

Sex Differences in Inflammatory Markers and Health Status Among Young Adults With Acute Myocardial Infarction Results From the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) Study

Yuan Lu, ScD; Shengfan Zhou, MS; Rachel P. Dreyer, PhD; Erica S. Spatz, MD, MHS; Mary Geda, MSN; Nancy P. Lorenze, DNSc; Gail D'Onofrio, MD; Judith H. Lichtman, PhD, MPH; John A. Spertus, MD; Paul M. Ridker, MD; Harlan M. Krumholz, MD, SM

Background—Young women (≤ 55 years of age) with acute myocardial infarction (AMI) have higher mortality risk than similarly aged men. Elevated inflammatory markers are associated with an increased risk of cardiovascular outcomes after AMI, but little is known about whether young women have higher inflammatory levels after AMI compared with young men.

Methods and Results—We assessed sex differences in post-AMI inflammatory markers and whether such differences account for sex differences in 12-month health status, using data from 2219 adults with AMI, 18 to 55 years of age, in the United States. Inflammatory markers including high-sensitivity C-reactive protein (hsCRP) and lipoprotein-associated phospholipase A2 were measured 1 month after AMI. Overall, women had higher levels of hsCRP and lipoprotein-associated phospholipase A2 after AMI compared with men, and this remained statistically significant after multivariable adjustment. Regression analyses showed that elevated 1-month hsCRP was associated with poor health status (symptom, function, and quality of life) at 12 months. However, the association between hsCRP and health status became nonsignificant after adjustment for sociodemographics, comorbidities, and treatment factors. Half of these patients had residual inflammatory risk (hsCRP > 3 mg/L) compared with a third who had residual cholesterol risk (Low-density lipoprotein cholesterol > 100 mg/dL).

Conclusions—Young women with AMI had higher inflammatory levels compared with young men. Elevated 1-month hsCRP was associated with poor health status at 12 months after AMI, but this was attenuated after adjustment for patient characteristics. Targeted anti-inflammatory treatments are worthy of consideration for secondary prevention in these patients if ongoing trials of anti-inflammatory therapy prove effective. (*Circ Cardiovasc Qual Outcomes*. 2017;10:e003470. DOI: 10.1161/CIRCOUTCOMES.116.003470.)

Key Words: biomarkers ■ C-reactive protein ■ inflammation ■ myocardial infarction ■ women

Young women (≤ 55 years of age) with acute myocardial infarction (AMI) have a significantly higher risk of mortality and morbidity after AMI compared with similarly aged men.¹ Although the cause of increased risk in young women is not completely understood, one hypothesis is that young women may have a higher inflammatory state after AMI. Inflammation is important in AMI prognosis: elevations of inflammatory markers such as high-sensitivity C-reactive

protein (hsCRP) after AMI are associated with an increased risk of recurrent cardiovascular events.^{2,3} Lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme produced by inflammatory cells, has also been shown to be associated with cardiovascular events independent of hsCRP.⁴ However, as inflammatory markers are not routinely measured in post-AMI care, we know little about whether young women have higher inflammatory levels after AMI compared with men and

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From the Center for Outcomes Research and Evaluation, Yale–New Haven Hospital, CT (Y.L., S.Z., R.P.D., E.S.S., H.M.K.); Section of Cardiovascular Medicine, Department of Internal Medicine (Y.L., S.Z., R.P.D., E.S.S., H.M.K.), Section of General Internal Medicine, Department of Internal Medicine (M.G., N.P.L.), Robert Wood Johnson Foundation Clinical Scholars Program, Department of Internal Medicine (H.M.K.), and Department of Emergency Medicine (R.P.D., G.D.), Yale School of Medicine, New Haven, CT; Department of Chronic Disease Epidemiology (J.H.L.) and Department of Health Policy and Management (H.M.K.), Yale School of Public Health, New Haven, CT; University of Missouri–Kansas City (J.A.S.); Saint Luke's Mid America Heart Institute, Kansas City, MO (J.A.S.); and Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Harvard Medical School, Boston, MA (P.M.R.).

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Correspondence to Harlan M. Krumholz, MD, SM, Yale School of Medicine, 1 Church St, Suite 200, New Haven, CT 06510. E-mail harlan.krumholz@yale.edu

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WHAT IS KNOWN

- Young women (≤ 55 years of age) with AMI have higher mortality risk than similarly aged men.
- Elevated inflammatory markers are associated with an increased risk of cardiovascular outcomes after AMI.

WHAT THE STUDY ADDS

- Young women with AMI had higher inflammatory levels compared with young men.
- Elevated 1-month hsCRP was associated with poor health status at 12 months after AMI, but this was attenuated after adjustment for patient characteristics.
- Half of the young patients had residual inflammatory risk (hsCRP > 3 mg/L) compared with one third who had residual cholesterol risk (LDL-C > 100 mg/dL).

whether the potential sex differences in inflammatory markers account for the sex differences in outcomes.

Previous evidence of sex differences in inflammatory markers is mostly derived from the general population. Studies have shown that hsCRP levels are higher in women compared with men across all ethnic subgroups, even after adjusting for traditional cardiovascular risk factors.⁵⁻⁷ The magnitude of increase is about 30% to 50%.⁵⁻⁷ However, no study has compared inflammatory markers after AMI in young women with those in men. Characterizing sex differences in post-AMI inflammatory markers may provide insight into sex differences in long-term outcomes and may provide a target to reduce the excess risk in young women with AMI. Furthermore, the proportion of young women with AMI who are afflicted primarily by residual cholesterol risk compared with residual inflammatory risk is uncertain, which has important implications for the selection of appropriate secondary prevention treatment to reduce residual risk in these patients.⁸

We used data from the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) study⁹ to assess sex differences in post-AMI inflammatory markers and whether such differences account for sex differences in health status (symptom, function, and quality of life) at 12 months after hospital discharge for AMI. We hypothesized that young women would have higher levels of inflammatory markers after AMI compared with men and that sex differences in inflammatory markers would partially explain women's worse health status after AMI. We compared the sex differences in inflammatory markers in VIRGO study with those in a nationally representative sample of the population in the United States. We also examined the proportion of VIRGO study patients who have residual cholesterol risk compared with residual inflammatory risk. Findings from this study may enhance our understanding of inflammatory markers and their potential contributions to sex differences in health status among young women and men with AMI.

Methods

Participants and Study Design

This study is a prespecified analysis of VIRGO study. Details about the design of VIRGO study have been described previously.⁹ In brief, VIRGO study is a prospective observational study designed to investigate the demographic, clinical, psychosocial, biological, and behavioral factors associated with the higher mortality in young women with AMI.¹ Between August 2008 and May 2012, patients 18 to 55 years of age were recruited into the VIRGO study from 103 United States (US), 24 Spanish, and 3 Australian hospitals. Of the 6538 patients screened at contributing sites, 3572 were eligible and enrolled. These consisted of 2985 patients from the US, 516 from Spain, and 71 from Australia. Given that the inflammatory markers were measured only in participants enrolled in the US, we limited our study population to the US participants, which represent 84% of the overall VIRGO study population. Participants were recruited using a 2:1 female to male enrollment design to enrich the study's inclusion of young women.

Participants were eligible for the study if they had increased cardiac biomarkers indicative of myocardial necrosis (with at least 1 cardiac biomarker above the 99th percentile of the upper reference limit) within 24 hours of admission and evidence of acute myocardial ischemia, including symptoms of ischemia, ECG changes indicative of new ischemia, or imaging evidence of infarction. We excluded individuals who met any of the following criteria: died before baseline interview, unable to provide informed consent, previous enrollment in VIRGO study, neither English nor Spanish speaking, development of elevated cardiac markers because of elective coronary revascularization, or AMI caused by physical trauma.⁹ We also excluded participants who did not have laboratory measurements at 1 month after hospital discharge or who were lost to follow-up by 1 month (Figure 1). Institutional review board approval was obtained at each participating institution, and participants provided informed consent for study participation including baseline hospitalization and follow-up interviews.

