

# BMJ Open C reactive protein level as a marker for dyslipidaemia, diabetes and metabolic syndrome: results from the Korea National Health and Nutrition Examination Survey

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## ABSTRACT

**Objective** Plasma C reactive protein (CRP) is a marker of inflammation, and increased plasma CRP is reported in many diseases, including cardiovascular disease, diabetes, metabolic syndrome, arthritis and malignancies. The aim of the study was to evaluate the association between plasma CRP levels and cardiovascular disease, metabolic syndrome, malignancies and other comorbidities.

**Design** A retrospective, cross-sectional survey study.

**Setting** Large population survey in Korea.

**Methods** A total of 5887 (weighted n=40 251 868) participants aged 19 years or older from the 2016 Korea National Health and Nutrition Examination Survey were included for analysis. Weighted prevalence and OR of comorbidities were analysed according to the continuous variable of log plasma high-sensitivity CRP levels.

**Results** The mean age was 46.7±0.37 years and the median plasma CRP was 0.58 mg/L (IQR 0.36–1.09). The mean plasma CRP levels were higher in participants with cardiovascular diseases and cardiovascular risk factors, osteoarthritis, rheumatoid arthritis, pulmonary tuberculosis, and several cancers, including gastric, colon, breast and cervix, than in the general population. In the multivariable analysis, plasma CRP concentration was associated with increased prevalence of hypertriglyceridaemia (OR 1.157, 95% CI 1.040 to 1.287, p=0.007), diabetes (OR 1.204, 95% CI 1.058 to 1.371, p=0.005) and metabolic syndrome (OR 1.228, 95% CI 1.112 to 1.357, p<0.001) after adjustment for socioeconomic and lifestyle characteristics. There was no significant association between plasma CRP level and cancers.

**Conclusion** Plasma CRP was associated with an increased risk of dyslipidaemia, diabetes and metabolic syndrome in the general population.

## INTRODUCTION

Plasma C reactive protein (CRP) is an acute-phase reactant produced by hepatocytes, and its production is regulated by interleukin-6 (IL-6) and other inflammatory cytokines.<sup>1</sup> Plasma CRP is a useful non-specific biomarker, and plasma CRP measurement is

## Strengths and limitations of this study

- This study analysed the association between plasma C reactive protein (CRP) and comorbidities using nationwide representative samples of the Korean adult population.
- The study evaluated the socioeconomic and lifestyle characteristics relevant to comorbidities and adjusted for these factors in the analysis.
- Definition of myocardial infarction or angina, stroke, cancers, and other comorbidities depended on the information reported by participants during the interview.
- This study was unable to assess the use of medications, such as non-steroidal anti-inflammatory drugs or corticosteroids, that may have affected plasma CRP levels.
- This cross-sectional study may have potential unknown inherent biases and confounding factors.

used as a screening test for organic diseases, assessment of disease activity in inflammatory conditions such as rheumatological diseases, diagnosis and management of infection, and the differential diagnosis or classification of inflammatory diseases.<sup>1</sup> Plasma CRP levels reflect the disease course of certain diseases, including infections, inflammatory disease, necrosis, trauma and malignancy. Plasma CRP measurement was found to be associated with increased risk of all-cause mortality in the Copenhagen City Heart Study, and this study revealed that a doubling of plasma CRP levels correlated with a 1.43-fold risk of cardiovascular mortality and a 1.38-fold risk of cancer mortality.<sup>2</sup> Plasma CRP levels are also strongly associated with the risk of hypertension and coronary heart disease, stroke, and diabetes.<sup>3–6</sup> Plasma CRP levels are also directly involved in vascular pathology via the

activation of inflammatory cells, including macrophages, endothelial cells and vascular smooth muscle cells.<sup>7</sup> Metabolic syndrome is a cluster of cardiovascular risk factors and is associated with the development of cardiovascular diseases (CVDs) and type 2 diabetes mellitus. Plasma CRP is associated with metabolic syndrome and its components.<sup>8</sup> In addition, increased plasma CRP concentrations have been reported in many types of solid malignancies and lymphoma.<sup>9 10</sup> Tumour growth causes tissue inflammation and subsequently increases production of inflammatory protein. Thus, plasma CRP could be an indicator of an immune response to tumour antigens.<sup>11</sup>

Evidence regarding the association between plasma CRP concentration and risk of major disease from studies involving large populations would be useful for routine clinical practice. However, the relationship between plasma CRP and overall comorbidities, including CVD, cancers and other comorbidities, has not been thoroughly investigated in the Korean population. In recent large-scale observational studies, the reported prevalence of metabolic syndrome, diabetes and hypertension was 27.4%, 11.4% and 30.3%, respectively, in the Korean adult population.<sup>12–14</sup> Therefore, it is important to recognise metabolic syndrome or cardiovascular risk factors in their early phase to promote public health. Plasma CRP may be a sensitive biochemical indicator in routine clinical practice. The purpose of this study was to evaluate the association between plasma CRP and comorbidities in the Korean adult population using a nationwide survey.

