

Research Paper

Significant association between *Helicobacter pylori* infection and serum C-reactive protein

Yoshiko Ishida¹, Koji Suzuki², Kentaro Taki³, Toshimitsu Niwa³, Shozo Kurotsuchi⁴, Hisao Ando⁵, Akira Iwase⁶, Kazuko Nishio¹, Kenji Wakai¹, Yoshinori Ito¹, Nobuyuki Hamajima¹

1. Department of Preventive Medicine/Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, Nagoya, Japan
2. Department of Public Health, Fujita Health University School of Health Sciences
3. Department of Clinical Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan
4. Department of Obstetrics and Gynecology, Toyota Kosei Hospital, Toyota, Japan
5. Center for Reproductive Medicine, Toyohashi Municipal Hospital, Toyohashi, Japan.
6. Department of Obstetrics and Gynecology and Department of Maternal and Perinatal Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Correspondence to: Ms. Yoshiko Ishida, Department of Preventive Medicine / Biostatistics and Medical Decision Making, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550 Japan, TEL:+81-52-744-2132, FAX:+81-52-744-2971, e-mail: mitton@med.nagoya-u.ac.jp

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Background: *Helicobacter pylori* (*H. pylori*) infection in gastric mucosa may cause systemic inflammatory reaction. This study aimed to examine the association between the infection and serum high sensitivity C-reactive protein (hsCRP).

Methods: Subjects were comprised of three groups; 453 health checkup examinees from Yakumo town inhabitants in Hokkaido, Japan (YTI, 153 males and 300 females), 449 health checkup examinees (ENUH, 273 males and 176 females), and 255 female patients of an infertility clinic (PIC), Nagoya University Hospital. Twenty participants with hsCRP more than 1 mg/dl were excluded from the analysis. Those with hsCRP more than 0.1mg/dl were defined as high hsCRP individuals. *H. pylori* infection status was examined with a serum IgG antibody test.

Results: When the three groups were combined, the geometric mean of hsCRP concentration was significantly higher among the seropositives (0.047mg/dl) than among the seronegatives (0.035mg/dl); $p < 0.0001$ by a *t*-test. The percentage of high hsCRP individuals was also higher in the seropositives than in the seronegatives among any group; 23.3% and 20.1% in YTI, 22.0% and 16.0% in ENUH, and 32.7% and 18.7% in PIC, respectively, although the difference was significant only in ENUH. The summary odds ratio of the high hsCRP for the seropositives relative to the seronegatives was 1.38 (95% confidence interval, 1.01-1.89), when age, sex, body mass index, smoking, and subject group were adjusted by a logistic model.

Conclusions: In three groups, hsCRP was higher among the infected individuals. The summary odd ratio indicated that *H. pylori* infection could influence the serum hsCRP level.

Key words: C-reactive protein, *Helicobacter pylori* infection, inflammation, serum antibody, smoking

1. Introduction

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacterium that inhabits the stomach mucosa in more than 50% of Japanese adults, and further more from child to elderly in developing countries [1]. This bacterium can elicit lifelong inflammatory and immune responses with release of various bacterial and host-dependent cytotoxic substances [2], resulting in chronic gastritis, peptic ulcer, and gastric cancer [3].

Epidemiological studies have suggested that *H. pylori* infection might be involved in the pathogenesis of coronary heart disease [4-6]. The suspicion about *H. pylori* involvement in the pathological lesions is based on the following: (i) local inflammation can have systemic effects; (ii) *H. pylori* gastric infection is a chronic process that lasts for decades; and (iii) persistent infection induces chronic inflammatory and immune responses that can induce lesions both local and remote sites from the primary infection site [7, 8]. The

manifestation may be caused by potential mechanisms with direct or indirect actions [9]. The direct effects on the vascular wall could include endothelial injury and dysfunction through circulating endotoxins, smooth muscle proliferation, and local inflammation. The indirect effects are more often pronounced, including elevation of inflammatory mediators with proinflammatory, procoagulant, and atherogenic action, production of cross-reactive antibodies, as well as nutrient/vitamin malabsorption and metabolic disturbances such as overproduction of ammonia by the bacterium.