Blood Analysis

We measured inflammatory markers by standardized assay at 1 month after hospital discharge. We delayed the measurement to allow the perturbation associated with the acute event to reside. Specifically, concentrations of CRP were determined using fixed-rate nephelometry (Quest Diagnostics, Madison, NJ),¹⁰ the most sensitive test available at study initiation; the technique sensitively quantifies levels that are > 0.8 mg/L. Levels below this were defined as not detectable. Lp-PLA2 mass concentration was measured by in-house enzyme-linked immunoassays. In addition, a VAP (vertical auto profile) lipid profile, which included total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels, was measured by a blood draw according to standard procedures. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation¹¹ if triglycerides were < 400 mg/dL and was measured directly if triglycerides were ≥ 400 mg/dL. All inflammatory markers and lipid profiles were measured at Quest Diagnostics, and the laboratory was certified by the National Heart, Lung, and Blood Institute and Centers for Disease Control and Prevention Lipid Standardization Program.

Data Collection and Variables

We collected baseline information on patients' sociodemographics, clinical presentation, cardiac risk factors, noncardiac comorbidities, and treatment from medical chart abstraction and standardized in-person interviews administered by trained personnel during the index AMI admission. Follow-up telephone interviews at 1 and 12 months were conducted by the Yale Follow-Up Center, and in-person blood tests were collected at 1 month.

At 12 months after hospital discharge, we measured angina-specific and overall health status (symptom, function, and quality of life) for each patient. Angina frequency, angina-related physical limitations, and angina-related quality of life were assessed with the Seattle Angina Questionnaire (SAQ).¹² General health status was measured with the 12-item Short-Form Health Survey (SF-12) physical component summary (PCS) and mental component summary scores.¹³

Health-related quality of life was assessed by the EuroQol (EQ-5D) utility index and visual analog scale.¹⁴ The EQ-5D utility index generates scores between 0 and 1, whereas all other scales are scored between 0 and 100. On all measures, a higher value indicated better symptoms, functioning, or quality of life.

We quantified patients' socioeconomic status by defining marital status, highest level of education, health insurance, employment status, and financial hardship (not having enough money to make ends meet or having just enough money to make ends meet versus having some money left over at the end of the month). We assessed the clinical severity of AMI presentations by final AMI diagnosis (ST-segment–elevation myocardial infarction [STEMI]), Global Registry of Acute Coronary Events (GRACE) risk score,¹⁵ left ventricular ejection fraction <40%, hemodynamic instability, and whether the patients present in hospital >6 hours after symptom onset. We included other cardiac risk factors and comorbidities, such as history of heart disease, diagnosis of hypertension, diabetes mellitus, and dyslipidemia extracted from the medical record, obesity (body mass index ≥ 30 kg/m²), prospectively measured waist circumference (high classified as >88 cm for women and >102 cm for men), smoking, physical activity, and depression. Self-reported physical activity was measured with the Behavioral Risk Factor Surveillance Survey physical activity instrument, which has high reliability and validity among young adults.¹⁶ We also assessed reperfusion treatment during hospitalization and use of statin, estrogen, aspirin, β -blockers, and angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers at hospital discharge. High-intensity statins were defined as statins dosed at a level expected to lower LDL-C by at least 50% according to the American College of Cardiology/American Heart Association recommendation.¹⁷

Statistical Analyses

Descriptive statistics of patient characteristics at baseline and 1 month were calculated for the overall study population and compared between men and women. We calculated frequencies for categorical variables and medians with interquartile ranges (IQRs) for continuous variables. We determined statistical differences between women and men using χ^2 , Student *t*, and Wilcoxon rank-sum tests, where appropriate.

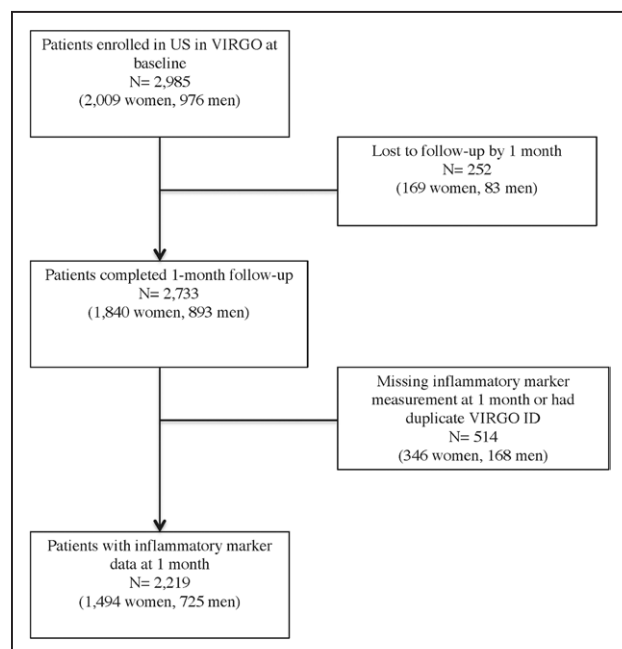


Figure 1. Flowchart of sample selection for post-acute myocardial infarction inflammatory analysis in the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) study.

To describe inflammatory markers by sex, we plotted the distributions of inflammatory markers at 1 month after AMI for men and women separately. We reported the median levels with IQRs of inflammatory markers and also categorized them into clinically meaningful and interpretable groups. hsCRP was categorized into < 1, 1 to 3, 3 to 5, and ≥ 5 mg per liter based on the Centers for Disease Control and Prevention/American Heart Association guidelines.¹⁸ We compared the distributions of inflammatory markers in VIRGO study with those in the NHANES (National Health and Nutrition Examination Survey) 2011 to 2012. NHANES uses a multistage, stratified, clustered probability sampling design and provided a representative sample of the noninstitutionalized population in the US.¹⁹ We included individuals aged 40 to 55 years (median age of 47 years) to have an age distribution similar to that of VIRGO study. We accounted for the complex survey design in NHANES to make the estimates representative of the corresponding sex group in the national population. We also used Spearman correlation coefficients to evaluate and compare the relationships between inflammatory marker levels and metabolic risk factor levels in men and women.

We conducted bivariate analyses and multivariable regression analyses to identify factors that differed between men and women and might explain the sex differences in inflammatory markers. We considered continuous hsCRP, Lp-PLA2 mass, and elevated hsCRP (1–3 and ≥ 3.0 versus <1 mg/L) as the dependent variables and developed separate models for each. We transformed continuous hsCRP and Lp-PLA2 to the log scale because their distributions were not normal. For categorical hsCRP, we used proportional odds models to assess different categories of hsCRP elevation. We included patient sex, age, race, current smoking, hypertension, diabetes mellitus, body mass index, statin use at discharge, and LDL-C at 1 month as covariates in the models because these variables were previously known to be associated with elevated inflammatory markers.^{2,3}

We also conducted multivariable linear regression analyses to assess the relationship between sex, 1-month hsCRP, and 12-month health status. Health status scores (SAQ angina frequency, angina-related physical limitation, angina-related quality of life, SF-12 PCS score, SF-12 mental component summary scores, EQ-5D utility index, and EQ-5D visual analog scale) served as dependent variables in these models. Explanatory variables included patient sex, 1-month hsCRP, 1-month health status score, and other covariates such as age, race, education, current smoking status, hypertension, diabetes mellitus, body mass index, statin use at discharge, and LDL-C at 1 month. For each dependent variable, 3 models were developed: model 1 included sex only, model 2 included sex and hsCRP, and model 3 included sex, hsCRP, and all other covariates. We compared models with and without adjustment for 1-month hsCRP to assess whether controlling for hsCRP reduced estimated sex differences in health status. We calculated the percentage of reduction in the sex effect after adjusting for hsCRP and after additionally adjusting for other covariates. In a secondary analysis, we repeated the analysis among patients with type I AMI classified by the Third Universal Definition of MI because these patients were in relatively severe condition and expected to have high inflammatory risk.²⁰ We also conducted sensitivity analysis in STEMI and non-STEMI patients separately to assess whether the results change by AMI type. Missing covariate data were minimal in our analysis, with 14.7% of patients missing any covariate data. Missing covariates were imputed using a multiple imputation approach in R 3.10 (The R Foundation for Statistical Computing), which allowed incorporation of all patients into multivariable models.

