Original Article

Associations between Inflammatory Markers and Subclinical Atherosclerosis in Middle-aged White, Japanese-American and Japanese Men: The ERA-JUMP Study

Shin-ya Nagasawa1, 2, Takayoshi Ohkubo2, 3, Kamal Masaki4, Emma Barinas-Mitchell5, Katsuyuki Miura2, 6, Todd B. Seto4, Aiman El-Saed5, Takashi Kadowaki2, Bradley J. Wilcox4, Daniel Edmundowicz7, Aya Kadota2, 6, 8, Rhobert W. Evans5, Sayaka Kadowaki2, Akira Fujiyoshi2, Takashi Hisamatsu2, 6, 9, Marianne H. Bertolet5, Tomonori Okamura10, Yasuyuki Nakamura11, Lewis H. Kuller5, Hirotsugu Ueshima2, 6, Akira Sekikawa5, for the ERA-JUMP (Electron-Beam Tomography, Risk Factor Assessment Among Japanese and U.S. Men in the Post-World War II Birth Cohort) Study Group

1 Department of Epidemiology and Public Health, Kanazawa Medical University, Uchinada, Ishikawa, Japan
2 Department of Public Health, Shiga University of Medical Science, Otsu, Shiga, Japan
3 Department of Hygiene and Public Health, Teikyo University School of Medicine, Tokyo, Japan
4 Department of Geriatric Medicine, John A. Burns School of Medicine, University of Hawaii, and Kuakini Medical Center, Honolulu, HI, USA
5 Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA
6 Center for Epidemiologic Research in Asia, Shiga University of Medical Science, Otsu, Shiga, Japan
7 Department of Medicine, Temple University, Philadelphia, PA, USA
8 Department of School Nursing and Health Education, Osaka Kyoiku University, Osaka, Japan
9 Department of Cardiovascular and Respiratory Medicine, Shiga University of Medical Science, Otsu, Shiga, Japan
10 Department of Preventive Medicine and Public Health, School of Medicine, Keio University, Tokyo, Japan
11 Department of Cardiovascular Epidemiology, Kyoto Women's University, Kyoto, Japan

Aim: To examine whether the inflammatory markers C-reactive protein (CRP) and fibrinogen are associated with biomarkers of atherosclerosis [carotid intima-media thickness (IMT) and coronary artery calcification (CAC)] in the general male population, including Asians.

Methods: Population-based samples of 310 Japanese, 293 Japanese-American and 297 white men 40-49 years of age without clinical cardiovascular disease underwent measurement of IMT, CAC and the CRP and fibrinogen levels as well as other conventional risk factors using standardized methods. Statistical associations between the variables were evaluated using multiple linear or logistic regression models.

Results: The Japanese group had significantly lower levels of inflammatory markers and subclinical atherosclerosis than the Japanese-American and white groups (P-values all < 0.001). The mean level of CRP was 0.66 vs. 1.11 and 1.47 mg/L, while that of fibrinogen was 255.0 vs. 313.0 and 291.5 mg/dl, respectively. In addition, the mean carotid IMT was 0.61 vs. 0.73 and 0.68 mm, while the mean prevalence of CAC was 11.6% vs. 32.1% and 26.3%, respectively. Body mass index (BMI) showed significant positive associations with both the CRP and fibrinogen levels. Although CRP showed a significant positive association with IMT in the Japanese men, this association became non-significant following adjustment for traditional risk factors or BMI. In all three populations, CRP was not found to be significantly associated with the prevalence of CAC. Similarly, fibrinogen did not exhibit a significant association with either IMT or the prevalence of CAC.

Conclusions: The associations between inflammatory markers and subclinical atherosclerosis may merely reflect the strong associations between BMI and the levels of inflammatory markers and incidence of subclinical atherosclerosis in both Eastern and Western populations.


