Association Between Obesity, High-Sensitivity C-Reactive Protein ≥2 mg/L, and Subclinical Atherosclerosis

Implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis

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Objective—High-sensitivity C-reactive protein (hsCRP) levels are closely associated with abdominal obesity, metabolic syndrome, and atherosclerotic cardiovascular disease. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial has encouraged using hsCRP ≥2 mg/L to guide statin therapy; however, the association of hsCRP and atherosclerosis, independent of obesity, remains unknown.

Methods and Results—We studied 6760 participants from the Multi-Ethnic Study of Atherosclerosis (MESA). Participants were stratified into 4 groups: nonobese/low hsCRP, nonobese/high hsCRP, obese/low hsCRP, and obese/high hsCRP. Using multivariable logistic and robust linear regression, we described the association with subclinical atherosclerosis, using coronary artery calcium (CAC) and carotid intima-media thickness (cIMT). Mean body mass index was 28.3 ± 5.5 kg/m², and median hsCRP was 1.9 mg/L (0.84 to 4.26). High hsCRP, in the absence of obesity, was not associated with CAC and was mildly associated with cIMT. Obesity was strongly associated with CAC and cIMT independently of hsCRP. When obesity and high hsCRP were both present, there was no evidence of multiplicative interaction. Similar associations were seen among 2083 JUPITER-eligible individuals.

Conclusion—High hsCRP, as defined by JUPITER, was not associated with CAC and was mildly associated with cIMT in the absence of obesity. In contrast, obesity was associated with both measures of subclinical atherosclerosis independently of hsCRP status. (Arterioscler Thromb Vasc Biol. 2011;31:1430-1438.)

Key Words: coronary artery disease • electron beam computed tomography • epidemiology • obesity • vascular biology

High-sensitivity C-reactive protein (hsCRP) is an inflammatory marker that is closely associated with abdominal obesity,1 metabolic syndrome,2 and atherosclerotic cardiovascular disease (CVD).3 The recent Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial has encouraged the use of hsCRP ≥2 mg/L as a screening tool for statin therapy.4 This approach is useful for identifying increased absolute risk,5,6 although the mechanism of increased cardiovascular risk associated with hsCRP and its relationship to obesity remain unclear.

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Indeed, although hsCRP has previously been described as having an independent mechanistic role in atherosclerosis,7 several lines of evidence call into question a causal role for C-reactive protein (CRP).8 For example, a large population-based study9 and a mendelian randomization study10 have not supported a causal association of hsCRP with atherosclerosis. In prior studies of subclinical atherosclerosis, variable or negative associations have been seen with inflammatory markers,11–14 whereas measures of overweight and obesity have been strongly associated with atherosclerosis.15–18

In the wake of the JUPITER trial, a more thorough understanding of hsCRP is required. To further explore the implications of hsCRP as an indicator of increased risk, we conducted a stratified analysis describing the relationship between obesity, high hsCRP, and subclinical atherosclerosis using data from the Multi-Ethnic Study of Atherosclerosis (MESA).
Methods

MESA

We used baseline data from the National Institutes of Health/National Heart, Lung, and Blood Institute–funded MESA (2000 to 2002). The MESA study design and participant recruitment have been previously published. In summary, MESA enrolled 6814 men and women from 4 different ethnic groups (whites, Chinese, black, and Hispanic), aged 45 to 84, into a population-based prospective cohort study aimed at describing the prevalence, progression, and significance of subclinical atherosclerosis. Patients were enrolled from 6 geographically distinct centers in the United States. All participants were free of known CVD at enrollment. All participants gave informed consent, and the study was approved by the institutional review boards at all 6 MESA field centers.

Patient Population

All MESA participants had anthropomorphic measurements of obesity taken at baseline. A total of 6762 (99%) individuals had baseline measurement of hsCRP. At baseline (2000 to 2002), all participants received 2 baseline cardiac computed tomography (CT) scans for the evaluation of coronary artery calcium (CAC), and 6726 (99%) had a baseline carotid ultrasound for measurement of carotid intima/media thickness (cIMT). Participants without baseline hsCRP or cIMT measurements were more likely to be female and black.

For subsequent analyses, we identified a subset of our study who fit JUPITER entry criteria (retaining the low-hsCRP group for this analysis): men aged 50 and above, women aged 60 and above, low-density lipoprotein cholesterol (LDL-C) <130 mg/dL, not on lipid-lowering therapy, free of diabetes, triglycerides ≤500 mg/dL, and creatinine ≤2 mg/dL.

At baseline, 417 men were younger than 50 years old, 1546 women were younger than 60 years old. 2167 participants had LDL-C ≥130 mg/dL. 1101 were on lipid-lowering therapy, 971 had diabetes, 34 had triglycerides ≥500 mg/dL, and 34 had a creatinine >2 mg/dL. Excluding these individuals resulted in a MESA JUPITER subpopulation of 2083 participants (see study flow diagram in the Supplemental Figure, available online at http://atvb.ahajournals.org).

Definition of Obesity and Metabolic Syndrome

Obesity was defined as a body mass index (BMI) ≥30 kg/m² or a waist circumference >102 cm for males and >88 cm for females when BMI was ≥25 kg/m². Overweight was defined as BMI 25 to 29.9 kg/m².

