ORIGINAL ARTICLE

# Elevated C-reactive protein level, obesity, and quality of life

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## Abstract

**Objective:** To investigate the association between serum C-reactive protein level and health-related quality of life, and to assess the relationship between the two in terms of controlling for obesity and other covariates.

**Methods:** The cross-sectional study was conducted retrospectively at university hospital in Yangsan from January to December 2017 using the nationally representative 2015 Korea National Health and Nutrition Examination Survey (KNHANES). High C-reactive protein was defined as level ≥1.0mg/L. Health-related quality of life was assessed using the Euro-Quality of Life-5 dimensions tool. The association between high C-reactive protein and health-related quality of life was analysed using logistic regression analysis and was adjusted for variables. The subjects were categorised into four groups according to the level of C-reactive protein, and the presence of obesity was analysed.

**Results:** Of the 3376 subjects, 1,413(42%) were men and 1,963(58%) were women. C-reactive protein level was <1.0 in 2490(73.7%) subjects and ≥1.0 in 886(26.2%). High CRP level was associated with low health-related quality of life for mobility and usual activities ($p<0.05$). However, in multivariable logistic model, the associations ceased to be statistically significant ($p>0.05$) after adjusting for the presence of obesity.

**Conclusion:** Obesity was found to play an important role in the association between C-reactive protein and health-related quality of life in Korean population.

**Keywords:** Obesity, C-reactive protein, Quality of life. (JPMA 69: 1771; 2019) **DOI:10.5455/JPMA.298182**

## Introduction

Systemic inflammation has a key role in the pathogenesis of cardiovascular disease, type 2 diabetes mellitus (T2DM) and cancer.[1-3] Pro-inflammatory cytokines, such as serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-α), are biomarkers associated with systemic inflammation.[4] In particular, CRP has been recognised as a clinically useful biomarker of acute and chronic inflammation.[5] Obesity has been linked to systemic inflammation and has close connections with inflammatory biomarkers such as CRP and IL-6.[6,7]

CRP was originally identified as a biological marker that is produced by Kupffer cells in the liver, and that indicates an acute phase of inflammation. CRP had also been associated with low-grade, chronic inflammation.[5] Several studies have reported that high CRP levels are related to various diseases, including obesity, insulin resistance (IR), sleepapnoea, cancer and cardiovascular disease.[7-11] Notably, there is a close, positive association between obesity, when assessed on the basis of body mass index (BMI), and CRP level.

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Recently, there has been increased interest in associations between systemic chronic inflammation and health-related quality of life (HRQoL), and strong connections between these factors have been observed in patients with various diseases.[8,10,12,13] To date, however, relatively few studies have examined associations between CRP and HRQoL in the general population.[14-16] A study of 92 healthy adults found that CRP level had significant association with lower qualities of physical health and well-being after controlling for the effects of BMI and other relevant covariates.[14] Studies also found that chronic inflammation, as measured by CRP level, was associated with HRQoL in older adults.[15,16] However, previous studies have had small sample sizes, and have identified relationships between CRP and HRQoL without using specific cut-off values for CRP. This has limited their ability to thoroughly assess the potential clinical applicability of CRP as a marker related to HRQoL. In addition, because obesity is closely correlated with CRP, and because obesity and CRP could both affect HRQoL, more comprehensive investigations are needed to understand the inter-relationship involving obesity, CRP and HRQoL.

The current study was planned to validate and extend upon previous findings by using a national database to examine the associations between CRP level and HRQoL in the Korean population, and to evaluate the relationship between CRP level and HRQoL after controlling for the

effects of obesity and other relevant covariates. It also aimed at evaluating the potential of CRP as a marker for HRQoL along with obesity.

