Title

High-sensitivity C-reactive protein elevation in patients with prior myocardial infarction in the United States

Authors

Pagidipati, Neha J
Hellkamp, Anne S
Sharma, Puza P
et al.

Publication Date

2018-10-01

DOI

10.1016/j.ahj.2018.07.014

Peer reviewed

HHS Public Access

Author manuscript

Am Heart J. Author manuscript; available in PMC 2022 December 27.

Published in final edited form as:

Am Heart J. 2018 October ; 204: 151–155. doi:10.1016/j.ahj.2018.07.014.

High-sensitivity C-reactive protein elevation in patients with prior myocardial infarction in the United States

Neha J. Pagidipati, MD, MPH[a], **Anne S. Hellkamp, MS**[a], **Puza P. Sharma, MBBS, MPH, PhD**[b], **Tracy Y. Wang, MD, MHS, MSc**[a], **Gregg C. Fonarow, MD**[c], **Michael Pencina, PhD**[a]

[a]Duke Clinical Research Institute, Duke University, Durham, NC

[b]Novartis Pharmaceutical Corporation, East Hanover, NJ

[c]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA

Abstract

Importance—The extent to which levels of high-sensitivity C-reactive protein (hs-CRP), a known marker of increased cardiovascular risk, are elevated and are associated with standard cardiovascular risk factors in patients with a history of myocardial infarction (MI) is unknown.

Objectives—To determine the pattern and determinants of the distribution of hs-CRP in those with a prior MI in the United States using a nationally representative sample.

Design and Participants—Adults with hs-CRP data in the National Health and Nutrition Examination Surveys from 1999–2010.

Results—Among 1296 individuals in our cohort, the median age was 65 years and the median hs-CRP level was 2.69 mg/L, measured an average of 7.1 years after the MI. Among these patients, 22% had hs-CRP levels of <1 mg/L, 61% had ≥2 mg/L, and 48% had ≥3 mg/L. Increasing hs-CRP was associated in a multivariable model with increasing body mass index (partial R^2 [pR^2] 0.113, P< .001), increasing non-high-density lipoprotein [HDL] (pR^2 0.030, P< .001), increasing age (pR^2 0.008, P = .017), and decreasing HDL (pR^2 0.005, P = .046). Adjusted mean hs-CRP was also higher in women (3.6 vs 2.7 mg/L; P< .001), in people with hypertension (3.5 vs. 2.8, P = .030), and among smokers (4.2 vs 2.3 mg/L; P< .001), and lower in people with hyperlipidemia (2.8 vs. 3.5, P = .007). Standard cardiovascular risk factors accounted for only 22% of the variability in hs-CRP levels.

Reprint requests: Neha J. Pagidipati, MD, MPH, Duke Clinical Research Institute, Duke University School of Medicine, PO Box 17969, Durham, NC 27715. neha.pagidipati@dm.duke.edu.

Disclosures:NJP: Ownership: Freedom Health, Inc; Physician Partners, LLC; RXAdvance, LLC; Florida Medical Associates, LLC.
ASH: None.
PPS: Employed by Novartis Pharmaceutical Corp.
TYW: Research grants to the Duke Clinical Research Institute from AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly, Gilead Sciences, Novartis, Pfizer, and Regeneron, as well as consulting or honoraria from Merck, Gilead, and Pfizer, Inc.
GCF: Consulting: Amgen, Janssen, Novartis.
MP: Grant from Novartis to Duke.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2018.07.014.

Conclusions and Relevance—Among patients with prior MI, elevated hs-CRP is prevalent several years after the MI, and standard cardiovascular risk factors explain only a small proportion of hs-CRP variability. In light of emerging evidence on the importance of inflammation in the pathogenesis of cardiovascular disease, the high prevalence of elevated hs-CRP in patients with prior MI in the United States may have public health implications.

