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Soluble Tumor Necrosis Factor Receptor 1 Level Is Associated With Left Ventricular Hypertrophy: The Northern Manhattan Study

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Abstract

BACKGROUND—Although inflammatory markers may be associated with risk of cardiovascular events, few data are available regarding these markers and their association with left ventricular hypertrophy (LVH). We sought to evaluate whether inflammatory markers were independently associated with LVH in a multiethnic population in northern Manhattan.

METHODS—A population-based cross-sectional study was conducted in 660 participants without stroke, who had undergone both transthoracic echocardiography and testing for soluble tumor necrosis factor receptor (sTNFR) 1, interleukin (IL)-6, and high-sensitivity C-reactive protein (hsCRP). LV mass was calculated according to an established formula. LVH was defined as LV mass greater than the 90th percentile of the participants.

RESULTS—The mean age was 67.4 ± 8.8 years, 35.5% were men, 61.7% were Hispanic, 19.7% were black, and 18.6% were white. In univariate analyses, hsCRP, IL-6 and sTNFR1 were significantly associated with LV mass. Multiple linear regression analyses demonstrated that sTNFR1 ($P = 0.0008$) was associated with LV mass after adjusting for demographic and medical risk factors, but hsCRP and IL-6 were not. When all markers were included in the same model, sTNFR1 remained significant, but hsCRP and IL-6 did not. Compared with the lowest quartile of

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sTNFR1, those in the highest quartile were more likely to have LVH (Odds ratio = 1.84, 95% Confidence interval, 0.97 to 3.64, $P = 0.06$).

CONCLUSIONS—Soluble TNFR1, but not hsCRP nor IL-6, is independently associated with increased LV mass. Chronic subclinical inflammation including the TNFR1-associated system may contribute to LVH.

Keywords

echocardiography; epidemiology; left ventricular hypertrophy; inflammation

Left ventricular hypertrophy (LVH), or increased LV mass, is an independent risk factor for cardiovascular and cerebrovascular diseases.[1] Echocardiographic LVH is associated with increased risk of all-cause mortality and cardiovascular disease morbidity and mortality in population-based investigations.[1,2] LVH reflects subclinical organ damage from risk factors, particularly arterial hypertension, and may provide a noninvasive gauge of the extent of atherosclerotic heart disease.[3,4]

Several epidemiological studies have provided evidence that serum markers of inflammation are associated with risk factors for cardiovascular and cerebrovascular events.[5–7] Elevated levels of these markers also predict recurrent events after a first acute coronary artery disease or ischemic stroke.[8–10] High-sensitivity C-reactive protein (hsCRP) has most consistently been associated with cardiovascular outcome events; however, interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, soluble TNF receptors (sTNFRs), and other molecules have been associated with cardiovascular outcome events as well.[11] Of these, TNF-alpha is difficult to measure in large-scale epidemiological studies because of its limited half-life. Consequently, sTNFRs might be more stable markers of atherosclerotic burden, and might reflect a long-term average with greater sensitivity and reliability than TNF-alpha itself.[12,13]

On the other hand, cytokines including TNF-alpha and TNFRs have been implicated in the pathogenesis of myocardial remodeling, dysfunction and hypertrophy.[14,15] Of these, the TNF receptor 1 (TNFR1)-mediated pathway is known to be deleterious in cardiac myocytes. TNF-alpha-induced cardiotoxic effects are initiated by binding to TNFR1.[16] In addition, IL-6 adversely affects myocyte contractility and promotes cardiac hypertrophy through activated glycoprotein 130-linked signaling as well as angiotensin II stimulation.[17,18] Although there are many pathogenic reports regarding the association between cytokines and LVH, only a few studies are available regarding inflammatory markers, including soluble TNFR1 (sTNFR1), IL-6 and hsCRP, and their association with LVH in a population-based sample. We sought to determine whether inflammatory markers are associated with LVH in a cross-sectional analysis of a stroke-free, multiethnic population living in a single community.