## Patients and Methods

The cross-sectional study was conducted retrospectively at university hospital in Yangsan from January to December 2017 using the nationally representative 2015 Korea National Health and Nutrition Examination Survey (KNHANES) which was conducted jointly by the Ministry of Health and Welfare and the Korea Centre for Disease Control using a stratified, multistage, probability sampling design.[17] It included health interview survey (HIS), health examination (HE), and nutrition survey (NS) components, and looked to generate statistical data on the general health and nutrition status of South Koreans. Data had been collected from 7,380 participants via household interviews, and standardised physical examinations had been conducted at mobile examination centres. For the purpose of the current study, we excluded participants aged <20 or >70 years; participants with relevant but unavailable laboratory results (such as for CRP), questionnaire responses (such as for the Euro-Quality-of-Life-5 five dimensions [EQ-5D] questionnaire, which is an indicator of HRQoL), health examination survey findings, or nutrition survey responses; participants who had been diagnosed with cancer, chronic kidney disease, liver cirrhosis, tuberculosis, or rheumatoid arthritis; participants who were pregnant; and participants with serum CRP levels ≥10mg/L (since acute inflammation status could not be ruled out). The study was approved by the Institutional Review Board at Pusan National University Yangsan Hospital (05-2017-115).

Height (cm) and weight (kg) were measured to the first place past the decimal point, and body mass index (BMI) was calculated as body-weight divided by height squared (kg/m$^2$). Using a tape measure (SECA 200, SECA Deutschland), waist circumference (WC) (cm) was measured from the halfway point between the lower line of the last rib and the upper line of the iliac crest. Measurements were taken when the participant exhaled, and were also recorded to the first place past the decimal point. Blood pressure (BP) was measured three times with an interval of 30 seconds after resting for five minutes in a seated position. The final BP was defined as the average BP of the second and third measurements.

Blood samples were collected from the antecubital vein following an eight-hour fast. Plasma blood glucose, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), alanine transaminase (ALT), and creatinine levels were measured (Hitachi automatic analyzer 7600-210, Hitachi, Japan). CRP level was analysed using immunoturbidimetry with a Cobasanalyser (Roche, Germany). A high CRP level was defined as CRP ≥1.0mg/L. The cut-off of 1.0mg/L was equal to the fourth quartile value of CRP levels.

HRQoL was assessed using the EQ-5D questionnaire, which consisted of five dimensions: mobility, self-care, usual activity, pain/discomfort, and depression/anxiety. For each dimension, responses were divided into three categories: 'no problem', 'moderate problem', or 'extreme problem'. Because of the frequency of 'extreme problem' responses, the responses were then dichotomised into 'no problem' vs. 'problem'. The average EQ-5D index scores were calculated to assess HRQoL, which is a preference-based health status index.[17]

Income, marriage status, and chronic diseases were assessed in interviews conducted by the researchers, and social history was obtained through questionnaires. Income was categorised as low, middle-low, middle-high, or high. Marriage status and current smoking status were reported as dichotomous variables. Obesity was defined as BMI ≥25kg/m$^2$ according to Asian-Pacific standards.[18] Comorbidity was also assessed as a dichotomous variable, as was considered to be present if the participant reported a physician-diagnosed medical history of one or more of the following diseases: T2DM, hypertension (HTN), dyslipidemia, stroke, myocardial infarction (MI), or angina pectoris. The analysis of nutritional values (including total calories, protein, fat, fibre, and sodium) was performed by trained dieticians based on the participants' 24-hour dietary recall.