C-reactive protein (CRP) is an acute-phase reactant that originates from the liver. CRP has many clinical and biological effects and can be used for the diagnosis and follow-up of various inflammatory and traumatic processes [10]. There is strong evidence that CRP is a powerful predictor of incident cardiovascular events independent of levels of LDL cholesterol, all levels of the Framingham risk score, and the metabolic syndrome [11-19]. The basal CRP level in individuals free from acute illness is reproducible [20]. Its determinants reportedly include age and smoking [21], while substantial heritability (35-40%) was also reported in familial aggregation studies [22].

Examining the association between *H. pylori* infection and serum CRP levels seemed important to elucidate the relevance of *H. pylori* infection with coronary heart disease, especially atherosclerosis. The previous studies on the association, however, provided inconsistent results [23, 24]. This study aimed to examine the association in three different Japanese groups.

2. Subjects and methods

Study subjects

The first group (YTI) was 524 apparently healthy inhabitants, who attended a health check-up at Yakumo town, Hokkaido, Japan in 2006. Among them, 505 agreed to participate in the study with written informed consent. Lifestyle data collected with a self-administered questionnaire, as well as residual blood samples, were available from 459 subjects. Six subjects with serum high-sensitivity CRP (hsCRP) > 1 mg/dl were excluded from the analysis, because they might have an inflammatory disease. Remaining 453 subjects (153 males and 300 females) aged from 39 to 90 years were used for the present study.

The second group (ENUH) incorporated health checkup examinees at Department of Clinical Preventive Medicine, Nagoya University Hospital, who visited the department between June 2003 and February 2004. After the explanation of the study, 476 agreed lifestyle questionnaire and donation of 7ml peripheral

blood for research purposes. Among them, 453 subjects could determine the presence of *H. pylori* infection and measure the hsCRP. Those with hsCRP more than 1 mg/dl were also excluded, remaining 449 subjects (273 males and 176 females) aged from 17 to 89 years for the present study.

The third group (PIC) consisted of 264 female patients at an infertility clinic, who underwent treatment for infertility at Department of Obstetrics and Gynecology or Department of Maternal and Perinatal Medicine, Nagoya University Hospital between February 2001 and December 2004. Stored blood samples of the patients were available for research purposes. Those with hsCRP more than 1 mg/dl were similarly excluded, remaining 255 females aged from 21 to 48 years. All the three studies were approved by the Ethics Committee of Nagoya University School of Medicine (approval number 398, 52, 278 for YTI, ENUH and PIC, respectively).

Determination of serum H. pylori infection and hsCRP value

Sera were separated from blood samples immediately after blood draw. They were kept in a deep freezer at -80 °C until analyses. A commercially available direct ELISA kit ("E Plate 'Eiken' *H. pylori* Antibody" from Eiken Kagaku, Tokyo, Japan) was used to determine the presence of *H. pylori* infection. The seropositive was defined as *H. pylori* IgG antibody more than 10 U/ml. The hsCRP was measured with a particle-enhanced immunoturbidometric latex agglutination assay by SRL Co. Ltd., Tokyo. The assay could detect 0.004 mg/dl of CRP. Undetectable CRP values were recorded as 0.002 mg/dl. The staff in the laboratory was blinded to the seropositivity of *H. pylori* antibody.

Statistical analysis

The difference in geometric mean of serum hsCRP between *H. pylori* positive subjects and negative subjects was statistically tested with a *t*-test, because log_e-transformed hsCRP distributed symmetrically with one peak. Participants with hsCRP more than 0.1 mg/dl were defined as high hsCRP individuals in this study. The proportion of high hsCRP subjects was compared between the seropositives and the seronegatives with a Fisher's exact test. Odds ratios (ORs) and 95% confidence intervals (CIs) of the seropositives compared with the seronegatives for high hsCRP were calculated using unconditional logistic regression models, adjusting for age (<30, 30-39, 40-49, 50-59, 60-69, or ≥70 years), sex, body mass index (BMI) (<25, or ≥25kg/m²), smoking (never, former, current, or unknown), and study group. The heterogeneity in the OR among study groups was tested with the Q statis-

tic. The data were analyzed by the statistical software "STATA/SE version 9.0" (College Station, TX, USA).