Finally, in this post-AMI population, we assessed the proportion of individuals with residual cholesterol risk (ie, LDL-C >100 mg/dL) compared with the proportion of those with residual inflammatory risk (ie, hsCRP >3 mg/L). We also reported the numbers using the alternative cut-points of LDL-C ≥ 70 mg/dL and hsCRP ≥ 2 mg/L. We consider a 2-sided $P < 0.05$ as statistically significant. All analyses were conducted with SAS 9.3 (SAS Institute Inc, Cary, NC) and R 3.10 (The R Foundation for Statistical Computing), using the most recent version of the VIRGO database.

Table 1. Baseline Characteristics of Study Participants, Stratified by Sex

Characteristics	Overall (N=2219)	Men (n=725)	Women (n=1494)	P Value
Sociodemographics				
Age, median (IQR), y	49 (44–52)	48 (44–52)	49 (44–52)	0.05
Race, n (%)				
White	1720 (77.7)	610 (84.3)	1110 (74.4)	<0.01
Black	358 (16.2)	60 (8.3)	298 (20.0)	
Other	137 (6.2)	54 (7.5)	83 (5.6)	
Married/living with a partner as if married, n (%)	1161 (52.4)	430 (59.3)	731 (49.0)	<0.01
Education, n (%)				
<High school	42 (1.9)	11 (1.5)	31 (2.1)	0.64
High school	858 (38.9)	279 (38.7)	579 (39.0)	
>High school	1304 (59.2)	431 (59.8)	873 (58.9)	
Ability to pay for medication, n (%)				
Health insurance	1738 (78.6)	560 (77.7)	1178 (79.0)	0.47
Used (work full or part time)	1419 (63.9)	533 (73.5)	886 (59.3)	<0.01
Finances at end of month				
Some money left over	704 (31.8)	291 (40.2)	413 (27.7)	0.01
Just enough to make ends meet	798 (36)	251 (34.7)	547 (36.6)	
Not enough to make ends meet	715 (32.3)	182 (25.1)	533 (35.7)	
AMI severity, n (%)				
AMI type				
NSTEMI	1109 (50.0)	312 (43.0)	797 (53.3)	<0.01
STEMI	1110 (50.0)	413 (57.0)	697 (46.7)	
GRACE risk score >99	194 (8.9)	61 (8.5)	133 (9.1)	0.67
Left ventricular ejection fraction <40%	214 (10.1)	70 (10.0)	144 (10.1)	0.97
Hemodynamic instability	166 (7.5)	57 (7.9)	109 (7.3)	0.70
Present >6 h after symptom onset	959 (43.4)	272 (37.6)	687 (46.2)	<0.01
Comorbidities and CVD risk factors, n (%)				
Previous heart disease (CAD, angina, and heart failure)	690 (31.1)	214 (29.5)	476 (31.9)	0.26
Hypertension	1441 (64.9)	456 (62.9)	985 (65.9)	0.16
Diabetes mellitus	664 (29.9)	153 (21.1)	511 (34.2)	<0.01
Dyslipidemia	1128 (50.9)	397 (54.9)	731 (49.0)	0.01
Obesity (BMI \geq 30 kg/m ²)	1162 (52.4)	346 (47.7)	816 (54.6)	<0.01
High waist circumference (women >88 cm, men >102 cm)	1270 (71.1)	321 (53.3)	949 (80.1)	<0.01
Current smoking	1211 (54.6)	391 (54.0)	820 (54.9)	0.73
Physical activity				
Recommended	849 (38.5)	313 (43.4)	536 (36.1)	<0.01
Insufficient	654 (29.6)	192 (26.6)	462 (31.1)	
Inactive	703 (31.9)	216 (30)	487 (32.8)	
Depression	6 (2–12)	5 (2–9)	7 (3–13)	<0.01
Baseline health status, mean (SD)				
SF-12 PCS score	44 (12)	46 (11.6)	43 (12)	<0.01
SF-12 MCS score	46 (12.2)	48 (11.4)	45 (12.3)	<0.01

(Continued)

Table 1. Continued

Characteristics	Overall (N=2219)	Men (n=725)	Women (n=1494)	P Value
SAQ angina frequency score	84 (20.5)	86 (18.1)	82 (21.4)	<0.01
SAQ angina-related physical limitation score	82 (25)	87 (20.8)	79 (26.5)	<0.01
SAQ angina-related quality of life score	58 (24.6)	62 (22.5)	56 (25.4)	<0.01
EQ-5D utility index score	0.8 (0.22)	0.8 (0.2)	0.7 (0.23)	<0.01
EQ-5D visual analog scale score	65 (21.1)	67 (19.8)	65 (21.7)	0.05
Reperfusion in hospital, n (%)				
None	859 (42.1)	227 (34.1)	632 (45.9)	<0.01
Fibrinolytic therapy	98 (4.8)	47 (7.1)	51 (3.7)	
PCI	1085 (53.1)	391 (57.8)	694 (50.4)	
Discharge medication, n (%)				
Statin use				
High-intensity statin	868 (39.1)	310 (42.8)	558 (37.3)	0.15
Low- and moderate-intensity statin	1167 (52.6)	381 (52.5)	786 (52.6)	
None	184 (8.3)	34 (4.7)	150 (10.1)	
Aspirin	2142 (98.2)	712 (98.9)	1430 (97.9)	0.13
β-Blockers	2031 (97.1)	638 (98.5)	1348 (96.4)	0.01
ACE inhibitors or ARBs	1416 (70.8)	512 (77.3)	904 (67.5)	<0.01
Estrogen use	35 (2.3)	...

All percentages are calculated by excluding missing values of the related variables. ACE indicates angiotensin-converting enzyme; AMI, acute myocardial infarction; ARBs, angiotensin II receptor blockers; BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease; GRACE, Global Registry of Acute Coronary Events; IQR, interquartile range; MCS, mental component summary; NSTEMI, non-ST-segment-elevation myocardial infarction; PCS, physical component summary; SAQ, Seattle Angina Questionnaire; and STEMI, ST-segment-elevation myocardial infarction.

Results

Sample Characteristics

There were 2219 adults with AMI in the VIRGO study included in this analysis (725 men and 1494 women; Figure 1). The median age was similar for both sexes (48 years for men and 49 years for women). The majority of patients were white (77.7%), were married (52.4%), had more than a high school education (59.2%), and had health insurance (78.6%). About half presented with STEMI, and one third had previous heart disease. Cardiovascular risk factors (eg, hypertension, diabetes mellitus, dyslipidemia, and obesity) were common (Table 1). Nearly half of the women were postmenopausal, and 2.3% of postmenopausal women were taking estrogen therapy at the time of their AMI. The median LDL-C level was 66 mg/dL (IQR, 66–106), whereas the median hsCRP was 2.9 mg/L (IQR, 1.2–6.4). Two percent of patients died during 12-month follow-up.