Data was analysed using SPSS 18. The statistical analysis accounted for the complex sampling design of the KNHANES[17] to minimise selection errors; the estimates reported in this study were obtained considering the primary sampling unit, stratification variables, and sampling weights.[19-22] Descriptive data was expressed as the mean ± standard error or frequencies and percentages. Independent t-test and chi-square test were used to evaluate differences between the two CRP-based groups in terms of general characteristics, socio-demographic parameters, anthropometric parameters, biochemical results, dietary parameters, EQ-5D dimension, and EQ-5D index values. Multiple logistic regression analysis was used to evaluate associations between high CRP (≥1.0 mg/L, analysed as an independent variable) and life quality (as represented by EQ-5D categories, and analysed as dependent variable). The odds ratios (ORs) were estimated in analyses that

adjusted for age, gender, smoking status, comorbidity and the presence of obesity. In order to evaluate the relationships involving obesity, CRP and EQ-5D dimensions, the participants were classified into four groups according to CRP level and the presence of obesity. Multiple logistic regression was performed, including the four groups in the model and adjusting for variables including age, gender, smoking status and comorbidity. P-values were two-sided and p<0.05 was considered statistically significant.

## Results

Of the 7,380 participants assessed by KNHANES, 3,376(45.7%) were included in the current study. Of them, 1,413(42%) were men and 1,963(58%) were women. CRP level was <1.0 in 2490(73.7%) subjects who had a mean age of 43.0 ±0.4 years, and ≥1.0 in 886(26.2%) whose mean age was 44.3±0.6 years. Participants in the high CRP group were older, mostly male, and more likely to be current smokers (p<0.05 each). However, household income and marital status did not differ between the two CRP groups. BMI, WC and BP were significantly higher in the high CRP group (p<0.05 each). Plasma blood glucose, TC, LDL-C, HDL-C, TG and ALT were greater in the high CRP group than in the non-high CRP group (p<0.05 each). However, no significant differences in nutritional values (including daily energy) were observed between the groups (p>0.05). More participants had comorbidities in the high CRP group (p<0.001) (Table-1).

Table-1: Characteristics of the study cohort, as stratified by CRP subgroup.

| | CRP | | P value |
|---|---|---|---|
| | <1.0 (n=2490) | ≥1.0 (n=886) | |
| Age, y | 43.0 ± 0.4 | 44.3 ± 0.6 | 0.033 |
| Gender, male % | 996 (35.7) | 417 (47.1) | 0.002 |
| Quartile of household income, % | | | 0.160 |
| Lowest | 290 (10.0) | 121 (11.2) | |
| Low-intermediate | 595 (22.2) | 232 (25.5) | |
| High-intermediate | 744 (31.6) | 255 (31.4) | |
| Highest | 849 (36.3) | 275 (31.9) | |
| Married, % | 2035 (74.6) | 747 (76.2) | 0.528 |
| Current smoker, % | 396 (20.2) | 200 (27.3) | 0.001 |
| Body mass index, kg/m$^2$ | 23.2 ± 0.1 | 25.7 ± 0.2 | <0.001 |
| Waist circumference, cm | 80.3 ± 0.2 | 87.4 ± 0.4 | <0.001 |
| Systolic BP, mm/Hg | 114.3 ± 0.4 | 118.6 ± 0.6 | <0.001 |
| Diastolic BP, mm/Hg | 75.2 ± 0.3 | 77.0 ± 0.4 | <0.001 |
| Fasting plasma glucose, mg/dL | 96.4 ± 0.5 | 104.1 ± 1.3 | <0.001 |
| ALT, IU/L | 20.6 ± 0.4 | 29.9 ± 1.3 | <0.001 |
| Creatinine, mg/dL | 0.84 ± 0 | 0.85 ± 0 | 0.035 |
| CRP, mg/L | 0.45 ± 0.01 | 2.46 ± 0.08 | <0.001 |
| Total cholesterol, mg/dL | 190.2 ± 0.8 | 195.7 ± 1.4 | <0.001 |
| LDL-cholesterol, mg/dL | 113.0 ± 0.7 | 120.5 ± 1.3 | <0.001 |
| HDL-cholesterol, mg/dL | 53.2 ± 0.3 | 47.0 ± 0.5 | <0.001 |
| Triglyceride, mg/dL | 130.4 ± 3.2 | 166.0 ± 5.5 | <0.001 |
| Energy, Kcal/day | 2197.9 ± 27.0 | 2242.2 ± 44.0 | 0.375 |
| Protein, g/day | 78.8 ± 1.6 | 77.9 ± 1.8 | 0.694 |
| Fat, g/day | 52.1 ± 1.1 | 51.6 ± 1.6 | 0.814 |
| Carbohydrate, g/day | 319.7 ± 3.4 | 332.0 ± 5.8 | 0.055 |
| Comorbidity*, % | 599 (17.8) | 266 (24.3) | <0.001 |

