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Relationship of CRP, IL-6, and Fibrinogen with Right Ventricular Structure and Function: The MESA-Right Ventricle Study

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Abstract

Background/objectives—Inflammation contributes to the pathogenesis of disease associated with the left ventricle (LV); yet, our understanding of the effect of inflammation on the right ventricle (RV) is quite limited.

Methods and results—The relationships of C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen with RV morphology and function (from cardiac MRI) were examined in participants free of clinical cardiovascular disease (n=4,009) from the Multi-Ethnic Study of Atherosclerosis

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(MESA)-RV study. Multivariable regressions (linear, quantile [25th and 75th] and generalized additive models [GAM]) were used to examine the independent association of CRP, IL-6 and fibrinogen with RV mass, RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RV stroke volume (RVSV) and RV ejection fraction (RVEF). Unadjusted and adjusted analyses revealed strong inverse associations between both CRP and IL-6 with RV mass, RVEDV, RVESV and RVSV (all $p < 0.01$); there were no associations with RVEF. These relationships remained significant after adjustment for the respective LV parameters and lung function. However, GAM models suggested that extreme values of CRP and IL-6 might have positive associations with RV parameters. Fibrinogen showed significant associations in unadjusted models, but no associations after adjustment or in sensitivity analyses.

Conclusion—Levels of CRP and IL-6 are independently associated with RV morphology even after adjustment for the respective LV measure in this multi-ethnic population free of cardiovascular disease. Systemic inflammation may contribute to RV structural changes independent of effects on the LV.

Keywords

Systemic inflammation; right ventricle; heart failure; Multi-Ethnic Study of Atherosclerosis

INTRODUCTION

A large body of literature supports inflammation as an important determinant of left ventricular (LV) morphology. While systemic vascular disease and subsequent LV changes are well defined, our understanding of the processes that affect the right ventricle (RV) is limited. C-reactive protein (CRP) [1, 2, 3] and interleukin-6 (IL-6) [4, 5] levels are associated with LV hypertrophy and remodeling. Further, higher levels of CRP [6–8], IL-6 [9, 10], and fibrinogen [8, 11, 12] have been linked with an increased risk of cardiovascular events, supporting a role of inflammation in long term cardiovascular outcomes.

Studies have suggested that CRP has adverse effects on the vascular endothelium and smooth muscle by decreasing prostacyclin and nitric oxide release and increasing endothelin-1 production [13–15], however the causal role of CRP itself (rather than CRP being an indicator of systemic inflammation) is unclear [16, 17]. Increased levels of IL-6 have been found in lung samples of patients with pulmonary hypertension (PH) [18, 19], and circulating IL-6 levels are increased in patients with pulmonary arterial hypertension (PAH), characterized by increased RV afterload leading to hypertrophy and eventual RV failure [20]. A recent mendelian randomization study [21] and meta-analysis [22] confirmed a causal role for IL-6 in LV disease. A causal link between fibrinogen and LV pathology has not been established [23] but there are considerable observational data suggesting a role in LV structure and function [8]. Further, circulating fibrinogen is elevated in patients with PAH [24], and a recent study of idiopathic PAH patients found increased levels of fibrinogen isoformgamma-A and fibrinogen isoformgamma-B compared with controls [25]. Thus, CRP, IL-6 and fibrinogen could be linked to RV structure and function either by directly acting on the myocardium or via their effects on the pulmonary vasculature.

A prior analysis in a subset of the Multi-Ethnic Study of Atherosclerosis (MESA)-RV study population suggested that higher plasma matrix metalloproteinase (MMP)-9 (a measure of inflammation) levels were associated with lower RV mass independent of LV mass [26]. This contradicts the traditional wisdom that more inflammation always leads to hypertrophy and ventricular dilation. In the present study, we sought to examine the association of well-defined inflammatory markers, CRP, IL-6 and fibrinogen, with RV structure and function in adults free of clinical cardiovascular disease. We hypothesized that these three biomarkers

would be positively associated with increased RV mass, larger RV end-diastolic volume (RVEDV) and RV end-systolic volume (RVESV), and lower RV stroke volume (RVSV) and RV ejection fraction (RVEF).