METHODS

The Northern Manhattan Study (NOMAS) is an ongoing population-based, prospective cohort study designed to determine stroke incidence, risk factors, and prognosis in a multiethnic urban population. Northern Manhattan consists of the region of New York City north of 145th street and south of 218th street, bordered on the west by the Hudson River and on the east by the Harlem River. In 1990, nearly 260,000 people lived in the community, with 40% over 40 years of age and a race-ethnic mixture consisting of 20% black, 63% Hispanic, and 15% white residents.[19] Race-ethnicity was defined by self-identification in response to a questionnaire modeled after the US census and conforming to the standard definitions outlined by Directive 15.[20]

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Selection of NOMAS Cohort

The methods of participant recruitment and enrollment into NOMAS have been previously described.[21] Stroke-free community subjects were identified by random digit dialing with dual-frame sampling to identify both published and unpublished numbers. Community participants were enrolled if they (1) had never been diagnosed with stroke, (2) were over 40 years of age, and (3) resided in northern Manhattan for ≥ 3 months in a household with a telephone. The study was approved by the Institutional Review Board of Columbia University Medical Center. All participants gave consent directly or through a surrogate when appropriate.

Index Evaluation of Subjects

Data were collected through interviews by trained research assistants, physical examinations by study physicians, in-person measurements, and fasting blood specimens as described elsewhere.[21] When possible, data were obtained directly from participants with standardized data collection instruments. When the participant was unable to provide answers, a proxy knowledgeable about the participant's history was interviewed. Direct participant data were obtained from 99% of stroke-free participants. Assessments were conducted in English or Spanish depending on the primary language of the participant. All participants classifying themselves as white without any Hispanic origin or black without any Hispanic origin were classified as white non-Hispanic or black non-Hispanic, respectively. Standardized questions were adapted from the Behavioral Risk Factor Surveillance System[22] by the Centers for Disease Control and Prevention (CDC) regarding the following conditions: hypertension, diabetes mellitus, hypercholesterolemia, peripheral vascular disease, transient ischemic attack, current smoking, ever smoking, coronary artery disease, congestive heart failure, atrial fibrillation, other arrhythmias, and valvular heart disease. Standard techniques were used to measure blood pressure, height, weight, and fasting blood glucose.[23] Fasting lipid panels including total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride were measured with a Hitachi 705 automated spectrometer (Boehringer Mannheim). Blood pressure was measured with mercury sphygmomanometers and cuffs of appropriate size. Hypertension was defined as a systolic blood pressure recording ≥ 140 mmHg or a diastolic blood pressure recording ≥ 90 mmHg based on the mean of two blood pressure measurements, a subject's self-report of a history of hypertension, or antihypertensive medication use. These two blood pressure measurements were performed with the participants in the seated position after at least 5 minutes of rest, and were repeated after an interval of at least 30 minutes. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dL, the subject's self-report of such a history, or insulin or oral hypoglycemic medication use. Coronary artery disease included history of myocardial infarction, coronary angioplasty, or coronary artery bypass surgery. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Because it has been emphasized that patients with chronic kidney disease, as well as hypertensives with normal renal function, are at high risk for cardiovascular atherosclerosis and LVH, serum creatinine was also evaluated. Medications were classified as aspirin, lipid-lowering agents, insulin, oral hypoglycemic agents, and anti-hypertensive agents.

Echocardiographic Evaluation

Transthoracic echocardiography was performed according to the guidelines of the American Society of Echocardiography[24] using Philips Medical Systems SONOS 1000 and 2500 equipment. LV end-diastolic diameter (LVDD), LV end-systolic diameter (LVSD), interventricular septum (IVS) thickness, and posterior wall (PW) thickness at end-diastole were measured. LV mass was calculated using the American Society of Echocardiography method[25] as follows:

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$$\text{LV mass}=0.8(1.04[(\text{IVS}+\text{LVDD}+\text{PW})^3-\text{LVDD}^3]+0.6)$$

Echocardiographic studies were interpreted by researchers blinded to the participants' clinical and demographic characteristics. Interobserver variability for the variables measured ranged between 8% and 10%.