The metabolic syndrome was identified according to the modified National Cholesterol Education Program Adult Treatment Panel III definition. In summary, at least 3 of the following 5 criteria must be met: waist circumference >102 cm in males and >88 cm in females; fasting glucose ≥100 mg/dL or on hypoglycemic therapy; high-density lipoprotein cholesterol (HDL-C) <40 mg/dL in men and <50 mg/dL in women; triglycerides ≥150 mg/dL; and systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, or on antihypertensive medication. Metabolic syndrome score is the total number of National Cholesterol Education Program Adult Treatment Panel III criteria present.

hsCRP and Study Covariates

hsCRP was determined by BNII nephelometer (N High Sensitivity CRP, Dade Behring Inc, Deerfield, IL). The lower limit of detection was 0.17 mg/L. As established by the JUPITER trial, hsCRP ≥2 mg/L was considered elevated.

Family history was obtained by asking the participants whether any immediate family member (parents, siblings, and children) had a prior myocardial infarction. Participants were classified as current cigarette smokers, former smokers, or never smokers. Medication use was defined as present use of prescription medications for the treatment of hypertension or hypercholesterolemia.

Using a Dinamap Pro 1000 automated oscillometric sphygmomanometer (Critikon), resting blood pressure was measured 3 times, with the participant in the seated position. The average of the last 2 measures was used in the analyses. A central laboratory (University of Vermont, Burlington, VT) measured levels of total and HDL-C, triglycerides, plasma glucose, and hsCRP in blood samples obtained after a 12-hour fast. Diabetes was defined according to American Diabetes Association guidelines as a fasting plasma glucose level >126 mg/dL, or a history of medical treatment for diabetes. Replacement of smoking and diabetes with pack-years and fasting glucose in the study models resulted in minimal change, with no overall impact on study conclusions.

Cardiac CT Protocol

Cardiac CT was performed at 3 sites using a cardiac-gated electron-beam CT scanner (Imatron C-150XL, GE-Imatron, San Francisco, CA) and at 3 sites using a 4-slice multidetector CT instrument. All participants were scanned over phantoms of known physical calcium concentration. Participants were scanned twice, and scores were averaged. Images were read at the MESA CT reading center (Harbor–University of California, Los Angeles).

The MESA scanning protocol has been described previously. Image slices were obtained with the participant supine, with no couch angulation, during a single breath hold. A minimum of 35 contiguous images were obtained, beginning above the left main coronary artery and proceeding below both ventricles. Section thickness of 3 mm, field of view 35 cm, and matrix 512×512 were used to reconstruct the raw data. Nominal section thickness was 3.0 mm for electron beam CT and 2.5 mm for 4-detector row CT.

Spatial resolution, expressed as the smallest voxel able to be discriminated, was 1.38 mm³ (0.68×0.68×3.00 mm) for electron beam CT and 1.15 mm³ (0.68×0.68×2.50 mm) for 4-detector row CT. The x statistic for agreement on presence of CAC was 0.92, and the mean rescan percentage absolute difference in CAC >0 was 20.1%.

For this study, CAC was considered both as a binary measure (present versus not present) and a continuous measure (Agatston score).

Carotid Ultrasound

The right and left common carotid arteries were imaged by trained technicians according to a common scanning protocol using high resolution B-mode ultrasonography with a Logiq 700 machine (General Electric Medical Systems, Waukesha, Wisconsin). The MESA ultrasound reading center (Tufts Medical Center) measured maximal intima-media thickness of the common carotid artery as the mean of the maximum intima-media thickness of the near and far walls on the right and left sides.

For this study, cIMT was considered both as a binary measure (≥75th percentile among MESA participants, as suggested in some guidelines31) and as continuous measure.

Statistical Analysis

We divided our total and MESA JUPITER populations into 4 study groups: group 1, nonobese, hsCRP <2 mg/L (reference group); group 2, nonobese, hsCRP ≥2 mg/L; group 3, obese, hsCRP <2 mg/L; group 4, obese, hsCRP ≥2 mg/L. For secondary analyses, similar study groups were constructed stratifying by National Cholesterol Education Program Adult Treatment Panel III metabolic syndrome in place of obesity.

We analyzed baseline characteristics of the study participants according to the 4 main study groups. Frequencies and proportions were reported for categorical variables, and either means with standard deviations or medians with interquartile ranges were reported for continuous variables based on normality of distribution. χ² tests, Fisher exact tests, 1-way ANOVA, or Kruskal-Wallis tests were used for comparison of variables between groups. To examine correlations, a Spearman correlation matrix between BMI, waist circumference, and hsCRP was constructed.

Multivariable regression models were used to determine the independent associations between our study groups and subclinical atherosclerosis. When considering measures of subclinical atherosclerosis as categorical variables, we conducted prevalence regres-
sion using a generalized estimating equation with logit link and 
binomial distribution. The measure of association from this model 
was interpreted as the prevalence ratio. When considering measures 
of subclinical atherosclerosis as continuous variables, we used robust 
linear regression.