METHODS

MESA is a multicenter prospective cohort study to investigate the prevalence, correlates and progression of subclinical cardiovascular disease in whites, African-Americans, Hispanics, and Chinese. In 2000–2002, MESA recruited 6,814 men and women aged 45–84 years old from six U.S. communities: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles, CA. Exclusion criteria included clinical cardiovascular disease (physician diagnosis of heart attack, stroke, transient ischemic attack, heart failure, angina, current atrial fibrillation, any cardiovascular procedure), weight > 136 kg (300 lbs), pregnancy, or impediment to long-term participation. No other specific pathologies (such as blood disorders or immune diseases) were considered as exclusion criterion. The protocols of MESA and all studies described herein were approved by the Institutional Review Boards of all collaborating institutions and the National Heart Lung and Blood Institute.

The MESA-Right Ventricle Study is an ancillary study focused on measuring RV morphology in MESA participants eligible for MRI (without metal implants, device or fragment) with interpretable studies at the baseline examination.

Cardiac Magnetic Resonance Imaging Measures

The cardiac MRI protocol and methods for interpretation of LV and RV parameters have been previously reported [27, 28]. All imaging was performed with 1.5-T magnets with a 4-element phased-array surface coil positioned anteriorly and posteriorly and ECG gating. Imaging consisted of fast gradient echo cine images with temporal resolution 50 milliseconds. Cardiac MRI examinations were transmitted to the reading center at Johns Hopkins University in Baltimore, MD, with the digital imaging and communications in medicine (DICOM) transfer protocol. Image analysis was done on Windows workstations with QMASS software (version 4.2; Medis, the Netherlands). Images were magnified to 250%. Image contrast was set to 55; image brightness was set to 55; and window width and level were set with the auto function in QMASS to minimum and maximum pixel values of 0 and 238, respectively.

The endocardial and epicardial borders of the RV were traced manually on the short-axis cine images at the end-systolic and end-diastolic phases. Full visualization of the correct placement of RV contours relied on evaluation of cine images to determine the demarcation between the right atrium and the RV. Contours were modified at basal slices of the heart by careful identification of the tricuspid valve so as to exclude the right atrium and to avoid overestimation of the volumes. The outflow tract was included in the RV volume.

RVEDV and RVESV were calculated using Simpson's rule by summation of areas on each slice multiplied by the sum of slice thickness and image gap. RV mass was determined at enddiastole as the difference between end-diastolic epicardial and endocardial volumes multiplied by the specific gravity of the heart (1.05 g/cm^3) [28]. RVSV was calculated by subtracting RVESV from RVEDV; RVEF was calculated by dividing RVSV by RVEDV. The intrareader intraclass correlation coefficient from random, blinded rereads of 229 scans for RV mass was 0.94 and for RVEDV and RVEF from 230 scans was 0.99 and 0.89. The interreader intraclass correlation coefficients from random, blinded rereads of 240 scans for RV mass, RVEDV, and RVEF were 0.89, 0.96, and 0.80, respectively.

Biomarkers

Fasting blood samples were drawn, processed and stored using standardized procedures [29]. All plasma biomarkers were measured in the Laboratory for Clinical Biochemistry Research at University of Vermont (Burlington, VT). CRP was measured using the BNII nephelometer (N High Sensitivity CRP; Dade Behring Inc., Deerfield, IL). This instrument utilizes a particle enhanced immunonephelometric assay to determine CRP. Polystyrene particles are coated with monoclonal antibodies to CRP that agglutinate in the presence of antigen (CRP) to cause an increase in the intensity of scattered light. The increase in scattered light is proportional to the amount of CRP in the sample. The assay range is 0.175 – 1100 mg/L. Expected values for CRP in normal, healthy individuals are 3 mg/L. Intra-assay CVs range from 2.3 – 4.4% and inter-assay CVs range from 2.1 – 5.7%.

