involvement in autoimmunity? *World J Diabetes*. 2013; 4:219–25. [PubMed: 24147206]
12. Beatty AL, Zhang MH, Ku IA, Na B, Schiller NB, Whooley MA. Adiponectin is associated with increased mortality and heart failure in patients with stable ischemic heart disease: data from the Heart and Soul Study. *Atherosclerosis*. 2012; 220:587–92. [PubMed: 22196150]
13. Steffes MW, Gross MD, Lee DH, Schreiner PJ, Jacobs DR Jr. Adiponectin, visceral fat, oxidative stress, and early macrovascular disease: the Coronary Artery Risk Development in Young Adults Study. *Obesity*. 2006; 14:319–26. [PubMed: 16571859]
14. Gustafsson S, Lind L, Zethelius B, Venge P, Flyvbjerg A, Soderberg S, et al. Adiponectin and cardiac geometry and function in elderly: results from two community-based cohort studies. *European journal of endocrinology/European Federation of Endocrine Societies*. 2010; 162:543–50. [PubMed: 20008076]
15. Bidulescu A, Liu J, Musani SK, Fox ER, Samdarshi TE, Sarpong DF, et al. Association of adiponectin with left ventricular mass in blacks: the Jackson Heart Study. *Circulation Heart failure*. 2011; 4:747–53. [PubMed: 21840935]
16. McManus DD, Lyass A, Ingelsson E, Massaro JM, Meigs JB, Aragam J, et al. Relations of circulating resistin and adiponectin and cardiac structure and function: the Framingham Offspring Study. *Obesity*. 2012; 20:1882–6. [PubMed: 21350435]
17. Mitsuhashi H, Yatsuya H, Tamakoshi K, Matsushita K, Otsuka R, Wada K, et al. Adiponectin level and left ventricular hypertrophy in Japanese men. *Hypertension*. 2007; 49:1448–54. [PubMed: 17420337]
18. Gidding SS, Liu K, Colangelo LA, Cook NL, Goff DC, Glasser SP, et al. Longitudinal determinants of left ventricular mass and geometry: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Circulation Cardiovascular imaging*. 2013; 6:769–75. [PubMed: 23922005]
19. Steffes MW, Gross MD, Schreiner PJ, Yu X, Hilner JE, Gingerich R, et al. Serum adiponectin in young adults—interactions with central adiposity, circulating levels of glucose, and insulin resistance: the CARDIA study. *Annals of epidemiology*. 2004; 14:492–8. [PubMed: 15301786]

20. Cnop M, Havel PJ, Utzschneider KM, Carr DB, Sinha MK, Boyko EJ, et al. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. *Diabetologia*. 2003; 46:459–69. [PubMed: 12687327]
21. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography*. 2005; 18:1440–63. [PubMed: 16376782]
22. Gardin JM, Brunner D, Schreiner PJ, Xie X, Reid CL, Ruth K, et al. Demographics and correlates of five-year change in echocardiographic left ventricular mass in young black and white adult men and women: the Coronary Artery Risk Development in Young Adults (CARDIA) study. *Journal of the American College of Cardiology*. 2002; 40:529–35. [PubMed: 12142122]
23. Chirinos JA, Segers P, De Buyzere ML, Kronmal RA, Raja MW, De Bacquer D, et al. Left ventricular mass: allometric scaling, normative values, effect of obesity, and prognostic performance. *Hypertension*. 2010; 56:91–8. [PubMed: 20458004]
24. Sjöberg S, Sundh F, Schlegel T, Maynard C, Ruck A, Wagner G, et al. The relationship between electrocardiographic left ventricular hypertrophy criteria and echocardiographic mass in patients undergoing transcatheter aortic valve replacement. *Journal of electrocardiology*. 2015
25. Drazner MH, Dries DL, Peshock RM, Cooper RS, Klassen C, Kazi F, et al. Left ventricular hypertrophy is more prevalent in blacks than whites in the general population: the Dallas Heart Study. *Hypertension*. 2005; 46:124–9. [PubMed: 15939807]
26. Giannessi D, Caselli C, Del Ry S, Maltinti M, Pardini S, Turchi S, et al. Adiponectin is associated with abnormal lipid profile and coronary microvascular dysfunction in patients with dilated cardiomyopathy without overt heart failure. *Metabolism: clinical and experimental*. 2011; 60:227–33. [PubMed: 20199784]
27. Kamari Y, Shimoni N, Koren F, Peleg E, Sharabi Y, Grossman E. High-salt diet increases plasma adiponectin levels independent of blood pressure in hypertensive rats: the role of the renin-angiotensin-aldosterone system. *J Hypertens*. 2010; 28:95–101. [PubMed: 19770680]
28. Koh KK, Lim S, Choi H, Lee Y, Han SH, Lee K, et al. Combination pravastatin and valsartan treatment has additive beneficial effects to simultaneously improve both metabolic and cardiovascular phenotypes beyond that of monotherapy with either drug in patients with primary hypercholesterolemia. *Diabetes*. 2013; 62:3547–52. [PubMed: 23863812]
29. Koh KK, Quon MJ, Han SH, Lee Y, Kim SJ, Shin EK. Atorvastatin causes insulin resistance and increases ambient glycemia in hypercholesterolemic patients. *Journal of the American College of Cardiology*. 2010; 55:1209–16. [PubMed: 20298928]
30. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *The New England journal of medicine*. 1990; 322:1561–6. [PubMed: 2139921]

Figure 1.
Participants included in the current analysis

Figure 2. Relation between left ventricular mass index and adiponectin
Figures are stratified by hypertension status.