Multivariable analyses were conducted in 3 groups: total study 
population (age, gender, race adjusted), MESA JUPITER population 
(age, gender, race adjusted), MESA JUPITER population (fully 
adjusted model). The fully adjusted model included the following 
covariates: age, gender, race, systolic blood pressure, diastolic blood 
pressure, smoking (never/former/current), LDL-C, HDL-C, triglyc-
erides, and antihypertensive medications. Additional models were 
conducted including BMI and hsCRP as continuous measures to 
adjust for the possibility of residual confounding. Interaction terms 
for age, gender, and race were tested, and they were discarded 
because of nonsignificance. Education, a measure of socioeconomic 
status, was tested in the models but discarded because of lack of 
significance.

To confirm the prognostic significance of our findings, we also 
constructed age-, gender-, and race-adjusted Cox proportional hazards 
models for our 4 study groups for the prediction of coronary heart 
disease (CHD) and CVD events. CHD events consisted of myocardial 
infarction, death from CHD, definite angina, probable angina followed 
by coronary revascularization, or resuscitated cardiac arrest. CVD 
events consisted of myocardial infarction, angina, resuscitated 
cardiac arrest, stroke (not transient ischemic attack), CHD death, 
stroke death, other atherosclerotic death, or other CVD death. A 
complete description of the MESA follow-up methods is available 

All analyses used a 5%, 2-sided significance level. Calculations 
were performed using Stata software, version 8.2.

Results

Baseline Characteristics: Entire MESA Population
The mean age of the 6760 study participants was 62±10 
years. Approximately 53% were female, with a mean calculated 
10-year Framingham risk for the entire cohort of 
8.2±7%. The mean BMI was 28.3±5.5 kg/m², and median 
hsCRP was 1.9 mg/L (0.84 to 4.26). Approximately 52% 
were obese, and 48% had high hsCRP.

In general, females were more likely to be obese and have 
high hsCRP. For females, 25% were nonobese with low 
hsCRP, whereas 43% of males fit into this group. Approximately 44% of females were both obese and had high hsCRP, 
whereas just 22% of males fit this group (Figure 1).

The number of participants in the 4 study groups and their 
characteristics are shown in Table 1. Patients in the obese, 
high-hsCRP group were more likely to be black and have hypertension, diabetes, and a family history of myocardial 
infarction. In this group, levels of HDL-C were lower and triglyceride levels were higher, which is characteristic of 
increasing metabolic syndrome prevalence. However the 
traditional 10-year Framingham risk score for CHD, which 
does not include obesity, hsCRP, or metabolic syndrome, was 
slightly lower in this group. The number of JUPITER-eligible 
participants in the 4 study groups is shown in Figure 1.

Both obesity and subclinical inflammation are considered 
central features of the metabolic syndrome. Therefore, we 
conducted a focused comparison of metabolic variables 
between the nonobese, high-hsCRP group (group 2) and the 
obese, low-hsCRP group (group 3). Participants in the obese, 
low-hsCRP group were more likely to have features of the 
metabolic syndrome than the nonobese, low-hsCRP group. 
Fasting glucose, blood pressure, and triglycerides were higher 
and HDL-C lower in this group, corresponding to more 
features of the metabolic syndrome.

Correlation of BMI, Waist Circumference, and 
hsCRP: Entire MESA Population
BMI and hsCRP were found to be correlated (Spearman 
rank correlation coefficient 0.42, P<0.0001). There was a 
greater correlation between anthropomorphic measures of 
obesity and hsCRP among women compared with men 
(Table 2). In women, the correlation coefficient between 
BMI and hsCRP was ρ=0.48 (P<0.0001), and between 
waist circumference and hsCRP it was ρ=0.44 (P<0.0001) 
For men, these correlation coefficients were ρ=0.35 and 
ρ=0.37, respectively (P<0.0001, gender/BMI interaction 
term P<0.0001).

Stated in clinically applicable terms, there was a 71% 
probability that obese females had high hsCRP. When hsCRP 
was high, approximately 77% of females were found to be 
obese. For males, the probabilities were 53% and 56%, 
respectively.

Association between Obesity, hsCRP, and 
Subclinical Atherosclerosis
Table 3 shows the results of the primary multivariable 
analyses. The reference group for these analyses was the 
nonobese, low-hsCRP group (group 1).
Correlation coefficient between:
hsCRP: MESA (2000 to 2002)

<table>
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<tr>
<th>Table 2. Correlation of BMI, Waist Circumference, and hscrp: MESA (2000 to 2002)</th>
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<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td></td>
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<tr>
<td>BMI, kg/m²</td>
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<tr>
<td>Waist circumference, cm</td>
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<td>hsCRP, mg/L</td>
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<tr>
<td>CAC</td>
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<tr>
<td>Scanning</td>
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<tr>
<td>If obese, likelihood of hsCRP ≥2 mg/dL</td>
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<tr>
<td>If hsCRP ≥2 mg/dL, likelihood obese</td>
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</table>

All individual correlation coefficients were statistically significant at P<0.001.

After adjustment for age, race, and gender, individuals in group 2 (nonobese, high hsCRP) had a minimal association with CAC >0, which was not apparent in the MESA JUPITER subpopulation (prevalence ratio 1.11, 95% CI 0.85 to 1.47). In contrast, individuals in group 3 (obese, low hsCRP) had a strong association with CAC >0, which remained similar in the MESA JUPITER population (prevalence ratio 1.68, 95% CI 1.26 to 2.22). Among MESA JUPITER individuals in group 4 (obese, high hsCRP), the prevalence ratio was 1.28 (95% CI 1.00 to 1.64), consistent with no multiplicative interaction between obesity and high hsCRP.

