Glucocorticoid Receptor Gene, Low-Grade Inflammation, and Heart Failure: The Heart and Soul Study

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Context: A common haplotype of the glucocorticoid receptor (GR) gene has been associated with increased susceptibility to coronary heart disease (CHD). Whether this haplotype predisposes to heart failure (HF) is unknown.

Objective: The objective of the study was to determine whether GR haplotype 3 is associated with HF and whether this association is explained by low-grade inflammation (C-reactive protein).

Design: In a prospective cohort study, participants were genotyped for common GR gene polymorphisms (ER22/23EK, Bcl I C/G, N363S, 9/H9252 A/G). Haplotype analyses were conducted.

Setting: The study was conducted at one university medical center, two Veterans Affairs medical centers, and nine public health clinics.

Patients: Patients included 526 white outpatients with stable CHD.

Main Outcome Measures: Echocardiographic evidence of ventricular dysfunction, self-reported heart failure, and subsequent hospitalization for heart failure were measured.

Results: After adjusting for age, sex, smoking, and body mass index, participants with two copies of haplotype 3 were more likely than those with 0 or 1 copy to report heart failure [hazard ratio (HR) 4.15, 95% confidence interval (CI) 1.5–11.3, \( P = 0.01 \)], have systolic dysfunction (left ventricular ejection fraction <50%) (HR 3.0, 95% CI 0.9–9.9, \( P = 0.07 \)), and be hospitalized for HF during a mean follow-up of 6 yr (HR 3.0, 95% CI 1.3–7.0, \( P = 0.01 \)). These associations were attenuated after adjustment for higher C-reactive protein levels in patients with two copies of haplotype 3.

Conclusions: We found that the GR gene haplotype 3 was associated with prevalent HF, systolic dysfunction, and subsequent HF hospitalization in patients with CHD. This association was partly mediated by low-grade inflammation. (J Clin Endocrinol Metab 95: 2885–2891, 2010)

As mortality from coronary heart disease (CHD) improves in the acute setting, improving care and outcomes for those with stable CHD assumes greater importance for public health. Avoiding hospitalization for heart failure (HF) is an important goal for this population, and understanding predictors of HF is the first step toward targeted prevention measures. HF appears to result not only from cardiac overload or injury but also from a complex interplay among genetic, neurohormonal, inflammatory, and biochemical alterations (1).
Within this context, endogenous glucocorticoid action has come under close scrutiny in the past years (2, 3). It is known that sensitivity to glucocorticoids varies considerably between individuals (4). Four common polymorphisms of the glucocorticoid receptor (GR) gene (ER22/23EK = rs6190; BclI C/G = rs41423247; N363S = rs6195; 9β A/G = rs 6198) (5–7) appear to modulate glucocorticoid sensitivity. A common haplotype of the GR gene, which includes the minor allele of the 9β A/G polymorphism (haplotype 3), has recently been associated with the development of CHD and myocardial infarction (8, 9).

How GR gene haplotype 3 is associated with cardiovascular disease is not known; however, haplotype 3 has also been linked to low-grade inflammation (8). Thus, one possible mechanism by which this haplotype might be associated with CHD and HF is altered inflammatory activity, a well-known risk factor for cardiovascular disease (1). C-reactive protein (CRP), a plasma protein synthesized by the liver, is a sensitive and dynamic systemic marker of inflammation. Its concentration in the circulation can increase by up to 10,000-fold during acute responses to serious infection or major tissue damage. Long-term circulating concentrations of CRP show a similar year-to-year consistency within individuals to levels of some more extensively studied risk factors such as blood cholesterol concentration and blood pressure. In recent years, CRP has been studied as a potential marker of more subtle and persistent systemic alterations that may be loosely called low-grade inflammation.

In this study, we sought to examine the association of GR gene haplotype 3 with self-reported HF, ventricular dysfunction, and subsequent HF hospitalization and determine the extent to which any association between haplotype 3 and HF was explained by low-grade inflammation. We evaluated a sample of 526 white patients with stable CHD who were enrolled in the Heart and Soul Study. Based on previous reports, we hypothesized that GR gene haplotype 3 would be associated with HF and that this association would be at least partly mediated by low-grade inflammation (CRP).