3. Results

The sex, age, hsCRP level, BMI, and smoking habits of the participants according to the study group are summarized in Table 1. In YTI, females were dominant (66.2%), and 65.3% were participants aged 60 years or older. In ENUH, males were dominant (60.8%), and age was distributed over a wider range. PIC was the group of only females aged under 50 years, because they were sampled from patients of an infertility clinic. The hsCRP distributed from undetectable level close to 1 mg/dl in any group, and the frequency of high hsCRP individuals was comparable among the three groups. The prevalence of *H. pylori* infection in YTI was 62.1% (95/153) in males and 54.7% (164/300) in females, 39.9% (109/273) and 36.9% (65/176) in ENUH, respectively, and 20.4% (52/255) in PIC. In total, the prevalence was 47.9% (204/426) in males and 38.4% (281/731) in females.

Table 1 Characteristics of subjects from three study groups

Characteristics	YTI* (n=453)	ENUH† (n=449)	PIC‡ (n=255)	Total (n=1,157)
Sex				
Males	153 (33.8)	273 (60.8)	0 (0.0)	426 (36.8)
Females	300 (66.2)	176 (39.2)	255 (100.0)	731 (63.2)
Age (years)				
19-29	0 (0.0)	19 (4.2)	53 (20.8)	72 (6.2)
30-39	5 (1.1)	97 (21.6)	177 (69.4)	279 (24.1)
40-49	34 (7.5)	111 (24.7)	25 (9.8)	170 (14.7)
50-59	118 (26.0)	116 (25.8)	0 (0.0)	234 (20.2)
60-69	171 (37.7)	80 (17.8)	0 (0.0)	251 (21.7)
≥70	125 (27.6)	26 (5.8)	0 (0.0)	151 (13.1)
BMI (kg/m²)				
<25	296 (65.3)	358 (79.7)	0 (0.0)	654 (56.5)
≥25	157 (34.7)	91 (20.3)	0 (0.0)	248 (21.4)
Unknown	0 (0.0)	0 (0.0)	255 (100.0)	255 (22.1)
hsCRP (mg/dl)				
≤0.1	354 (78.1)	370 (82.4)	200 (78.4)	924 (79.9)
>0.1	99 (21.9)	79 (17.6)	55 (21.6)	233 (20.1)
Geometric mean	0.047	0.038	0.038	0.040
1st-3rd quartile	0.022-0.090	0.019-0.072	0.011-0.076	0.018-0.082
Range	0.002-0.973	0.002-0.923	0.002-0.994	0.002-0.994
Smoking				
Never	280 (61.8)	230 (51.2)	0 (0.0)	510 (56.7)
Former	97 (21.4)	126 (28.1)	0 (0.0)	223 (24.8)
Current	76 (16.8)	91 (20.3)	0 (0.0)	167 (18.6)
Unknown	0 (0.0)	2 (0.5)	255 (100.0)	257 (22.2)

YTI: Yakumo Town Inhabitants, ENUH†: Examinees of Nagoya University Hospital, PIC‡: Patients of Infertility Clinic, Nagoya University Hospital.

Percentages are shown in parentheses.

Table 2 shows associations of categorized hsCRP (≤ 0.1 mg/dl or >0.1 mg/dl) with background factors. In YTI, ENUH and whole participants, no significant difference was found in the prevalence of hsCRP between sexes, although the high hsCRP was more prevalent in males of YTI and in females of ENUH. There was no significant difference in the hsCRP level across age groups. The geometric mean of hsCRP level was 0.051 mg/dl for *H. pylori* positive subjects and 0.042 mg/dl for *H. pylori* negative subjects in YTI, 0.043 mg/dl and 0.036 mg/dl in ENUH, 0.045 mg/dl and 0.028 mg/dl in PIC, respectively. Corresponding 1st-3rd quartile was 0.025-0.094 and 0.020-0.082 in YTI, 0.023-0.072 and 0.018-0.071 in ENUH, and 0.016-0.143 and 0.010-0.061 in PIC. In total, the geometric mean of hsCRP level was 0.047mg/dl for *H. pylori* positive subjects and 0.035mg/dl for *H. pylori* negative subjects, with the 1st-3rd quartile of 0.023-0.093 and 0.015-0.073, respectively. The hsCRP geometric mean was significantly higher in subjects with *H. pylori* positive subjects than in those without ($p < 0.0001$ by a *t*-test).