Adjusted for age, race, and gender, individuals in group 2 (nonobese, high hsCRP) had a modestly increased prevalence ratio for cIMT >75th percentile that was similar, but no longer significant, in the MESA JUPITER subpopulation (prevalence ratio 1.35, 95% CI 0.99 to 1.83). In contrast, in group 3 (obese, low hsCRP) there was a persistent statistically significant increase in cIMT (prevalence ratio 1.43, 95% CI 1.05 to 1.95) among the MESA JUPITER population. The prevalence ratio for the MESA JUPITER population in group 4 (obese, hsCRP) was 2.33 (95% CI 1.78 to 3.05). Formal testing revealed no evidence of multiplicative interaction (P=0.35) between obesity and high hsCRP.

<table>
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<tr>
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<th>Odds Ratio</th>
<th>β-Coefficient</th>
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<tr>
<td></td>
<td>CAC &gt;0</td>
<td>cIMT (&gt;75th Percentile)</td>
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<td>Nonobese/hsCRP &lt;2</td>
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<td>1 (Reference)</td>
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<td>Nonobese/hsCRP ≥2</td>
<td>1.18 (1.00 to 1.40)</td>
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<td>1.51 (1.29 to 1.76)</td>
<td>1.63 (1.36 to 1.95)</td>
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<td>1.51 (1.32 to 1.74)</td>
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<tr>
<td>Nonobese/hsCRP &lt;2</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Nonobese/hsCRP ≥2</td>
<td>1.11 (0.85 to 1.47)</td>
<td>1.35 (0.99 to 1.83)</td>
</tr>
<tr>
<td>Obese/hsCRP &lt;2</td>
<td>1.68 (1.26 to 2.22)</td>
<td>1.43 (1.05 to 1.95)</td>
</tr>
<tr>
<td>Obese/hsCRP ≥2</td>
<td>1.28 (1.00 to 1.64)</td>
<td>2.33 (1.78 to 3.05)</td>
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<td>MESA JUPITER population,* fully adjusted†</td>
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<tr>
<td>Nonobese/hsCRP &lt;2</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
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<tr>
<td>Nonobese/hsCRP ≥2</td>
<td>1.04 (0.79 to 1.38)</td>
<td>1.31 (0.96 to 1.80)</td>
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<td>Obese/hsCRP &lt;2</td>
<td>1.44 (1.07 to 1.94)</td>
<td>1.28 (0.93 to 1.77)</td>
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<tr>
<td>Obese/hsCRP ≥2</td>
<td>1.01 (0.78 to 1.31)</td>
<td>2.10 (1.58 to 2.80)</td>
</tr>
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</table>

β-Coefficient should be interpreted as the absolute difference between each category and the reference category.

*MESA JUPITER population (N=2083): men aged ≥50 and women aged ≥60 with LDL-C <130 mg/dL, not on lipid-lowering therapy, without diabetes, triglycerides ≤500 mg/dL, and creatinine ≤2 mg/dL.

†Adjusted for age, gender, race, systolic blood pressure, diastolic blood pressure, smoking, LDL-C, HDL-C, triglycerides, and antihypertensive medications.

Similar trends were seen when CAC was considered as a continuous variable (Table 3). Group 2 (nonobese, high hsCRP) was not associated with CAC. Within group 3 (obese, low hsCRP), there was a strong association with CAC ($\beta=0.63$, 95% CI 0.32 to 0.93). In group 4, when both obesity and high hsCRP were present, the $\beta=0.47$ (95% CI 0.20 to 0.74), indicating no multiplicative interaction.

Similar trends were also seen when cIMT was considered as a continuous variable (Table 3). Group 2 (nonobese, high hsCRP) was mildly associated with increased cIMT ($\beta=0.37$, 95% CI 0.18 to 0.55). Within group 3 (obese, low hsCRP), there was a moderate association with cIMT ($\beta=0.50$, 95% CI 0.31 to 0.69). The strongest absolute difference was seen when both obesity and high hsCRP were present (group 4: $\beta=0.68$, 95% CI 0.51 to 0.85). Formal testing revealed no evidence of multiplicative interaction ($P=0.56$) between obesity and high hsCRP.

The results for the fully adjusted model in the total population are shown in Supplemental Table I. We also conducted similar analyses after substituting overweight for obesity (Supplemental Table II). Overall results and conclusions were similar to the analyses using obesity described above.

Association of Metabolic Syndrome, hsCRP, and Subclinical Atherosclerosis

Table 4 shows the results of the multivariable analysis stratifying by hsCRP status and presence of metabolic syndrome. In general, results were similar to those above stratifying by hsCRP and obesity. High hsCRP was associated with cIMT but not CAC in the absence of metabolic syndrome. Metabolic syndrome was strongly correlated with both CAC and cIMT. When both metabolic syndrome and cIMT were present, there was no evidence of multiplicative interaction.

Figure 2 summarizes the age and gender-adjusted prevalence ratios for the 4 study groups in graphical form (MESA JUPITER subpopulation).