## MATERIALS AND METHODS

### Study population

The Korea National Health and Nutrition Examination Survey (KNHANES) is a nationwide survey conducted periodically by the Korea Centers for Disease Control and Prevention to investigate the health and nutritional status of the Korean population.<sup>15</sup> This survey assesses general health and nutrition status of individuals in South Korea through interviews about health and nutritional and basic health assessments. Participants were selected using the proportional allocation-systematic sampling method with multistage stratification to derive a representative Korean population. Although individual participants are not generally representative of the Korean population, this survey provided a representative estimates of the non-institutionalised Korean civilian population by using the power of sample weight. Every year, 10 000–12 000 individuals in approximately 3800–4600 households are selected from a panel based on the National Census Data. Participation rates of selected households in the past several cycles of the KNHANES have been high, from 75% to 80%. This study analysed data from the 2016 KNHANES. In the 2016 KNHANES, 10 806 individuals from 4416 households were selected and the participation rate was 75.4%. Among 8150 participants in the 2016 KNHANES, 1768 participants were excluded as they were younger than 19 years of age. Of the remaining 6382 participants,

495 participants for whom serum plasma CRP levels were missing were excluded. Finally, a total of 5887 participants were selected for analysis.

### Demographic variables and data collection

The KNHANES was conducted by four special research teams, each composed of eight experts including nurses, nutritionists and students majoring in public health. The selected professional investigator was placed at the investigation site after completing 1 month of education and practice. Subsequently, the ability to conduct research was verified through regular education and onsite quality management. A standardised interview was performed in participants' homes, and an established questionnaire was used to collect information on demographic variables and socioeconomic characteristics. Specifically, data on age, sex, income, region, education, marital status, alcohol consumption and smoking status were collected. Alcohol consumption was categorised into the following four groups based on the frequency of alcohol consumption during the past year: (1) never, (2)  $\leq 1$  day/week, (3) 2–3 days/week and (4)  $\geq 4$  days/week. Income level was categorised into quartiles based on the average individual monthly income. Urban and rural areas were classified by the administrative district. High physical activity was defined as continuous high-intensity sports, exercise or leisure activities that lasted more than 10 min for more than 3 days a week. If physical activity occurred less than 3 days a week, it was defined as low physical activity. Blood pressure (BP) was measured by nurses with a standard protocol. After at least 5 min of rest and with the participant in a sitting position, BP was measured on the right arm using a mercury sphygmomanometer. BP was measured three times and the mean of the second and third BP was calculated. The mean BP was used for analysis. Blood samples were collected from each participant after at least 8 hours of fasting. All blood samples were immediately refrigerated and transported in cold storage to the central testing facility. Plasma high-sensitivity CRP (subsequently referred to as plasma CRP throughout the manuscript) levels were measured by immunoturbidimetry (Roche Diagnostics, Penzberg, Germany) using Roche Cardiac C-Reactive Protein High Sensitive (Roche Diagnostics). Total cholesterol and triglyceride levels were measured using an enzymatic method with the Hitachi Automatic Analyzer 7600–210 (Hitachi, Tokyo, Japan). High-density lipoprotein (HDL) cholesterol levels were measured with a homogeneous enzymatic colourimetric method using the Hitachi Automatic Analyzer 7600–210 (Hitachi). Glucose levels were measured using a hexokinase ultra-violet method with the Hitachi Automatic Analyzer 7600–210 (Hitachi). Low-density lipoprotein (LDL) was calculated using the Friedewald formula: LDL cholesterol = total cholesterol – HDL cholesterol – triglyceride/5.<sup>16</sup> Height and weight were assessed using standardised techniques and equipment. Briefly, height was measured to the nearest 0.1 cm using a portable stadiometer Seca 225 (Seca, Hamburg, Germany). Weight was measured to the

nearest 0.1 kg using a GL-6000–20 (G-tech, Gyenggi-do, Korea). Body mass index (BMI) was calculated as weight divided by height squared ( $\text{kg}/\text{m}^2$ ). For measurement of waist circumference, participants were asked to breathe out, and the waist girth at the midpoint between the lower margin of the ribs and the iliac crest was measured to the nearest 0.1 cm using the Seca 200 (Seca).