In PIC, the high hsCRP level was observed more frequently among subjects with *H. pylori* infection than among those without it, with a statistically significant difference; 32.7% vs. 18.7%, $p=0.037$ (Table 3). A similar difference in the prevalence of high hsCRP level was also detected in the pooled population (23.5% vs. 17.7%, $p=0.017$). In YTI and ENUH groups, the proportion of high hsCRP level was similarly higher in those with *H. pylori* infection compared with those without it, but the difference was not significant; $p=0.491$ for YTI and $p=0.127$ for ENUH.

Table 3 also shows OR and 95% CI of *H. pylori* seropositivity for the high hsCRP. The ORs were 1.18 (95% CI, 0.74-1.90) in YTI, 1.37 (95% CI, 0.81-2.31) in ENUH, and 2.20 (95% CI, 1.11-4.37) in PIC, after adjustment for age, sex, BMI, and smoking habits. The Q test for heterogeneity showed the differences in the OR among the three groups was not significant ($p=0.337$). The summary OR was 1.38 (95% CI, 1.01-1.89), with allowance for study groups; 1.20 (95% CI, 0.73-1.95) in males and 1.61 (95% CI, 1.09-1.38) in females. Because the median of the age in pooled data was 52, we divided the data into two groups at the age; the younger group (age ≤ 52 years) and the older group (age >52 years). The summary OR of the younger group adjusted for sex, BMI, smoking, and subject groups was 1.60 (95% CI, 1.00-2.55), while the corresponding OR of the older group was 1.27 (95% CI, 0.85-1.90).

Table 2 Associations between the serum level of hsCRP and background factors

Characteristics	YTI* (n=453)		ENUH† (n=449)		PIC‡ (n=255)		Total (n=1,157)	
	Low§	High¶	Low§	High¶	Low§	High¶	Low§	High¶
Sex								
Males	111 (72.5)	42 (27.5)	228 (83.5)	45 (16.5)	0 (0.0)	0 (0.0)	339 (79.6)	87 (20.4)
Females	243 (81.0)	57 (19.0)	142 (80.7)	34 (19.3)	200 (78.4)	55 (21.6)	585 (80.0)	146 (20.0)
p-value¶	0.054		0.449		-		0.879	
Age (year)								
19-29	0 (0.0)	0 (0.0)	17 (89.5)	2 (10.5)	39 (73.6)	14 (26.4)	56 (77.8)	16 (22.2)
30-39	5 (100.0)	0 (0.0)	82 (84.5)	15 (15.3)	140 (79.1)	37 (20.9)	227 (81.4)	52 (18.6)
40-49	29 (85.3)	5 (14.7)	94 (84.7)	17 (15.3)	21 (84.0)	4 (16.0)	144 (84.7)	26 (15.3)
50-59	97 (82.2)	21 (17.8)	93 (80.2)	23 (19.8)	0 (0.0)	0 (0.0)	190 (81.2)	44 (18.8)
60-69	130 (76.0)	41 (24.0)	63 (78.8)	17 (21.2)	0 (0.0)	0 (0.0)	193 (76.9)	58 (23.1)
≥70	93 (74.4)	32 (25.6)	21 (80.8)	5 (19.2)	0 (0.0)	0 (0.0)	114 (75.5)	37 (24.5)
p-value¶	0.371		0.793		0.575		0.255	
BMI (kg/m²)								
<25	249 (84.1)	47 (15.9)	302 (84.4)	56 (15.6)	0 (0.0)	0 (0.0)	551 (84.3)	103 (15.8)
≥25	105 (66.9)	52 (33.1)	68 (74.7)	23 (25.3)	0 (0.0)	0 (0.0)	173 (69.8)	75 (30.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	200 (78.4)	55 (21.6)	200 (78.4)	55 (21.6)
p-value¶	<0.001		0.044		-		<0.001	
Smoking								
Never	225 (80.4)	55 (19.6)	190 (82.6)	40 (17.4)	0 (0.0)	0 (0.0)	415 (81.4)	95 (18.6)
Former	73 (75.3)	24 (24.7)	103 (81.8)	23 (18.3)	0 (0.0)	0 (0.0)	176 (78.9)	47 (21.1)
Current	56 (73.7)	20 (26.3)	75 (82.4)	16 (17.6)	0 (0.0)	0 (0.0)	131 (78.4)	36 (21.6)
Unknown	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)	200 (78.4)	55 (21.6)	202 (78.6)	55 (21.4)
p-value¶	0.324		0.990		-		0.589	
Total	354 (78.1)	99 (21.9)	370 (82.4)	79 (17.6)	200 (78.4)	55 (21.6)	924 (79.8)	233 (20.1)