IL-6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN). The lower detection limit is <0.0094 pg/mL with a detection range of 0.156–10.0 pg/mL. A monoclonal anti-IL6 antibody is coated on the plastic support and a polyclonal anti-IL6 antibody is used as the sandwich antibody. The amount of IL-6 bound is determined by a color reaction. The expected normal range per the manufacturer is 0.24 to 12.5 pg/mL. The laboratory CV for this assay is 6.3%.

Fibrinogen antigen was measured using the BNII nephelometer (N Antiserum to Human Fibrinogen; Dade Behring Inc., Deerfield, IL). The amount of fibrinogen present in the sample is quantitatively determined by immunochemical reaction. Complexes formed between antigen and antibody molecules scatter light passing through the sample. The intensity of the scattered light is proportional to the concentration of the antigen (fibrinogen) in the sample. Expected values for fibrinogen in normal, healthy individuals are 180 – 350 mg/dl. The intra-assay and inter-assay CVs are 2.7% and 2.6%, respectively.

Other Covariates

Race/ethnicity was self-reported during the baseline MESA exam according to 2000 US Census criteria. Height was measured to the nearest 0.1 cm with the subject in stocking feet and weight was measured to the nearest pound with the subject in light clothing using a balanced scale. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or current use of anti-hypertension medication. Presence of diabetes mellitus was based on self-reported physician diagnosis, use of medication for hyperglycemia, or a fasting glucose value ≥ 126 mg/dL, the latter measured by rate reflectance spectrophotometry (Johnson & Johnson Clinical Diagnostics, Inc., Rochester, NY). Fasting glucose = 100–125 mg/dL was considered impaired fasting glucose. Spirometry, urine cotinine, and computed tomographic (CT) lung density measures were available for a subset of 2,680 (67%) participants [30, 31].

Statistical Analysis

Continuous variables are expressed as means and standard deviations or ranges. Categorical variables are expressed as percents. A multivariate generalized linear model was used to assess the relationship of each biomarker with RV mass, RVEDV, RVSV, and RVEF. Shapiro-Wilks tests for normality and quantile plots were used to assess the distribution of each biomarker, leading to the log-transformation of CRP and IL-6 for the analysis. Initial models were adjusted for age, sex, race/ethnicity, height, and weight. Adjustment for height and weight in all analyses avoided the assumptions made in indexing the RV measures to certain parameters of body size (e.g., body surface area), while achieving the same end of accounting for differences in body size between participants. Models were then further adjusted for smoking, hypertension, diabetes mellitus, impaired glucose tolerance, and systolic and diastolic blood pressure, as well as for the respective LV parameter. Adjustment

for LV parameters was performed to account for the contribution of LV abnormalities to RV changes (for example, increased LV mass causing pulmonary venous hypertension leading to increased RV mass), to better account for differences in body size, and to examine RV-specific associations (rather than more general associations with bi-ventricular morphology). To examine the stability of our estimates we examined the coefficients at the 25th and 75th percentiles. We estimated generalized additive models (GAM) in our primary study sample for each of the three biomarkers to detect non-linear relationships.

We performed further adjusted analyses in the subgroup of participants (n=2,680, 67%) with available data for percent of emphysema-like lung as measured in the lung windows of cardiac computed tomography, forced expiratory volume in 1 second/forced vital capacity ratio (FEV1/FVC), (continuous), and cotinine (continuous) (from the MESA-Lung ancillary study). Statistical significance was defined as $P < 0.05$. Analyses were performed using STATA 12.0 (StataCorp, College Station, TX). Post-estimation analyses of residuals and removal of observations with high leverage values did not result in a change in the direction, significance or effect size of the primary models.