### Definition of comorbidities

Definitions of hypertension, prehypertension, diabetes, impaired fasting glucose, hypercholesterolaemia and hypertriglyceridaemia were taken from the KNHANES.<sup>15</sup> Hypertension was defined as a mean systolic BP (SBP)  $\geq 140$  mm Hg or diastolic BP (DBP)  $\geq 90$  mm Hg or the use of antihypertensive agents. Prehypertension was defined as an average SBP of 120–139 mm Hg or a DBP of 80–89 mm Hg. Diabetes mellitus was defined as a fasting plasma glucose  $\geq 126$  mg/dL and/or current use of antidiabetic drugs or insulin due to a previous diagnosis of diabetes. Impaired fasting glucose was defined by a range of fasting plasma glucose levels of 100 mg/dL to  $< 126$  mg/dL. Diagnosis of hypercholesterolaemia was defined as a total plasma cholesterol level of  $\geq 240$  mg/dL after 8 hours of fasting or current use of cholesterol-lowering agents. Hypertriglyceridaemia was defined as a triglyceride level of  $> 200$  mg/dL after 12 hours of fasting. Metabolic syndrome was defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (ATP III) definition.<sup>17</sup> Current ATP III criteria define metabolic syndrome as the presence of any three of the following five traits: (1) central obesity (waist circumference  $\geq 90$  cm in Asian men or  $\geq 80$  cm in Asian women), (2) hypertriglyceridaemia (fasting serum triglycerides  $\geq 150$  mg/dL or drug treatment for elevated triglycerides), (3) decreased HDL cholesterol (serum HDL cholesterol  $< 40$  mg/dL in men and  $< 50$  mg/dL in women or drug treatment for low HDL cholesterol), (4) elevated BP (SBP  $\geq 130$  mm Hg and/or DBP  $\geq 85$  mm Hg or drug treatment for elevated BP), and (5) hyperglycaemia (fasting plasma glucose  $\geq 100$  mg/dL or drug treatment for elevated blood glucose). Stroke was defined in the questionnaire as 'stroke diagnosed by a physician' through a standardised interview. We asked 'Was your stroke diagnosed by a physician?' and there were three possible responses ('Yes', 'No' and 'I have never been sick before'). Participants who chose 1 (yes) were classified into the stroke group. Each interview was conducted individually by a trained professional investigator. Other comorbidities were defined in the same way as the stroke diagnosis. Information was collected on other comorbidities diagnosed by a physician, including myocardial infarction or angina, osteoarthritis, rheumatoid arthritis, osteoporosis, pulmonary tuberculosis, asthma, thyroid disease, atopic dermatitis, and allergic rhinitis. Information on malignancies diagnosed by a physician, including gastric cancer, breast cancer, cervical cancer, lung cancer and thyroid cancer, was also collected.

### Statistical analyses

To reflect representative estimates of the non-institutionalised Korean civilian population, survey sample weights were applied in the analyses. Sample weights were calculated by considering the sampling rate, response rate and age/sex proportions of the reference population (2005 Korean National Census Registry). Because the distribution of plasma CRP was highly skewed, log-transformed plasma CRP was used for analyses. To analyse the effect of plasma CRP on morbidity, univariable logistic regression models were computed with comorbidities as dependent variables and log plasma CRP level as an independent variable. Variables associated with p value outcomes  $\leq 0.05$  in univariable analysis were included in the multivariable analysis. Multivariable logistic regression analysis was performed with adjustments for age, income, region, education, marriage, smoking, alcohol consumption, BMI and physical activity. The strength of associations was estimated using ORs and 95% CIs. Multivariable linear regression analysis was used to estimate the association between metabolic syndrome and plasma CRP levels. A receiver operating characteristics (ROC) curve was used to analyse the specificity, sensitivity, and negative and positive predictive values of plasma CRP for metabolic syndrome, hypertriglyceridaemia and diabetes. The maximum value of the Youden's index was selected as the optimum cut-off point. Statistical analyses were performed using SAS V.9.4. All p values were two-sided, and a p value  $< 0.05$  was considered statistically significant.

### Patient and public involvement

The KNHANES data were released after anonymisation. The study population was not involved in the design of this study.

### RESULTS

The clinical characteristics of the study population are shown in [table 1](#). The mean age was  $46.7 \pm 0.37$  years, and 50.3% of the population were male. The mean plasma CRP level of the study population was  $1.23 \pm 0.03$  mg/L and the median plasma CRP concentration was 0.58 mg/L (IQR 0.36–1.09). Distribution of plasma CRP was markedly skewed, and 91.3% of participants had a plasma CRP  $\leq 3$  mg/L. The mean concentration of plasma CRP according to each of the comorbidities is presented in [figure 1](#). Mean plasma CRP levels were higher in participants with CVDs and cardiovascular risk factors, osteoarthritis, rheumatoid arthritis, pulmonary tuberculosis, and several cancers, including gastric, colon, breast and cervix, than in the general population. The mean plasma CRP was significantly higher in subjects with CVDs and cardiovascular risk factors than in those without CVDs or cardiovascular risk factors ([table 2](#)). In the univariable analysis, increased log plasma CRP was significantly associated with an increased probability of stroke, myocardial infarction or angina, hypercholesterolaemia, hypertriglyceridaemia, diabetes, hypertension, and metabolic syndrome.



**Table 1** Demographic, clinical and laboratory characteristics of the study population

Variables	Value (unweighted n=5887, weighted n=40 251 869)
Age, years	46.74±0.37
Male	2568 (50.3)
Income	
Low	1464 (25.8)
Mid-low	1468 (24.4)
Mid-high	1476 (25.0)
High	1458 (24.8)
Education	
Elementary school	1189 (15.1)
Middle school	576 (9.1)
High school	1794 (36.2)
College graduation	2045 (39.6)
Marital status	
Married	4970 (77.3)
Not married	917 (22.7)
Region	
Urban	4740 (84.3)
Rural	1147 (15.7)
Alcohol consumption	
Never	1610 (22.9)
≤1 day/week	2889 (52.7)
2–3 days/week	877 (16.8)
≥4 days/week	418 (7.6)
Smoking	
Never smoked	3490 (56.2)
Ex-smoker	1204 (20.9)
Current smoker	1098 (22.9)
Physical activity	
Low	5258 (92.2)
High	357 (7.8)
Body mass index (kg/m <sup>2</sup> )	24.0±0.1
Fasting glucose (mg/dL)	100.4±0.4
Total cholesterol (mg/dL)	193.1±0.6
HDL cholesterol (mg/dL)	51.1±0.2
LDL cholesterol (mg/dL)	113.9±0.6
Triglyceride (mg/dL)	144.8±2.8
Antihypertensive agents users	1333 (17.9)
Lipid-lowering agents users	664 (9.2)
Oral hypoglycaemic agents or insulin users	549 (7.4)
Plasma C reactive protein (mg/L), median (IQR)	1.23±0.03, 0.58 (0.36–1.09)