Key words: Obesity, C-reactive protein, Fibrinogen, Intima-media thickness, Coronary artery calcification
Introduction

It is well established that inflammation plays a pivotal role in atherogenesis, with inflammatory markers, such as C-reactive protein (CRP) and fibrinogen, having been shown to be useful for detecting individuals with higher cardiovascular risks\textsuperscript{1-7}. The presence of subclinical atherosclerosis, characterized by an increased intima-media thickness (IMT) or coronary artery calcification (CAC), has been reported to independently predict future cardiovascular events\textsuperscript{8-10}. However, evidence for the relationships between inflammatory markers and subclinical atherosclerosis is inconsistent. Although two meta-analyses showed positive associations between IMT and CRP and/or fibrinogen\textsuperscript{11, 12}, other studies have not confirmed this association after adjusting for traditional cardiovascular risk factors, including measurements of adiposity\textsuperscript{13-15}. On the other hand, a small number of studies have reported a relationship between CAC and inflammatory markers. However, the majority of these studies showed no significant relationships after adjusting for traditional risk factors, particularly measurements of adiposity\textsuperscript{12, 16-18}, although two studies showed that fibrinogen, but not CRP, is weakly and independently associated with CAC\textsuperscript{19, 20}.

It also remains to be elucidated whether the effects of inflammatory markers on atherosclerosis differ in various populations with different genetic or environmental backgrounds. To our knowledge, no previous studies have examined the relationship between inflammatory markers and CAC in Asian general populations living in Asia, including Japanese subjects. We previously reported the levels of subclinical atherosclerosis (i.e., CAC and IMT) in population-based samples of 868 men 40-49 years of age (281 Japanese living in Japan and 281 Japanese Americans and 306 whites living in the USA) in the Electron-Beam Tomography, Risk Factor Assessment Among Japanese and U.S. Men in the Post-World War II Birth Cohort (ERA-JUMP) Study\textsuperscript{21}. Using data collected in that study, we examined whether the inflammatory markers CRP and fibrinogen are associated with subclinical atherosclerosis evaluated using CAC and IMT in three general middle-aged populations:

Methods

Design

We analyzed data obtained from the ERA-JUMP study, a population-based multi-center cross-sectional study of 904 men 40 to 49 years of age. The study employed highly standardized methods to measure subclinical atherosclerosis and all other variables.

Study Participants

The details of the study population have been described previously\textsuperscript{21, 22}. Between 2002 to 2006, 926 men 40 to 49 years of age were selected randomly for enrollment. The study group included 313 Japanese men from Kusatsu, Shiga, Japan, 310 white men from Allegheny County, Pennsylvania and 303 Japanese-American men from a representative sample of offspring of fathers who participated in the Honolulu Heart Program, Honolulu, Hawaii\textsuperscript{23}. The offspring were third- or fourth-generation Japanese Americans without ethnic admixture. At baseline, all participants were without clinical cardiovascular disease, type 1 diabetes or other severe diseases. We excluded 27 participants with missing data, leaving a final study group that included 310 Japanese, 293 Japanese-American and 297 white men. Informed consent was obtained from all participants, and the study protocol was approved by the Institutional Review Boards of Shiga University of Medical Science, the University of Pittsburgh and Kuakini Medical Center.

Data Collection

Body mass index (BMI) and blood pressure (BP) were measured using standardized methods, as previously described\textsuperscript{21, 22}. The fasting glucose and serum lipid levels, including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), were also determined as previously described\textsuperscript{21, 22}. Diabetes mellitus was defined as the use of anti-diabetic medication(s) or a fasting glucose level of $\geq 7.0$ mmol/L (126 mg/dL). Hypertension was defined as the use of anti-hypertensive medication(s) or a systolic/diastolic BP of $\geq 140/90$ mmHg. The CRP level was determined using a calorimetric competitive enzyme-linked immunosorbent assay, and the fibrinogen level was measured using an automated clot rate assay (Diagnostic Stago, Parsippany, NJ, USA). The serum samples were stored at $-80^\circ$C and shipped on dry ice to the University of Pittsburgh for testing. The coeffi-
Intima-Media Thickness of the Carotid Arteries

The scanning procedures have been described elsewhere\textsuperscript{21, 22}. Before the study began, sonographers at all centers received training for carotid scanning provided by the Ultrasound Research Laboratory, University of Pittsburgh. Toshiba 140A scanners equipped with a 7.5-MHz linear array imaging probe were used in Japan and Pittsburgh, while a Siemens Acuson Cypress scanner was used in Hawaii. The sonographers scanned the right and left common carotid arteries, carotid bulbs and internal carotid arteries. For the common carotid artery segment, both the near and far walls were examined 1-cm proximal to the bulb. For the bulb and internal carotid artery areas, only the far walls were examined. The scans were recorded on videotape and sent to a central laboratory for scoring. Trained readers digitized the best image for scoring and subsequently used the automated software program to measure the IMT values over 1-cm segments of the near and far walls of the common carotid artery and far walls of the carotid bulb and internal carotid artery on both sides. The measurements obtained from each location were then averaged to determine the mean IMT. The readers were blinded to the characteristics of the participants and the study centers. The correlation coefficients of the mean IMT between the sonographers and between readers were 0.96 and 0.99, respectively\textsuperscript{24}.