Results

MESA included 6,814 participants. Of these, 5,098 had cardiac MRIs of which 5,004 were interpretable for LV measures. The MESA-Right Ventricle Study selected 4,634 scans from the 5,004 (without regard to age, sex, or race), and attempted to read 4,424, of which 4,204 were available and interpretable for RV morphology. Table 1 shows the characteristics of the study sample with complete biomarker and covariate data ($N = 4,009$), compared to those excluded ($N = 2,805$). The mean age of the study sample was 61.4 years, 47.3% were male, 39.5% were white, 25.9% were African-American, 21.9% were Hispanic, and 12.7% were Chinese. The mean BMI of the study sample was 27.9 kg/m^2 ($SD = 4.9$). The study sample was similar to those excluded in terms of age, gender, race/ethnicity, educational achievement, comorbidities, smoking, and glucose levels. Biomarker values were similar between those in the study sample and those excluded who had available data. Formal statistical testing is not appropriate for such comparisons, which are descriptive rather than inferential [32]. The mean RV mass in the study sample was $21.1 \pm 4.5 \text{ g}$, the mean RVEDV was $124.2 \pm 31.1 \text{ mL}$, and the mean RVSV was $86.9 \pm 20.7 \text{ mL}$. The mean RVEF was $70.5 \pm 6.5 \%$.

We found effect modification (all p values for interaction < 0.05) by race/ethnicity for CRP (with RVEDM, RVEDV, RVESV and RVSV) and fibrinogen (with RVEDV and RVSV) with RV morphology though effect estimates for all races/ethnicities were in the same direction (just of different magnitudes). Specifically, the effect sizes were greater among African Americans than in Caucasians, Hispanic Americans and Chinese-Americans. There were no differences (effect modification) in the association of IL-6 or fibrinogen with RV morphology between races/ethnicities (all p values for interaction > 0.10).

Higher CRP levels were associated with lower RV mass (per 1 $\ln$ CRP = -0.25 g , $p < 0.001$) in the base model using linear regression (Table 2). Adjustment for covariates did not affect this result, whereas additional adjustment for LV mass attenuated the effect estimate, which was still statistically significant. The difference in RV mass between the first and fourth quartile of $\ln$ CRP was -0.41 g . There were also significant inverse associations between CRP levels and RV volumes. Higher CRP levels were associated with smaller RVEDV and RVESV in basic and fully adjusted linear regression models, even after adjusting for the respective LV volumes. Higher CRP levels were also significantly associated with lower RVSV (per 1 $\ln$ CRP = -1.62 mL , $p < 0.001$). There were no associations between CRP levels and RVEF.

Analyses using GAMs (which is a more flexible modeling approach which allows for nonlinearity in the relationship) revealed that CRP had a non-linear relationship with RVEDM, RVEDV, RVESV and RVSV, but not RVEF. Visual inspection of the GAM models, in addition to quantile regressions at the 25th and 75th percentile, confirmed the strong inverse associations seen with linear regression in the range of CRP values of most of the population with possible direct associations at the very highest CRP values (> 20 mg/L, ~97thile) (Figure 1). Linear regression analyses in the subset with available lung function data after controlling for FEV1/FVC, cotinine, % of emphysema-like lung, and machine type used for computed tomography showed similar though attenuated results of the relationship with CRP with the inverse relationship remaining in the fully adjusted model for all RV measures other than RVEF ($p < 0.05$ for all) (Table E1).

Analyses of IL-6 showed results similar to those of CRP (Table 3). Higher levels of IL-6 were associated with lower RV mass in the basic model using linear regression (per 1 ln IL-6 = -0.31 g, $p < 0.001$). This result was unchanged after adjusting for confounders and was attenuated (but still present) after adjustment for LV mass (per 1 ln IL-6 = -0.19 g, $p < 0.001$). The difference in RV mass between the upper and lower quartile of ln IL-6 was -0.35 g. Higher IL-6 levels were also associated with significantly lower RV volumes even after adjustment for confounders and the respective LV volumes. There were weak (and non-significant) direct associations between IL-6 and RVEF, which were statistically significant after adjustment for LV ejection fraction.