Values are presented as mean±SD or unweighted n (weighted %). HDL, high-density lipoprotein; LDL, low-density lipoprotein.

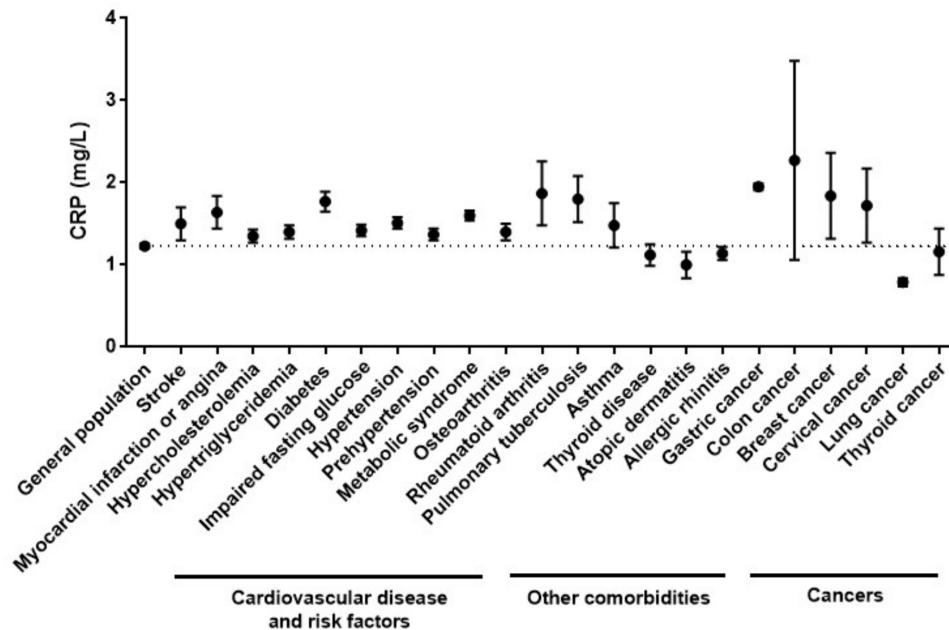
As the log plasma CRP value increased, the likelihood of metabolic syndrome increased, and the OR was 1.71. Increased log plasma CRP was significantly associated

with increased prevalence of osteoarthritis, osteoporosis, pulmonary tuberculosis and allergic rhinitis (table 3). There was no association between solid malignancy and log plasma CRP level. In the multivariable analysis, increased log plasma CRP was significantly associated with increased prevalence of hypertriglyceridaemia, diabetes, impaired fasting glucose, metabolic syndrome and pulmonary tuberculosis after adjustment for age, sex, income, region, education, alcohol consumption, BMI, smoking and physical activity (table 4). Stroke, myocardial infarction or angina, and hypertension were not significantly associated with log plasma CRP level after adjustment. Multivariable linear regression was performed to inspect the association between plasma CRP levels and individual components of metabolic syndrome and lipid profiles (table 5). A number of components of metabolic syndrome were positively associated with log plasma CRP. Fasting glucose, triglyceride and waist circumference were positively associated with log plasma CRP level after adjustment for age, income, region, education, marital status, smoking, alcohol consumption, BMI and physical activity. Total cholesterol and LDL cholesterol were positively associated with plasma CRP level, and HDL cholesterol was negatively associated with log plasma CRP level.

ROC curve analysis was performed to evaluate the diagnostic value of serum plasma CRP concentration for metabolic syndrome, hypertriglyceridaemia and diabetes. A plasma CRP concentration cut-off value of >0.54 mg/L showed 68.5% sensitivity, 56.6% specificity, 48.1% positive predictive value, 75.4% negative predictive value and 61.0% accuracy for metabolic syndrome. In hypertriglyceridaemia, a plasma CRP concentration cut-off value of 0.56 mg/L had 70.8% sensitivity, 51.3% specificity, 20.8% positive predictive value, 90.6% negative predictive value and 54.3% accuracy. In diabetes, a plasma CRP concentration cut-off value of >0.53 mg/L showed 67.7% sensitivity, 48.9% specificity, 16.3% positive predictive value, 91.1% negative predictive value and 51.3% accuracy. Based on the cut-off value of metabolic syndrome ascertained by the ROC curve analysis, we defined lower inflammation as a plasma CRP concentration of <0.54 mg/L and higher inflammation as a plasma CRP concentration of ≥0.54 mg/L. Table 6 shows the prevalence of cardiovascular risk factors, metabolic syndrome, comorbidities and cancer according to lower and higher inflammation. The prevalence of stroke, hypercholesterolaemia, hypertriglyceridaemia, diabetes, impaired fasting glucose, hypertension, prehypertension, metabolic syndrome, osteoarthritis, osteoporosis and thyroid disease was significantly higher in the higher inflammation group than in the lower inflammation group.