No Residual Confounding With Exposure Dichotomization or Gender Interaction

When anthropomorphic variables and hsCRP were included into the models as continuous variables, hsCRP was not significantly associated with either CAC or cIMT, whereas BMI and waist circumference were significantly associated with both CAC and cIMT. There was no statistically significant interaction between the 4 main study groups and age (study group×age, $P=0.14$), gender (study group×gender, $P=0.41$), or race (study group×race, $P=0.56$) in the prediction of subclinical atherosclerosis among MESA JUPITER participants.

No Effect Modification by JUPITER Inclusion/Exclusion Criteria

LDL-C greater than or less 130 mg/dL, use of cholesterol-lowering therapy, and diabetes status were not statistically significant effect modifiers of the association between hsCRP and subclinical atherosclerosis.
Correlation With CHD and CVD Events
Median follow-up of the participants was 5.8 years. Within the MESA JUPITER population, there were 82 CHD events and 117 CVD events in all. Trends were similar to those seen for subclinical atherosclerosis, although results did not achieve statistical significance because of limited power. The multivariable adjusted hazard ratios for CHD and CVD events for group 2 (nonobese, high hsCRP) were 0.88 (95% CI 0.46 to 1.73) and 1.05 (95% CI 0.59 to 1.90), respectively.

For group 3 (obese, low hsCRP), the hazard ratios for CHD and CVD events were 1.25 (95% CI 0.69 to 2.29) and 1.11 (95% CI 0.66 to 1.90), respectively, and for group 4 (obese, high hsCRP), they were 1.33 (95% CI 0.73 to 2.32) and 1.39 (95% CI 0.87 to 2.21).


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<th>Odds Ratio</th>
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<td></td>
<td>CAC &gt;0</td>
<td>CAC Score</td>
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<td>(&gt;75th Percentile)</td>
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<td>1.08 (0.93 to 1.25)</td>
<td>1.43 (1.21 to 1.70)</td>
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<td>1.72 (1.49 to 1.99)</td>
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<td>1.96 (1.43 to 2.70)</td>
<td>1.78 (1.29 to 2.45)</td>
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<tr>
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<td>1.49 (1.15 to 1.95)</td>
<td>2.42 (1.83 to 3.21)</td>
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<td>MESA JUPITER population,* fully adjusted†</td>
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<tr>
<td>No Met Syn/hsCRP ≥2</td>
<td>0.97 (0.76 to 1.24)</td>
<td>1.60 (1.21 to 2.12)</td>
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<tr>
<td>Met Syn/hsCRP &lt;2</td>
<td>1.69 (1.21 to 2.35)</td>
<td>1.52 (1.10 to 2.12)</td>
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<tr>
<td>Met Syn/hsCRP ≥2</td>
<td>1.24 (0.94 to 1.63)</td>
<td>2.13 (1.58 to 2.87)</td>
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β-Coefficient should be interpreted as the absolute difference between each category and the reference category. Met Syn indicates metabolic syndrome.

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Figure 2. Association between obesity, metabolic syndrome (MS), hsCRP ≥2, and subclinical atherosclerosis in the MESA JUPITER population: MESA (2000 to 2002). MS indicates metabolic syndrome; CIMT, carotid intima-media thickness. In models adjusted for age, gender, and race, hsCRP ≥2 was weakly associated with subclinical atherosclerosis in the absence of obesity or metabolic syndrome. In contrast, obesity and metabolic syndrome were associated with increased atherosclerosis independently of hsCRP status. There was no multiplicative interaction between hsCRP, obesity/metabolic syndrome, and CAC or cIMT.
Discussion

In this large multiethnic cohort of participants free of baseline clinical CVD, high hsCRP in the absence of obesity was not associated with CAC and was mildly associated with cIMT. Obesity was strongly associated with CAC and cIMT independently of hsCRP. When obesity and high hsCRP were both present, there was no evidence of multiplicative interaction. Similar associations were seen in when considering only the MESA JUPITER subpopulation.

Obesity and hsCRP

One proposed mechanistic link between obesity and the development of atherosclerosis is subclinical inflammation, resulting from innate and acquired immune responses. CRP is an acute phase plasma protein that is synthesized in the liver in response to inflammatory cytokines and therefore is used as a nonspecific marker of inflammation. Our study confirms the close correlation between measures of obesity and hsCRP seen in other, more homogenous cohorts. Indeed, among more than 19,000 participants in the Reasons for Geographic and Racial Differences in Stroke study, obesity was more strongly correlated with elevated hsCRP than any other demographic or clinical variable.

Results from our study indicate that circulating levels of hsCRP do not fully account for the association between obesity and atherosclerosis. As illustrated by the metabolic syndrome clinical phenotype, the vascular biology of obesity is complex, with links to several other emerging atherosclerotic risk factors, including prediabetes, atherogenic dyslipidemia, decreased adiponectin, leptin resistance, decreased plasminogen activator inhibitor-1, and endothelial dysfunction, including microalbuminuria. In our study, the addition of hsCRP as the sole marker of inflammation did not add to the association between the metabolic syndrome and subclinical atherosclerosis.