Analyses using GAMs revealed that IL-6 had possible non-linear relationships with RVEDM, RVEDV, and RVSV, but not RVEF, though this relationship was weaker when adjusting for LVEDV in the RVEDV model ($p = 0.03$). Similar to CRP, visual inspection of the GAM models, in addition to quantile regressions at the 25th and 75th percentile, suggest robust negative associations for the vast majority of participants with possible positive associations at the very highest IL-6 values (> 4 pg/ml level, ~96thile) (Figure 2). Further linear regression analyses in the subset with available lung function data after controlling for FEV1/FVC, cotinine, % of emphysema-like lung, and machine type used for computed tomography showed the same results (Table E2).

Levels of CRP and IL-6 were independently associated with RV morphology in linear regression models with both variables (data not shown). Analyses of fibrinogen showed significant associations with RV parameters in the unadjusted models, however none were significant after adjustment for confounders (Table 4).

Discussion

In a multi-ethnic sample of adults without clinical cardiovascular disease at baseline, we have shown that higher plasma CRP and IL-6 levels were associated with lower RV mass and smaller RVEDV, RVESV, and RV stroke volume in most individuals. These associations were independent of a variety of confounders, including demographics, body size, smoking history, diabetes, blood pressure, use of an anti-hypertensive medication or statins, and even the respective LV parameters. At extremely high levels of CRP and IL-6 (affecting only a few percent of the population), there may be increased RV mass and volumes. Sensitivity analyses in a subset of patients with available spirometric measures and CT lung density did not change the findings from the full sample. There were no associations between fibrinogen and RV morphology.

Figures 1 and 2 demonstrate the possible complex relationship between CRP and IL-6 and RV morphology in the general adult population. In the most common range (~10 mg/L for CRP and about 3 pg/ml for IL-6) of these biomarkers (including > 90% of the population),

there were inverse relationships between biomarker levels and RV size. In adults with extremely high biomarker levels, there were direct associations with RV size. At clinical thresholds of CRP and IL-6 the findings are consistent with a large body of literature that supports inflammation as an important determinant of LV morphology [1, 3, 14, 33–35]. While established as an indicator of systemic inflammation, some have suggested that CRP may have a mechanistic role in heart and lung disease. Recent studies focusing on genetic variation in CRP production in coronary artery disease and COPD suggest that CRP is not causal but rather a reflection of the role of inflammation in the disease process [17, 36, 37].

A variety of studies of patients with pulmonary hypertension have shown that elevated CRP levels are linked to adverse outcomes. Quarck et al. examined the association of CRP levels in patients with PAH and chronic thromboembolic disease [38]. These investigators found an independent association between elevated CRP levels and worse survival. Those patients whose CRP levels decreased to normal during treatment had a better outcome than that of patients whose CRP levels remained elevated. Sztrymf et al. found that PAH patients who died after admission to the ICU had higher CRP levels than those of patients who survived the ICU [39].

IL-6 has been directly implicated in the pathogenesis of pulmonary vascular disease. IL-6 levels are elevated in (PAH)[40, 41] and an animal model that overexpresses IL-6 develops pulmonary hypertension [42]. Higher IL-6 levels are associated with an increased risk of death in PAH [19]. IL-6 levels are also increased in patients with congestive heart failure and diastolic dysfunction, and cause increased hepatic production of CRP and fibrinogen [5, 39, 43]. In our study, the associations of IL-6 and CRP were independent, suggesting the importance of each individually.