C-reactive protein is an acute-phase reactant that is a marker of cardiovascular risk in both the primary and secondary prevention populations.[1,2] There is also increasing evidence that chronic inflammation plays a role in the initiation and progression of atherosclerotic cardiovascular disease. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study demonstrated prospectively that statin therapy improves cardiovascular outcomes in individuals with an elevated high-sensitivity-CRP (hs-CRP) but no prior history of coronary heart disease.[3]

There has also been a growing interest in exploring the relationship between cardiovascular disease and inflammation in the secondary prevention population. Bohula et al demonstrated that post-myocardial infarction (MI) patients with an hs-CRP level of <2 mg/L have improved long-term cardiovascular outcomes compared with those with an hs-CRP level of ≥2 mg/L.[4] The recently published CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial showed that among patients with prior MI and hs-CRP ≥2 mg/L, a monoclonal antibody targeting interleukin-1β was associated with fewer cardiovascular events, independent of lipid-level lowering.[5] This large, randomized placebo-controlled trial lends support to the hypothesis that inflammation plays a critical role in the pathogenesis of cardiovascular disease.

However, it is not known what proportion of patients with prior MIs have elevated hs-CRP levels, or how much of the variation of hs-CRP can be explained by standard cardiovascular risk factors. If a large proportion of patients with prior MI in the United States have elevated hs-CRP levels, this could have wide-ranging public health consequences, both in terms of risk of subsequent disease and in terms of appropriate risk management. Using a nationally representative sample of adults, our goal was to determine the pattern and determinants of the distribution of hs-CRP in those with a prior MI in the United States.

Methods

We used data from the National Health and Nutrition Examination Survey (NHANES), which contains a representative sample of the US civilian, non-institutionalized population.[6] NHANES interviews approximately 10,000 people, of whom 95% have laboratory data collected, in 2-year cycles. From the continuous surveys in which hs-CRP data were collected (1999–2010, N = 62,160), we identified a subset of subjects who reported a prior MI and had hs-CRP data available (N = 1296). Only 7% of individuals with a prior MI who were in the randomly-selected laboratory subsample did not have hs-CRP data available. Their characteristics are shown in eTable I.

All analyses were performed according to NHANES analytic guidelines, utilizing sample weights to account for the complex, multistage probability-sampling design of NHANES, nonresponse rates, and oversampling of certain segments of the population.[7,8] We

determined the distribution of hs-CRP in the US population of patients with prior MI. For ease of presentation, we also summarized clinical characteristics using the clinically relevant threshold of 2 mg/L[3,4] and the exploratory threshold of 3 mg/L. We performed univariable linear regression models to evaluate the association of hs-CRP with cardiovascular disease risk factors. Laboratory values that required fasting (low-density lipoprotein cholesterol, triglycerides, glucose) were collected in ~30% of patients. To limit the undue influence of large observations, hs-CRP was log-transformed in all models.

To develop a multiple regression model for hs-CRP, we used 733 patients who had complete data for all predictors of interest; these patients were similar in baseline characteristics to the patients not included (data not shown). We used backward selection among the following candidate predictors, chosen as standard cardiovascular risk factors based on clinical input: age, sex, race (white, black, Hispanic, or other), body mass index (BMI), current smoking status, hypertension, antihypertensive medication use, hyperlipidemia, use of lipid lowering agent, diabetes, systolic blood pressure, high-density lipoprotein cholesterol (HDL-C), non-HDL-C, glycated hemoglobin (HbA1c), and estimated glomerular filtration rate (eGFR). Non-HDL-C was chosen rather than low-density lipoprotein cholesterol (LDL-C) because it is a better predictor of cardiovascular disease.[9,10] Prior to variable selection, continuous predictors were evaluated for the linearity of their relationship with hs-CRP, using restricted cubic splines, and only slight non-linearity was detected; therefore, to provide easily interpretable coefficients, all were entered into the multivariable model using linear terms. To address the possibility that the relationship between BMI and hs-CRP differs by sex, an interaction between sex and BMI was tested, and because this was significant, estimation for BMI was carried out within each sex. Estimation in the final model was based on 959 patients with complete data for the selected predictors. For categorical predictors, the least squares mean was used to illustrate the relationship with hs-CRP; for continuous predictors, the beta-coefficient was used. As in the univariable analyses, hs-CRP was log-transformed in the model, but then exponentiated to return to the original scale in the presentation. Partial R^2 was calculated as: $(R^2_{full} - R^2_{reduced})/(1 - R^2_{reduced})$ where $R^2_{reduced}$ is the R^2 from the model without the variable.