Assessment of Inflammatory Markers

For the measurement of serum inflammatory markers, blood was drawn into a 10-ml EDTA tube with minimally traumatic venipuncture by an experienced research phlebotomist trained in the protocol. The tube was immediately spun at 3000g at 4 degrees for 20 minutes. Plasma was divided equally into six 1.5-ml Eppendorf tubes. The samples were frozen and stored at −70 degrees. Inflammatory marker levels were measured in batched samples and assays were performed blinded to echocardiographic status of participants. HsCRP was measured using the BNII nephelometric assay system (Dade-Behring, Deerfield, IL). IL-6 and sTNFR1 were measured by enzyme-linked immunosorbent assays according to instructions provided by the manufacturer (Biosource International). Only participants enrolled in NOMAS after July 1999 had blood sampled in this way and were included in this analysis.

Statistical Analysis

Data are reported as mean ± SD for continuous variables and as proportions for categorical variables. Differences between proportions were assessed by the *chi*-square test, and differences between means were assessed by the paired Student's *t*-test. Regression analysis was performed using each inflammatory marker level as a continuous independent variable and LV mass as the dependent variable. The unit of each inflammatory marker was the standard deviation of the marker. Based on these preliminary analyses, further analyses of sTNFR1 and hsCRP were carried out. Participants were divided into quartiles defined by sTNFR1 levels, and hsCRP levels were categorized according to CDC/American Heart Association (AHA) threshold criteria (low level, < 1 mg/L; intermediate level, 1 to 3 mg/L; and high level, > 3 mg/L).[26] Multivariate linear regression analysis, using a non-automated procedure incorporating demographic and clinical variables, was then used to build models for the association between inflammatory markers and LV mass. For the first model, atherosclerotic risk factors were chosen on the basis of association with LV mass in simple linear regression analysis, or on the basis of findings in previous analyses in our population. Analyses were then conducted using multivariable logistic regression to determine the effect of inflammatory markers on LVH as a dichotomous variable, using a cutoff of LV mass ≥ 90th percentile among the participants without conditions associated with LVH such as hypertension, diabetes mellitus, obesity, and cardiovascular diseases.[27] Statistical significance was determined at the alpha = 0.05 level with the use of 2-sided tests. Statistical analyses were conducted with SAS computer software version 9.1 (SAS Institute, Cary, NC).

RESULTS

The mean age of the 660 participants for whom there were hsCRP, IL-6, sTNFR1 and LV mass data was 67.4 ± 8.8 years, and 35.5% (n = 234) were male; 18.6% of the participants (n = 123) were white non-Hispanic, 19.7% (n = 130) were black non-Hispanic, and 61.7% (n = 407) were Hispanic. Approximately 70% of the participants (n = 453) were hypertensive; 21.3% by blood pressure measurements, 27.3% were by self-report of a history of hypertension or taking anti-hypertensive medication, and 51.3% met both criteria. In

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hypertensive participants, 68.0% (n = 308) had systolic blood pressure recording of ≥ 140 mmHg. The distributions of sociodemographic factors, comorbid vascular diseases, medical risk factors, and inflammatory marker levels are shown in Table 1. There were no significant race-ethnic differences in the levels of the various inflammatory markers.

In a simple linear regression analysis, hsCRP, IL-6, and sTNFR1 were associated with LV mass in this population sample. After adjusting for demographic factors including age, sex, race-ethnicity, and completed high school education, the association with LV mass for hsCRP, IL-6, and sTNFR1 remained significant. After adjusting for demographic factors and medical risk factors including hypertension, diabetes mellitus, body mass index, ever smoking, history of coronary artery disease, and serum creatinine, the association remained significant for sTNFR1, but did not remain significant for hsCRP and IL-6 (Table 2). When both hsCRP and sTNFR1 were included in the same model, TNFR1 was still associated with LV mass, but hsCRP was not. Similarly, when IL-6 and sTNFR1 were included in the same model, sTNFR1 was still associated with LV mass, but IL-6 was not. After further adjusting for medications, sTNFR1 was still significantly associated with LV mass (Table 2).

Participants were also divided into 3 hsCRP groups according to the CDC/AHA guideline regarding use of hsCRP for cardiovascular risk classification. Compared to those with hsCRP < 1 mg/L, those with hsCRP > 3 mg/L had increased LV mass, but those with intermediate levels of hsCRP did not. Although the association remained after adjusting for demographic factors, hsCRP > 3 mg/L was not associated with LV mass after further adjusting for medical risk factors and medications (Table 3).