Table 1

Year 15 demographic and clinical characteristics and year 25 echocardiographic variables stratified by year 25 hypertensive status.

Demographic or Clinical Variable	Normotensive (N=1718)	Hypertensive (N=801)	P value
Age	40±4	41±4	<0.0001
White (%)	1121 (65%)	280 (35%)	<0.0001
Male (%)	756 (44%)	341 (43%)	0.50
BMI (kg/m ²)	27±6	31±7	<0.0001
Systolic blood pressure (mm Hg)	107±10	123±16	<0.0001
Diabetes (%)	42 (2%)	80 (10%)	<0.0001
LDL (mg/dl)	112±31	116±34	0.003
HDL (mg/dl)	52±14	49±14	<0.0001
Smokers	290 (17%)	200 (25%)	<0.0001
Alcohol Users	955 (56%)	377 (47%)	<0.0001
LV Mass (g)	158±45	187±60	<0.0001
LV Mass Index (g/m ^{1.7})	64±16	77±23	<0.0001
Posterior Wall Thickness (mm)	8.6±1.6	9.5±1.7	<0.0001
Ventricular Septal Thickness (mm)	8.8±1.5	9.7±1.8	<0.0001
LV Diastolic Dimension (mm)	50.9±5.0	52.1±5.6	<0.0001
LVEF (%)	62±7	61±8	0.59

Values are noted as mean±SD or number (% of total).

Risk factor adjusted echocardiographic variables stratified by adiponectin quintile: Adiponectin concentrations (mg/L) are noted for each quintile.

Table 2

Echo Variable	Adiponectin Quintile				
	I 1.0–5.0	II 6.0–8.0	III 8.4–11.0	IV 12.0–15.0	V 15.6–64.0
Normotensive					
LV mass (g)	167±3	158±2 [‡]	159±2 [‡]	156±2 [‡]	155±2 [‡]
LV mass index (g/m ^{1.7})	66±1	64±1	64±1 [‡]	63±1 [‡]	62±1 [‡]
Posterior Wall Thickness (mm)	8.9±0.1	8.6±0.1 [‡]	8.6±0.1 [‡]	8.6±0.1 [‡]	8.5±0.1 [‡]
Ventricular Septal Thickness (mm)	9.2±0.1	8.8±0.1 [‡]	8.8±0.1 [*]	8.7±0.1 [*]	8.6±0.1 [*]
LV Diastolic Dimension (mm)	50.7±0.3	50.9±0.3	51.1±0.2	50.8±0.3	50.9±0.3
LV Ejection Fraction (%)	61.8±0.4	61.3±0.4	61.7±0.4	61.7±0.4	61±0.4
Hypertensive					
LV mass (g)	184±4	185±4	183±4	192±5	200±6 [‡]
LV mass index (g/m ^{1.7})	75±2	76±2	75±2	79±2	81±2 [‡]
Posterior Wall Thickness (mm)	9.4±0.1	9.4±0.1	9.4±0.1	9.4±0.2	9.8±0.2
Ventricular Septal Thickness (mm)	9.7±0.1	9.6±0.1	9.7±0.1	9.6±0.2	9.8±0.2
LV Diastolic Dimension (mm)	51.6±0.4	52.0±0.4	51.7±0.4	52.8±0.5	52.9±0.6
LV Ejection Fraction (%)	61.1±0.6	60.9±0.6	62.4±0.7	60.3±0.8	62.5±0.9

Values are compared to quintile I.

^{*} p 0.0005,

[‡] p 0.005,

[‡] p 0.05. Mean±SE are noted.

Table 3

Risk factor adjusted regression analysis of echocardiographic variables; Models are for adiponectin. Model 1: Linear model. Model 2: Quadratic term from the quadratic model.

Echo Variable	Normotensive			Hypertensive		
	N	Model 1	Model 2	N	Model 1	Model 2
LV mass (g)	1594	-4±1 [‡]	2±1	711	4±2	6±2 [*]
LV mass index (g/m ^{1.7})	1593	-1.6±0.5 [‡]	0.4±0.4	710	1.5±1.0	2.6±0.6 [*]
Posterior Wall Thickness (mm)	1596	-0.12±0.05 [‡]	0.07±0.04	711	0.03±0.08	0.18±0.05 [*]
Ventricular Septal Thickness (mm)	1596	-0.20±0.05 [*]	0.08±0.03 [‡]	711	-0.04±0.08	0.17±0.05 [‡]
LV Diastolic Dimension (mm)	1593	0.1±0.2	-0.1±0.1	709	0.6±0.2 [‡]	0.1±0.2
LV Ejection Fraction (%)	1636	-0.1±0.2	-0.2±0.2	739	0.2±0.4	0.3±0.3

Values are noted as B±SE and are risk factor-adjusted. A 1 unit increase in log2adiponectin represents a doubling of the adiponectin level.

^{*} p 0.0005,

[‡] p 0.005,

[‡] p 0.05.