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Original Contribution

Low-Density Lipoprotein Cholesterol Concentrations and Association of High-Sensitivity C-Reactive Protein Concentrations With Incident Coronary Heart Disease in the Multi-Ethnic Study of Atherosclerosis

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High-sensitivity C-reactive protein (hs-CRP) has been associated with coronary heart disease (CHD) in numerous but not all observational studies, and whether low levels of low-density lipoprotein cholesterol (LDL-C) alter this association is unknown. In the Multi-Ethnic Study of Atherosclerosis (2000–2012), we prospectively assessed the association of hs-CRP concentrations with incident CHD in participants who did not receive lipid-lowering therapy, as well as in those with LDL-C concentrations less than 130 mg/dL ($n = 3,106$) and those with LDL-C concentrations of 130 mg/dL or greater ($n = 1,716$) at baseline (2000–2002). Cox proportional hazard analyses were used to assess the associations after adjustment for socioeconomic status, traditional risk factors, body mass index, diabetes, aspirin use, kidney function, and coronary artery calcium score. Log_e hs-CRP was associated with incident CHD in participants with LDL-C concentrations of 130 mg/dL or higher (hazard ratio (HR) = 1.29, 95% confidence interval (CI): 1.05, 1.60) but not in those with LDL-C concentrations less than 130 mg/dL (HR = 0.88, 95% CI: 0.74, 1.05; *P* for interaction = 0.003). As a whole, log_e hs-CRP was not associated with incident CHD in participants who had not received lipid-lowering therapy at baseline (HR = 1.05, 95% CI: 0.92, 1.20) and who had mean LDL-C concentrations less than 130 mg/dL. These findings suggest that LDL-C concentrations might be a moderator of the contribution of hs-CRP to CHD.

coronary heart disease; high-sensitivity C-reactive protein; low-density lipoprotein cholesterol

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein-cholesterol; MESA, Multi-Ethnic Study of Atherosclerosis.

C-reactive protein (CRP), which is a member of the pentraxin protein family, is mainly synthesized in the liver after stimulation by proinflammatory cytokines (1). Additionally, CRP is also produced by extra-hepatic cells, such as aortic endothelial cells, under oxidative stress or inflammatory stimulation (2–4). CRP is present in atherosclerotic lesions and has been found to interact with some modified low-density lipoproteins, possibly leading to progression of atherosclerotic plaque (4, 5).

In the past 15 years, higher concentrations of high-sensitivity CRP (hs-CRP) within the normal range have been associated with a higher risk of future coronary heart disease (CHD) in multiple observational studies and clinical trials (6–9). Measurement of hs-CRP has become a part of prevention guidelines in the United States, particularly for persons at intermediate risk of cardiovascular disease (CVD) (10).

Notably, the association between hs-CRP concentration and CHD risk was mainly observed in community-based cohort studies before 2000, when the general population had higher mean concentrations of low-density lipoprotein cholesterol (LDL-C) (7, 8). In contrast, hs-CRP concentrations were not associated with incident CHD in the Multi-Ethnic Study of Atherosclerosis (MESA) (11, 12). Whether the low baseline LDL-C concentrations in MESA participants

altered the association with hs-CRP is not known. Therefore, we aimed to study in greater depth the association between hs-CRP concentrations and CHD events in MESA participants with lower LDL-C concentrations and in those with higher LDL-C concentrations.

METHODS

Study population and data collection

The study design for MESA has previously been published elsewhere (13). In brief, MESA is a longitudinal cohort study designed to investigate the prevalence, correlates, and progression of subclinical CVD in individuals without clinical CVD at baseline. The cohort includes 6,814 women and men recruited from 6 US communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minneapolis) who were 45–84 years of age at the baseline examination (July 2000 to August 2002). Thirty-eight percent of the participants were white, 28% were black, 22% were Hispanic, and 12% were Chinese. The study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

Of the 6,814 participants, 3 had missing medication histories and 1,100 had received lipid-lowering therapy at baseline. We excluded those with a hs-CRP concentration higher than 10 mg/L to avoid confounders such as occult infectious disease and those with missing data about hs-CRP and LDL-C concentrations and relevant covariates, leaving a sample of 4,822 participants for analysis. Of these, 3,106 had an LDL-C concentration lower than 130 mg/dL and 1,716 had an LDL-C concentration of 130 mg/dL or higher. Figure 1 shows the criteria used to select study participants.