YTI: Yakumo Town Inhabitants, ENUH†: Examinees of Nagoya University Hospital, PIC‡: Patient of Infertility Clinic, Nagoya University Hospital, Low§: hsCRP ≤ 0.1mg/dl, High¶: hsCRP > 0.1mg/dl, and p-value¶: Fisher's exact test.

Percentages are shown in parentheses.

Table 3 Associations of the serum level of hsCRP with *H. pylori* seropositivity and odds ratio (OR) and 95% confidence interval (CI) of *H. pylori* for hsCRP

	<i>H. pylori</i>	Low*	High†	OR (95% CI)	aOR‡ (95% CI)	aOR§ (95% CI)
YTI¶	Seronegative	155 (79.9)	39 (20.1)	1 [Reference]	1 [Reference]	1 [Reference]
n=453	Seropositive	199 (76.8)	60 (23.2)	1.20 [0.76-1.89]	1.13 [0.71-1.79]	1.18 [0.74-1.90]
ENUH¶	Seronegative	220 (84.0)	42 (16.0)	1 [Reference]	1 [Reference]	1 [Reference]
n=449	Seropositive	131 (78.0)	37 (22.0)	1.49 [0.92-2.44]	1.38 [0.83-2.32]	1.37 [0.81-2.31]
PIC**	Seronegative	165 (81.4)	38 (18.7)	1 [Reference]	1 [Reference]	1 [Reference]
n=255	Seropositive	35 (67.3)	17 (32.7)	2.11 [1.07-4.16]	2.20 [1.11-4.37]	-
Pooled††	Seronegative	553 (82.3)	119 (17.7)	1 [Reference]	1 [Reference]	1 [Reference]
n=1,157	Seropositive	371 (76.5)	114 (23.5)	1.45 [1.07-1.97]	1.37 [1.01-1.86]	1.38 [1.01-1.89]

Low*: hsCRP ≤ 0.1mg/dl, High†: hsCRP > 0.1mg/dl, †Sex-, and age-adjusted odds ratios (aOR‡), †Sex-, age- smoking- and BMI-adjusted odds ratios (aOR§), YTI¶: Yakumo Town Inhabitants, ENUH¶: Examinees of Nagoya University Hospital, PIC**.: Patients of Infertility Clinic, Nagoya University Hospital, Pooled††: three studies were combined, and the ORs were adjusted additionally for the study groups using dummy variables.

Percentages are shown in parentheses.

4. Discussion

The present paper examined the association of *H. pylori* seropositivity with hsCRP in the range of 0.002 to 1.0 mg/dl, based on three different Japanese groups with 1,157 subjects in total. Although the background of the three groups was different, the sex, age, BMI, and smoking adjusted OR of the seropositive for hsCRP > 0.1 mg/dl relative to hsCRP ≤ 0.1 mg/dl was larger than unity in all three groups. The summary OR was 1.38 (95% CI, 1.01-1.89), indicating that

H. pylori seropositivity was associated with a higher hsCRP among those with hsCRP ≤ 1 mg/dl. We tested the heterogeneity of the OR for high CRP levels in relation to the seropositivity among three groups. Because no significant differences in the OR were found among study groups, we pooled the data derived from three different populations.