To further understand the potential significance of an elevated hs-CRP level in the population of patients with a prior MI, we evaluated the proportion of prior MI patients who had hs-CRP ≥2 mg/L, but who did not have other standard risk factors including diabetes mellitus, hypertension, hyperlipidemia, and current smoking status. All analyses were performed with SAS version 9.4 or higher (SAS Institute, Cary, NC). Survey-specific procedures (SURVEYMEANS, SURVEYFREQ, and SURVEYREG) were used.

Results

We identified 1296 individuals who had a prior MI, representing approximately 6.3 million people (3.5% of the US population). As expected, the hs-CRP distribution was skewed to the left, with a mean of 5.84 mg/L and a median of 2.69 mg/L (25th, 75th percentiles 1.06, 6.40) (Figure 1). Approximately 61% (95% CI 58%–65%) of the prior MI population had hs-CRP ≥2 mg/L. These patients, versus those with hs-CRP <2 mg/L, were younger, more frequently female and non-white, and had a higher rate of smoking, hyperlipidemia, and stroke history

(Table I). Individuals with hs-CRP ≥2mg/L less frequently had a history of hypertension or were on statin therapy. Clinical characteristics are also displayed using the hs-CRP threshold of 3 mg/L in eTable II.

Univariable regression revealed that hs-CRP was most strongly associated with BMI (R^2 0.10, P< .0001), non-HDL-C (R^2 0.05, P< .0001), current smoking status (R^2 0.04, P < .0001), HDL-C (R^2 0.03, P < .0001), triglycerides (R^2 0.03, P = .0056), female sex (R^2 0.03, P < .0001), and antihypertensive medication use (R^2 0.01, P = .0006). In the multivariable model, BMI was the most significant continuous predictor of hs-CRP. There was a significant interaction (P = .010) between sex and BMI; hs-CRP increased by a factor of 1.09 (95% CI 1.07–1.10) for every 1 kg/m^2 increase in women and by a factor of 1.05 (1.03–1.07) for every 1 kg/m^2 increase in men. Overall, BMI accounted for 11.3% of the variation in hs-CRP (Table II). Non-HDL-C and HDL-C were also significant continuous predictors of hs-CRP, with a 1.05 (95% CI 1.03–1.07) -fold and a 1.05 (95% CI 1.00–1.11) -fold increase per 10 mg/L increase of non-HDL-C and 10 mg/L decrease of HDL-C, respectively (eFigure 1). Greater age, current smoking, female sex, hypertension, and absence of hyperlipidemia were also associated with higher hs-CRP levels (Table II).

The overall R^2 of the regression model was 0.22, indicating that only 22% of the variation in hs-CRP level in the US population with a prior MI can be explained by other traditional cardiovascular risk factors that were included in this analysis. Among individuals with a prior MI in the United States, 6% (95% CI 4–7%) had an elevated hs-CRP ≥2 mg/L, but did not have other standard modifiable risk factors such as diabetes, hypertension, hyperlipidemia, or current smoking status. Among all prior MI patients with an elevated hs-CRP ≥2 mg/L, 9% (95% CI 7–12%) did not have any of the standard modifiable risk factors listed above.

Discussion

C-reactive protein is a known marker of cardiovascular risk in patients with a history of MI. Our results indicate that an estimated 61% of individuals with a prior MI in the United States have an elevated hs-CRP level (≥2 mg/L). Increasing hs-CRP is associated with increasing BMI, non-HDL-C, and age, decreasing HDL-C, female sex, smoking, hypertension, and absence of hyperlipidemia. However, standard cardiovascular risk factors account for only 22% of the variability in hs-CRP. Further, 6% of individuals with a prior MI in the United States have an elevated hs-CRP level as their only major modifiable risk factor.

The proportion of individuals with a prior MI who have hs-CRP ≥2 mg/L in our study is greater than the proportion of the general U.S. population with elevated hs-CRP. A prior analysis of NHANES data revealed that an estimated 52% of patients in the general U.S. adult population have hs-CRP levels ≥2 mg/L.[11] This higher prevalence of hs-CRP elevation in the prior MI population, along with the apparent independence of the distribution from other cardiovascular risk factors, lend some support to the hypothesis that inflammation may lie in the causal pathway of vascular disease. This hypothesis is further bolstered by the CANTOS trial, which showed cardiovascular benefit of canakinumab, a monoclonal antibody targeting interleukin-1β.[5] There are other ongoing trials to evaluate the potential

benefit of inflammation reduction in cardiovascular disease. The Colchicine Cardiovascular Outcomes Trial (COLCOT) will assess whether long-term colchicine therapy reduces cardiovascular events in patients after MI.[12] The effect of methotrexate on patients with prior MI and diabetes or metabolic syndrome is being assessed in the Cardiovascular Inflammation Reduction Trial (CIRT).[13] If inflammation does indeed lie in the causal pathway of cardiovascular disease, then the high prevalence of inflammation in individuals with prior MI, as is evidenced in this study, is of public health concern.