## DISCUSSION

We investigated the relationship between plasma CRP and overall comorbidities in the Korean adult population. We determined that elevated plasma CRP level was significantly associated with the increase in the prevalence of



**Figure 1** Mean plasma C reactive protein (CRP) concentration according to cardiovascular diseases and cardiovascular risk factors, other comorbidities, and cancers. The dotted line represents mean plasma CRP concentration of the total subjects included in the study.

dyslipidaemia, diabetes and metabolic syndrome. Plasma CRP was not associated with solid malignancy after adjustment for age, income, region, education, marital status, smoking, alcohol consumption, BMI and physical activity in this study. In this study, the median plasma CRP was 0.58 mg/L (IQR 0.36–1.09). In the Copenhagen General Population Study of 63 500 individuals, the median plasma CRP concentration was 1.53 mg/L (IQR 1.14–2.51).<sup>18</sup> In the US National Health and Nutrition Examination Survey (NHANES) that included 21 004 participants, the mean plasma CRP was  $4.3 \pm 7.7$  mg/L, and the median was 2.1 mg/L (IQR 0.8–4.7).<sup>19</sup> The mean plasma CRP concentration in the Korean adult population seems to be lower than that of the Western population. Considering plasma CRP is strongly correlated with BMI,<sup>20</sup> lower mean plasma CRP levels in the Korean population may be due to relatively lower BMI in Asian people compared with people in Western countries. Plasma CRP levels closely correlate with mean BMI at a population level across ethnic groups.<sup>21</sup> However, obesity does not completely explain the plasma CRP levels. Race and gender differences exist in the distribution of plasma CRP.<sup>22</sup> Genome-wide association studies using the Women's Health Initiative SNP Health Association Resource reported the ancestry-specific genetic variants associated with plasma CRP concentration.<sup>23</sup> East Asian ancestry was associated with lower age and lower BMI-adjusted plasma CRP compared with African-American ancestry. The TREM2 (triggering receptors expressed by the myeloid cells 2) variant associated with higher plasma CRP is common in African-American individuals, but is much less common in Asian populations.

We determined that an increased plasma CRP level was associated with increased odds of diabetes and impaired

fasting glucose. Plasma CRP level was positively associated with fasting glucose level in this study. The NHANES revealed that plasma CRP level was elevated in participants with diabetes compared with those with normal fasting glucose in the US adult population.<sup>24</sup> Elevated plasma CRP concentration was positively associated with haemoglobin A1c levels in patients with diabetes.<sup>25</sup> Subjects with elevated acute-phase proteins were more likely to develop type 2 diabetes in the Insulin Resistance Atherosclerosis Study.<sup>26</sup> Hyperglycaemia may contribute to inflammation by inducing endothelial dysfunction and stimulating reactive oxygen species generation.<sup>27 28</sup> Elevated plasma CRP was significantly associated with increased mean fasting insulin concentration.<sup>29</sup> Plasma CRP induces endothelial insulin resistance and dysfunction through the spleen tyrosine kinase and RhoA-activation signalling pathway.<sup>30</sup> The results of this study suggest an association between glycaemic control and systemic inflammation. Although we could not infer the cause and effect relationship due to the cross-sectional design, our findings indicate that chronic systemic inflammation may be of aetiological significance in insulin resistance and diabetes.

This study determined that plasma CRP was related to metabolic syndrome. US nationwide data revealed that participants with metabolic syndrome had significantly elevated plasma CRP levels compared with participants without metabolic syndrome in the NHANES III.<sup>31</sup> Numerous studies have now confirmed that plasma CRP levels are elevated in patients with metabolic syndrome.<sup>32</sup> We determined that plasma CRP was positively associated with a number of metabolic syndrome components. This finding corresponds well with previous studies that have found that mean levels of plasma CRP increased according to the increased number of metabolic

**Table 2** Plasma mean CRP levels according to the presence of cardiovascular disease and cardiovascular risk factors and the OR of each comorbidity according to log plasma CRP levels