Demographic, medical history, anthropometric, and laboratory data for the present analysis were obtained from the first examination of MESA. Body mass index was calculated as weight in kilograms divided by height in meters squared. Smoking status was defined as current, former, or never smoker from self-report. Resting blood pressure was measured 3 times at 1-minute intervals while participants were seated, and the mean of the second and third measurements was recorded. Diabetes mellitus was defined as having a fasting glucose level of 126 mg/dL or higher or using hypoglycemic medications. Glomerular filtration rate was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation (14). Total cholesterol and high-density lipoprotein cholesterol levels were measured from blood samples obtained after a 12-hour fast. LDL-C concentration was estimated using the

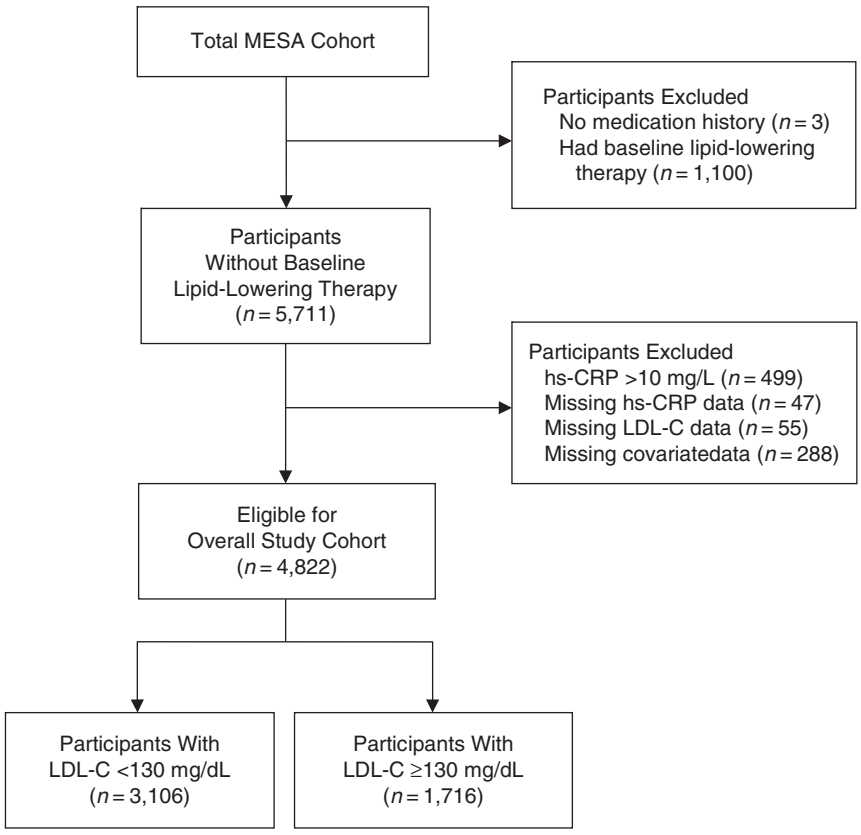

Figure 1. Flow chart of the selection criteria for the eligible overall study cohort, the subcohort with low-density lipoprotein cholesterol (LDL-C) concentrations less than 130 mg/dL, and the subcohort with LDL-C concentrations of 130 mg/dL or higher for the analysis of the association between high-sensitivity C-reactive protein (hs-CRP) concentrations and incident coronary heart disease, Multi-Ethnic Study of Atherosclerosis (MESA), 2000–2012.

Friedewald equation in participants with a triglyceride concentration less than 400 mg/dL (15).

We assessed medication use at clinic visits by reviewing participants' medication containers. The Laboratory for Clinical Biochemistry Research (University of Vermont, Burlington, Vermont) measured serum hs-CRP concentrations using the BN II nephelometer (Dade Behring Inc., Deerfield, Illinois) and urinary albumin/creatinine ratio (mg of albumin/g of creatinine) on a single spot morning collection using nephelometry and the rate-Jaffe reaction. Analytical intra-assay coefficients of variation of hs-CRP ranged from 2.1% to 5.7%, with a detection concentration of 0.18 mg/L. Microalbuminuria and macroalbuminuria were defined as having urinary albumin/creatinine ratios of 30–299 mg/g and ≥300 mg/g, respectively. Family history of CHD was defined as self-report of any immediate family member (parents or siblings) with fatal or nonfatal myocardial infarction at any age.