### Coronary Calcium Score (CCS)

Scanning was performed at all three centers according to a standardized protocol using a GE-Imatron C150 EBT scanner (GE Medical Systems, San Francisco, CA, USA). A total of 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart. The images were recorded during maximal breath holding using ECG-guided triggering of 100-m second exposures during the same phase of the cardiac cycle. CAC was considered to be present for three contiguous pixels (area=1 mm\textsuperscript{2}) \(\geq 130\) Hounsfield Units. One trained reader at the Cardiovascular Institute, University of Pittsburgh read the images using a Digital-Imaging-and-Communications-in-Medicine workstation and software package (AccuImage Diagnostic Corporation, San Francisco, CA, USA) that calculated the coronary calcium score (CCS) according to the Agatston scoring method\textsuperscript{25}. The prevalence of CAC was defined as a CCS of \(\geq 10\). We selected the cutoff point of 10 for the following reasons: (1) its clinical significance\textsuperscript{10}, (2) the possibility that a score of 0-10 may be due to imaging artifacts from spurious noise\textsuperscript{26} and (3) our intention to keep the cutoff point consistent with our previous studies\textsuperscript{9, 22}. The reader was blinded to the characteristics of the participants and the study centers. The intra-examiner reproducibility of non-zero CCS had an intra-class correlation of 0.98.

### Statistical Analysis

The levels of risk factors for atherosclerosis were compared between the three populations using an analysis of variance for continuous variables and the \(\chi^2\)-test for proportions. Multiple linear regression analyses were used to calculate the standardized regression coefficients for the associations between inflammatory markers and IMT in each population and the total study group. The associations between the inflammatory markers with the prevalence of CAC in each population and the total study group were examined using multiple logistic regression models. The odds ratios and 95% confidence intervals for the prevalence of CAC with a 1-SD increment in the levels of the inflammatory markers were then calculated.

In both multivariate analyses, model 2 was adjusted for age, systolic blood pressure, LDL-cholesterol, HDL-cholesterol, fasting glucose, smoking and alcohol consumption, while model 3 was adjusted for age and BMI. Logarithmic values of CRP were used in both regression models to normalize the distribution.

In order to examine potential confounding effects, we performed sensitivity analyses restricted to non-smokers, non-drinkers, non-hypertensives, non-diabetics, subjects without obesity and those not taking hyperlipidemia medications. These factors were selected because they may influence the levels of inflammatory markers. A \(P\) value of <0.05 was considered to be significant. All statistical tests were two-sided. The IBM SPSS statistics 19 software program (IBM Inc., NY, USA) was used for all statistical analyses.

### Results

The baseline characteristics of the participants in the three populations are shown in Table 1. The Japanese men exhibited the highest prevalence of current cigarette smoking and alcohol drinking among the three populations. On the other hand, the Japanese
men were the least obese. The Japanese men also had a favorable profile, with lower levels of HDL-C, inflammatory markers (CRP and fibrinogen) and atherosclerosis.

The multiple linear regression analysis showed a significant and positive association between the CRP levels and mean IMT after adjusting for age in the Japanese men and the total study group (Model 1 in Table 2). However, following additional adjustment for traditional risk factors or BMI, the positive associations were diminished and became non-significant (Models 2 and 3 in Table 2). Non-significant but positive trends in the American men and the total study group also disappeared after additional adjustment for traditional risk factors or BMI. Although there was a significant and positive association between the fibrinogen level and IMT in the total study group, this association was attenuated and became non-significant after additional adjustment for traditional risk factors or BMI.
were not independent of traditional risk factors or BMI in three populations of men with genetically or environmentally different backgrounds. As we found that BMI was associated strongly with both CRP and fibrinogen in all three populations, the relationships between inflammatory markers and subclinical atherosclerosis may reflect the strong associations between BMI and inflammatory markers.