Inflammation, hsCRP, and Atherosclerosis

Although there is a clear role for hsCRP in cardiovascular risk prediction independent of obesity and physical fitness, there is currently controversy over whether CRP plays a causal role in atherosclerotic CVD. Studies supporting a causal role point to evidence that CRP binds to LDL and is present in atherosclerotic plaques. However, recent basic science research has questioned a direct atherogenic mechanism. For example, direct injection of CRP into mice and rats elicits relatively little cellular level activity and little vascular inflammation. Transgenic rabbits that express high amounts of human CRP have no additional aortic or coronary atherosclerosis, despite evidence of human CRP within the vessel wall.

Several recent large clinical studies have added to the basic science evidence suggesting that CRP is not causal. For example, Zacho et al studied a large population-based sample, showing that polymorphisms in the CRP gene are associated with marked increases in CRP levels yet do not predict the incidence of adverse ischemic cardiovascular events. Elliott et al carried out a mendelian randomization study of the most closely associated single-nucleotide polymorphism in the CRP locus, as well as other well-established CRP genetic variants, among more than 100,000 patients. The single-nucleotide polymorphism and other variants were associated with CRP levels but not with incidence of CHD. This suggests that hsCRP may reflect a secondary inflammatory response, and not the cause, of atherosclerosis.

Our study adds to prior studies demonstrating a weak association between hsCRP and subclinical atherosclerosis by studying a large multiethnic sample, stratifying by obesity, and including both CAC and cIMT. Because atherosclerosis underlies the development of most clinical cardiovascular events, our findings suggest that if CRP does indeed have a causal role in CVD, the mechanism for its effect likely relies on pathways other than increased subclinical atherosclerosis. Additional research is needed to define the role of CRP in nonatherosclerotic pathways, such as thrombosis, reduced fibrinolysis, and plaque instability.

In our study, the association of high hsCRP with cIMT >75th percentile was stronger than that seen with CAC >0. Prior studies using different cutpoints have suggested a strong association between CRP and cIMT, as compared with CAC. The implications of atherosclerosis in these vascular beds may be different. The stronger association of hsCRP with cIMT may explain why some studies have found hsCRP to be more predictive of stroke than CHD. Within MESA, CAC predicts all cardiovascular events (CHD, stroke, and fatal CVD) better than cIMT, although cIMT is more strongly predictive of stroke. The MESA JUPITER Subpopulation

In our study, there were similar mild associations between high hsCRP and subclinical atherosclerosis in the entire MESA population and in the MESA JUPITER subpopulation. Neither LDL <130, exclusion of diabetes, nor exclusion of patients on prior lipid-lowering therapy modified the relationship between hsCRP and subclinical atherosclerosis. As such, the biology of hsCRP does not appear to differ for the specific MESA JUPITER population. Because prior research indicates that high hsCRP (at least in single biomarker approaches) appears to be associated with increased absolute risk, our results suggest a continuing need to define the mechanism of hsCRP-related risk in all populations.

Limitations

This study is limited by its cross-sectional nature. Although we were able to describe the statistical associations of obesity, hsCRP, and subclinical atherosclerosis, we were unable to establish the temporal relationships or causality. Although our events analysis shows the same trends as those seen for subclinical atherosclerosis, these results must be considered exploratory given the small number of events when defining small subgroups within MESA.

Although the multiethnic makeup of this study increases generalizability, it may limit precise characterization of obesity. Waist circumference, which was an integral part of our definition of obesity, varies for different ethnicities and geographic locations. The impact of different waist circumference thresholds according to ethnicity has not yet been determined.
thoroughly described within MESA. Another limitation is that hsCRP was measured just once, at baseline, in MESA.

Conclusions and Future Directions

In this study, we showed that high hsCRP as defined by JUPITER (≥2 mg/L) was weakly associated with subclinical atherosclerosis in the absence of obesity. In contrast, obesity was associated with increased atherosclerosis independently of hsCRP status. Further research, of a longitudinal nature, is needed to understand the potential independent mechanisms of risk imparted by obesity, subclinical inflammation as measured by hsCRP, and the possibility of their synergistic combination. Based on our study, it does not appear that isolated identification of hsCRP ≥2 mg/L is an optimal tool for identifying individuals expected to have an increased burden of atherosclerosis. Identifying obesity may be more valuable for this purpose.

Acknowledgments

The authors thank the other investigators, the staff, and the participants of the MESA study for their valuable contributions. A full list of participating MESA investigators and institutions can be found at http://www.mesa-nhlbi.org.

Sources of Funding

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Disclosures

Dr Budoff is on the Speaker’s Bureau for GE Healthcare.

References


Association Between Obesity, High-Sensitivity C-Reactive Protein ≥2 mg/L, and Subclinical Atherosclerosis: Implications of JUPITER from the Multi-Ethnic Study of Atherosclerosis

Blumenthal and Khurram Nasir

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6,814 MESA participants

1,512 with LDL ≥ 130 mg/dL

769 on lipid-lowering therapy

380 with diabetes

0 with triglycerides ≥ 500 mg/dL

9 with creatinine > 2 mg/dL

“JUPITER ELIGIBLE” STUDY POPULATION
N = 2,083
Supplemental Table I: Association between obesity, metabolic syndrome, hsCRP ≥2, and subclinical atherosclerosis in the fully adjusted total population - MESA (2000-2002).