Compared with men, women were more likely to be black, to be single, have diabetes mellitus, have previous stroke, and have congestive heart failure. In particular, women were much more likely than men to have obesity (54.6% versus 47.7%) and a high waist circumference (80.1% versus 53.3%). However, women were less likely to have dyslipidemia and present with STEMI. Women were also less likely to receive in-hospital reperfusion treatment and statin, β-blockers, and

angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers at discharge. Women had significantly lower observed generic and disease-specific health status scores than men at baseline, 1 month post-AMI, and 12 months post-AMI. The proportion of women without any angina symptoms were 44.1%, 59.7%, and 6.7% at baseline, 1 month post-AMI, and 12 months post-AMI, respectively. The corresponding numbers in men were 48.4%, 67.0%, and 73.8%.

Overall, the proportion of these post-MI patients with residual cholesterol risk (ie, LDL-C >100 mg/dL) was 32.5% (34.6% in women versus 28.2% in men), whereas the proportion of these post-MI patients with residual inflammatory risk (ie, hsCRP >3 mg/L) was 49.1% (53.6% in women versus 39.5% in men). Among all patients, 14.7% had only the hsCRP goal achieved (LDL >100 mg/dL and hsCRP ≤3 mg/L), 30.8% had only the LDL goal achieved (LDL ≤100 mg/dL and hsCRP >3 mg/L), 36.4% had both goals achieved (LDL ≤100 mg/dL and hsCRP ≤3 mg/L), and 18.1% had neither goal achieved (LDL >100 mg/dL and hsCRP >3 mg/L). Using the alternative cut-points of LDL-C ≥70 mg/dL and hsCRP ≥2 mg/L, 25.0% of patients had only the hsCRP goal achieved (LDL >70 mg/dL and hsCRP ≤2 mg/L), 15.5% had only the LDL goal achieved (LDL ≤70 mg/dL and hsCRP >2 mg/L), 13.6% had both goals achieved (LDL ≤70 mg/dL and hsCRP ≤2 mg/L), and 43.9% had neither goal achieved (LDL >70 mg/dL and hsCRP >2 mg/L).

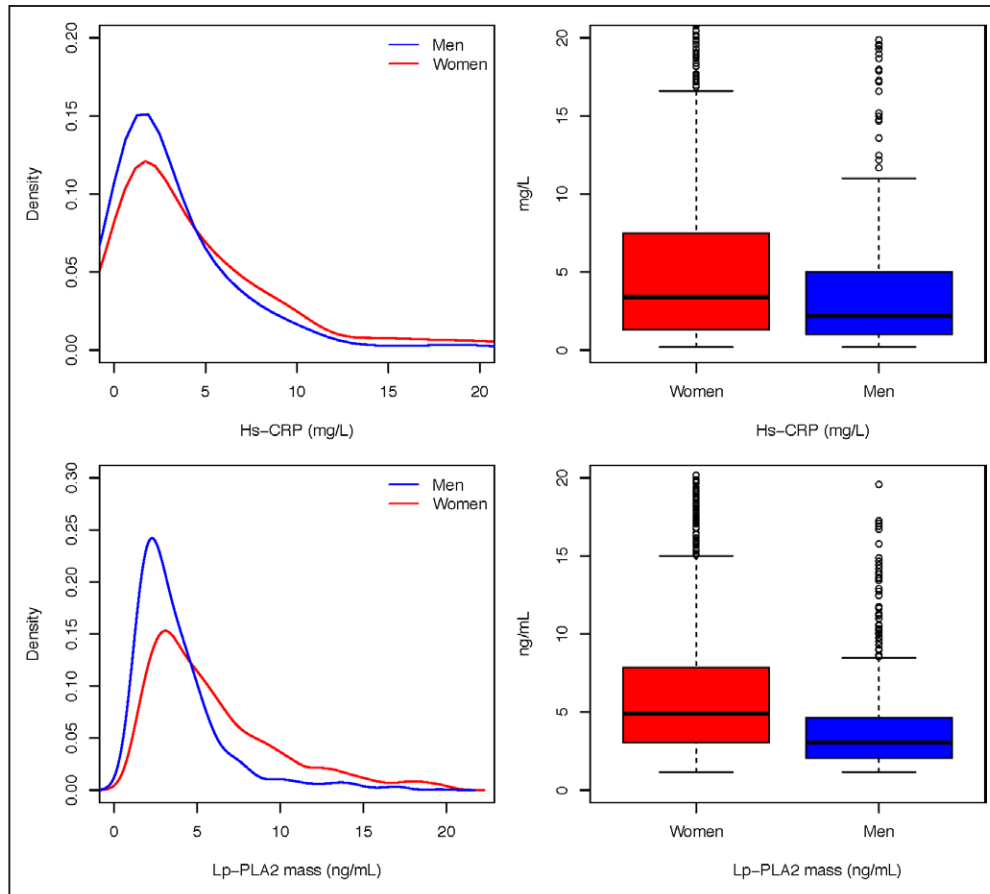


Figure 2. Distributions of inflammatory markers at 1 mo after discharge for acute myocardial infarction, by sex (men=blue, women=red). hsCRP indicates high-sensitivity C-reactive protein; and Lp-PLA2, lipoprotein-associated phospholipase A2.

Sex Differences in Inflammatory Markers at 1 Month After AMI

Women had significantly higher levels of inflammatory markers at 1 month after AMI compared with men (Figure 2; Table 2). The median (IQR) of hsCRP was 3.4 (1.3–7.3) mg/L for women and 2.2 (1.0–5.0) mg/L for men ($P<0.01$). These values were substantially higher than those in the similarly aged general population captured in NHANES (1.9 [0.7–4.4] mg/L for women and 1.3 [0.6–3.0] mg/L for men; Table I in the Data Supplement). When hsCRP was categorized into groups, there were more women (35.8%) with very high hsCRP (≥ 5 mg/L) compared with men (25.2%; $P<0.01$). The percentage of high hsCRP (3–5 mg/L) was also larger in women (15.8% versus 14.3%). In addition, women had higher levels of Lp-PLA2 (4.8 [3.1–7.8] versus 3.0 [2.1–4.7] ng/mL; $P<0.01$). Both hsCRP and Lp-PLA2 have significantly stronger correlations with body mass index and waist circumference in women compared with those in men (Table 3).

The regression analyses demonstrated the independent effect of sex on inflammatory markers (Table 4). Adjustment for patient characteristics in the multivariable regression models reduced the sex differences in hsCRP and in Lp-PLA2, but the effect of sex remained statistically significant. On the log scale, women had 0.21 mg/L higher hsCRP and 0.35 ng/mL higher Lp-PLA2 than men

in the fully adjusted models (both P values <0.01). When hsCRP was used as a categorical variable, women were 1.41 times more likely than men to have high or moderate hsCRP ($P<0.01$). In particular, older age, smoking status, diabetes mellitus, and higher body mass index at baseline, and higher 1-month LDL-C were all associated with high or moderate hsCRP at 1 month after AMI. These variables were also associated with a significantly higher hsCRP and Lp-PLA2 levels.

Sex, Inflammatory Markers, and 12-Month Health Status

At 12 months after AMI, women had significantly worse angina, more disease-specific physical limitations, and a poorer quality of life than men as measured by the SAQ ($P<0.01$ for all; Table 5). In addition, women had a significantly worse physical and mental generic health status than men as measured by the SF-12 ($P<0.01$ for all). Women also had lower EQ-5D index and visual analog scale scores ($P<0.01$ for all).