Several caveats should be considered when interpreting our results. Because these are observational data, our analyses may be affected by residual confounding, despite adjustment for multiple possible confounders. In addition, the trajectory of hs-CRP levels over time and the clinical outcomes of participants are unknown, since NHANES is a cross-sectional study rather than a prospective cohort study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding:

Novartis Pharmaceutical Corporation.

References

1. Ridker PM, Cushman M, Stampfer MJ, et al. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9. [PubMed: 9077376]
2. Sabatine MS, Morrow DA, Jablonski KA, et al. Prognostic significance of the Centers for Disease Control/American Heart Association high-sensitivity C-reactive protein cut points for cardiovascular and other outcomes in patients with stable coronary artery disease. Circulation 2007;115:1528–36. [PubMed: 17372173]
3. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195–207. [PubMed: 18997196]
4. Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation 2015;132:1224–33. [PubMed: 26330412]
5. Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med 2017;377:1119–31. [PubMed: 28845751]
6. Liese AD, Hense HW, Lowel H, et al. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. Epidemiology 1999;10:391–7. [PubMed: 10401873]
7. Johnson CL, Paulose-Ram R, Ogden CL, et al. National health and nutrition examination survey: analytic guidelines, 1999–2010. Vital Health Stat 2013;2:1–24.
8. Bos MJ, Koudstaal PJ, Hofman A, et al. Uric acid is a risk factor for myocardial infarction and stroke: the Rotterdam study. Stroke 2006;37:1503–7. [PubMed: 16675740]
9. Arsenault BJ, Boekholdt SM, Kastelein JJ. Lipid parameters for measuring risk of cardiovascular disease. Nat Rev Cardiol 2011;8:197–206. [PubMed: 21283149]
10. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA 2012;307:1302–9. [PubMed: 22453571]

11. Woloshin S, Schwartz LM. Distribution of C-reactive protein values in the United States. N Engl J Med 2005;352:1611–3.
12. Johnson RJ, Kang DH, Feig D, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension 2003;41:1183–90. [PubMed: 12707287]
13. Ridker PM. Testing the inflammatory hypothesis of atherothrombosis: scientific rationale for the cardiovascular inflammation reduction trial (CIRT). J Thromb Haemost 2009;7(Suppl 1):332–9. [PubMed: 19630828]
14. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–54. [PubMed: 16908915]