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>$\beta$-coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC&gt;0</td>
<td>CIMT (&gt;75th percentile)</td>
</tr>
<tr>
<td><strong>Total Population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fully adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Normal weight/hsCRP≥2</td>
<td>1.07 (0.90 – 1.28)</td>
<td>1.23 (1.01 – 1.50)</td>
</tr>
<tr>
<td>Obese/hsCRP&lt;2</td>
<td>1.26 (1.07 – 1.49)</td>
<td>1.45 (1.20 – 1.75)</td>
</tr>
<tr>
<td>Obese/hsCRP≥2</td>
<td>1.17 (1.01 – 1.36)</td>
<td>1.83 (1.55 – 2.17)</td>
</tr>
<tr>
<td><strong>Total population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fully adjusted</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Met Syn/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>No Met Syn/hsCRP≥2</td>
<td>1.02 (0.88 – 1.18)</td>
<td>1.35 (1.13 – 1.61)</td>
</tr>
<tr>
<td>Met Syn/hsCRP&lt;2</td>
<td>1.35 (1.13 – 1.62)</td>
<td>1.55 (1.28 – 1.88)</td>
</tr>
<tr>
<td>Met Syn/hsCRP≥2</td>
<td>1.42 (1.21 – 1.65)</td>
<td>1.95 (1.64 – 2.31)</td>
</tr>
</tbody>
</table>

* Adjusted for age, gender, race, systolic blood pressure, diastolic blood pressure, smoking, LDL-C, HDL-C, triglycerides, anti-hypertensive medications

** Adjusted for age, gender, race, systolic blood pressure, diastolic blood pressure, smoking, LDL-C, anti-hypertensive medications

$\beta$-coefficient should be interpreted as the absolute difference between each category and the reference category.
Supplemental Table II: Association between overweight, hsCRP ≥2, and subclinical atherosclerosis in the MESA JUPITER population - MESA (2000-2002).

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
<th>β-coefficient</th>
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<tbody>
<tr>
<td></td>
<td>CAC&gt;0</td>
<td>CIMT (&gt;75th percentile)</td>
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<tr>
<td><strong>Total Population</strong></td>
<td></td>
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<tr>
<td>Age, gender, race adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Normal weight/hsCRP≥2</td>
<td>1.30 (1.03 – 1.63)</td>
<td>1.20 (0.92 – 1.57)</td>
</tr>
<tr>
<td>Overweight/hsCRP&lt;2</td>
<td>1.23 (1.04 – 1.47)</td>
<td>1.64 (1.34 – 2.01)</td>
</tr>
<tr>
<td>Overweight/hsCRP≥2</td>
<td>1.27 (1.06 – 1.52)</td>
<td>2.27 (1.85 – 2.80)</td>
</tr>
<tr>
<td><strong>MESA JUPITER population</strong></td>
<td></td>
<td></td>
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<tr>
<td>Age, gender, race adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Normal weight/hsCRP≥2</td>
<td>1.17 (0.82 – 1.67)</td>
<td>1.16 (0.76 – 1.78)</td>
</tr>
<tr>
<td>Overweight/hsCRP&lt;2</td>
<td>1.33 (1.00 – 1.78)</td>
<td>1.78 (1.28 – 2.48)</td>
</tr>
<tr>
<td>Overweight/hsCRP≥2</td>
<td>1.25 (0.93 – 1.68)</td>
<td>2.67 (1.91 – 3.73)</td>
</tr>
<tr>
<td><strong>MESA JUPITER population</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fully adjusted**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal weight/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Normal weight/hsCRP≥2</td>
<td>1.13 (0.78 – 1.63)</td>
<td>1.20 (0.77 – 1.88)</td>
</tr>
<tr>
<td>Overweight/hsCRP&lt;2</td>
<td>1.18 (0.88 – 1.60)</td>
<td>1.71 (1.22 – 2.42)</td>
</tr>
<tr>
<td>Overweight/hsCRP≥2</td>
<td>1.06 (0.78 – 1.44)</td>
<td>2.62 (1.84 – 3.72)</td>
</tr>
</tbody>
</table>

* MESA JUPITER population (N=2,083): Men age ≥50 and women ≥60 with LDL-C <130 mg/dL, not on lipid-lowering therapy, without diabetes, triglycerides ≤500 mg/dL, and creatinine ≤2 mg/dL
** Fully adjusted model: Adjusted for age, gender, race, systolic blood pressure, diastolic blood pressure, smoking, LDL-C, HDL-C, triglycerides, anti-hypertensive medications

β-coefficient should be interpreted as the absolute difference between each category and the reference category.
hsCRP보다 비만 자체가 동맥경화증과 관련이 있다

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삼성서울병원 내분비대사내과

Summary

목적
hsCRP(high sensitivity C-reactive protein) 수치는 복부비만, 대사증후군, 심혈관질환과 밀접하게 연관이 있다. JUPITER(The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) 연구는 hsCRP 2mg/L 이상의 환자에서 심혈관질환의 1차 예방 목적으로 스타틴 치료가 효과적임을 보여주었지만, 비만 여부와 상관없이 hsCRP가 동맥경화와 연관되는지는 여전히 불확실하다.