Coronary artery calcium was measured using either electron beam computed tomography or multidetector computed tomography. Participants were scanned twice at a single examination, and images were interpreted at a centralized reading center (Harbor–UCLA Medical Center, Los Angeles, California). The coronary artery calcium scores from the 2 scans were averaged (16).

Ascertainment of incident CHD

Incident CHD events were defined as myocardial infarction, CHD death, resuscitated cardiac arrest, or definite or probable angina if followed by coronary revascularization. CHD events were adjudicated by a committee that included cardiologists, physician epidemiologists, and neurologists. A description of the adjudication process has been reported previously (17).

Statistical analysis

In the primary analysis, we examined the association of hs-CRP concentrations with incident CHD in participants with LDL-C concentrations less than 130 mg/dL and in those with LDL-C concentrations of 130 mg/dL or higher. We also investigated the association of hs-CRP concentrations with incident CHD in participants who had received lipid-lowering therapy at baseline.

In the analysis, we used the follow-up time from the first MESA examination with censoring at the first occurrence of incident CHD, loss to follow-up, or end of follow-up (December 31, 2012). hs-CRP concentrations were treated as continuous variables by $\log_e$ transformation. Cox proportional hazard regression analyses were used to assess the multivariable associations of $\log_e$ hs-CRP with incident CHD in the groups, with adjustment for potential confounders.

In model 1, we adjusted for age, sex, race/ethnicity, study site, educational level, and total family income. In model 2, we additionally adjusted for body mass index, diabetes, smoking status, family history of CHD, systolic blood pressure, total cholesterol level, high-density lipoprotein cholesterol level, aspirin use, and antihypertensive therapy. In model 3, we adjusted for the variables in models 1 and 2 and estimated glomerular filtration rate, microalbuminuria, macroalbuminuria, and coronary artery calcium score ($\log_2$ transformation). Finally, in model 4, we adjusted for the variables in all previous models and the interim use of lipid-lowering medications. Formal testing for interaction for the hs-CRP association between the subcohorts defined by LDL-C concentration were performed by pooling the 2 subcohorts and introducing into the statistical model an indicator variable for 1 subcohort together with the product of that indicator variable with $\log_e$ hs-CRP. A 2-tailed P value <0.017 was considered significant. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 1 shows the baseline characteristics of the study participants. As shown in Table 2, over an average of 10.3 years of follow-up, there were 299 (6.2%) CHD events in the overall cohort, 168 (5.4%) in the subcohort with LDL-C concentrations less than 130 mg/dL, and 131 (7.6%) in the subcohort with LDL-C concentrations of 130 mg/dL or higher. In the subcohort with LDL-C concentrations of 130 mg/dL or higher, $\log_e$ hs-CRP was associated with incident CHD independent of traditional risk factors, body mass index, diabetes, renal function, coronary artery calcium score, and interim use of lipid-lowering medication in the multivariable analyses.

In the subcohort with LDL-C concentrations less than 130 mg/dL, all associations were nonsignificant. In addition, the associations with risk of incident CHD differed significantly between the subcohorts in the multivariable analyses (P value for interaction from model 1 to model 4: 0.002, 0.007, 0.003, and 0.003, respectively). In the overall cohort in which mean LDL-C concentration was less than 130 mg/dL, $\log_e$ hs-CRP was not associated with incident CHD in the multivariable analyses.

As shown in Appendix Table 1, $\log_e$ hs-CRP was associated with incident CHD in the model 1 analysis (HR = 1.34, 95% confidence interval (CI): 1.08, 1.66). Associations were slightly attenuated in the model 2 and model 3 analyses (in both, HR = 1.22, 95% CI: 0.96, 1.55). As compared with having a hs-CRP concentration less than 3 mg/L, having a concentration of 3 mg/L or higher was associated with higher risk of incident CHD in model 1 (HR = 2.21, 95% CI: 1.46, 3.36), model 2 (HR = 2.00, 95% CI: 1.28, 3.12), and model 3 (HR = 1.93, 95% CI: 1.24, 3.02).

DISCUSSION

In MESA participants who were had not received lipid-lowering therapy at baseline, higher hs-CRP concentrations were associated with a higher risk of CHD only if their LDL-C concentration was at least 130 mg/dL. Higher hs-CRP concentrations while receiving treatment were associated with higher risk of incident CHD in those who had received lipid-lowering therapy at baseline, 94% of whom used statins.