Variables	n	Plasma CRP (mg/L), mean±SE	P value	OR (95% CI)	P value
Stroke			0.174		0.019
Yes	121	1.50±0.20		1.24 (1.04 to 1.48)	
No	5523	1.22±0.03		Ref	
Myocardial infarction or angina			0.042		0.010
Yes	165	1.64±0.20		1.28 (1.06 to 1.54)	
No	5475	1.21±0.03		Ref	
Hypercholesterolaemia			0.089		<0.001
Yes	1209	1.35±0.08		1.12 (1.10 to 1.30)	
No	4481	1.20±0.04		Ref	
Hypertriglyceridaemia			0.013		<0.001
Yes	677	1.40±0.08		1.46 (1.33 to 1.59)	
No	3729	1.18±0.04		Ref	
Glucose			<0.001		<0.001
Diabetes	744	1.77±0.12		1.67 (1.51 to 1.84)	
Impaired fasting glucose	1385	1.42±0.07		1.45 (1.34 to 1.56)	
Normal	3561	1.06±0.04		Ref	
Blood pressure			<0.001		<0.001
Hypertension	1909	1.51±0.07		1.64 (1.51 to 1.78)	
Prehypertension	1409	1.37±0.07		1.41 (1.31 to 1.52)	
Normal	2552	0.99±0.04		Ref	
Metabolic syndrome			<0.001		<0.001
Yes	2193	1.60±0.06		1.71 (1.59 to 1.85)	
No	3694	1.04±0.04		Ref	

CRP, C reactive protein; Ref, reference.

syndrome components.<sup>33–36</sup> Among metabolic syndrome components, hyperglycaemia, low HDL, hypertriglyceridaemia and central obesity were associated with plasma CRP in this study. BP was not significantly associated with plasma CRP. Previous studies reported that plasma CRP was significantly associated with all metabolic syndrome components, and among those components central obesity revealed the strongest association with plasma CRP levels.<sup>33–35</sup> In a centrally obese population, waist circumference and triglycerides were significantly associated with plasma CRP after adjustment for age, smoking status, alcohol consumption and other metabolic syndrome components.<sup>8</sup> BP and HDL were not significantly associated with plasma CRP. These findings indicate that metabolic syndrome and a variety of components of metabolic syndrome are associated with low-grade systemic inflammation. The mechanisms of proinflammatory status and metabolic syndrome are not yet fully understood. Adipocytes release tumour necrosis factor- $\alpha$  and IL-6 into circulation in patients with metabolic syndrome, and they stimulate plasma CRP production in the liver and induce insulin resistance.<sup>37–38</sup> Plasma CRP is also released in the

adipocytes of body fat, and plasma CRP is independently associated with total body fat, central fat and insulin resistance.<sup>39</sup> Besides, in a genome-wide association study among 6345 healthy women, it was reported that seven loci were associated with plasma CRP levels.<sup>40</sup> Protein products of six of these seven loci are directly involved in metabolic syndrome, insulin resistance, beta cell function, weight homeostasis and/or premature atherosclerosis. Common variations in several genes involved in metabolic and inflammatory regulation have significant effects on plasma CRP levels. The results of these studies suggest plasma CRP may be a useful biomarker of vascular disease and diabetes.

Metabolic syndrome is associated with incident CVD and diabetes.<sup>41</sup> Men with metabolic syndrome show significantly increased cardiovascular mortality, even in the absence of baseline CVD and diabetes.<sup>42</sup> Although plasma CRP was associated with diabetes and metabolic syndrome, plasma CRP was not significantly associated with stroke and myocardial infarction or angina after adjustment for age, income, region, education, marital status, smoking, alcohol consumption, BMI and physical

**Table 3** Plasma mean CRP levels according to the presence of other medical comorbidities and solid cancers and OR for each comorbidity according to log plasma CRP levels

Variables	n	Plasma CRP (mg/L), mean±SE	P value	OR (95% CI)	P value
Osteoarthritis			0.067		<0.001
Yes	639	1.40±0.10		1.22 (1.12 to 1.34)	
No	5000	1.21±0.03		Ref	
Rheumatoid arthritis			0.095		0.149
Yes	125	1.87±0.39		1.19 (0.94 to 1.51)	
No	5514	1.21±0.03		Ref	
Osteoporosis			0.046		<0.001
Yes	485	1.46±0.12		1.24 (1.12 to 1.38)	
No	5154	1.21±0.03		Ref	
Pulmonary tuberculosis			0.040		0.003
Yes	223	1.80±0.28		1.25 (1.08 to 1.45)	
No	5416	1.20±0.03		Ref	
Asthma			0.330		0.261
Yes	157	1.48±0.27		1.12 (0.92 to 1.37)	
No	5482	1.22±0.03		Ref	
Thyroid disease			0.404		0.785
Yes	223	1.12±0.13		1.02 (0.87 to 1.21)	
No	5415	1.23±0.03		Ref	
Atopic dermatitis			0.175		0.076
Yes	152	1.00±0.16		0.79 (0.61 to 1.03)	
No	5486	1.23±0.03		Ref	
Allergic rhinitis			0.269		0.023
Yes	784	1.14±0.08		0.88 (0.80 to 0.98)	
No	4854	1.24±0.04		Ref	
Gastric cancer			0.118		0.269
Yes	42	1.95±0.04		1.27 (0.83 to 1.93)	
No	5596	1.22±0.03		Ref	
Colon cancer			0.394		0.062
Yes	23	2.27±1.21		1.47 (0.98 to 2.20)	
No	5615	1.22±0.03		Ref	
Breast cancer			0.338		0.744
Yes	30	1.84±0.52		1.06 (0.76 to 1.46)	
No	5608	1.22±0.03		Ref	
Cervical cancer			0.397		0.752
Yes	38	1.72±0.45		0.94 (0.62 to 1.42)	
No	5600	1.22±0.03		Ref	
Lung cancer			0.070		0.613
Yes	11	0.79±0.05		0.86 (0.47 to 1.56)	
No	5627	1.22±0.03		Ref	
Thyroid cancer			0.816		0.981
Yes	59	1.16±0.28		0.99 (0.76 to 1.30)	
No	5579	1.22±0.03		Ref	