Adjustment for 1-month hsCRP levels attenuated these sex differences, but they remained statistically significant (Table 5). The reductions in sex effect after adjustment for hsCRP ranged from 6.5% for SF-12 mental component summary to 23.9% EQ-5D visual analog scale score. Compared with patients with low hsCRP values, those with high hsCRP

Table 2. Sex Differences in Inflammatory Markers and Lipid Profiles at 1 mo After Discharge

	Overall (N=2219)	Men (n=725)	Women (n=1494)	P Value
hsCRP, median (IQR), mg/L	2.9 (1.2–6.4)	2.2 (1.0–5.0)	3.4 (1.3–7.3)	<0.01
hsCRP category, n (%)				
Very high (≥ 5 mg/L)	709 (33.7)	172 (25.2)	537 (37.8)	<0.01
High (3–5 mg/L)	323 (15.4)	98 (14.3)	225 (15.8)	
Moderate (1–3 mg/L)	676 (32.1)	262 (38.2)	414 (29.1)	
Low (<1 mg/L)	395 (18.8)	153 (22.3)	242 (17.1)	
Lp-PLA2 mass, median (IQR), ng/mL	4.1 (2.6–6.7)	3.0 (2.1–4.7)	4.8 (3.1–7.8)	<0.01
Lipid profile, median (IQR), mg/dL				
Total cholesterol	153 (129–182)	145 (126–174)	157 (132–185)	<0.01
LDL cholesterol	85 (66–106)	81 (65–104)	86 (67–107)	0.01
HDL cholesterol	37 (30–46)	33 (28–39)	39 (32–48)	<0.01
Triglyceride	122 (86–181)	130 (91–193)	119 (83.5–173)	<0.01

All percentages are calculated by excluding missing values of the related variables.

HDL indicates high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL, low-density lipoprotein; and Lp-PLA2, lipoprotein-associated phospholipase A2.

values had significantly worse scores in angina frequency, angina-related physical limitation, angina-related quality of life, SF-12 PCS, SF-12 mental component summary, EQ-5D utility index, and EQ-5D visual analog scale (Table 5). For those with moderate hsCRP values, the scores were significantly worse for SF-12 PCS and EQ-5D visual analog scale but not statistically different for others.

Additional adjustment of all other covariates further reduced the sex differences in health status. The reductions in sex effect after adjustment for hsCRP and all other covariates ranged from 43.8% for angina-related quality of life score to 63.4% SF-12 PCS score. There were no significant sex differences in angina frequency, angina-related physical limitation, and the EQ-5D visual analog scale. However, women still had a significantly poorer quality of life, worse physical and mental generic health status as measured by the SF-12, and lower EQ-5D index score than men. The association of hsCRP with health status was also attenuated in the fully adjusted model. Compared with patients with low hsCRP levels, patients with high or moderate hsCRP levels were not significantly different with regard to all health status scores. Interaction terms between sex and hsCRP levels (high and moderate versus low) were not statistically significant in any of the fully adjusted models for 12-month health status, indicating that the association of 1-month hsCRP with health status did not vary between men and women. Our sensitivity analysis among type I AMI patients, STEMI patients, or non-STEMI patients showed results consistent with the main analysis (Tables II through VII in the Data Supplement).

Discussion

Among young and middle-aged AMI patients, women had significantly higher levels of inflammatory markers after AMI compared with their male counterparts. There were 53.6% and 37.8% of women with hsCRP ≥ 3 and ≥ 5 mg/L

at 1 month after AMI compared with only 39.5% and 25.2% in men. The higher hsCRP level in women with AMI was partially explained by a higher prevalence of smoking, diabetes mellitus, and obesity in that group, as well as higher 1-month LDL-C level. Post-AMI inflammatory marker was associated with poor health status in young and middle-aged AMI patients, and adjustment for 1-month hsCRP partially attenuated the observed sex difference in health status 12 months after AMI. However, the association between hsCRP and health status became nonsignificant after adjustment for sociodemographics, comorbidities, and treatment factors, suggesting that hsCRP may be a marker of other factors associated with poor health status.

Our study extends previous literature in several important ways. First, it demonstrates a significant sex difference in inflammatory markers at 1 month after an AMI. Previous studies have focused on the general population,^{5–7} and data on AMI patients are limited. Assessing sex difference in inflammatory markers among AMI patients is important, not only because it is essential for monitoring the rise in acute-phase reactants after an AMI but also because it helps identify potential factors that may account for the excess adverse outcomes in women. Second, our study shows that sex differences in post-AMI inflammatory markers are partially explained by the differences in comorbidities between men and women. For instance, compared with men, women had a much higher rate of obesity and a stronger correlation between obesity and inflammatory markers. Women also had higher rates of smoking and diabetes mellitus and experienced greater stress and depression but were less likely to receive high-intensity statins, all of which contribute to higher levels of inflammatory markers in women. Hence, interventions that recognize and address these predictors of inflammatory markers would be beneficial for inflammation management in men and women with AMI.

Third, our study shows that elevated hsCRP is associated with poor health status (symptom, function, and

Table 3. Spearman Correlations Between Inflammatory Markers and Metabolic Risk Factors at 1 mo After Discharge

	hsCRP			Lp-PLA2 Mass		
	Men	Women	<i>P</i> Value*	Men	Women	<i>P</i> Value*
Body mass index†	0.24	0.40	<0.01	0.18	0.32	<0.01
Waist circumference†	0.25	0.40	<0.01	0.21	0.31	0.02
Total cholesterol	0.13	0.05	0.08	0.08	0.04	0.38
LDL cholesterol	0.18	0.11	0.11	0.12	0.10	0.66
HDL cholesterol	-0.24	-0.32	0.06	-0.10	-0.20	0.02
Triglyceride	0.14	0.25	0.01	0.06	0.11	0.27

HDL indicates high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and Lp-PLA2, lipoprotein-associated phospholipase A2.

*The *P* value shows the significance of the difference in correlation coefficients between men and women.

†Body mass index and waist circumference were measured at baseline and carried over to 1 mo.

quality of life) among young and middle-aged patients with AMI. Earlier analyses of VIRGO study documented worse physical functioning, mental health status, and quality of life in women than in men at 12 months post-AMI.²¹ The current study found this gap to be partially attenuated after adjustment for differential levels of 1-month hsCRP between men and women. It was additionally attenuated after adjustment for other comorbidities, indicating that hsCRP is correlated with factors associated with poor health status. Although the association of hsCRP with health status may not involve a causal relationship, the strong association suggests that post-AMI hsCRP may be a useful prognostic marker for health outcomes in young and

middle-aged AMI patients. Further studies that examine the underlying pathways responsible for post-AMI health status and potential sex differences may help identify novel therapeutic interventions.

