High-sensitivity C-reactive protein (hsCRP) is an inflammatory marker that is closely associated with abdominal obesity, metabolic syndrome, and atherosclerotic cardiovascular disease (CVD). 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 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;31:00-00.)

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

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;31:00-00.)

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

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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.19 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. Baseline weight of more than 300 pounds was an exclusion criterion for MESA.

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 calcification (CAC), and 6726 (99%) had a baseline carotid ultrasound for measurement of carotid intima-media thickness (cIMT). Patients 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 subgroup 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 ≥80 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 measurements 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. Patients 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.20 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 k 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 regression 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, triglycerides, 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 TIA), CHD death, stroke death, other atherosclerotic death, or other CVD death. A complete description of the MESA follow-up methods is available at http://www.mesa-nhlbi.org.

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 male, 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 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 \( r=0.48 \) (\( P<0.0001 \)), and between waist circumference and hsCRP it was \( r=0.44 \) (\( P<0.0001 \)). For men, these correlation coefficients were \( r=0.35 \) and \( r=0.37 \), 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.
### Table 1. Baseline Characteristics of the Study Group: MESA (2000 to 2002)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N=6760)</th>
<th>Nonobese, hsCRP &lt;2 (N=2248)</th>
<th>Nonobese, hsCRP ≥2 (N=1016)</th>
<th>Obese, hsCRP &lt;2 (N=1246)</th>
<th>Obese, hsCRP ≥2 (N=2250)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>62.2±0.10</td>
<td>61.7±0.11</td>
<td>63.0±0.10</td>
<td>62.5±0.10</td>
<td>62.0±0.10</td>
</tr>
<tr>
<td>Gender, women</td>
<td>53%</td>
<td>39%</td>
<td>47%</td>
<td>52%</td>
<td>69%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>39%</td>
<td>40%</td>
<td>40%</td>
<td>41%</td>
<td>35%</td>
</tr>
<tr>
<td>Chinese</td>
<td>12%</td>
<td>24%</td>
<td>12%</td>
<td>7%</td>
<td>2%</td>
</tr>
<tr>
<td>Black</td>
<td>27%</td>
<td>20%</td>
<td>25%</td>
<td>28%</td>
<td>36%</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22%</td>
<td>16%</td>
<td>23%</td>
<td>24%</td>
<td>26%</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.3±5</td>
<td>24.2±3</td>
<td>24.8±3</td>
<td>30.6±4</td>
<td>32.9±5</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>98.2±14</td>
<td>87.3±9</td>
<td>88.9±8</td>
<td>106±10</td>
<td>109±12</td>
</tr>
<tr>
<td>hsCRP, mg/L</td>
<td>1.92</td>
<td>0.74</td>
<td>3.81</td>
<td>1.08</td>
<td>4.71</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>(0.84 to 4.26)</td>
<td>(0.43 to 1.20)</td>
<td>(2.70 to 6.18)</td>
<td>(0.68 to 1.49)</td>
<td>(3.16 to 5.54)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>127±22</td>
<td>122±21</td>
<td>126±22</td>
<td>128±21</td>
<td>130±21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>45%</td>
<td>33%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>105±31</td>
<td>100±24</td>
<td>102±35</td>
<td>105±28</td>
<td>110±35</td>
</tr>
<tr>
<td>Diabetes</td>
<td>14%</td>
<td>10%</td>
<td>9%</td>
<td>15%</td>
<td>20%</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.96±0.3</td>
<td>0.96±0.2</td>
<td>0.96±0.2</td>
<td>0.96±0.3</td>
<td>0.94±0.4</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>37%</td>
<td>36%</td>
<td>36%</td>
<td>37%</td>
<td>38%</td>
</tr>
<tr>
<td>Current</td>
<td>13%</td>
<td>11%</td>
<td>19%</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>117±31</td>
<td>116±31</td>
<td>117±32</td>
<td>118±31</td>
<td>118±32</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>51±15</td>
<td>53±16</td>
<td>52±17</td>
<td>49±13</td>
<td>49±13</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>111 (78 to 161)</td>
<td>95 (69 to 138)</td>
<td>108 (78 to 156)</td>
<td>120 (85 to 165)</td>
<td>125 (88 to 181)</td>
</tr>
<tr>
<td>Family history of heart attack</td>
<td>43%</td>
<td>37%</td>
<td>40%</td>
<td>46%</td>
<td>48%</td>
</tr>
<tr>
<td>Metabolic Syndrome Score</td>
<td>2.2±1.4</td>
<td>1.3±1.1</td>
<td>1.6±1.2</td>
<td>2.8±1.1</td>
<td>3.0±1.1</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>41%</td>
<td>15%</td>
<td>22%</td>
<td>57%</td>
<td>67%</td>
</tr>
<tr>
<td>Medications for hypertension</td>
<td>37%</td>
<td>26%</td>
<td>32%</td>
<td>42%</td>
<td>48%</td>
</tr>
<tr>
<td>Medications for cholesterol</td>
<td>16%</td>
<td>15%</td>
<td>12%</td>
<td>22%</td>
<td>17%</td>
</tr>
<tr>
<td>10-year FRS</td>
<td>8.2±7%</td>
<td>8.1±7%</td>
<td>9.0±8.9</td>
<td>8.7±7%</td>
<td>7.6±7%</td>
</tr>
<tr>
<td>CAC</td>
<td>50%</td>
<td>48%</td>
<td>51%</td>
<td>54%</td>
<td>48%</td>
</tr>
<tr>
<td>cIMT, mm</td>
<td>0.870±0.19</td>
<td>0.837±0.19</td>
<td>0.876±0.20</td>
<td>0.884±0.19</td>
<td>0.893±0.19</td>
</tr>
</tbody>
</table>