CRP, C reactive protein; Ref, reference.

activity in this study. However, previous studies reported that plasma CRP is an independent risk factor for atherosclerosis, atherothrombosis, hypertension and myocardial

infarction.<sup>43–46</sup> Inflammation plays a key role in the development of atherosclerosis.<sup>47</sup> Plasma CRP may be involved in all phases of atherosclerosis by direct proinflammatory



**Table 4** Multivariable logistic regression analysis for OR and 95% CI of comorbidities according to log plasma C reactive protein levels

Variables	OR (95% CI)	P value
Stroke	0.902 (0.730 to 1.115)	0.337
Myocardial infarction or angina	0.949 (0.743 to 1.212)	0.673
Hypercholesterolaemia	0.999 (0.980 to 1.112)	0.989
Hypertriglyceridaemia	1.157 (1.040 to 1.287)	0.007
Diabetes	1.204 (1.058 to 1.371)	0.005
Impaired fasting glucose	1.117 (1.016 to 1.229)	0.022
Hypertension	1.083 (0.978 to 1.200)	0.126
Prehypertension	1.074 (0.992 to 1.162)	0.078
Metabolic syndrome	1.146 (1.035 to 1.270)	0.009
Osteoarthritis	0.952 (0.834 to 1.086)	0.461
Osteoporosis	1.087 (0.945 to 1.252)	0.240
Pulmonary tuberculosis	1.187 (1.017 to 1.386)	0.029
Allergic rhinitis	1.006 (0.905 to 1.118)	0.910

Adjusted for age, sex, income, region, education, marital status, alcohol consumption, body mass index, smoking, marital status and physical activity.

effects via complement activation, apoptosis, vascular cell activation, monocyte recruitment, lipid accumulation and thrombosis.<sup>48</sup> In this study, while the definitions of diabetes, dyslipidaemia and metabolic syndrome were based on the laboratory test results, the diagnoses of myocardial infarction, angina and stroke depended on the information provided by the participants during the

**Table 5** Association between log plasma C reactive protein level and individual components of metabolic syndrome and lipid profiles in multivariable linear regression analysis

Variables	$\beta$	SE	P value
Number of metabolic syndrome component	0.104	0.024	<0.001
Individual component			
Fasting glucose (mg/dL)	0.014	0.003	<0.001
HDL cholesterol (mg/dL)	-1.714	0.237	<0.001
Triglyceride (mg/dL)	0.043	0.010	<0.001
Waist circumference (cm)	0.463	0.077	<0.001
Systolic blood pressure (mm Hg)	0.405	0.253	0.112
Diastolic blood pressure (mm Hg)	0.179	0.179	0.320
Total cholesterol (mg/dL)	1.939	0.735	0.009
LDL cholesterol (mg/dL)	1.943	0.619	0.020

Adjusted for age, sex, income, region, education, marital status, alcohol consumption, body mass index, smoking, marital status and physical activity.

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

interview. Although the interview was conducted individually by a trained professional investigator, recall bias should be considered.

We analysed cut-off values for metabolic syndrome, as well as hypertriglyceridaemia and diabetes. The plasma CRP cut-off value for metabolic syndrome was 0.54 mg/L with 68.5% sensitivity and 48.1% specificity. The plasma CRP concentration was likely to be low because this was a study of the general population rather than hospitalised patients. The Centers for Disease Control and Prevention and the American Heart Association suggested that levels of  $\geq 3$  mg/L be used to determine high cardiovascular risk.<sup>49</sup> However, low levels of plasma CRP also provide important prognostic information on the cardiovascular risk. Ridker and Cook<sup>50</sup> reported that the predictive value of plasma CRP for cardiovascular events is linear across a full range of values, including low levels of plasma CRP. Cardiovascular risk was very low for individuals at the end of the spectrum with plasma CRP levels <0.5 mg/L. In participants with plasma CRP levels between 0.5 and 1.0 mg/L, the relative risk of cardiovascular event was 1.6 (95% CI 1.1 to 2.5) when compared with those with plasma CRP levels <0.5 mg/L after adjustment for Framingham Risk Score and additionally for diabetes. The cut-off values for hypertriglyceridaemia and diabetes were 0.56 mg/L and 0.53 mg/L, respectively. In hypertriglyceridaemia and diabetes, the sensitivity of the cut-off value was about 70% and the specificity was about 50%, which were similar to that of metabolic syndrome. This sensitivity is not very high (70%) and the specificity is low (50%). Therefore, the incorporation of plasma CRP into the diagnostic criteria for metabolic syndrome or cardiovascular risk factors is not suggested, based on the results of the current study. More studies on plasma CRP and other inflammatory markers are needed. However, these results suggest that people with completely normal plasma CRP levels are less likely to have metabolic syndrome, hypertriglyceridaemia and diabetes.