Finally, our study is also among the first to address the population prevalence of residual cholesterol risk compared with residual inflammatory risk.⁸ Consistent with previous data,²² the proportion of individuals in whom post-MI risk is predominantly on the basis of a persistent proinflammatory response was higher than the proportion in whom post-MI risk is predominantly on the basis of persistently elevated levels of LDL-C. These data have implications for the use of further LDL-lowering agents (such as PCSK9 inhibitors) compared

Table 4. Patient Characteristics Associated With Inflammatory Markers at 1 mo After Hospital Discharge

Characteristics	Categorical hsCRP (High [≥ 3 mg/L], Moderate [1–3 mg/L], and Low [< 1 mg/L])		Continuous hsCRP on Log Scale, mg/L		Continuous Lp-PLA2 Mass on Log Scale, ng/mL	
	Unadjusted Odds Ratio (<i>P</i> Value)	Adjusted Odds Ratio (<i>P</i> Value)*	Unadjusted Coefficient (<i>P</i> Value)	Adjusted Coefficient (<i>P</i> Value)*	Unadjusted Coefficient (<i>P</i> Value)	Adjusted Coefficient (<i>P</i> Value)*
Women (vs men)	1.65 (<0.01)	1.41 (<0.01)	0.36 (<0.01)	0.21 (<0.01)	0.41 (<0.01)	0.35 (<0.01)
Age at baseline (per 5-y increase)	...	1.10 (0.01)	...	0.07 (<0.01)	...	0.04 (<0.01)
White race (vs nonwhite)	...	0.83 (0.1)	...	-0.14 (0.02)	...	-0.18 (<0.01)
Current smoking at baseline	...	1.91 (<0.01)	...	0.38 (<0.01)	...	0.15 (<0.01)
Hypertension at baseline	...	1.09 (0.38)	...	0.15 (<0.01)	...	0.02 (0.41)
Diabetes mellitus at baseline	...	1.71 (<0.01)	...	0.29 (<0.01)	...	0.14 (<0.01)
Body mass index at baseline	...	1.1 (<0.01)	...	0.05 (<0.01)	...	0.02 (<0.01)
Statin use at discharge						
Nonstatin	...	Reference category	...	Reference category	...	Reference category
Low- or moderate-intensity statin	...	0.87 (0.26)	...	-0.17 (0.01)	...	-0.01 (0.69)
High-intensity statin	...	1.08 (0.51)	...	-0.04 (0.50)	...	0.04 (0.30)
LDL cholesterol at 1 mo (per 10 mg/dL increase)	...	1.09 (<0.01)	...	0.04 (<0.01)	...	0.02 (<0.01)

HsCRP indicates high-sensitivity C-reactive protein; LDL, low-density lipoprotein; and Lp-PLA2, lipoprotein-associated phospholipase A2.

*Model was also adjusted for patient age, race, current smoking, hypertension, diabetes mellitus, body mass index, statin use at discharge, and LDL-cholesterol at 1 mo.

Table 5. Adjusted 12-mo Health Status Associated With Sex and hsCRP at 1 mo, Coefficient (P Value)

Health Status at 12-mo Follow-Up	Unadjusted, Women (vs Men)	After Adjustment for 1-mo hsCRP				Reduction in Sex Effect After Adjustment for CRP, %	After adjustment for 1-mo hsCRP and Other Covariates*		
		Women (vs Men)	1-mo hsCRP		Women (vs Men)		Moderate (vs Low)	High (vs Low)	Reduction in Sex Effect After Adjustment for CRP and Other Covariates, %
			Moderate (vs Low)	High (vs Low)					
SAQ angina frequency	-2.25 (<0.01)	-2.05 (0.01)	-1.40 (0.20)	-2.18 (0.03)	8.9	-0.87 (0.24)	0.04 (0.96)	-0.42 (0.68)	61.3
SAQ angina-related physical limitation	-2.24 (<0.01)	-1.97 (0.01)	-0.55 (0.60)	-2.12 (0.04)	12.1	-0.96 (0.22)	0.02 (0.98)	0.10 (0.92)	57.1
SAQ angina-related quality of life	-6.51 (<0.01)	-6.09 (<0.01)	-1.96 (0.19)	-3.84 (<0.01)	6.5	-3.66 (<0.01)	-0.37 (0.77)	-0.63 (0.64)	43.8
SF-12 PCS score	-3.72 (<0.01)	-3.07 (<0.01)	-1.77 (0.02)	-5.35 (<0.01)	17.5	-1.36 (<0.01)	0.19 (0.77)	-0.06 (0.92)	63.4
SF-12 MCS score	-3.31 (<0.01)	-3.05 (<0.01)	0.05 (0.92)	-1.62 (0.01)	7.9	-1.69 (<0.01)	0.05 (0.93)	-0.65 (0.31)	48.9
EQ-5D utility index score	-0.05 (<0.01)	-0.04 (<0.01)	-0.01 (0.33)	-0.06 (<0.01)	20.0	-0.02 (0.01)	0.003 (0.77)	-0.01 (0.27)	60.0
EQ-5D visual analog scale	-4.22 (<0.01)	-3.21 (<0.01)	-2.70 (0.03)	-7.60 (<0.01)	23.9	-1.59 (0.07)	-0.83 (0.47)	-2.19 (0.09)	62.3

Results are reported as coefficients and *P* values. EQ-5D indicates EuroQol; MCS, mental component summary; PCS, physical component summary; SAQ, Seattle Angina Questionnaire; and SF-12, Short Form-12.

*Model was also adjusted for patient age, race, education, current smoking, hypertension, diabetes mellitus, body mass index, statin use at discharge, 1-mo LDL-cholesterol, and the corresponding 1-mo value of the outcome variable.

with potential anti-inflammatory treatment strategies such as low-dose methotrexate or canakinumab.

This study has several limitations. First, VIRGO study was an observational study that required patients to be healthy enough at baseline to participate; thus, we were unable to enroll those who were too ill to be enrolled. Second, about 9% of patients were lost to follow-up at 1 month after AMI. If they had different characteristics compared with the remaining patients and were disproportionately distributed between men and women, our estimated sex difference in inflammatory markers may be biased. However, we found that the lost-to-follow-up rates were comparable between men and women and baseline sociodemographic and clinical characteristics were generally similar between those who were lost to follow-up and those who remained in the sample. Third, we did not measure inflammatory markers at baseline and were unable to examine change in inflammatory markers during follow-up.

In conclusion, there was a significantly higher level of post-AMI inflammatory markers in young women compared with similarly aged men. An elevated level of hsCRP at 1 month was associated with poor health status at 12 months after AMI, but this was attenuated after adjusting for sociodemographics, comorbidities, and treatment factors. In half of the men and women with AMI, the post-AMI risk is predominantly on the basis of a persistent proinflammatory response. Targeted anti-inflammatory treatments are worthy of consideration for secondary prevention in these patients if the ongoing clinical trials of anti-inflammatory therapy prove effective at cardiovascular event reduction.

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Sex Differences in Inflammatory Markers and Health Status Among Young Adults With Acute Myocardial Infarction: Results From the VIRGO (Variation in Recovery: Role of Gender on Outcomes of Young Acute Myocardial Infarction Patients) Study

Yuan Lu, Shengfan Zhou, Rachel P. Dreyer, Erica S. Spatz, Mary Geda, Nancy P. Lorenze, Gail D'Onofrio, Judith H. Lichtman, John A. Spertus, Paul M. Ridker and Harlan M. Krumholz

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SUPPLEMENTAL MATERIAL

Supplemental Table 1: Comparison of sex differences in post-AMI inflammatory markers and lipid profiles in VIRGO with those in NHANES 2011-2012

Supplemental Table 2: Sex differences in inflammatory markers and lipid profile at 1 month after discharge among type I AMI patients

Supplemental Table 3: Spearman correlations between inflammatory markers and metabolic risk factors at 1 month after discharge among type I AMI patients

Supplemental Table 4: Patient characteristics associated with inflammatory markers at 1 month after hospital discharge among type I AMI patients

Supplemental Table 5: Adjusted 12-month health status associated with sex and hsCRP at 1 month among type I AMI patients, coefficient (p value)

Supplemental Table 6: Adjusted 12-month health status associated with sex and hsCRP at 1 month among STEMI patients, coefficient (p value)

Supplemental Table 7: Adjusted 12-month health status associated with sex and hsCRP at 1 month among NSTEMI patients, coefficient (p value)

Appendix Table 1: Comparison of sex differences in post-AMI inflammatory markers and lipid profiles in VIRGO with those in NHANES 2011-2012