Data are expressed as mean ± standard error or number (%).
P values are from two-sample t-tests or chi-square tests.
BP, blood pressure; ALT, alanine aminotransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; EQ-5D, EuroQol-5 Dimension
*One or more diseases, including diabetes mellitus, hypertension, dyslipidemia, stroke, myocardial infarction, and/or angina pectoris.

Table-2: Comparison of the total EQ-5D index, each of the 5 included dimensions between CRP groups.

| | CRP | | P value |
|---|---|---|---|
| | <1.0 (n=2490) | ≥1.0 (n=886) | |
| EQ-5D index | 0.97 ± 0 | 0.96 ± 0 | 0.016 |
| Mobility (n) | 193 (5.8) | 93 (8.7) | 0.005 |
| Self-care (n) | 53 (1.7) | 20 (1.7) | 0.982 |
| Usual activities (n) | 127 (4.0) | 59 (6.3) | 0.021 |
| Pain/discomfort (n) | 519 (18.0) | 198 (21.5) | 0.053 |
| Anxiety/depression (n) | 238 (8.1) | 80 (7.9) | 0.908 |

Data are expressed as numbers ± standard.
P values are from two-sample t-tests or chi-square tests.
CRP, C-reactive protein; EQ-5D, EuroQol-5 Dimension.

The EQ-5D index score was lower in the high CRP group than in the non-high CRP group, indicating lower quality of life with higher CRP (Table-2). There were significant differences between the CRP groups for the EQ-5D dimensions of mobility and usual activities (p<0.05 each). The dimension of pain/discomfort differed between the groups, but not significant (p>0.05). Additionally, self-care and depression/anxiety dimensions did not (p>0.05 each).

Logistic regression analysis showed that perceived problems with mobility (OR: 1.553, 95% confidence interval [CI]: 1.145-2.107) and usual activity (OR: 1.599, 95% CI: 1.072-2.386) were associated with high CRP level. The EQ-5D dimensions of self-care, pain/discomfort, and anxiety/depression were not associated with high CRP (Table-3).

After adjusting for age, gender, smoking status and comorbidity, the mobility and usual activity dimensions of quality of life were still associated with high CRP (Model 1). However, after adjusting for the presence of obesity (BMI ≥25kg/m$^2$) in addition to the other variables from Model 1, high CRP no longer had a significant association with any of the EQ-5D dimensions (p>0.05 each).

In multiple logistic regression analysis, adjusting for several covariates, mobility, usual activities, and

Table-3: Relationships between CRP level and each dimension of the EQ-5D descriptive system for assessing quality of life.

| Outcome variable | Crude OR (95% CI) ≥1.0 | P-value | Model 1 OR (95% CI) ≥1.0 | P-value | Model 2 OR (95% CI) ≥1.0 | P-value |
|---|---|---|---|---|---|---|
| Mobility | 1.553 (1.145-2.107) | 0.020 | 1.380 (1.009-1.888) | 0.044 | 1.279 (0.909-1.799) | 0.157 |
| Self-care | 0.982 (0.526-1.931) | 0.908 | 0.877 (0.470-1.639) | 0.681 | 0.784 (0.420-1.462) | 0.443 |
| Usual activities | 1.599 (1.072-2.386) | 0.022 | 1.501 (1.020-2.210) | 0.039 | 1.385 (0.899-2.134) | 0.140 |
| Pain/discomfort | 1.246 (0.998-1.555) | 0.052 | 1.220 (0.975-1.528) | 0.082 | 1.147 (0.903-1.456) | 0.260 |
| Anxiety/depression | 0.981 (0.902-1.370) | 0.908 | 0.965 (0.683-1.363) | 0.838 | 0.981 (0.685-1.404) | 0.915 |