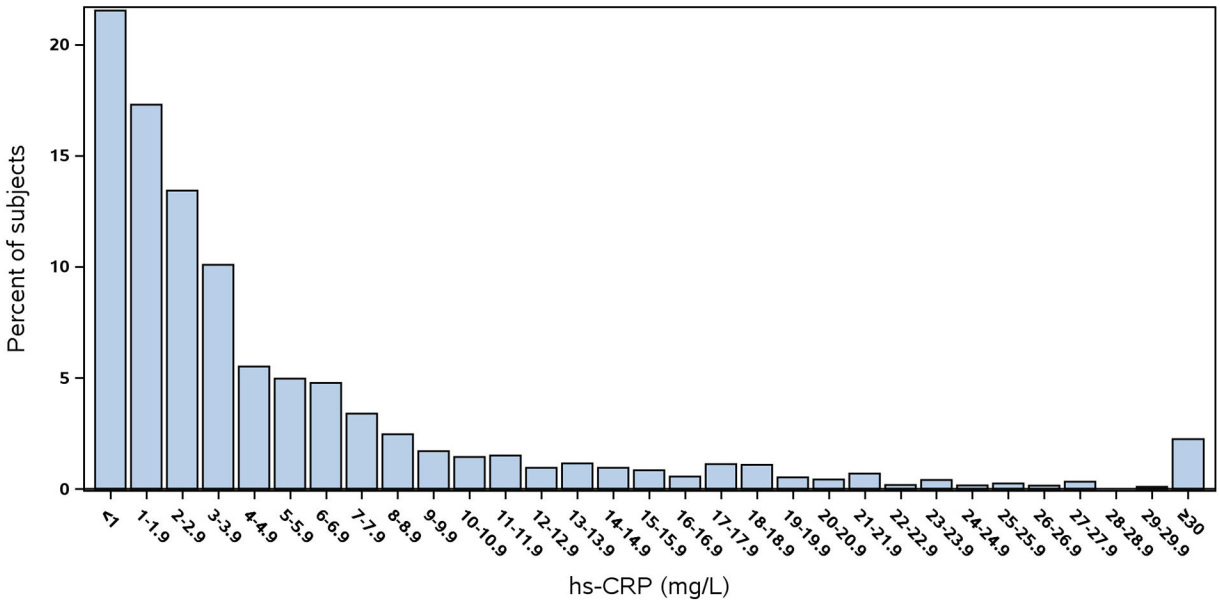

Figure 1.

Distribution of high-sensitivity C-reactive protein (hs-CRP) values among individuals with a prior myocardial infarction.

Am Heart J. Author manuscript; available in PMC 2022 December 27.

Table I.

Baseline characteristics by hs-CRP level(threshold = 2 mg/L)

	Individuals with Prior MI		
Characteristic	**Overall**	**hs-CRP< 2 mg/L**	**hs-CRP ≥ 2 mg/L**
N: sample	1296	480	816
N: population	6,315,925	2,461,930 (39%)	3,853,995 (61%)
Demographics			
Age, y (up to 80 y)	65 (55, 75)	67 (56, 76)	64 (53, 74)
Age categories			
≤50 y	15% (12, 17)	12% (8, 16)	16% (12, 20)
51–64 y	32% (28, 35)	30% (24, 35)	33% (29, 38)
65–75 y	28% (25, 31)	29% (25, 34)	27% (23, 31)
≥76 y	26% (23, 28)	29% (24, 34)	24% (20, 27)
Female	35% (32, 38)	28% (23, 32)	39% (35, 44)
Race			
White	81% (78, 84)	83% (80, 86)	79% (76, 83)
Black	9% (7, 11)	6% (4, 8)	11% (9, 13)
Hispanic	6% (4, 7)	6% (4, 8)	6% (4, 8)
Other	4% (3, 6)	5% (3, 8)	4% (2, 6)
Risk Factors			
BMI, kg/m^2	29.0 (25.4, 33.1)	27.1 (24.3, 30.4)	30.5 (26.2, 34.6)
Current smoker	24% (21, 27)	15% (11, 19)	30% (26, 33)
Hypertension	45% (41, 49)	52% (47, 58)	40% (36, 44)
Antihypertensive medication use	65% (62, 68)	60% (55, 66)	68% (64, 72)
Hyperlipidemia	59% (55, 62)	55% (49, 61)	61% (57, 65)
Statin use	60% (57, 64)	65% (60, 70)	58% (53, 62)
Diabetes	26% (23, 29)	26% (21, 31)	26% (22, 29)
Prior stroke	16% (14, 18)	14% (10, 17)	18% (15, 21)
Years since prior MI*	7.1 (2.5, 13.4)	7.6 (2.4, 14.3)	6.7 (2.6, 12.9)
Measurements and Labs			
hs-CRP, mg/L	2.7 (1.1, 6.4)	0.8 (0.5, 1.2)	5.1 (3.0, 9.7)