In categorical analyses of sTNFR1, those in the highest sTNFR1 quartile had increased LV mass compared with those in the lowest quartile. After adjustment for demographics and risk factors except serum creatinine, the association remained significant (mean difference per category change = 14.06 g, $P = 0.02$). However, the association did not remain significant after further adjustment for serum creatinine and medications (Table 3). Those in the highest quartile of sTNFR1, compared with those in the lowest quartile, were also more likely to have LVH, even after adjusting for demographics, medical risk factors and medications. HsCRP > 3mg/L was not associated with LVH after adjusting for demographic, medical risk factors, and medications (Table 4).

DISCUSSION

This cross-sectional study provides evidence of an association between serologic markers of inflammation and LV mass in a multi-ethnic population living in a single community. We found a significant association between sTNFR1 and increased LV mass, independent of hsCRP and IL-6.

TNFR1 and LVH

TNF-alpha is a potent inflammatory cytokine. The main source of TNF-alpha is activated mononuclear leukocytes, although it is also secreted by a wide variety of other immune and non-immune cell types, such as smooth muscle cells, astrocytes, neurons and fibroblasts. Cardiofibroblasts originate from fibroblasts, monocytes, or circulating progenitor cells. sTNFR1 (also known as p55) and sTNFR2 (also known as p75) are both soluble receptors that are shed by the many cell types on which they reside. Elevation of TNF-alpha and sTNFRs occurs in a variety of infectious, inflammatory, autoimmune, and neoplastic diseases. Elevation of sTNFRs may also be a reflection of inflammatory mechanisms involved in subclinical atherosclerotic diseases. sTNFRs might be a more stable marker of inflammatory burden than TNF-alpha itself. For example, we have previously shown different relationships between TNF-alpha, sTNFRs and carotid plaque thickness.[28] At

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physiological concentration, sTNFRs may act as a “slow-release reservoir” of bioactive TNF-alpha, thus increasing its half-life. Because TNF-alpha induces shedding of its soluble receptors, it is possible that elevated sTNFRs simply reflect activation of the cytokine. sTNFRs can be sensitive serum markers of TNF-alpha activation. Additionally, because several other inflammatory cytokines promote shedding of sTNFRs, sTNFRs can mirror systemic pan-inflammatory status more closely than a single cytokine level such as TNF-alpha.

It is well established that TNF-alpha plays an important role in cardiac contractile dysfunction, cardiac hypertrophy[15], and cardiac myocyte apoptosis[16] through reactive oxygen species and mitogen-activated protein kinase pathways, as well as through interactions with the renin-angiotensin system in experimental settings.[29–31] Both TNFR1 and TNFR2 are expressed in most cells including cardiac myocytes. The cytoplasmic domains of TNFR1 and TNFR2 are different, and each receptor activates both distinct and overlapping intracellular signal pathways. Of these, TNFR1-associated pathways contribute cardiotoxic effects including cardiac hypertrophy, whereas TNFR2-associated pathways elicit cardioprotective effects.[32] The origin of elevated circulating sTNFRs is still a matter of debate. They have been shown to arise from several extracardiac sources, including peripheral skeletal muscles[33], and immune system activation.[34] Further pathogenic studies of the relationship between sTNFRs, particularly sTNFR1, and adverse cardiac effects such as LVH are needed; however, the magnitude of the effect of elevated sTNFR1 on increased LV mass in this present study may have clinical importance.

Although the importance of sTNFR1 as a systemic inflammatory marker is emphasized, there have been few reports regarding sTNFR1 as an independent predictor of cardiovascular disease in epidemiological studies. It has been reported that sTNFR1 emerges among all cytokine parameters as the strongest and most accurate prognostic marker of chronic heart failure[35] and sTNFR1 also remains the only independent predictor of death and heart failure after myocardial infarction among several inflammatory markers.[36,37] These findings in both experimental and epidemiological studies suggest that systemic overexpression of TNFR1 might have independent significance in terms of subclinical organ damage such as LVH.