Model 1: Adjusted for age, sex, current smoking status, and comorbidity. The variables were adjusted for using the following categorizations: age, 10 years; sex, male vs. female; smoking status, current smoker vs. non-smoker (never or former smoker); and comorbidity, none vs. one or more diseases, including diabetes mellitus, hypertension, dyslipidemia, stroke, myocardial infarction, and angina pectoris.
Model 2: Model 2 + adjusted for the presence of obesity (BMI >25 kg/m$^2$)
CRP, C-reactive protein; EQ-5D, EuroQol-5 Dimension; OR, odds ratios; 95% CI, 95% confidence interval.

Table-4: Relationships between obesity, CRP, and EQ-5D dimensions.

| | Normal CRP & Non-obese (N=1705) | Normal CRP & Obese (N=785) | High CRP & Non-obese (N=404) | High CRP & Obese (N=482) | P for trend |
|---|---|---|---|---|---|
| Mobility | 1 | 1.556 (1.059-2.287) | 1.507 (0.866-2.621) | 1.740 (1.173-2.580) | 0.024 |
| Self-care | 1 | 0.265 (0.576-2.780) | 0.306 (0.100-0.936) | 1.452 (0.710-2.970) | 0.080 |
| Usual activities | 1 | 1.716 (1.082-2.722) | 1.842 (0.964-3.522) | 1.862 (1.195-2.901) | 0.013 |
| Pain/discomfort | 1 | 1.594 (1.250-2.034) | 1.549 (1.107-2.169) | 1.365 (1.028-1.813) | 0.001 |
| Anxiety/depression | 1 | 0.961 (0.679-1.360) | 1.037 (0.637-1.687) | 0.885 (0.576-1.358) | 0.092 |

Data are expressed as odds ratios and 95% confidence interval
Adjusted for age, sex, current smoking status, and comorbidity
Normal CRP: CRP level below 1.0mg/L.
Obesity: BMI over 25 kg/m$^2$
High CRP: CRP level over 1.0 mg/L.
CRP, C-reactive protein; EQ-5D, EuroQol-5 Dimension.

pain/discomfort components of HRQoL differed in the four groups ($p<0.05$ each). The presence of obesity was a crucial factor associated with the mobility, usual activities, and pain/discomfort HRQoL components (Table-4).

## Discussion

The study confirmed that high CRP level was associated with low HRQoL in the general population. Participants with high CRP levels had a high probability of self-reported impediments to mobility and usual activities. However, when applying a multivariable logistic model to the results, these initial associations disappeared after adjusting for the presence of obesity, which suggests that obesity status is a confounding factor for the correlations between CRP level and the life quality dimensions of mobility and continuation of usual activities. Categorising the participants into four groups according to quartiles of CRP level and obesity status revealed meaningful differences in mobility, usual activities, and pain/discomfort.

Previous studies have reported correlations between inflammation and poor HRQoL, and that serum CRP is a useful marker of chronic inflammation in chronic medical conditions.[7-13] In relatively healthy adults, similar outcomes have also been suggested.[14-16] Among the relatively few studies that have investigated general populations, one reported that increased CRP level was also associated with pain and overall physical health in healthy participants, independent of their BMIs.[14] Non-specific pain, fatigue, and lower overall quality of physical health were all associated with higher CRP level, but depression symptoms and other indices of mental/emotional wellbeing did not have associations with CRP level. These results continued to be observed after adjusting for age, gender, BMI and socioeconomic status. The findings were similar to our findings, at least in terms of the relationships between high CRP level and low values of the mobility, usual activity and pain/discomfort dimensions of HRQoL. Nevertheless, CRP level did not show statistically significant associations with the pain/discomfort domain in our study.