Characteristic	Individuals with Prior MI		
	Overall	hs-CRP< 2 mg/L	hs-CRP ≥ 2 mg/L
hs-CRP by years since MI *			
0–1 y	2.2 (1.0, 5.8)	0.9 (0.5, 1.2)	5.3 (3.2, 7.2)
2–5 y	3.3 (1.2, 7.7)	0.7 (0.4, 1.2)	5.4 (3.3, 11.4)
>5 y	2.6 (1.0, 6.3)	0.8 (0.5, 1.2)	4.9 (2.8, 10.1)
Systolic blood pressure, mmHg	127 (114, 142)	126 (111, 140)	127 (115, 144)
Total cholesterol, mg/dL	183.3 (156.3, 214.3)	176.1 (150.4, 206.7)	186.6 (160.8, 217.6)
LDL-C, mg/dL †	100.0 (78.4, 124.9)	97.5 (70.6, 119.8)	101.7 (82.9, 128.7)
HDL-C, mg/dL	44.4 (37.0, 55.9)	46.4 (38.6, 57.3)	43.3 (35.6, 54.7)
Non-HDL-C, mg/dL	130.9 (106.3, 160.2)	121.0 (97.9, 148.8)	136.6 (113.2, 166.0)
Triglycerides, mg/dL †	133.0 (93.0, 202.8)	116.6 (85.5, 189.3)	141.9 (97.3, 210.3)
eGFR ‡	79.0 (62.4, 95.3)	78.0 (59.2, 92.7)	80.2 (64.0, 98.5)
Glucose, mg/dL †	106.0 (97.8, 121.6)	105.7 (97.8, 121.3)	106.7 (97.6, 121.6)
HbA1c, %	5.6 (5.3, 6.2)	5.5 (5.3, 6.0)	5.7 (5.4, 6.3)

Continuous variables are shown as medians (25th, 75th percentiles) estimated in the US population. Categorical variables are shown as estimated proportions of the US population, with 95% confidence intervals.

BMI, Body mass index; *eGFR*, estimated glomerular filtration rate; *HbA1c*, glycated hemoglobin; *HDL-C*, high-density lipoprotein cholesterol; *hs-CRP*, high-sensitivity C-reactive protein; *LDL-C*, low-density lipoprotein cholesterol; *MI*, myocardial infarction.

* Years since MI can be calculated for 72% of the sample, where age at MI was reported and where the subject was younger than 80 years at the time of interview (because all ages >80 are set to 80 to ensure privacy).

† LDL-C (n = 604), triglycerides (n = 646), and glucose (n = 644) were collected in a subset of patients who were fasting.

‡ Estimated by the Modification of Diet in Renal Disease formula.[14]

Table II.

Multivariable model for hs-CRP (continuous) and various factors*

Factor		Individuals with Prior MI hs-CRP†	Partial R^2‡	*P*-value
BMI			0.1127	<.001
Interaction with Sex				.010
Female		1.09 (1.07–1.10) increase per 1 point increase		
Male		1.05 (1.03–1.07) increase per 1 point increase		
Current smoker	Yes	4.24 (3.67–4.90)	0.0501	<.001
	No	2.30 (2.07–2.54)		
Non-HDL-C, mg/dL		1.05 (1.03–1.07) increase per 10 mg/dL increase	0.0304	<.001
Sex	Female	3.61 (3.12–4.17)	0.0234	<.001
	Male	2.70 (2.42–3.01)		
Hyperlipidemia	Yes	2.77 (2.48–3.11)	0.0118	.007
	No	3.51 (3.08–4.00)		
Hypertension	Yes	3.48 (3.13–3.86)	0.0082	.030
	No	2.80 (2.39–3.27)		
Age		1.04 (1.01–1.08) increase per 5 year increase	0.0079	.017
HDL-C, mg/dL		1.05 (1.00–1.11) increase per 10 mg/dL decrease	0.0048	.046

BMI, Body mass index; *HDL-C*, high-density lipoprotein cholesterol; *hs-CRP*, high-sensitivity C-reactive protein; *MI*, myocardial infarction.

*Overall model R^2 = 0.22.

†For continuous predictors, the relationship is illustrated with parameter estimates, which show the amount (factor) of change in CRP for each given change in the predictor, with 95% confidence intervals. For categorical predictors, the relationship is illustrated with subgroup least squares CRP means, with 95% confidence intervals. Because there is a significant interaction between BMI and sex, BMI estimates are shown by sex; least squares means for each sex are averaged across BMI levels.

‡Partial R^2 estimates the amount (%) of variability in hs-CRP accounted for by each individual predictor. It is calculated as $(R^2_{full} - R^2_{reduced})/(1 - R^2_{reduced})$ where $R^2_{reduced}$ is the R^2 from the model without the variable. For BMI and sex, the $R^2_{reduced}$ is calculated from a model that also omits the interaction term.