Similar to other findings in MESA-RV, increasing levels of these inflammatory biomarkers (in the range of most participants) were associated with lower RV mass and smaller RV volumes. While traditional thinking would suggest that more inflammation always leads to hypertrophy and ventricular dilation in the RV, our data do not support this contention. We (and others) have shown that older age is associated with lower (rather than higher) RV mass [27]. Other markers of inflammation, such as impaired fasting glucose and higher levels of MMP-9, were also associated with lower RV mass and smaller RV volumes in MESA [26]. While of a small magnitude, these associations were independent of LV mass, suggesting RV-specific (or disproportionate) effects. It is possible that RV diastolic abnormalities could explain these findings, as increased RV stiffness could reduce RV filling. The negative relationship between CRP and IL-6 and RV mass might be due to the generalized 'wasting' of muscle mass or frailty that accompanies inflammation [44]. The impact on cardiac morphology may indeed differ depending on the biomarker levels, with atrophy and increased stiffness being seen at lower levels of inflammation and hypertrophy and dysfunction seen at higher levels.

Study limitations

There are some limitations in the present study. Confounding by unmeasured covariates or residual confounding is possible, however MESA included extensive measurements and assessments of known confounders, which we used in multivariate analyses. The lack of large, epidemiologic studies of RV structure and function in disease-free older adults make it difficult to judge whether the effect estimates amount to “clinically important” associations but they were similar in magnitude to those of traditional cardiovascular risk factors with LV morphologic changes. For example, the difference in RV mass between extreme quartiles of both CRP and IL-6 was approximately 3%, compared to that seen with LV mass for smoking (5.3%) or diabetes mellitus (2.8%) [27].

Additionally, we analyzed several biomarkers making Type I error possible. Furthermore, newer MRI sequences may be more precise (steady-state free precession imaging); however, potential error in MRI measurements should bias toward the null hypothesis, so the associations may be even stronger than we have shown. We performed cross-sectional analyses of observational data using assessments made at the baseline MESA examination. Therefore, it is not possible to prove temporality or causality, although we know of no data supporting a role of RV structure and function in determining the biomarker levels studied. Additionally, short-term variability in the biomarkers, from diurnal or seasonal fluctuations, if present, would have biased towards the null. Finally, this analysis did not examine gene polymorphisms for CRP, IL-6 or fibrinogen.

Conclusion

In sum, we found robust inverse relationships between CRP and IL-6 and RV size for most adults without dramatic elevations in these biomarkers. However, with extreme elevations in these inflammatory biomarkers, higher levels were associated with increased RV mass and volumes. Inflammation may play an important role in clinical cardiovascular disease-free individuals and those with increased RV afterload from pulmonary vascular disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This report was reviewed by the MESA investigators for scientific content and consistency of data interpretation with previous MESA publications, and significant comments were incorporated before submission for publication. We thank the other investigators, staff members, and participants of the MESA and MESA-Lung studies for their valuable contributions. A full list of participating MESA investigators and institutions can be found at <http://www.mesa-nhlbi.org>.

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A

B

Figure 1.

- Generalized additive model of the association between CRP and right ventricular end-diastolic mass
- Generalized additive model of the association between CRP and right ventricular end-diastolic volume

A

B

Figure 2.

- Generalized additive model of the association between IL-6 and right ventricular end-diastolic mass
- Generalized additive model of the association between IL-6 and right ventricular end-diastolic volume