HsCRP, IL-6 and LVH

Epidemiological studies have generally shown that several acute phase reactant proteins are associated with atherosclerosis, coronary heart disease, and stroke. In particular, hsCRP has many features that suggest it as a molecular marker of risk of inflammation.[11] The mechanism by which hsCRP may be associated with cardiac hypertrophy remains unclear. HsCRP elevation might be an epiphenomenon, or a marker of the inflammation that is present in atherosclerosis, but not directly responsible for it. HsCRP itself decreases production of nitric oxide by endothelial cells and upregulates angiotensin type-I receptor expression. These known actions of hsCRP on angiotensin II receptors and in the production of nitric oxide can offer causative links between inflammation, the renin-angiotensin system, and LVH.[38] On the other hand, hsCRP is produced by the liver in response to stimulation by IL-6, and is also produced by smooth cells and adipocytes. In several experimental studies, IL-6-assocated pathways played an important role in cardiomyocyte hypertrophy and cardiac fibroblast proliferation, and these effects were mediated by angiotensin II via the angiotensin type-I receptor as well as activated glycoprotein 130-linked signaling pathways.[17,18]

Although hsCRP is associated with measures of the burden of atherosclerosis such as carotid artery intima-media thickness,[39] hsCRP might be a more specific predictor of plaque vulnerability and hence future cardiovascular events, rather than of the extent of

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atherosclerosis in many epidemiological studies. IL-6 also increases with the acute-phase response and these elevations may be a marker for plaque instability. On the other hand, several studies reported that renal insufficiency was independently associated with elevated inflammatory markers, in particular, hsCRP, and renal insufficiency predicted LVH independently in subjects with chronic renal disease.[40] Because of the established association of endothelial function and LVH, these pathways could be accelerated in subjects with chronic renal disease.[40–42] In our study, both hsCRP and IL-6 were associated with LVH, but sTNFR1 was more strongly associated with LVH than these markers, and its associations persisted even after adjusting for other risk factors including serum creatinine. Other investigators have reported that hsCRP and IL-6 were more strongly associated with risk for coronary artery disease than sTNFR1 and sTNFR2.[13] These data suggest that although hsCRP and IL-6 might be associated with plaque weakening, rupture and coronary artery disease, sTNFR1 might be associated with progression of subclinical disease or cardiac remodeling. However, it is possible that some of the effects of these other risk factors on LVH are mediated through hsCRP or IL-6-associated inflammatory system.

Study limitations

Our study has several limitations. Because of its cross-sectional design, we were not able to derive a temporal or causal relationship between inflammatory markers and increased LV mass. We also did not have data on clinical infection and therefore were not able to make statements about potential underlying infectious causes of the elevated inflammatory marker levels. However, our population was generally healthy, and infection is unlikely to be a common cause of elevations in markers. Moreover, our study assesses a measure of subclinical diseases and LVH, rather than clinical end points such as stroke or myocardial infarction, which might be considered more relevant to clinical practice. Several recent studies have provided evidence that measures of subclinical diseases are predictive of clinical ischemic events.[1,2] These measures thus have the potential to allow stratification of patients for intervention to prevent outcome events. Further prospective studies of the relationship between sTNFRs and other inflammatory markers and LVH are needed. It is also possible that there is residual confounding by other conditions, including heart failure. Levels of TNF-alpha are elevated in congestive heart failure patients, and could be elevated in patients in our study for that reason. However, the prevalence of heart failure in our sample was low (5.8%)[28], though not all of the enrolled patients had LV diastolic function measurements using transthoracic Doppler echocardiography. Additional studies in unrelated populations would be necessary to extend our finding to other groups.

In conclusion, our study suggests an association between elevated sTNFR1, IL-6 and hsCRP levels and increased LV mass in this multiethnic population, independent of clinically overt cardiovascular disease and cardiovascular risk factors. sTNFR1 is more strongly associated with increased LV mass than IL-6 and hsCRP levels. Confirmation of the role of inflammatory markers in cardiac hypertrophy from larger, prospective studies might lead to clinical trials with novel anti-inflammatory therapies for atherosclerosis or for prevention of incident and recurrent cardiovascular events.