On the basis of current evidence, some modified low-density lipoproteins (LDLs), such as oxidized LDLs, which are generally correlated with plasma concentrations of LDL-C, could initiate vascular inflammation by stimulating endothelial cells to secrete CRP (5, 18). CRP in turn increases the release of lectin-like oxidized LDL receptor 1 from macrophages,

Table 1. Baseline Characteristics of Participants Who Did Not Receive Lipid-Lowering Therapy Stratified by Low-Density Lipoprotein and High-Sensitivity C-Reactive Protein Concentrations, Multi-Ethnic Study of Atherosclerosis, 2000–2012

Characteristic	Overall ($n = 4,822$)				LDL-C <130 mg/dL ($n = 3,106$)				LDL-C ≥130 mg/dL ($n = 1,716$)			
	hs-CRP ≥3 mg/L ($n = 1,461$)		hs-CRP <3 mg/L ($n = 3,361$)		hs-CRP ≥3 mg/L ($n = 892$)		hs-CRP <3 mg/L ($n = 2,214$)		hs-CRP ≥3 mg/L ($n = 569$)		hs-CRP <3 mg/L ($n = 1,147$)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	61.5 (9.8)		61.2 (10.5)		61.6 (10.0)		61.3 (10.7)		61.1 (9.5)		61.0 (10.1)	
Sex, female		62.3		45.9		60.2		45.9		65.6		45.8
Race												
White		36.6		39.2		36.4		38.0		36.9		41.6
Black		30.3		22.9		31.1		23.5		29.0		21.7
Hispanic		28.5		20.5		28.4		19.5		28.8		22.3
Chinese		4.6		17.4		4.2		19.0		5.3		14.4
Cigarette smoking												
Current		17.5		11.3		17.0		12.3		18.3		9.2
Former		35.9		35.4		38.1		35.3		32.5		35.6
Never		46.5		53.3		44.8		52.4		49.2		55.2
Body mass index[a]	30.2 (5.6)		26.7 (4.5)		30.2 (5.7)		26.5 (4.6)		30.1 (5.4)		26.9 (4.3)	
Diabetes		12.2		8.8		13.7		9.4		9.8		7.7
SBP, mm Hg	128.8 (21.5)		123.3 (20.9)		128.5 (21.8)		123.3 (21.1)		129.4 (21.2)		124.1 (20.5)	
Antihypertensive therapy		37.7		27.9		40.5		29.5		33.4		24.9
Aspirin therapy		20.4		20.7		20.6		21.6		20.0		19.0
Total cholesterol, mg/dL	198.1 (36.4)		195.3 (34.1)		177.5 (25.4)		178.3 (24.0)		230.5 (25.9)		228.1 (25.6)	
LDL-C level, mg/dL	121.5 (33.1)		119.4 (30.8)		101.0 (20.6)		102.4 (19.2)		153.6 (21.4)		152.3 (20.8)	
HDL-C level, mg/dL	50.0 (14.5)		51.8 (15.1)		50.6 (15.8)		52.3 (16.2)		49.1 (12.1)		50.7 (12.5)	
Triglycerides, mg/dL	132.9 (64.7)		120.4 (64.6)		129.1 (66.3)		117.6 (66.9)		138.9 (61.9)		125.8 (59.5)	
eGFR, mL/min/1.73 m^2	81.3 (17.8)		82.2 (18.6)		81.2 (18.2)		83.1 (17.2)		81.5 (17.2)		80.5 (21.0)	
Albuminuria		10.8		7.6		11.2		7.8		10.2		7.1
CAC score, Agatston[b]	0 (0, 64.5)		0 (0, 65.4)		0 (0, 62.5)		0 (0, 61.5)		1.9 (0, 68.0)		0 (0, 73.6)	
Interleukin-6 level, pg/mL	1.9 (1.2)		1.2 (0.9)		2.0 (1.3)		1.2 (0.9)		1.8 (1.1)		1.1 (0.9)	
hs-CRP level, mg/L	5.2 (1.9)		1.2 (0.8)		5.2 (1.9)		1.2 (0.8)		5.3 (1.9)		1.3 (0.8)	

Abbreviations: CAC, coronary artery calcium; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

[a] Weight (kg)/height $(m)^2$.

[b] CAC score was presented as median (25th percentile, 75th percentile).