Participants and Methods

Participants
Details regarding our recruitment procedures have been published previously (10, 11). We used administrative databases to identify outpatients with documented coronary disease at two Veterans Affairs medical centers (San Francisco Veterans Affairs Medical Center and the Veterans Affairs Palo Alto Health Care System, Palo Alto CA), one university medical center (University of California, San Francisco), and nine public health clinics in the Community Health Network of San Francisco. Patients were eligible to participate if they had at least one of the following: a history of myocardial infarction, angiographic evidence of 50% or greater stenosis in one or more coronary vessels, prior evidence of exercise-induced ischemia by treadmill or nuclear testing, or a history of coronary revascularization. A total of 1024 participants enrolled and completed a day-long study appointment at the San Francisco Veterans Affairs Medical Center.

Two (N363S and ER 22/23) of the four polymorphisms do not occur in Asians (12, 13). Therefore, to minimize confounding due to population stratification (14, 15), we examined genotypes only in white patients, the largest race/ethnic group in the Heart and Soul study (n = 595). Our protocol was approved by the appropriate institutional review boards. After complete description of the study to the subjects, written informed consent was obtained.

Genotyping
Polymorphism-spanning fragments were amplified by the PCR and genotyped by template-directed dye-terminator incorporation assay with fluorescence polarization detection, using the AcyclolPrime-FP II kit (PerkinElmer, Norwalk, CT) per the manufacturer’s instructions. Plates were read on the EnVision fluorescence polarization plate reader (PerkinElmer) and genotypes scored with software (Excel macro) provided by PerkinElmer. Standard PCR conditions were: 5 μl reaction in 384-well plates with 2.4 ng dried genomic DNA, 0.12–0.24 μM each primer, 0.1–0.2 U Platinum Taq (Invitrogen, Carlsbad, CA), 0.05 mmol/liter deoxyribonucleotide triphosphates, and 2.5–3.5 mmol/liter MgCl2. Cycling conditions were 95°C for 2 min; 45 cycles of 92°C for 10 sec, 58°C for 20 sec, 68°C for 30 sec, followed by 68°C for 10 min. All plates contained positive and negative controls. Genotyping was performed by investigators blinded to clinical status.

The four polymorphisms we examined (ER22/23EK = rs6190; BclI = rs41423247; N363S = rs6195, 9β = rs 6198) are common variants of the glucocorticoid receptor gene (NR3C1) that have all been associated with changes in glucocorticoid sensitivity (5, 16). Figure 1 schematically depicts the GR gene, the location of the four investigated polymorphisms, and their specific nucleotide variations.
Individual haplotype assignments for the four polymorphisms were estimated using PHASE (17). Only haplotypes with a frequency greater than 1% were included in the analyses. Linkage disequilibrium among the four variants was expressed as D’ and r² using Haploview (Massachusetts Institute of Technology/Harvard Broad Institute, Cambridge, MA). For each haplotype, three combinations were distinguished as carrying no, one, or two copies of the haplotype as in previous studies (8, 18).

CRP

Participants were instructed to fast for 12 h (except for medication, which they were able to take with water) and not to smoke for 5 h before their study appointment. Plasma and serum samples were stored at −70°C for measurement of CRP. The laboratory technicians who assayed the inflammatory markers were blinded to the results of genotyping and HF. We used the Integra high-sensitivity assay (Roche, Indianapolis, IN) or (owing to a change in the laboratory) the Extended Range assay (Beckman, Palo Alto, CA) to measure CRP as described previously (19). Results from these two assays were highly correlated (r = 0.99 in 185 participants). The Roche Integra high-sensitivity CRP assay has an interassay coefficient of variation of 3.2%, and the lowest detectable measurement of this assay is 0.25 mg/liter. The Beckman Extended Range high-sensitivity CRP assay has an interassay coefficient of variation of less than 6.7%, an intraassay coefficient of variation is 6.9–7.8%. The interassay coefficient of variation is 6.5–9.6%, and the lowest detectable measurement of this assay is 0.25 mg/liter. The interassay coefficient of variation of the CRP is 3.2%, and the lowest detectable measurement of this assay is 0.25 mg/liter. The Beckman Extended Range high-sensitivity CRP assay has an interassay coefficient of variation of less than 6.7%, an intraassay coefficient of variation of less than 6.2%, and a reportable range of 0.20–1140 mg/liter.