Christian LM et al.[15] showed that poorer self-rated health is associated with elevated serum CRP and IL-6 levels among generally healthy older adults, and also reported an inverse association with HRQoL after adjusting for age, gender, BMI and health conditions. In contrast with preceding studies, our results showed that adjustment for obesity status removed the statistically significant

associations between high CRP level and worse values of the mobility and usual activity dimensions of HRQoL. These changes suggest that obesity and CRP share a causal pathway, with respect to their relationships with poor HRQoL. In numerous studies, obesity status (based on BMI or WC) has been regarded as having a crucial relationship with high CRP levels.[6,8] The discordance between the results of the present study and previous research may be attributed to the fact that previous studies included small sample sizes and only observed relationships between CRP and HRQoL, without applying a specific cut-off value for CRP. In addition, high CRP levels can be seen in cases of acute illness,[5] which could affect HRQoL, but which were not excluded from previous studies. In the present study, categorising participants into four groups according to both CRP level and obesity status revealed significant differences in the mobility, usual activities, and pain/discomfort components of life quality, suggesting that participants with high CRP levels and obesity may have experienced limitations related to mobility, usual activity and pain/discomfort.

Depression and anxiety are reportedly related to increased levels of CRP,[23,24] but our results did not show an association between CRP level and reported depression/anxiety. The results are consistent with another study on the relationship between CRP level and physical and mental health.[14] Because the EQ-5D assessment has limitations related to the identification of symptoms of depression and anxiety, further studies are needed to evaluate the relationship between mental health and CRP level in South Korea.

Obesity, the excess accumulation of fat, results in chronic low-grade inflammation due to reduced blood supply and neutrophils, as well as resident macrophage infiltration into adipose tissue.[25,26] In obesity, the production of pro-inflammatory adipokines are upregulated and may promote obesity-related metabolic disorders, including IR, metabolic syndrome and cardiovascular disease.[27-] In addition, sustained inflammation can negatively affect individual HRQoL. Serum CRP appears to be a useful marker of inflammation relative to HRQoL, and may be useful as an index of quality of life, considering both CRP level and obesity status.

The current study has several limitations. First, because it had a cross-sectional design, a causal relationship between serum CRP and HRQoL could not be established. Second, although we excluded several confounding factors that could have affected CRP level (including cancer, chronic kidney disease, liver cirrhosis, tuberculosis, and rheumatoid arthritis), other diseases and unidentified cases of disease could have been present, and might have affected the associations. Third, the EQ-5D is a relatively simple method of evaluating HRQoL and might not have been sufficient to provide a thorough evaluation of HRQoL, and the value of the questionnaires may have differed, depending on the dimension of assessment. Finally, in our study, the cut-off value for high CRP was 1mg/L, which was chosen to be equal to the fourth quartile value of CRP. This value is relatively low in comparison with other studies on CRP.[13,14] However, in a study that evaluated the combined relationships of systemic inflammation and body size with IR in a Japanese cohort, the fourth quartile of serum CRP level was 0.64 mg/dL(30.31). Further studies are necessary to define high CRP levels in different ethnic groups. Future studies should also investigate whether serum levels of CRP can predict physical and mental status in healthy individuals based on longitudinal observations.

Despite the limitations, we believe the findings are meaningful because the study has made a novel, large-scale attempt to evaluate CRP as a marker for HRQoL, along with obesity. Further, the study evaluated the relationships between CRP and HRQoL after controlling for the effects of obesity based on a nationally representative dataset of South Korean adults.

## Conclusion

High CRP level was associated with low HRQoL in terms of mobility and participation in usual activities in South Korean population. Obesity was found to play an important role in the association between CRP and HRQoL in South Korean population.

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**Conflict of Interest:** None.

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