방법 및 결과
MESA(the Multi-Ethnic Study of Atherosclerosis) 연구에 참여했던 6,760명을 4군, 즉, 비만(-)/낮은 hsCRP군, 비만(-)/높은 hsCRP군, 비만(+)/낮은 hsCRP군, 비만(+)/높은 hsCRP군으로 나누었다. 관상동맥 칼슘 수치(coronary artery calcium score)와 경동맥내막 두께(carotid intima-media thickness)를 이용해 동맥경화여부를 측정하였다. 평균 체질량지수는 28.3±5.5kg/m², hsCRP 중간값은 1.9mg/L(0.84-4.26)였다.

결론
JUPITER 연구에서 정의한 높은 hsCRP 수치는 비만이 없는 경우 관상동맥 칼슘 수치와 연관이 없었고, 경동맥내막 두께와는 약간의 관련성이 관찰되었다. 비만의 경우 hsCRP와 독립적으로 관상동맥 칼슘 수치 및 경동맥내막 두께가 각각의 연관성이 관찰되었다. 비만 및 높은 hsCRP 2가지가 존재하더라도 곧@email의 상호작용은 관찰되지 않았다. JUPITER 연구 참여자 조건에 해당하는 2,083명에서도 비슷한 결과가 나타났다.
 Commentary

hsCRP는 혈중 표지자로 복부비만, 대사증후군, 동맥경화성 심혈관질환과 밀접하게 관련된다. 최근 JUPITER 연구를 통해 hsCRP가 2mg/L 이상인 경우 스타틴 치료가 심혈관질환의 1차 예방에 효과가 있음을 관찰되었다. 하지만 hsCRP 자체가 직접적으로 동맥경화의 직접적 치료는 불확실하며, 기존 대규모 주택을 대상으로 한 연구에서 직접적인 인과적 관계를 찾을 수 없었다.

기존 연구들은 혈중 표지자들과 동맥경화증 사이의 연관성은 있지만, 비만 자체는 동맥경화와 경증 연관성을 보고하였으나, JUPITER 연구 이후, 다수의 hsCRP 증가와 동맥경화 사이의 관계성이 조명을 받게 되어 다수의 대상으로 시행된 MESA 연구를 통하여 비만, hsCRP, 동맥경화증과의 관련성을 분석하였다. 비만이 동맥경화를 유발하여 기전 중 하나로, 후천적 혹은 선천적인 면역 반응을 통한 염증반응이 잘 알려져 있다.

CRP는 간에서 염증성 사이토카인에 반응하여 합성되는 급성 흙질단백으로 비특이적인 염증 표지자이다. CRP는 LDL관련 동맥경화반응에서 존재하여 동맥경화의 원인으로 여겨졌다. 그러나 최근 몰슬질실험에서 직접 CRP를 주사하는 경우 세포수증 활성도와 혈관 염증을 일으키는 정도가 증가하였다. 또한 실험에서 CRP 발현이 증가함으로 인해 동맥조직의 혈관조직을 관찰하지 않았다. 또한 CRP 수치 증가와 관련되는 CRP의 유전자의 형성이 있어서 혈액에서의 CRP는 증가하지만 심혈관 질환 발생은 높지 않았다. 이는 hsCRP 자체가 단지 이차적인 염증반응을 나타내는 표지자이고 동맥경화증의 원인이 아닐 가능성을 시사한다. hsCRP는 기존 연구에서처럼 본 연구에서도 비만과 연관이 있었다. 비만이 동맥경화를 일으키는 기전은 여러 가지로 언급된 구축성, 이상혈당증, 아포קבע산 감소, 혈관조짐, 혈관내피세포 기능 이상, P-1(Plasminogen activator inhibitor-1) 감소, 미세단백질 등이다. 따라서 hsCRP만으로 비만과 동맥경화 사이의 연관성이 존재하는 이유를 완벽히 설명할 수는 없다.

본 연구에서도 연중 표지자인 hsCRP는 비만과 동맥경화 사이의 연관성을 알았는데 추가적인 기여를 하지 못함을 보여주고 있다. JUPITER 연구대 상자들은 LDL 130mg/dL 미만이면서 염증, 고지혈증 치료를 받은 사람을 대상으로 한 연구에서도 마찬가지 결과를 보았다. 그러나 이번 연구는 환자단위 연구여서 시간적인 선호관계나 인증관계를 증명하기에 한계가 있다. 또한 단일 연구에서 일반화를 하기 전에 특정한 기준을 설정하고, hsCRP를 전반적으로 본 연구에서는 모든 인증에서 동일한 기준(체질량지수 30kg/m², 허리둘레 높이 102cm, 어깨 88cm)을 이용하여 인증한다. 다른 기준을 정립하기에 적용하지는 않았다. 또한 hsCRP는 한 번에 단일한 단점이 있었다.

결론적으로 hsCRP 2mg/L 이상은 비만이 없는 경우 동맥경화증과 약간 연관성을 보였으나, 비만은 hsCRP가 높지 않더라도 동맥경화증과 밀접한 관계가 있었다. 따라서 독립적으로 hsCRP 2mg/L 이상의 환자들은 비만과 더 맥락이 있는 것으로 생각되지만, 앞으로 연구관계를 장려하기 위하여 추가적인 연구가 필요하다.
REFERENCES