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Table 1

Characteristics of participants

	n	prevalence (%), or mean ± SD
Age (years)	660	67.4 ± 8.8
Male	234	35.5
Race-ethnicity		
Hispanic	407	61.7
Non-Hispanic Black	130	19.7
Non-Hispanic White	123	18.6
Completed high school education	284	43.0
History of coronary artery disease*	59	8.9
Body mass index (kg/m^2)	660	27.8 ± 5.4
Fasting blood glucose (mg/dL)	655	101.1 ± 46.8
Diabetes mellitus†	98	14.9
Systolic blood pressure (mmHg)	657	143.3 ± 21.1
Diastolic blood pressure (mmHg)	657	83.1 ± 10.8
Hypertension‡	453	68.6
Total cholesterol (mg/dL)	658	204.7 ± 40.1
LDL cholesterol (mg/dL)	648	132.0 ± 36.1
HDL cholesterol (mg/dL)	658	46.6 ± 14.9
Triglyceride (mg/dL)	658	132.5 ± 78.8
Serum creatitine (mg/dL)	658	0.93 ± 0.34
Current smoking	112	17.2
Ever smoking	538	81.6
Left ventricular mass (g)	660	177.7 ± 58.4
Inflammatory marker		
High-sensitive C-reactive protein (mg/L)	660	5.3 ± 8.0
Interleukin-6 (pg/mL)	654	2.0 ± 2.0
Soluble tumor necrosis factor receptor 1 (ng/mL)	660	2.5 ± 1.2
Medication usage		
Aspirin	176	26.8
Statin	127	19.3
Insulin	23	3.5
Oral hypoglycemic agents	58	8.8
Anti-hypertensive agents	305	46.2

*History of coronary artery disease was defined by history of myocardial infarction, angioplasty or bypass surgery.

†Diabetes mellitus was defined by fasting blood glucose level ≥ 126mg/dL, or participant's self report of such a history, or insulin or hypoglycemic use.

‡Hypertension was defined by systolic blood pressure ≥ 140mmHg, or diastolic blood pressure ≥ 90mmHg, or participant's self-report of a history of hypertension or anti-hypertensive medicine use.

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Table 2

Mean difference in left ventricular mass (g) by hsCRP, IL-6 and sTNFR 1 level*

	hsCRP			IL-6			sTNFR 1		
Model	***n***	**Estimate****	***P* value**	***n***	**Estimate****	***P* value**	***n***	**Estimate****	***P* value**
Unadjusted	660	6.21	0.002	654	6.30	0.004	660	15.67	<0.0001
Adjusted for demographic factors†	660	7.55	<0.0001	654	6.82	0.0009	660	14.49	<0.0001
Adjusted for demographic and medical risk factors‡	655	2.81	0.12	649	3.63	0.06	655	8.86	0.0008
Adjusted for demographic factors, medical risk factors‡ and sTNFR1/hsCRP	655	1.29	0.49	--	--	--	655	8.36	0.002
Adjusted for demographic factors, medical risk factors‡, medication§ and sTNFR1/hsCRP	432	4.93	0.04	--	--	--	432	7.10	0.03
Adjusted for demographic factors, medical risk factors‡ and sTNFR1/IL-6	--	--	--	646	0.34	0.87	646	10.41	0.0004
Adjusted for demographic factors, medical risk factors‡, medication§ and sTNFR1/IL-6	--	--	--	427	3.37	0.17	427	9.25	0.01

*Abbreviations: hsCRP = high-sensitive C-reactive protein, IL-6 = interleukin-6, sTNFR = soluble tumor necrosis factor receptor.

**Estimate means difference in LV mass (g) per standard deviation change of each inflammatory marker.

†Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education.

‡Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, and serum creatinine (See text for definitions of risk factors).

§Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, serum creatinine, and medication (See text for definitions of risk factors).