### 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).

### Table 2. Correlation of BMI, Waist Circumference, and hsCRP: MESA (2000 to 2002)

<table>
<thead>
<tr>
<th>Correlation coefficient between:</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho$ BMI and hsCRP</td>
<td>0.348</td>
<td>0.482</td>
</tr>
<tr>
<td>$\rho$ Waist circumference and hsCRP</td>
<td>0.365</td>
<td>0.438</td>
</tr>
<tr>
<td>$\rho$ BMI and waist circumference</td>
<td>0.881</td>
<td>0.859</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>If obese, likelihood of hsCRP ≥2 mg/dL</td>
<td>53%</td>
<td>71%</td>
</tr>
<tr>
<td>If hsCRP ≥2 mg/dL, likelihood obese</td>
<td>56%</td>
<td>77%</td>
</tr>
</tbody>
</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 1.21 to 1.69).
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.

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.
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 (ρ=0.42) 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,27,28 there is currently controversy over whether CRP plays a causal role in atherosclerotic CVD.8,29 Studies supporting a causal role point to evidence that CRP binds to LDL and is present in atherosclerotic plaques.30 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.31 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.32

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.33 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.10 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.11–14 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.34 Within MESA, CAC predicts all cardiovascular events (CHD, stroke, and fatal CVD) better than cIMT, although cIMT is more strongly predictive of stroke.35 cIMT also predicts stroke better than CAC among individuals 70 years old in the Cardiovascular Health Study.36

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 relation-
ship 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 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-nih.org.

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**Disclosures**

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

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

Michael J. Blaha, Juan J. Rivera, Matthew J. Budoff, Ron Blankstein, Arthur Agatston, Daniel H. O'Leary, Mary Cushman, Susan Lakoski, Michael H. Criqui, Moyses Szklo, Roger S. Blumenthal and Khurram Nasir

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Supplemental Figure I

Assembly of Study Population

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

147 with missing hsCRP or LDL-C

AGE CRITERIA
402 Men < 50 yrs
1512 Women < 60 yrs
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>Total Population</th>
<th>Odds Ratio</th>
<th>β-coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC&gt;0</td>
<td>CAC score (log CAC + 1)</td>
</tr>
<tr>
<td></td>
<td>CIMT (&gt;75th percentile)</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>0 (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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Total population</th>
<th>Odds Ratio</th>
<th>β-coefficient</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CAC&gt;0</td>
<td>CAC score (log CAC + 1)</td>
</tr>
<tr>
<td></td>
<td>CIMT (&gt;75th percentile)</td>
<td></td>
</tr>
<tr>
<td>Fully adjusted**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Met Syn/hsCRP&lt;2</td>
<td>1 (ref)</td>
<td>0 (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

β-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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CAC&gt;0</td>
<td>CIMT (&gt;75&lt;sup&gt;th&lt;/sup&gt; percentile)</td>
</tr>
<tr>
<td><strong>Total Population</strong></td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>1.13 (0.78 – 1.63)</td>
<td>1.20 (0.77 – 1.88)</td>
</tr>
<tr>
<td>Normal weight/hsCRP≥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 지, 비만(-)/낮은 hsCRP군, 비만(-)/높은 hsCRP군, 비만(+)/낮은 hsCRP군, 비만(+)/높은 hsCRP군으로 나누었다.