The association between inflammation and atherosclerosis is well established. The CRP level also independently predicts future cardiovascular events, as evidenced by its incorporation into the new clinical guidelines of the American Heart Association/American College of Cardiology. However, the associations between measurements of subclinical atherosclerosis (i.e., CAC and IMT) and CRP or other markers of inflammation are not well established. The results of previous studies reporting associations between inflammatory markers and subclinical atherosclerosis have been controversial. Although some studies have shown positive associations between inflammatory markers and IMT, the majority of these studies were based on univariate analyses or analyses adjusted for age and gender without adjustment for other traditional risk factors. A few studies using multivariate analyses have demonstrated significant posi-

Table 3. Associations between lnCRP or fibrinogen and coronary artery calcification (coronary calcium score ≥ 10)

<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>Japanese-American</th>
<th>US white</th>
<th>Total*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI) of CCS ≥ 10 for ln CRP</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.29 (0.90-1.85)</td>
<td>0.94 (0.73-1.21)</td>
<td>1.17 (0.88-1.56)</td>
<td>1.09 (0.92-1.29)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.23 (0.82-1.84)</td>
<td>0.88 (0.66-1.19)</td>
<td>0.92 (0.65-1.29)</td>
<td>0.96 (0.80-1.15)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.10 (0.74-1.64)</td>
<td>0.84 (0.63-1.11)</td>
<td>0.86 (0.61-1.20)</td>
<td>0.90 (0.74-1.09)</td>
</tr>
<tr>
<td>Odds ratio (95% CI) of CCS ≥ 10 for fibrinogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.29 (0.89-1.89)</td>
<td>1.08 (0.83-1.42)</td>
<td>1.27 (0.96-1.68)</td>
<td>1.21 (1.02-1.43)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.17 (0.75-1.82)</td>
<td>1.10 (0.82-1.47)</td>
<td>1.24 (0.93-1.65)</td>
<td>1.17 (0.98-1.39)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.20 (0.80-1.78)</td>
<td>1.04 (0.79-1.36)</td>
<td>1.12 (0.84-1.49)</td>
<td>1.11 (0.93-1.32)</td>
</tr>
</tbody>
</table>

The odds ratios were calculated for 1SD higher of lnCRP or fibrinogen, using the logistic regression analysis. CI, confidence interval.

Table 4. Correlation coefficients for BMI with CRP or fibrinogen

<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>Japanese-American</th>
<th>US white</th>
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</thead>
<tbody>
<tr>
<td>CRP</td>
<td>0.28</td>
<td>0.43</td>
<td>0.41</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.12</td>
<td>0.21</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Correlation coefficient calculated by Spearman's rank method.
tive associations between inflammatory markers and IMT. For example, Wang et al. studied an offspring cohort of the Framingham Heart Study and showed a graded association between CRP and IMT independent of traditional risk factors, including BMI, in women but not men\(^{13}\). Elias-Smale et al. also showed a graded association between CRP and IMT independent of traditional risk factors, including BMI, in elderly men and women in the Rotterdam Study\(^{30}\).

However, to our knowledge, no previous population-based studies in middle-aged men have reported significant positive associations between inflammatory markers and IMT after adjusting for measurements of obesity.

Although a smaller number of studies have examined associations with CAC versus IMT, the majority of these studies showed the associations between inflammatory markers and CAC to be weak, and significant associations, if any, disappeared after adjusting for traditional risk factors, including BMI or the use of medications, such as estrogen or statins\(^{12, 30, 31}\). Only two community-based studies have shown that the inflammatory marker fibrinogen is positively associated with CAC independent of BMI\(^{19}\). However, after adjusting for all traditional risk factors, including BMI, significant associations remained in women only, not in men\(^{19}\). A multi-ethnic study of atherosclerosis (MESA) showed that fibrinogen, but not CRP, was weakly associated with the prevalence of CAC, although in the participants with detectable CAC, neither inflammatory marker was significantly associated with the burden of CAC following adjustment for traditional risk factors\(^{20}\). Some studies have reported that measurements of obesity are important factors among traditional risk factors for the associations observed with IMT or CCS\(^{16, 18, 31, 32}\). However, the relationship of obesity to clinical cardiovascular disease is relatively weak compared to that associated with subclinical atherosclerosis.