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Table 3

Change in left ventricular mass by inflammatory marker levels

	Unadjusted		Adjusted for demographic factors[†]		Adjusted for demographic and medical risk factors[‡]		Adjusted for demographic, medical risk factors and medicines[§]	
	Mean Difference per Category Change (g)	*P* value	Mean Difference per Category Change (g)	*P* value	Mean Difference per Category Change (g)	*P* value	Mean Difference per Category Change (g)	*P* value
hsCRP Category[*]								
hsCRP <1 mg/L	0.00 (Ref)	--	0.00 (Ref)	--	0.00 (Ref)	--	0.00 (Ref)	--
hsCRP 1–3 mg/L	−2.96	0.64	1.49	0.80	−3.75	0.50	−6.42	0.38
hsCRP> 3 mg/L	8.46	0.15	17.07	0.002	2.39	0.66	5.38	0.45
sTNFR 1 Quartile								
Quartile 1	0.00 (Ref)	--	0.00 (Ref)		0.00 (Ref)	--	0.00 (Ref)	--
Quartile 2	−4.56	0.48	−2.32	0.70	−2.40	0.67	−4.20	0.56
Quartile 3	2.62	0.68	7.50	0.21	2.67	0.64	0.39	0.96
Quartile 4	23.16	0.0003	25.70	<0.0001	8.76	0.16	2.89	0.71

Abbreviations: hsCRP = high-sensitivity C-reactive protein, sTNFR = soluble tumor necrosis factor receptor.

[*] based on Centers for the Disease Control and Prevention/American Heart Association recommendations for cardiovascular risk assessment: hsCRP <1mg/L, hsCRP 1 to 3 mg/L, and hsCRP >3 mg/L.

[†] Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education.

[‡] Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, and serum creatinine (See text for definitions of risk factors).

[§] Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, serum creatinine, and medication (See text for definitions of risk factors).

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Table 4

Odds ratio of LVH* by inflammatory marker levels

	Unadjusted			Adjusted for demographic factors†			Adjusted for demographic and medical risk factors‡			Adjusted for demographic, medical risk factors and medication§		
	OR	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
hsCRP overall	1.20	1.04–1.39	0.01	1.23	1.05–1.44	0.009	1.05	0.90–1.22	0.57	1.06	0.85–1.32	0.63
hsCRP Category**												
hsCRP < 1mg/L	1.00 (Ref)	--	--	1.00 (Ref)	--	--	1.00 (Ref)	--	--	1.00 (Ref)	--	--
hsCRP 1–3 mg/L	0.77	0.48–1.24	0.29	0.85	0.52–1.37	0.50	0.67	0.40–1.12	0.12	0.64	0.33–1.24	0.18
hsCRP > 3mg/L	1.20	0.79–1.83	0.40	1.39	0.90–2.17	0.14	0.79	0.49–1.30	0.36	0.83	0.43–1.58	0.56
sTNFR 1 overall	1.46	1.25–1.71	<0.0001	1.58	1.28–1.95	<0.0001	1.41	1.11–1.80	0.005	1.49	1.10–2.00	0.009
sTNFR 1 Quartile												
Quartile 1	1.00 (Ref)	--		1.00 (Ref)	--	--	1.00 (Ref)	--	--	1.00 (Ref)	--	--
Quartile 2	1.12	0.69–1.83	0.65	1.25	0.75–2.07	0.39	1.31	0.77–2.23	0.32	1.19	0.61–2.31	0.62
Quartile 3	1.19	0.73–1.95	0.48	1.34	0.80–2.22	0.26	1.17	0.69–2.00	0.56	1.21	0.63–2.31	0.57
Quartile 4	2.46	1.54–3.94	0.0002	2.68	1.62–4.43	0.0001	1.84	1.07–3.20	0.03	1.88	0.97–3.64	0.06

Abbreviations: hsCRP = high-sensitivity C-reactive protein, sTNFR = soluble tumor necrosis factor receptor, OR = odds ratio, CI = confidence interval.

* LVH was defined as LV mass ≥ 90th percentile of the normal participants without conditions associated with LVH.

** based on the Centers for the Disease Control and Prevention/American Heart

† Association recommendations for cardiovascular risk assessment: hsCRP <1mg/L, hsCRP 1 to 3 mg/L, and hsCRP >3 mg/L.

‡ Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, and serum creatinine (See text for definitions of risk factors).

§ Adjusted for age, sex, race-ethnicity (white non-Hispanic, black non-Hispanic, or Hispanic), completed high school education, diabetes mellitus, hypertension, history of coronary artery disease, body mass index, smoking, serum creatinine, and medication (See text for definitions of risk factors).