Table 1

Characteristics

	Not Included (n=2,805) Mean or proportion	SD	Study Sample (n=4,009) Mean or proportion	SD
Age, years	63.2	+/- 10.3	61.4	+/- 10.1
Male sex, %	46.8		47.3	
Race/ethnicity, %				
White	37.0		39.5	
African American	30.4		25.9	
Hispanic	22.1		21.9	
Chinese	10.5		12.7	
Educational attainment, %				
No high school degree	20.52		16.3	
High school degree	18.04		18.3	
Some college, no bachelors	28.5		28.6	
Bachelors or graduate	33.0		36.8	
Height, cm	177.4	+/- 41.0	170.6	+/- 35.9
Weight, kg	166.3	+/- 10.1	166.4	+/- 9.9
BMI, kg/m ²	29.0	+/- 6.05	27.9	+/- 4.9
Waist circumference, cm	100.1	+/- 15.5	96.8	+/- 13.4
Hip circumference, cm	107.0	+/- 12.6	104.7	+/- 10.5
Systolic blood pressure, mmHg	128.3	+/- 22.0	125.4	+/- 21.0
Diastolic blood pressure, mmHg	72.0	+/- 10.4	71.8	+/- 10.2
Total cholesterol, mg/dL	193.6	+/- 36.8	194.5	+/- 35.0
HDL cholesterol, mg/dL	50.7	+/- 14.6	51.2	+/- 15.0
Triglycerides, mg/dL	133.1	+/- 98.7	130.5	+/- 81.2
Cigarette smoking status, %				
Never	47.3		52.5	
Former	38.6		35.2	
Current	14.2		12.3	
Smoking history, pack years	12.3	+/- 21.5	10.8	+/- 22.7
Diabetes mellitus, (treated or untreated), %	14.1	+/- 1.1	11.6	+/- 0.9
C-reactive protein, mg/dL	4.3	+/- 7.0	3.4	+/- 4.9
Fibrinogen, mg/dL	352.3	+/- 78.3	343.1	+/- 70.6
IL-6, mg/dL	1.7	+/- 1.3	1.5	+/- 1.2
Glucose, mg/dL	99.1	+/- 32.3	96.2	+/- 28.7
Statin use, %	15.1%		14.6%	
Blood pressure medication, %	36.0%		31.4%	
Cholesterol medication, %	16.2%		16.1%	
Any lipid-powering medication, %	16.1%		16.2%	
Diabetes medication, %	10.9%		9.0%	

	Not Included (n=2,805) Mean or proportion	SD	Study Sample (n=4,009) Mean or proportion	SD
<i>Left (LV) and right (RV) ventricle measures</i>				
LV end-diastolic mass, g	143.8	+/- 40.3	145.6	+/- 39.3
LV end-diastolic volume, ml	125.3	+/- 31.4	126.6	+/- 31.6
LV end-systolic volume, ml	39.5	+/- 17.3	40.1	+/- 17.1
LV stroke volume, ml	85.8	+/- 19.7	86.5	+/- 19.9
LV ejection fraction, %	69.1	+/- 7.4	69.0	+/- 7.4
RV end-diastolic mass, g	20.8	+/- 3.9	21.1	+/- 4.5
RV end-diastolic volume, ml	123.2	+/- 26.5	124.2	+/- 31.1
RV end-systolic volume, ml	37.5	+/- 12.4	37.3	+/- 14.3
RV stroke volume, ml	85.8	+/- 18.2	86.9	+/- 20.7
RV ejection fraction, %	69.9	+/- 6.2	70.5	+/- 6.5

Table 2Linear regression models of the association between C-reactive protein and the right ventricle (n=4,009)^{*}

	<i>Regression coefficient (95% CI)[*]</i>	<i>P-value</i>
RV End-Diastolic Mass (g)		
Model 1	−0.25 (−0.35, −0.15)	<0.001
Model 2	−0.21 (−0.31, −0.11)	<0.001
Model 3	−0.14 (−0.24, −0.05)	0.003
RV End-Diastolic Volume (mL)		
Model 1	−2.42 (−3.06, −1.78)	<0.001
Model 2	−1.91 (−2.55, −1.26)	<0.001
Model 3	−1.06 (−1.54, −0.58)	<0.001
RV End-Systolic Volume (mL)		
Model 1	−0.8 (−1.12, −0.48)	<0.001
Model 2	−0.64 (−0.97, −0.31)	<0.001
Model 3	−0.52 (−0.81, −0.22)	0.001
RV Stroke Volume (mL)		
Model 1	−1.62 (−2.09, −1.14)	<0.001
Model 2	−1.27 (−1.74, −0.79)	<0.001
Model 3	−0.55 (−0.9, −0.21)	0.002
RV Ejection Fraction (%)		
Model 1	0.07 (−0.11, 0.25)	0.47
Model 2	0.06 (−0.12, 0.25)	0.50
Model 3	0.08 (−0.09, 0.25)	0.37

Model 1: Adjusted for age, gender, race, weight, height.