결론
JUPITER 연구에서 정의된 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 두께와 강한 연관성이 관찰되었다. 비만 및 높은 hsCRP 2가지가 존재하더라도 급발의 상호작용은 관찰되지 않았다. JUPITER 연구 참여자 조건에 해당하는 2,083명에서도 비슷한 결과가 나타났다.
 Commentary

hsCRP는 혈중 표지자로 부부비만, 대사증후군, 동맥경화성 심혈관질환과 밀접하게 관련된다. 최근 JUPITER 연구를 통해 hsCRP가 2mg/L 이상인 경우 스트레스 치료가 심혈관질환의 1차 예방에 효과가 있음을 관찰되었다. 하지만 hsCRP 자체가 직접적으로 동맥경화의 직접적 원인인지는 불확실하며 기존 연구로 주로 대상으로 한 연구에서 직접적인 인과적 관계를 찾아내기 어렵다.

기존 연구들은 염증 표지자들과 동맥경화성 증후군의 연관성은 있지만 비만 자체는 동맥경화와 강한 연관성을 보고한 바 있다. JUPITER 연구 이후 다수 hsCRP 증가와 동맥경화 사이의 관련성이 증명을 받게 되며 다진환 자나 대상으로 시행한 MESA 연구를 통하여 비만, hsCRP, 동맥경화증과의 관련성을 분석하게 되었다. 비만이 동맥경화를 유발하는 기전 중 하나로 추정적 혹은 선행적인 연관성을 통한 염증반응이 강조되었다.

CRP는 간에서 염증성 사이토카인에 반응하여 활성화된 급성형성 반응으로 비특이적인 염증 표지자이다. CRP는 LDL와 결합하여 동맥경화증에 존재하여 동맥경화의 원인으로 여겨졌다. 그러나 최근 소동물실험에서 직접 CRP를 주사하는 경우 세포수증, 혈관장벽, 혈관막을 일으키는 정도가 미해하였다. 또한 사람의 CRP 발현이 증가할때 유전자가 조절한 톤과에서 추가적으로 대동맥 혹은 관상동맥에 동맥경화증이 관찰되지 않았다. 또한 CRP 수치 증가와 관련된 CRP의 유전자가 혈액에서의 CRP는 증가하지만 심혈관 질환 발생은 높지 않았었다. 이는 hsCRP 자체가 단지 이차적인 염증반응을 나타내는 표지자이고 동맥경화증의 원인이 아닐까 시사한다. hsCRP는 기존 연구에서처럼 본 연구에서도 비만과 연관이 있었다. 비만이 동맥경화를 일으키는 기전은 여러 가지로 언급된 적혈구, 이상직혈증, 아디포색소취산, 혈관내피세포 기능 이상, PAI-1(plasminogen activator inhibitor-1) 감소, 미세단백 등이다. 따라서 hsCRP만으로 비만과 동맥경화와의 연관성이 존재하는 이유를 완벽히 설명할 수는 없다.

본 연구에서도 염증 표지자인 hsCRP는 비만과 동맥경화 사이의 연관성을 입혀내는데 추가적인 기여를 하지 못함을 보여주고 있다. JUPITER 연구대상자들 LDL 130mg/dL 미만이면서 당뇨, 고지혈증 치료를 받은 사람을 제외한 경우에도 마찬가지 결과를 보였다. 그러나 이번 연구는 횡단면적인 연구에서 시간적인 선후관계나 동반관계를 증명하기에 한계가 있다. 또한 다진환 연구에서 일반화 하기 위해서는 당연하지만, 비만을 정의하는데 본 연구에서는 모든 인종에서 동일한 기준(체질량지수 30kg/m², 혈압 120cm, 여자 88cm)을 이용하여 인증마다 다른 기준을 정밀하게 적용하지는 않았다. 또한 hsCRP는 한변만 측정한 단점이 있었다.

결론적으로 hsCRP 2mg/L 이상은 비만이 없는 경우 동맥경화증과 악한 관계연관은 존재하지 않았지만, 비만은 hsCRP가 높지 않더라도 동맥경화증과 밀접한 관련성이 있었다. 따라서 독립적으로 hsCRP 2mg/L 이상의 환자를 찾는 것보다 비만을 찾아내는 노력이 동맥경화증 예방을 위한 핵심적인 방안으로 생각되지만, 앞으로 인과관계를 증명하기 위하여 전향적인 연구 디자인으로 비만과 hsCRP로 측정한 염증반응과 독립적으로 혹은 상호작용을 가지면서 동맥경화증을 일으키는지에 대한 추가적인 연구가 필요하다.
REFERENCES