	VIRGO			NHANES 2011-2012		
	Overall (N=2219)	Men (N=725)	Women (N=1494)	Overall (N=1731)	Men (N=843)	Women (N=888)
HsCRP, median (IQR), mg/L	2.9 (1.2-6.4)	2.2 (1.0-5.0)	3.4 (1.3-7.3)	1.6 (0.6-3.8)	1.3 (0.6-3.0)	1.9 (0.7-4.4)
HsCRP category, n (%) *						
Very high (≥ 5 mg/L)	709 (33.7%)	172 (25.2%)	537 (37.8%)	595 (19.3%)	141 (15.4%)	219 (23.1%)
High (3-5 mg/L)	323 (15.4%)	98 (14.3%)	225 (15.8%)	595 (13.4%)	90 (10.1%)	145 (16.7%)
Moderate (1-3 mg/L)	676 (32.1%)	262 (38.2%)	414 (29.1%)	521 (31.7%)	283 (36.1%)	238 (27.4%)
Low (<1 mg/L)	395 (18.8%)	153 (22.3%)	242 (17.1%)	503 (35.6%)	279 (38.4%)	224 (32.9%)
Lipid profile, median (IQR), mg/dL						
Total cholesterol	153 (129-182)	145 (126-174)	157 (132-185)	202 (177-228)	202 (175-228)	202 (179-227)
LDL cholesterol	85 (66-106)	81 (65-104)	86 (67-107)	120 (98-142)	126 (101-143)	115 (95-140)
HDL cholesterol	37 (30-46)	33 (28-39)	39 (32-48)	51 (41-62)	45 (37-54)	59 (41-71)
Triglyceride	122 (86-181)	130 (91-193)	119 (83.5-173)	99 (72-144)	109 (85-160)	87 (65-132)

All percentages are calculated by excluding missing, don't know, and patient refused.

* The percentages in NHANES were accounted for the sampling weight to make estimates representative of the national population.

HsCRP = high-sensitivity C-reactive protein; Lp-PLA2 = lipoprotein-associated phospholipase A2; LDL= low-density lipoprotein, HDL= high-density lipoprotein;

NHANES=National Health and Nutrition Examination Survey; VIRGO=Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients.

Appendix Table 2: Sex differences in inflammatory markers and lipid profile at 1 month after discharge among type I AMI patients

	Overall (N=1807)	Men (N=637)	Women (N=1170)	P-value
HsCRP, median (IQR), mg/L	3.0 (1.3-6.8)	2.2 (1.0-5.0)	3.6 (1.5-7.7)	<0.01
HsCRP category, n (%)				
Very high (≥ 5 mg/L)	602 (35.1%)	155 (25.8%)	447 (40.1%)	<0.01
High (3-5 mg/L)	268 (15.6%)	87 (14.5%)	181 (16.2%)	
Moderate (1 -3 mg/L)	538 (31.4%)	223 (37.1%)	315 (28.3%)	
Low (<1 mg/L)	308 (17.9%)	136 (22.6%)	172 (15.4%)	
Lp-PLA2 mass, median (IQR), ng/mL	4.2 (2.7-6.7)	3.1 (2.1-4.7)	5.0 (3.1-8.0)	<0.01
Lipid profile, median (IQR), mg/dL				
Total cholesterol	151 (128-180)	143 (125-174)	154 (130-182)	<0.01
LDL cholesterol	83 (65-105)	80 (64-103)	85 (66-106)	0.05
HDL cholesterol	36 (30-44)	32 (27-39)	38 (32-47)	<0.01
Triglyceride	124 (87-183)	130 (91-193)	122 (85-176)	0.02

All percentages are calculated by excluding missing, don't know, and patient refused.

HsCRP = high-sensitivity C-reactive protein; Lp-PLA2 = lipoprotein-associated phospholipase A2; LDL= low-density lipoprotein, HDL= high-density lipoprotein.

Appendix Table 3: Spearman correlations between inflammatory markers and metabolic risk factors at 1 month after discharge among type I AMI patients

	HsCRP			Lp-PLA2 mass		
	Men	Women	P-value *	Men	Women	P-value *
Body mass index †	0.25	0.37	<0.01	0.21	0.32	0.02
Waist circumference †	0.27	0.38	0.01	0.22	0.30	0.08
Total cholesterol	0.13	0.06	0.15	0.09	0.06	0.68
LDL cholesterol	0.18	0.11	0.15	0.12	0.12	0.95
HDL cholesterol	-0.23	-0.30	0.13	-0.10	-0.19	0.06
Triglyceride	0.13	0.22	0.06	0.08	0.08	0.92

* The P-value shows the significance of the difference in correlation coefficients between men and women.

† Body mass index and waist circumference were measured at baseline and carried over to 1 month.

HsCRP = high-sensitivity C-reactive protein; Lp-PLA2 = lipoprotein-associated phospholipase A2; LDL= low-density lipoprotein, HDL= high-density lipoprotein.

Appendix Table 4: Patient characteristics associated with inflammatory markers at 1 month after hospital discharge among type I AMI patients

Characteristics	Categorical hsCRP (High [≥ 3 mg/L], Moderate [1-3 mg/L], Low [< 1 mg/L])		Continuous hsCRP on log scale, mg/L		Continuous Lp-PLA2 mass on log scale, ng/mL	
	Unadjusted Odds ratio (P value)	Adjusted Odds ratio (P value) *	Unadjusted Coefficient (P value)	Adjusted Coefficient (P value) *	Unadjusted Coefficient (P value)	Adjusted Coefficient (P value) *
	Women (vs. men)	1.81 (<0.01)	1.48 (<0.01)	0.42 (<0.01)	0.25 (<0.01)	0.43 (<0.01)
Age at baseline (per 5 year increase)	-	1.09 (0.04)	-	0.06 (0.02)	-	0.03 (0.01)
White race (vs. non-white)	-	0.81 (0.09)	-	-0.15 (0.03)	-	-0.19 (<0.01)
Current smoking at baseline	-	1.85 (<0.01)	-	0.35 (<0.01)	-	0.12 (<0.01)
Hypertension at baseline	-	1.14 (0.22)	-	0.18 (<0.01)	-	0.03 (0.32)
Diabetes at baseline	-	1.68 (<0.01)	-	0.28 (<0.01)	-	0.1 (<0.01)
Body mass index at baseline	-	1.09 (<0.01)	-	0.04 (<0.01)	-	0.02 (<0.01)
Statin use at discharge						
Non-statin	-	Reference category	-	Reference category	-	Reference category
Low or moderate intensity	-	0.77 (0.07)	-	-0.27 (<0.01)	-	-0.01 (0.78)
High intensity	-	0.98 (0.85)	-	-0.13 (0.08)	-	0.03 (0.4)
LDL-cholesterol at 1 month (per 10 mg/dl increase)	-	1.09 (<0.01)	-	0.04 (<0.01)	-	0.02 (<0.01)

The models are developed based on cohorts that excluded missing values in all variables. HsCRP = high-sensitivity C-reactive protein; Lp-PLA2 = lipoprotein-associated phospholipase A2, LDL= low-density lipoprotein.

* Model was also adjusted for patient age, race, current smoking, hypertension, diabetes, body mass index, statin use at discharge, and LDL-cholesterol at 1 month.