Model 2: Model 1 + educational attainment, systolic and diastolic blood pressure, total & HDL cholesterol, triglycerides, current smoking status & pack years, diabetes (yes/no), waist & hip circumference, glucose, and an indicator for use of statins or hypertension medication.

Model 3: Model 2 + LV parameter

^{*}
per 1 ln increase in CRP level

Table 3

Linear regression models of the association between IL-6 and the right ventricle (n=4,009) *

	<i>Regression coefficient (95% CI) *</i>	<i>P-value</i>
RV End-Diastolic Mass (g)		
Model 1	−0.31 (−0.49, −0.14)	<0.001
Model 2	−0.28 (−0.45, −0.1)	0.002
Model 3	−0.19 (−0.35, −0.02)	0.025
RV End-Diastolic Volume (mL)		
Model 1	−3.31 (−4.42, −2.19)	<0.001
Model 2	−2.65 (−3.78, −1.52)	<0.001
Model 3	−1.15 (−1.99, −0.31)	0.007
RV End-Systolic Volume (mL)		
Model 1	−1.34 (−1.89, −0.78)	<0.001
Model 2	−1.22 (−1.79, −0.65)	<0.001
Model 3	−1.05 (−1.57, −0.54)	<0.001
RV Stroke Volume (mL)		
Model 1	−1.97 (−2.8, −1.14)	<0.001
Model 2	−1.43 (−2.27, −0.59)	0.001
Model 3	−0.06 (−0.67, 0.55)	0.85
RV Ejection Fraction (%)		
Model 1	0.18 (−0.13, 0.5)	0.25
Model 2	0.27 (−0.05, 0.59)	0.10
Model 3	0.36 (0.07, 0.66)	0.017

Model 1: Adjusted for age, gender, race, weight, height.

Model 2: Model 1 + educational attainment, systolic and diastolic blood pressure, total & HDL cholesterol, triglycerides, current smoking status & pack years, diabetes (yes/no), waist & hip circumference, glucose, and an indicator for use of statins or hypertension medication.

Model 3: Model 2 + LV parameter

*
per 1 ln increase in IL-6 level

Table 4

Linear regression models of the association between fibrinogen and the right ventricle (n=4,009)

	<i>Regression coefficient (95% CI)*</i>	<i>P-value</i>
RV End-Diastolic Mass (g)		
Model 1	−0.000 (−0.002, 0.001)	0.60
Model 2	0.000 (−0.001, 0.002)	0.55
Model 3	0.000 (−0.001, 0.002)	0.56
RV End-Diastolic Volume (mL)		
Model 1	−0.015 (−0.025, −0.004)	0.004
Model 2	−0.007 (−0.017, 0.004)	0.19
Model 3	−0.002 (−0.010, 0.005)	0.39
RV End-Systolic Volume (mL)		
Model 1	−0.003 (−0.008, 0.002)	0.18
Model 2	−0.002 (−0.007, 0.004)	0.46
Model 3	−0.003 (−0.007, 0.002)	0.18
RV Stroke Volume (mL)		
Model 1	−0.011 (−0.019, −0.004)	0.003
Model 2	−0.005 (−0.013, 0.002)	0.21
Model 3	0.002 (−0.004, 0.007)	0.59
RV Ejection Fraction (%)		
Model 1	−0.002 (−0.005, 0.001)	0.27
Model 2	−0.001 (−0.004, 0.002)	0.57
Model 3	0.000 (−0.002, 0.003)	0.54

Model 1: Adjusted for age, gender, race, weight, height.

Model 2: Model 1 + educational attainment, systolic and diastolic blood pressure, total & HDL cholesterol, triglycerides, current smoking status & pack years, diabetes (yes/no), waist & hip circumference, glucose, and an indicator for use of statins or hypertension medication.

Model 3: Model 2 + LV parameter