In the present study, Japanese men had significantly lower levels of inflammatory markers and BMI and included a significantly higher proportion of cigarette smokers than the other two populations. These characteristics of Japanese men are consistent with the results of previous studies\(^{8, 33-35}\). In particular, the CRP levels in the Japanese population have been reported to be approximately two to three times lower than those measured in white Americans\(^{34}\). Similarly, the plasma fibrinogen levels in Japanese subjects are lower than those noted in Japanese-Americans\(^{34}\). Although it is known whether cigarette smoking is positively associated with the levels of inflammatory markers\(^{36, 37}\), the Japanese men in the present study included a higher proportion of cigarette smokers and exhibited lower levels of inflammatory markers. This discrepancy may be due in part to the lower prevalence of obesity among Japanese men, as there is epidemiological evidence that obesity is positively related to the levels of inflammatory markers\(^{33, 34}\). There is also physiological evidence that adipocytes are a source of IL-6 and that fat stimulates monocytes and macrophages to become activated and release cytokines\(^{38, 39}\).

Both CRP and fibrinogen are acute-phase proteins secreted from hepatocytes following the induction of cytokines secreted by macrophages, T cells and other immune cells\(^{5-7}\). The present study, as well as numerous other studies\(^{11-18}\), demonstrated that the associations between these inflammatory markers and subclinical atherosclerosis are usually weak. Although immune cells are activated in atherosclerotic lesions, the levels of CRP or fibrinogen may be very low in the early stage of atherosclerosis, whereas the increase is likely to be high in more advanced stages of atherosclerosis. Therefore, the CRP and fibrinogen levels may reflect the extent of the atherosclerotic burden and predict cardiovascular events, although based on the findings of our study, it is not clear whether CRP and/or fibrinogen have biological effects on atherosclerosis.

Some limitations of our study warrant consideration. The sample size was relatively small, as the study participants were limited to only men 40 to 49 years of age. Therefore, the generalizability of the present findings to different age groups or women may be limited. However, we focused on this specific gender and age group for important reasons, one of which was to reduce the effects of confounding due to age, although statistical adjustments for age were taken into account. The other limitation is the similarity in the total cholesterol and BP levels throughout the lifespan in middle-aged Japanese and white men, unlike that observed in older individuals or women\(^{22, 40}\). This characteristic allowed us to investigate the genetic effects of associations between other risk factors and atherosclerosis. In addition, the ultrasound machine used in Honolulu differed from that employed in Japan and Pittsburgh. However, we evaluated the between-machine differences for mean IMT and found no greater variation than that noted between the sonographers (data not shown). We therefore consider that variations in measurement due to differences in the machine to be relatively small, as most of the variation came from the sonographers and the readers. We accounted for reader variation by using the same reader. Because the present study was cross-sectional, it may have underestimated the long-term effects of
inflammatory markers on atherosclerosis. The present study was therefore observational and we cannot exclude the possibility of residual or unmeasured confounding factors.

The present findings suggest that the associations between inflammatory markers and subclinical atherosclerosis may merely reflect the strong associations between BMI and the levels of inflammatory markers and subclinical atherosclerosis. Further prospective studies are needed to confirm the findings of the present study.

Acknowledgement

We are deeply grateful to the valuable assistance of Dr. J. David Curb, of the University of Hawaii and Kuakini Medical Center, who was the Principal Investigator at the Hawaii site of this project, who died on January 8th, 2012.

Conflicts of Interest

The authors declare no conflicts of interest.

Sources of Funding

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19) Bielak LF, Klee GG, Sheedy PF, 2nd, Turner ST, Schwartz...


Supplemental Table 1.
Sensitivity analysis of the associations between lnCRP or fibrinogen and the mean carotid intima-media thickness (standardized regression coefficient)