Appendix Table 5: Adjusted 12-month health status associated with sex and hsCRP at 1 month among type I AMI patients, coefficient (p value)

Health status at 12 month of follow up	Unadjusted, Women (vs Men)	After adjustment for 1-month hsCRP				Reduction in gender effect after adjustment for CRP	After adjustment for 1-month hsCRP and other covariates*			Reduction in gender effect after adjustment for CRP and other covariates
		Women (vs Men)	1-month hsCRP		Women (vs Men)		1-month hsCRP			
			Moderate (vs Low)	High (vs Low)			Moderate (vs Low)	High (vs Low)		
Angina frequency	-2.79 (<0.01)	-2.45 (<0.01)	-1.27 (0.30)	-1.88 (0.10)	12.2%	-1.05 (0.22)	-0.49 (0.67)	-0.59 (0.61)	62.4%	
Angina-related physical limitation	-2.41 (<0.01)	-2.27 (<0.01)	-0.75 (0.51)	-1.67 (0.12)	5.8%	-1.25 (0.13)	-0.10 (0.93)	0.20 (0.86)	48.1%	
Angina-related quality of life	-7.87 (<0.01)	-7.59 (<0.01)	-2.42 (0.14)	-3.31 (0.03)	3.6%	-4.83 (<0.01)	-1.21 (0.43)	-0.47 (0.76)	38.6%	
SF-12 PCS score	-4.44 (<0.01)	-3.75 (<0.01)	-2.07 (0.02)	-5.33 (<0.01)	15.5%	-1.80 (<0.01)	0.63 (0.44)	-0.94 (0.25)	59.5%	
SF-12 MCS score	-3.59 (<0.01)	-3.53 (<0.01)	-0.31 (0.69)	-1.62 (0.02)	1.7%	-1.90 (<0.01)	0.30 (0.67)	-0.32 (0.66)	47.1%	
EQ-5D utility index score	-0.06 (<0.01)	-0.05 (<0.01)	-0.01 (0.50)	-0.06 (<0.01)	16.7%	-0.02 (0.04)	0.002 (0.85)	-0.008 (0.51)	66.7%	
EQ-5D visual analog scale	-4.96 (<0.01)	-3.99 (<0.01)	-3.42 (0.02)	-7.71 (<0.01)	19.6%	-1.56 (0.12)	-1.45 (0.29)	-2.14 (0.12)	68.5%	

Results are reported as coefficients and p values. EQ-5D indicates EuroQol; MCS, Mental Component Summary; PCS, Physical Component Summary; and SF-12, Short Form-12.

*Model was also adjusted for patient age, race, education, current smoking, hypertension, diabetes, body mass index, statin use at discharge, 1-month LDL-cholesterol, and the corresponding 1-month value of the outcome variable.

Appendix Table 6: Adjusted 12-month health status associated with sex and hsCRP at 1 month among STEMI patients, coefficient (p value)

Health status at 12 month of follow up	Unadjusted, Women (vs Men)	After adjustment for 1-month hsCRP				Reduction in gender effect after adjustment for CRP	After adjustment for 1-month hsCRP and other covariates*			Reduction in gender effect after adjustment for CRP and other covariates
		Women (vs Men)	1-month hsCRP		Women (vs Men)		1-month hsCRP			
			Moderate (vs Low)	High (vs Low)			Moderate (vs Low)	High (vs Low)		
Angina frequency	-2.52 (0.01)	-2.03 (0.05)	-0.37 (0.79)	-1.44 (0.28)	19.4%	-0.56 (0.58)	1.05 (0.44)	0.65 (0.64)	77.8%	
Angina-related physical limitation	-3.17 (<0.01)	-2.92 (<0.01)	0.25 (0.85)	-2.60 (0.06)	7.9%	-1.48 (0.13)	1.58 (0.26)	-0.06 (0.97)	53.3%	
Angina-related quality of life	-7.92 (<0.01)	-7.07 (<0.01)	-0.22 (0.91)	-4.06 (0.03)	10.7%	-4.47 (<0.01)	1.00 (0.60)	-1.13 (0.56)	43.6%	
SF-12 PCS score	-4.38 (<0.01)	-3.61 (<0.01)	-0.95 (0.38)	-4.86 (<0.01)	17.6%	-1.53 (0.04)	0.87 (0.37)	0.22 (0.82)	65.1%	
SF-12 MCS score	-3.37 (<0.01)	-3.07 (<0.01)	-0.08 (0.92)	-2.67 (0.03)	8.9%	-1.97 (<0.01)	0.26 (0.77)	-1.82 (0.05)	41.5%	
EQ-5D utility index score	-0.06 (<0.01)	-0.04 (<0.01)	0.004 (0.81)	-0.06 (<0.01)	33.3%	-0.01 (0.25)	0.02 (0.16)	-0.01 (0.44)	83.3%	
EQ-5D visual analog scale	-4.73 (<0.01)	-3.67 (<0.01)	-2.64 (0.15)	-7.74 (<0.01)	22.4%	-1.46 (0.27)	-1.26 (0.47)	-3.22 (0.07)	69.1%	

Results are reported as coefficients and p values. STEMI indicates ST-elevation AMI; EQ-5D, EuroQol; MCS, Mental Component Summary; PCS, Physical Component Summary; a SF-12, Short Form-12.

*Model was also adjusted for patient age, race, education, current smoking, hypertension, diabetes, body mass index, statin use at discharge, 1-month LDL-cholesterol, and the corresponding 1-month value of the outcome variable.

Appendix Table 7: Adjusted 12-month health status associated with sex and hsCRP at 1 month among NSTEMI patients, coefficient (p value)

Health status at 12 month of follow up	After adjustment for 1-month hsCRP					After adjustment for 1-month hsCRP and other covariates*			
	Unadjusted, Women (vs Men)	1-month hsCRP			Reduction in gender effect after adjustment for CRP	1-month hsCRP			Reduction in gender effect after adjustment for CRP and other covariates
		Women (vs Men)	Moderate (vs Low)	High (vs Low)		Women (vs Men)	Moderate (vs Low)	High (vs Low)	
Angina frequency	-1.66 (0.19)	-1.36 (0.30)	-2.28 (0.18)	-2.69 (0.08)	18.1%	-0.72 (0.56)	-0.77 (0.63)	-0.85 (0.59)	56.6%
Angina-related physical limitation	-0.98 (0.42)	-0.56 (0.65)	-1.32 (0.41)	-1.31 (0.38)	42.9%	-0.10 (0.93)	-0.60 (0.71)	1.59 (0.33)	89.8%
Angina-related quality of life	-4.97 (<0.01)	-4.78 (<0.01)	-3.63 (0.09)	-3.51 (0.08)	3.8%	-2.54 (0.10)	-1.25 (0.53)	0.47 (0.81)	48.9%
SF-12 PCS score	-2.68 (<0.01)	-2.30 (0.01)	-2.52 (0.03)	-5.68 (<0.01)	14.2%	-1.43 (0.08)	-0.47 (0.65)	-0.59 (0.57)	46.6%
SF-12 MCS score	-3.34 (<0.01)	-3.23 (<0.01)	-0.02 (0.98)	-0.64 (0.48)	3.3%	-1.69 (0.01)	0.30 (0.73)	0.94 (0.29)	49.4%
EQ-5D utility index score	-0.044 (<0.01)	-0.040 (<0.01)	-0.03 (0.11)	-0.06 (<0.01)	9.1%	-0.02 (0.10)	-0.02 (0.17)	-0.01 (0.33)	54.5%
EQ-5D visual analog scale	-3.49 (0.01)	-2.48 (0.08)	-3.06 (0.10)	-7.55 (<0.01)	28.9%	-1.22 (0.37)	-0.40 (0.81)	-1.44 (0.41)	65.0%

Results are reported as coefficients and p values. NSTEMI indicates non ST-elevation AMI; EQ-5D, EuroQol; MCS, Mental Component Summary; PCS, Physical Component Summary; and SF-12, Short Form-12.

*Model was also adjusted for patient age, race, education, current smoking, hypertension, diabetes, body mass index, statin use at discharge, 1-month LDL-cholesterol, and the corresponding 1-month value of the outcome variable.