Table 2. Association of Log_e High-Sensitivity C-Reactive Protein With Incident Coronary Heart Disease, Multi-Ethnic Study of Atherosclerosis, 2000–2012

Study Group	CHD Events		Model 1[a]			Model 2[b]			Model 3[c]			Model 4[d]		
	No.	%	HR	95% CI	*P* for Interaction[e]	HR	95% CI	*P* for Interaction[e]	HR	95% CI	*P* for Interaction[e]	HR	95% CI	*P* for Interaction[e]
Overall	299	6.2	1.13	1.00, 1.28		1.04	0.91, 1.19		1.05	0.92, 1.20		1.06	0.93, 1.21	
LDL-C <130 mg/dL	168	5.4	0.94	0.79, 1.10	0.002	0.88	0.74, 1.05	0.007	0.88	0.74, 1.05	0.003	0.89	0.75, 1.06	0.003
LDL-C ≥130 mg/dL	131	7.6	1.43	1.17, 1.75		1.25	1.02, 1.55		1.29	1.05, 1.60		1.29	1.05, 1.60	

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol.

[a] Adjusted for age, sex, race, site, total family income, and educational level.

[b] Adjusted for the variables in model 1 and body mass index, diabetes, smoking status, family history of coronary heart disease, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol level, aspirin use, and antihypertensive therapy.

[c] Adjusted for the variables in models 1 and 2 and estimated glomerular filtration rate, macroalbuminuria, microalbuminuria, and coronary artery calcium score.

[d] Adjusted for the variables in models 1–3 and interim use of lipid-lowering medication.

[e] *P* value for interaction was examined for the difference in the associations with high-sensitivity C-reactive protein between the LDL-C <130 mg/dL subcohort and the LDL-C ≥130 mg/dL subcohort.

which can increase uptake of these modified LDLs (19). As a mediator of vascular inflammation, CRP might induce complement activation via lectin-like oxidized LDL receptor 1 (20). Activation of lectin-like oxidized LDL receptor 1 contributes to endothelial exudation, vasomotor dysfunction, and proatherogenic actions of CRP (21, 22). In clinical observations, hs-CRP concentrations were correlated with oxidized LDL concentrations in the general population (23) and had additive value to predict myocardial infarction and death in patients with acute coronary syndrome (24).

Previous studies of the associations of hs-CRP concentrations with vascular events have been done in populations with low LDL-C concentrations (8, 9, 25). In the Women's Health Study (8), they did not control for lipid-lowering therapy at baseline in their subgroup with a lower LDL-C concentration. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (9), the subgroup with lower LDL-C concentrations included participants with LDL-C concentrations less than the median of 150 mg/dL, many of whom had LDL-C concentrations of 130 mg/dL or higher. In the Justification for Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (25), even though hs-CRP concentrations were associated with CVD events in the subcohort comprising men who received the placebo, the association was not seen in the subcohort of women who received the placebo.

The strengths of the present study include the large array of covariates for which we adjusted and the carefully conducted adjudications for incident CHD. In contrast, our study had a relatively short follow-up period. In addition, residual confounding might have contributed to the inconsistent results for the hs-CRP association in our subgroup analyses despite the large array of covariates in the multivariable adjustment models.

In conclusion, these data suggest that LDL-C concentrations might be a moderator of the contribution of hs-CRP to vascular events. Whether the hs-CRP association in individuals with higher LDL-C concentrations is mediated by modified LDL or some factors that are correlated closely with LDL-C concentrations needs further investigation in the general population, including people who are and people who are not using lipid-lowering therapy.

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(Appendix follows)

Appendix Table 1. Association of High-Sensitivity C-Reactive Protein Concentrations With Incident Coronary Heart Disease in Participants Receiving Lipid-Lowering Therapy ($n = 963$), Multi-Ethnic Study of Atherosclerosis, 2000–2012

hs-CRP Variable	Model 1[a]		Model 2[b]		Model 3[c]	
	HR	95% CI	HR	95% CI	HR	95% CI
Log_e hs-CRP	1.34	1.08, 1.66	1.22	0.96, 1.55	1.22	0.96, 1.55
hs-CRP ≥3 mg/L vs. hs-CRP <3 mg/L	2.21	1.46, 3.36	2.00	1.28, 3.12	1.93	1.24, 3.02

Abbreviations: CI, confidence interval; HR, hazard ratio; hs-CRP, high-sensitivity C-reactive protein.

[a] Adjusted for age, sex, race, site, total family income, and educational level.

[b] Adjusted for the variables in model 1 and body mass index, diabetes, smoking status, family history of coronary heart disease, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol level, aspirin use, and antihypertensive therapy.

[c] Adjusted for the variables in models 1 and 2 and estimated glomerular filtration rate, macroalbuminuria, microalbuminuria, and coronary artery calcium score.