IL-6

IL-6 is a lymphokine produced by T cells, fibroblasts, macrophages, and other cells. One of its main functions is to stimulate synthesis of plasma proteins involved in acute phase responses. We used the Quantikine HS IL-6 Immunoassay (R&D Systems, Minneapolis, MN) to determine the concentration of IL-6 from EDTA plasma. The interassay coefficient of variation is 6.5–9.6%, and the intraassay coefficient of variation is 6.9–7.8%.

Twenty-four-hour urinary cortisol

Details regarding collecting 24-h urinary cortisol have been published previously (20). In brief, patients were instructed to collect all urine for 24 h between the end of their study appointment and the time when a researcher visited their house the next day. Research personnel arrived at patient homes exactly 24 h after their appointment to ensure accurately timed specimens and enhance compliance with the protocol. If subjects were unable to collect all urine for any reason or had urinary incontinence, their samples were deemed inadequate and no urinary cortisol data were recorded for these subjects.

Diastolic and systolic function

At baseline, all participants underwent resting echocardiography using an Acuson Sequoia ultrasound System (Mountain View, CA). We obtained standard two-dimensional views and performed planimetry with a computerized digitization system to determine left ventricular ejection fraction. We categorized participants as having diastolic dysfunction if their mitral inflow ratio of peak early-to-late diastolic filling velocity was more than 0.75 and if the velocity time integral in their pulmonary vein was greater during diastole than during systole (21). Systolic dysfunction was defined as a left ventricular ejection fraction less than 50%.

HF

Baseline

Self-reported heart failure was determined by asking participants, “Has a doctor or nurse had ever told you that you have congestive heart failure?”

Follow-up

We conducted annual telephone follow-up interviews with participants (or their proxy) to ask about hospitalizations. If any participant or proxy reported a hospitalization, we retrieved the medical records, and they were reviewed by two independent and blinded physician adjudicators. If both adjudicators agreed on the outcome classification, it was binding. If there was disagreement, they conferred, reconsidered their classification, and requested consultation from a third, blinded adjudicator as necessary. The outcome of interest, HF hospitalization, was defined as hospitalization for a clinical syndrome with more than two of the following: paroxysmal nocturnal dyspnea, orthopnea, increased jugular venous pressure, pulmonary rales, third heart sound, cardiomegaly on chest x-ray, or pulmonary edema on chest x-ray, as determined by the adjudicators from reviewing medical records. These clinical signs and symptoms must have represented a clear change from the normal clinical state of the patient and been accompanied by either failing cardiac output or peripheral or pulmonary edema. In addition to all the hospital records, supportive documentation of decreased cardiac index, increasing pulmonary capillary wedge pressure, decreasing oxygen saturation, and end-organ hypoperfusion, if available, were included in adjudication (11).

Other variables

Age, sex, smoking, and medical history were determined by self-report. Body mass index was calculated as weight in kilograms divided by the square of height in meters. The waist circumference was measured midway between the lower rib margin and the iliac crest. The hip circumference was measured at the level of the greater trochanters. The waist to hip ratio (WHR) was calculated as the waist circumference divided by the hip circumference. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. Medications were categorized using Epocrates Rx (San Mateo, CA).