<table>
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<th>Japanese</th>
<th>Japanese-American</th>
<th>US white</th>
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<tbody>
<tr>
<td></td>
<td>Coefficient</td>
<td>P value</td>
<td>(n)</td>
</tr>
<tr>
<td>lnCRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0.07</td>
<td>0.20</td>
<td>(310)</td>
</tr>
<tr>
<td>Non-drinker</td>
<td>-0.06</td>
<td>0.47</td>
<td>(158)</td>
</tr>
<tr>
<td>Non-hypertensive</td>
<td>0.05</td>
<td>0.58</td>
<td>(102)</td>
</tr>
<tr>
<td>Non-diabetic</td>
<td>0.00</td>
<td>0.95</td>
<td>(228)</td>
</tr>
<tr>
<td>Non-obese*</td>
<td>0.09</td>
<td>0.11</td>
<td>(291)</td>
</tr>
<tr>
<td>No medicine for hyperlipidemia**</td>
<td>0.07</td>
<td>0.20</td>
<td>(299)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>0.01</td>
<td>0.90</td>
<td>(310)</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>0.06</td>
<td>0.44</td>
<td>(158)</td>
</tr>
<tr>
<td>Non-drinker</td>
<td>0.06</td>
<td>0.52</td>
<td>(102)</td>
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<tr>
<td>Non-hypertensive</td>
<td>-0.05</td>
<td>0.43</td>
<td>(228)</td>
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<tr>
<td>Non-diabetic</td>
<td>0.02</td>
<td>0.80</td>
<td>(291)</td>
</tr>
<tr>
<td>Non-obese*</td>
<td>0.00</td>
<td>1.00</td>
<td>(299)</td>
</tr>
<tr>
<td>No medicine for hyperlipidemia**</td>
<td>0.01</td>
<td>0.93</td>
<td>(299)</td>
</tr>
</tbody>
</table>

Coefficient is standard regression coefficient in linear regression analyses. All models were adjusted for age and BMI.
*Non-obese was defined as participants whose BMI were under 30 kg/m².
**No medicine for hyperlipidemia was defined as participants without medicine for hyperlipidemia.

Supplemental Table 2.
Sensitivity analysis of the associations between lnCRP or fibrinogen and coronary artery calcification (coronary calcium score ≥ 10)

<table>
<thead>
<tr>
<th></th>
<th>Japanese</th>
<th>Japanese-American</th>
<th>US white</th>
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<tbody>
<tr>
<td>Odds ratio (95% CI) ∘ of CCS ≥ 10 for ln CRP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1.10 (0.74-1.64)</td>
<td>(310)</td>
<td>0.84 (0.63-1.11)</td>
</tr>
<tr>
<td>Non-drinker</td>
<td>1.20 (0.60-2.38)</td>
<td>(158)</td>
<td>0.85 (0.62-1.16)</td>
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<tr>
<td>Non-hypertensive</td>
<td>1.10 (0.56-2.17)</td>
<td>(102)</td>
<td>0.81 (0.55-1.19)</td>
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<tr>
<td>Non-diabetic</td>
<td>1.40 (0.88-2.21)</td>
<td>(228)</td>
<td>0.91 (0.64-1.29)</td>
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<tr>
<td>Non-obese*</td>
<td>1.13 (0.74-1.71)</td>
<td>(291)</td>
<td>0.86 (0.63-1.16)</td>
</tr>
<tr>
<td>No medicine for hyperlipidemia**</td>
<td>1.11</td>
<td>(0.74-1.67)</td>
<td>(299)</td>
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<tr>
<td>Odds ratio (95% CI) ∘ of CCS ≥ 10 for fibrinogen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>1.20 (0.80-1.78)</td>
<td>(310)</td>
<td>1.04 (0.79-1.36)</td>
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<td>Non-drinker</td>
<td>1.36 (0.75-2.47)</td>
<td>(158)</td>
<td>1.07 (0.79-1.45)</td>
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<td>Non-hypertensive</td>
<td>1.65 (0.86-3.15)</td>
<td>(102)</td>
<td>0.99 (0.68-1.43)</td>
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<tr>
<td>Non-diabetic</td>
<td>1.32 (0.84-2.08)</td>
<td>(228)</td>
<td>1.11 (0.79-1.56)</td>
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<tr>
<td>Non-obese*</td>
<td>1.23 (0.81-1.88)</td>
<td>(291)</td>
<td>0.92 (0.68-1.25)</td>
</tr>
<tr>
<td>No medicine for hyperlipidemia**</td>
<td>1.13</td>
<td>(0.75-1.70)</td>
<td>(299)</td>
</tr>
</tbody>
</table>

All models were adjusted for age and BMI.
The odds ratios were calculated for 1SD higher of lnCRP or fibrinogen, using the logistic regression analysis. CI, confidence interval.
*Non-obese was defined as participants whose BMI were under 30 kg/m².
**No medicine for hyperlipidemia was defined as participants without medicine for hyperlipidemia.