In this study, there was no association between plasma CRP and malignancy. Many case-control studies and prospective studies have demonstrated that plasma CRP is associated with increased cancer risks.<sup>51-54</sup> In a prospective study from Greece, 496 cases of cancer and 996 controls were analysed. This study reported higher plasma CRP levels in patients with cancer compared with controls. Plasma CRP levels have a strong association with the risk of cancers, including liver, lung, skin, kidney, bladder cancer and lymphoma/leukaemia, compared with other types of malignancy.<sup>53</sup> A Danish general population study of 10 408 individuals observed for up to 16 years showed that a baseline plasma CRP level more than 3 mg/L was associated with a 1.3-fold increased risk of any type of cancer compared with individuals with a plasma CRP level less than 1 mg/L.<sup>54</sup> However, other studies reported no significant association between plasma CRP and cancer.<sup>55-57</sup> In a US study of 28 345 healthy women aged 45 years or older who were followed prospectively, baseline plasma CRP was a reliable marker of risk of future CVD, but not



**Table 6** Prevalence of cardiovascular risk factors, metabolic syndrome, comorbidities and cancer according to lower and higher inflammation

Variables	n	Lower inflammation (plasma CRP <0.54 mg/L)	Higher inflammation (plasma CRP ≥0.54 mg/L)	P value
Stroke	121	41 (1.31)	80 (2.03)	0.037
Myocardial infarction or angina		68 (1.99)	97 (2.40)	0.332
Hypercholesterolaemia	1209	540 (16.58)	699 (21.57)	<0.001
Hypertriglyceridaemia	677	194 (9.83)	483 (22.15)	<0.001
Diabetes	744	243 (7.36)	501 (14.06)	<0.001
Impaired fasting glucose	1385	504 (17.48)	881 (28.85)	<0.001
Hypertension	1909	681 (20.87)	1228 (34.85)	<0.001
Prehypertension	1409	640 (24.32)	769 (26.96)	<0.001
Metabolic syndrome	2193	684 (21.81)	1509 (44.60)	<0.001
Osteoarthritis	639	250 (6.83)	389 (10.11)	<0.001
Rheumatoid arthritis	125	59 (1.76)	66 (1.68)	0.793
Osteoporosis	485	186 (4.76)	299 (7.35)	<0.001
Pulmonary tuberculosis	223	81 (2.91)	142 (4.31)	0.014
Asthma	157	64 (2.48)	93 (2.84)	0.483
Thyroid disease	223	114 (3.33)	109 (3.29)	0.007
Atopic dermatitis	152	81 (4.03)	71 (2.83)	0.053
Allergic rhinitis	784	390 (16.25)	391 (14.42)	0.117
Gastric cancer	42	20 (0.48)	22 (0.56)	0.654
Colon cancer	23	8 (0.17)	15 (0.31)	0.252
Breast cancer	30	15 (0.47)	15 (0.38)	0.608
Cervical cancer	38	20 (0.70)	18 (0.45)	0.215
Lung cancer	11	4 (0.10)	7 (0.19)	0.268
Thyroid cancer	59	27 (0.96)	32 (0.92)	0.906

Values are presented as unweighted n (weighted %).  
CRP, C reactive protein.

cancer.<sup>57</sup> In a Mendelian randomisation study, nine of the most common genotype combinations of four plasma CRP single nucleotide polymorphisms were associated with an increase in plasma CRP levels, but not with increased risk of cancers, suggesting that elevated plasma CRP does not cause cancer.<sup>55</sup> In this study, the number of participants with a diagnosis of cancer was small, and the study design was cross-sectional. We should consider reverse causation, survival bias or other confounding factors in the relationship between plasma CRP and cancers.

This study had several limitations. First, the definition of myocardial infarction or angina, stroke, cancer, and other comorbidities was dependent on the information provided by the participants during the interview. Although trained researchers asked participants in face-to-face interviews, participants may have misunderstood the information given by physicians. Second, we were unable to assess the use of medications, such as non-steroidal anti-inflammatory drugs or corticosteroids, that could have affected plasma CRP levels. Third, we could not exclude participants with acute inflammatory diseases, such as acute viral or bacterial infection. There

were no data about acute inflammatory conditions in this survey. In the participants with acute inflammatory disease, plasma CRP may not be suitable for estimation of the risk of comorbidities. Fourth, the causality could not be determined due to the cross-sectional design of this study. Fifth, we only analysed plasma CRP as an inflammatory marker. This was because IL-6 and other inflammatory cytokines were not included in the KNHANES data. Despite all these limitations, the strength of this study was that we analysed the association between plasma CRP and comorbidities using nationwide representative samples from the Korean adult population, adjusted for socioeconomic and lifestyle characteristics. Our comprehensive cross-sectional data provide additional information about the relationship between plasma CRP and comorbidities.

In conclusion, plasma CRP was positively associated with an increased risk of diabetes, dyslipidaemia and metabolic syndrome in the general population. The results of this study suggest that a low-grade inflammatory process may be related to cardiovascular risk factors. Clinicians should devote attention to glucose, lipid profile and central obesity in patients with elevated plasma CRP levels.

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