Statistical analysis

The goals of this study were to examine the association of GR gene haplotype 3 with self-reported HF, ventricular dysfunction, and subsequent HF hospitalization and evaluate the extent to which the association between haplotype 3 and HF is explained by low-grade inflammation (CRP). Because the proportion of participants with the combined HF outcome (systolic dysfunction, self-reported HF, or HF hospitalization) was identical in patients with no or one copy of haplotype 3, we combined these into one group for the analyses.

Differences in baseline characteristics between patients with two copies of GR gene haplotype 3 and those who had no or one copy were compared using univariate ANOVA for continuous variables and χ² tests for dichotomous variables. CRP and IL-6 were log transformed because they did not have a normal distribution. We used χ² tests to examine the distribution of established CRP cutoff categories indicating low (≤3 mg/liters).
TABLE 1. Characteristics of 526 white Heart and Soul study participants according to haplotype 3 of the glucocorticoid receptor gene

<table>
<thead>
<tr>
<th>Demographic</th>
<th>0 copies (n = 355)</th>
<th>1 copy (n = 154)</th>
<th>2 copies (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.6 ± 10.9</td>
<td>67.9 ± 11.0</td>
<td>65.2 ± 12.7</td>
<td>0.62</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>306 (86)</td>
<td>126 (82)</td>
<td>14 (82)</td>
<td>0.43</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.6 ± 4.8</td>
<td>28.1 ± 5.0</td>
<td>30.8 ± 11.1</td>
<td>0.10</td>
</tr>
<tr>
<td>WHR</td>
<td>0.97 ± 0.08</td>
<td>0.95 ± 0.08</td>
<td>0.99 ± 0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td>48 (14)</td>
<td>34 (22)</td>
<td>5 (29)</td>
<td>0.02</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>232 (65)</td>
<td>104 (68)</td>
<td>8 (47)</td>
<td>0.24</td>
</tr>
<tr>
<td>MI, n (%)</td>
<td>199 (56)</td>
<td>86 (56)</td>
<td>8 (47)</td>
<td>0.75</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>49 (14)</td>
<td>18 (12)</td>
<td>1 (6)</td>
<td>0.55</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>72 (20)</td>
<td>34 (22)</td>
<td>3 (18)</td>
<td>0.86</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor, n (%)</td>
<td>174 (49)</td>
<td>91 (59)</td>
<td>8 (47)</td>
<td>0.10</td>
</tr>
<tr>
<td>β-Blocker, n (%)</td>
<td>199 (56)</td>
<td>96 (62)</td>
<td>9 (53)</td>
<td>0.39</td>
</tr>
<tr>
<td>Statins, n (%)</td>
<td>234 (66)</td>
<td>102 (66)</td>
<td>9 (53)</td>
<td>0.54</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>119 ± 42</td>
<td>117 ± 42</td>
<td>114 ± 24</td>
<td>0.86</td>
</tr>
<tr>
<td>Glycosylated Hgb (%)</td>
<td>5.9 ± 1.1</td>
<td>5.8 ± 1.1</td>
<td>5.8 ± 1.0</td>
<td>0.70</td>
</tr>
<tr>
<td>HDL (mg/dl)</td>
<td>45 ± 14</td>
<td>47 ± 16</td>
<td>46 ± 17</td>
<td>0.31</td>
</tr>
<tr>
<td>Log CRP (mg/liter)</td>
<td>0.6 ± 1.3</td>
<td>0.8 ± 1.2</td>
<td>1.6 ± 1.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Log IL-6 (mg/liter)</td>
<td>0.97 ± 0.68</td>
<td>0.97 ± 0.75</td>
<td>1.19 ± 0.99</td>
<td>0.44</td>
</tr>
<tr>
<td>24-h cortisol (µg/d)</td>
<td>40.5 ± 20.9</td>
<td>39.6 ± 22.1</td>
<td>49.0 ± 27.2</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Mean and SD are shown except where indicated. BMI, Body mass index; MI, myocardial infarction; ACE, angiotensin-converting enzyme; HDL, high-density lipoprotein; Hgb, hemoglobin.