Although *H. pylori* infection is associated with coronary artery disease, the pathway to elevate the disease risk is not clear. There are several possibilities for the mechanism underlying a causal role of *H. pylori*

infection in endothelial dysfunction. First, *H. pylori* may have the direct effect on the structure and function of vascular endothelial cells. Extract of *H. pylori* has been reported to induce a disturbance of proliferation and apoptosis and to decrease viability of cultured vascular endothelial cells [25]. The second possibility is the nutritional effect of *H. pylori* [26]. An infection from *H. pylori* may cause malabsorption of folate, vitamin B6, and vitamin B12. This nutritional defect could lead to failure of methylation by 5-methyl-tetrahydrofolic acid and subsequent hyperhomocysteinemia, which is toxic to endothelial cells. In our past study, serum folate was examined as a molecule connecting *H. pylori* infection with systemic diseases, resulting in no association between the seropositivity and serum folate [27]. CRP is also one of the candidate molecules, but there were limited reports on the association with *H. pylori* infection.

A study on the effects of *H. pylori* eradication among 78 patients in Turkey reported that serum CRP was significantly reduced among 57 participants with successful eradication, but not among 21 participants in whom the eradication failed [23]. Another study reported that increasing age, smoking, symptoms of chronic bronchitis, *H. pylori* and Chlamydia pneumoniae infections, and BMI were all associated with raised concentrations of CRP [24]. The present study demonstrated that *H. pylori* infection may slightly elevate serum CRP, thereby may increase systemic disease risk.

CRP is an easily measurable substance in blood. Increased levels of this protein indicate acute inflammation. Many studies have shown that high levels of CRP also indicate an increased risk of suffering from a heart attack or stroke. The CRP test is not specific, and the levels fluctuate daily and throughout the day. The levels increase as a result of numerous factors including aging, alcohol use, smoking, eating a high protein diet, coffee consumption, low levels of physical activity, chronic fatigue, high blood pressure, BMI, high triglycerides, rheumatoid arthritis, rheumatic fever, insulin resistance and diabetes [28], as well as heart attack. Medicines containing estrogen (oral contraceptive and hormone replacement therapy) may also elevate CRP levels. In this study, we took factors, sex, age, BMI, and smoking into account, although information on BMI and smoking was not available for PIC group. Among the female subjects, smokers and fatty ladies were relatively rare.

The present study has several limitations. First, *H. pylori* infection was determined by only serum antibody, not by the other diagnosis methods with a higher sensitivity and specificity, such as a urease breath test. Since the present analysis was based on

stored blood samples from multi-purpose studies, alternative methods could not be applied for the detection of *H. pylori* infection. Second, the information on the other factors that affect serum CRP level was not available. For example, chronic infections other than *H. pylori* could confound the association with *H. pylori* infection, since it seemed plausible that *H. pylori* infected individuals might be vulnerable to other infections which elevate CRP. The adjustments of the potential confounding factors might not be enough to confirm the association with *H. pylori* infection. Third, this study was a cross-sectional study so that the causal inference was not possible directly. Finally, the effects of medication on CRP were not removed. Since several drugs, such as statins, were reported to influence CRP levels [29, 30], the adjustment for such medications could allow clear interpretation on the observed association.

If *H. pylori* has effects on the function of vascular endothelial cells, serum CRP could be one of the molecules to connect both. *H. pylori* infection stimulates the production of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL) -6, and IL-8 [31, 32]. *H. pylori* was detected not only in gastric mucosa but also in human atherosclerotic plaque [33, 34], and the expression of intercellular adhesion molecule-1 was higher in plaques containing *H. pylori* than in those without it [33]. The production of CRP is regulated by cytokines, principally interleukins [35, 36], whose effects are modified by other cytokines and growth factors [37], as well as by hormones such as cortisol and insulin [38]. Production of cytokines and stress hormones may be altered in conditions other than inflammation or injury. TNF- α is a potent inducer of IL-6 by various cells. Therefore, the association of CRP concentration with *H. pylori* infection could be explained by the actions of cytokines, hormones, or both.

In conclusion, the present cross-sectional study based on the three different subjects showed a significant association between *H. pylori* infection and serum hsCRP levels, supporting that *H. pylori* infection may increase the serum CRP. The possible attribution of *H. pylori* infection to CRP elevation could be a route to *H. pylori* negative subjects related coronary heart disease with the base of atherosclerosis. Since many factors influence the CRP levels, larger studies with information on potential confounding factors are necessary to confirm the association.

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Conflict of Interest

The authors have declared that no conflict of interest exists.

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