Results

Among the 595 white participants, successful genotyping for all four polymorphisms was achieved (and haplotypes estimated) in 526 participants. Reasons for missing genotypes included nonavailability of DNA and genotyping errors. The genotype distributions for the four polymorphisms did not deviate significantly from Hardy-Weinberg-Equilibrium (all P > 0.4).

Haplotypes

The observed haplotype structure (Fig. 1) corresponded to those previously reported (5, 8, 9, 23–25). The haplotype with the highest frequency (haplotype 1, 41.4%) consisted of the major alleles of the four single-nucleotide polymorphisms (SNPs). Haplotype 2 (34.8%) was characterized by the minor G allele of the BclI polymorphism. Three of the four polymorphisms were found to be mutually exclusive; only the minor codon 23 A allele was always present in combination with the minor 9β G allele (haplotype 4, 3.8%). However, the G allele of the exon 9β SNP was also observed independently from ER22/23EK (haplotype 3, 17.9%). The minor A allele of the N363S SNP was present in haplotype 5 (2.1%).
Haplotype 3 was associated with numerically but non-significantly higher 24-h urinary cortisol levels (Table 1, Cohen’s $d = 0.35$ homozygous carriers compared with noncarriers) and IL-6 values ($d = 0.26$).

**HF**

Among homozygous haplotype 3 carriers, eight of 17 (47%) had self-reported HF compared with 82 of 509 (16%) of those who had no or one copy of haplotype 3 (Fig. 3 and Table 2). Furthermore, four of 17 of homozygotes (24%) presented with systolic dysfunction according to echocardiography compared with 52 of 509 (10%) of those not homozygous for haplotype 3 (Fig. 3 and Table 2). We found no differences in diastolic dysfunction by haplotype 3 [four of 17 (24%) vs. 85 of 509 (17%), Table 2].

During a mean follow-up of 6 yr, 78 of 526 participants (14.8%) required hospital admission due to HF. The incidence of HF hospitalization during 6 yr of follow-up was 35% (six of 17) in participants homozygous for haplotype 3, compared with 14% (72 of 509) in those who were not homozygous for haplotype 3 (Fig. 3 and Table 2). These differences persisted after adjusting for potentially confounding variables (Table 2). We did not find any evidence that the association of GR haplotype 3 with any HF outcome varied by age, sex, smoking, body mass index, or CRP (all $P$ values for interaction $>0.10$).

When outcomes were combined, participants homozygous for haplotype 3 had a 4-fold increased odds of developing any HF outcome (self-reported heart failure, ventricular dysfunction, hospitalization for heart failure) (Fig. 3 and Table 2).

Supplemental Table 1 depicts the results separately for each group (two copies of haplotype 3 vs. one copy, two copies vs. no copies; one copy vs. no copies).

**Role of CRP**

After adjustment for higher CRP levels among patients with two copies of the haplotype 3 allele, the association of haplotype 3 with self-reported HF, systolic dysfunction, and subsequent hospitalization for HF was partly attenuated (Table 2).

**Discussion**

In a prospective cohort study of white patients with stable CHD, we found that having two copies of the GR gene haplotype 3 was associated with self-reported HF, systolic dysfunction, and subsequent hospitalization for HF during 6 yr of follow-up. After adjusting for age, sex, smoking, and body mass index, participants with two copies of haplotype 3 were three to four times more likely to have HF than those with no or one copy. The association between GR haplotype 3 and HF appeared to be at least partly explained by greater low-grade inflammation in patients with two copies of haplotype 3.

Previous studies found that GR haplotype 3 increases the risk of CHD, but the association between GR haplotype 3 and HF has not been previously evaluated. The Rotterdam study demonstrated an increased risk of CHD and myocardial infarction for GR haplotype 3 homozygotes in a population-based sample (8). Another recent study showed that GR haplotype 3 is associated with CHD in men with familial hypercholesterolemia (9). Our findings add to this growing literature by demonstrating that the risk of HF associated with being homozygous for GR haplotype 3 is of a comparable magnitude with other established cardiovascular risk factors such as smoking, hypertension, and diabetes (26).

Furthermore, we replicated findings from the Rotterdam study of increased CRP in homozygotes of GR haplotype 3. Thus, it seems likely that the mechanism by which GR haplotype 3 increases risk for CHD and HF includes inflammatory processes. Indeed, in our study the association between GR haplotype 3 and HF was markedly reduced after adjustment for CRP.
The 9β G allele, present in haplotype 3, is a plausible candidate for increased inflammatory activity because it leads to relative glucocorticoid resistance, i.e., reduced glucocorticoid sensitivity. This has been shown by functional studies that revealed a stabilizing effect of this variant on GR studies that revealed a stabilizing effect of this variant on glucocorticoid sensitivity. This has been shown by functional activity associated with relative glucocorticoid resistance. Thus, we cannot exclude that our results may not be applicable to other populations. It is noteworthy that one of the earlier studies found an association of haplotype 3 with CHD in men but not women (9). Furthermore, a sex-specific effect of the 9β A/G polymorphism was found in basal cortisol values (31) and the cortisol response to psychosocial stress (24). Again, in men, but not women, carriers of the 9β A/G polymorphism displayed greater basal cortisol and greater cortisol responses to stress compared with noncarriers. It appears that the 9β A/G polymorphism has stronger effects in men compared with women. Future studies should systematically explore sex effects of the 9β A/G polymorphism. Sensitivity to glucocorticoid differs not only among individuals but also in different tissues (muscle, fat, liver, brain, etc.). Therefore, a limitation of our study is that we did not perform ex vivo studies examining differences in glucocorticoid sensitivity among several tissues.

In summary, we found that a common haplotype of the GR gene, which includes the minor allele of the 9β A/G polymorphism (haplotype 3), is associated with HF. The association between GR haplotype 3 and HF was partly mediated by CRP. Thus, variation in the glucocorticoid receptor gene may be involved in the pathogenesis of HF, presumably involving inflammatory processes.

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**Table 2. Risk of self-reported HF, systolic dysfunction, and subsequent hospitalization for HF associated with having two copies of haplotype 3**

<table>
<thead>
<tr>
<th>Model</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>P value</th>
<th>HR (95% CI)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.6 (1.7–12.4)</td>
<td>0.002</td>
<td>2.9 (0.9–9.4)</td>
<td>0.07</td>
<td>3.1 (1.4–7.2)</td>
<td>0.007</td>
<td>4.3 (1.6–11.9)</td>
<td>0.005</td>
</tr>
<tr>
<td>2</td>
<td>4.6 (1.7–12.3)</td>
<td>0.002</td>
<td>3.1 (0.9–9.9)</td>
<td>0.06</td>
<td>3.6 (1.5–8.2)</td>
<td>0.003</td>
<td>4.6 (1.6–12.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>3</td>
<td>4.3 (1.6–11.7)</td>
<td>0.004</td>
<td>3.1 (1.0–10.1)</td>
<td>0.06</td>
<td>3.3 (1.4–7.7)</td>
<td>0.006</td>
<td>4.4 (1.6–12.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>4</td>
<td>4.2 (1.5–11.3)</td>
<td>0.005</td>
<td>3.0 (0.9–9.9)</td>
<td>0.07</td>
<td>3.0 (1.3–7.0)</td>
<td>0.01</td>
<td>4.0 (1.4–11.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>5</td>
<td>3.3 (1.1–9.3)</td>
<td>0.03</td>
<td>2.6 (0.7–9.4)</td>
<td>0.13</td>
<td>2.1 (0.8–5.5)</td>
<td>0.13</td>
<td>3.3 (1.1–9.8)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Model 1: unadjusted; model 2: age and sex adjusted; model 3: body mass index, age, and sex adjusted; model 4: smoking status, body mass index, age, and sex adjusted; model 5: CRP, smoking status, body mass index, age, and sex adjusted. OR, Odds ratio; CI, confidence interval.
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