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Sarcopenic obesity associated with high-sensitivity C-reactive protein in age and sex comparison: a two-center study in South Korea

Chul-Hyun Park,[1,2] Jong Geol Do,[1] Yong-Taek Lee,[1] Kyung Jae Yoon[1]

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Y-TL and KJY contributed equally.

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[1]Department of Physical & Rehabilitation Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea
[2]Department of Rehabilitation Medicine, Graduate School of Medicine, Chung-Ang University, Seoul, Korea

Correspondence to
Dr Yong-Taek Lee; yongtaek1.lee@gmail.com and Dr Kyung Jae Yoon; kint99@gmail.com

ABSTRACT

Objectives To evaluate the association between high-sensitivity C-reactive protein (hs-CRP) and sarcopenic obesity, and to determine age or sex differences underlying the relationship between hs-CRP and sarcopenic obesity.

Design Observational study.

Participants The study included 237 838 participants whose body composition and hs-CRP were analysed at the two health promotion centres in South Korea. Participants were divided into four groups based on body composition: normal, obesity only, sarcopenia only and sarcopenic obesity.

Primary measures The levels of hs-CRP and proportion of participants with high (≥1.0 mg/L) hs-CRP. Sarcopenic obesity was defined as subjects fulfilling the criteria for sarcopenia (below 2 SD of mean of Skeletal Muscle Mass Index for young adults) and obesity (waist circumference ≥90 cm for men and ≥85 cm for women).

Results The level of hs-CRP was highest in the sarcopenic obesity group. Following adjustment for various confounders including age, sex, comorbidities, metabolic, health-related behaviour and demographic factors, the adjusted ORs (95% CI) for subjects with high hs-CRP associated with obesity, sarcopenia and sarcopenic obesity compared with normal group (reference) were 1.17 (1.05 to 1.31), 2.23 (1.21 to 4.07) and 3.23 (2.71 to 3.83), respectively. In age subgroup analyses, multivariate logistic regression analysis revealed that the association of high hs-CRP with sarcopenic obesity was stronger in younger (<60 years) participants than in older (≥60 years) participants (p for interaction <0.001). In subgroup analyses for sex, the association of high hs-CRP with sarcopenic obesity was higher in female participants than in males (p for interaction <0.001).

Conclusions This study demonstrated that high level of hs-CRP was independently associated with sarcopenic obesity in Korean population. We found for the first time that there was a strong association between increased hs-CRP and sarcopenic obesity in female and younger (<60 years) subjects.

Strengths and limitations of this study

- This study was performed with a large sample of participants (n=237 838) to explore the relationship between high-sensitivity C-reactive protein (hs-CRP) and sarcopenic obesity.
- For the first time, we demonstrated age and sex differences in association between increased hs-CRP level and sarcopenic obesity.
- The association of high hs-CRP level with sarcopenic obesity was investigated after adjusting for potential confounders such as age, sex, comorbidities, metabolic, health-related behaviour and demographic factors. Nevertheless, there is always a potential of residual confounding given the observational design of the study.
- The potential for selection bias existed, as elderly subjects were relatively smaller than middle-aged subjects.

INTRODUCTION

Sarcopenia, described as the generalised loss of skeletal muscle, is an emerging health challenge in an ageing society.[1 2] Recent studies reported that the loss of skeletal muscle is associated with several chronic conditions such as cardiovascular disease, diabetes mellitus (DM), chronic lung disease and metabolic disorders.[3 4] However, sarcopenia often coexists with an increased fat mass, so-called sarcopenic obesity (SO).[5] Obesity is a well-known risk factor for cardiovascular, endocrine and metabolic disorders.[6 7] Therefore, a double metabolic burden due to sarcopenia and obesity (called SO) is assumed to potentiate each other and synergise their adverse health effects.[8]

C-reactive protein (CRP) is a critical marker of inflammation and a predictor of overall mortality.[9–11] However, the standard CRP assay plays a limited role in identifying low-grade inflammation because the standard CRP assay measured down to concentrations of 3–5 mg/L.[12 13] High-sensitivity CRP (hs-CRP) enables detection of even mild elevations of hs-CRP, as low as 0.1 mg/L.[13 14] Therefore, hs-CRP provides improved sensitivity for detection of low-grade inflammation including subclinical inflammation.[14]

Low-grade inflammation is a key feature of obesity.[15] Furthermore, recent reports demonstrated a strong association between elevated hs-CRP and abdominal obesity.[16 17] Sarcopenia is also closely linked to low-grade inflammation in a few studies.[18 19] However, few studies have demonstrated the relationship between hs-CRP and sarcopenia. Furthermore, the effects of coexisting sarcopenia and obesity on hs-CRP have been under-recognised. Additionally, because of variation in hs-CRP across age and gender,[20] the role of age and gender differences in the association between hs-CRP and SO needs to be established.

The aims of this study were (1) to investigate the association of hs-CRP with SO and (2) to evaluate age or sex differences in the relationship between hs-CRP and SO.

MATERIALS AND METHODS

Study population

A cross-sectional study was conducted to investigate the association of hs-CRP with SO in Korean population. Study participants were recruited from a medical health screening programme at the two health promotion centres of Kangbuk Samsung Hospital in Seoul and Suwon. Between January 2012 and December 2015, a total of 237 838 participants (18–89 years old) were included in the present study, and their hs-CRP and body composition were analysed.

Patient and public involvement

Neither patients nor public were involved in the development of the research question, in the study design and in drawing conclusions from the results.

Laboratory and anthropometric measurements

Data, including demographic characteristics, educational level (<college graduation vs ≥college graduation), alcohol history, smoking status, physical activity, total nutrient intake and medical history of hypertension (HTN), DM, heart disease, stroke and hyperlipidaemia, were collected by the examining physicians using standardised self-administered questionnaires. Subjects with alcohol consumption over 20 g/day were categorised into a heavy drinking group. Individuals with smoking history were grouped into never, former or current smoking categories. Physical activity was assessed using the International Physical Activity Questionnaire-Short Form. Regular physical activity was subjects who performed vigorous exercise >3 times/week for over 20 min/session or moderate exercise >5 times/week for over 30 min/session. Total nutrient intake (kcal/day) was assessed using a 103-item self-administered Food Frequency Questionnaire validated for usage in South Korea, and estimated using a food composition table developed by the Korean Nutrition Society.

Serum biochemical parameters and anthropometric measurements were collected by trained nurses. Blood specimens were collected from the antecubital vein in the morning after at least 10 hours of fasting. Serum biochemical parameters included hs-CRP, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, glycated haemoglobin, homoeostasis model assessment of insulin resistance (HOMA-IR) and alanine aminotransferase (ALT). Insulin resistance was calculated using the following formula: HOMA-IR=-fasting serum insulin (μU/mL) x fasting serum glucose (mg/dL)/405. Serum creatinine assays were analysed using an enzyme caloric method by a Hitachi Automatic Analyzer 7600 (Hitachi, Japan) and calibrated with the isotope dilution mass spectroscopic standard. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) was applied to obtain estimated glomerular filtration rate (eGFR). CKD was defined as eGFR <60 mL/min per 1.73 m^2.[21] Waist circumference (WC) (cm) was measured as the smallest circumference between the lower end of the sternum (xiphoid process) and the umbilicus. Skeletal muscle mass (kg) was estimated using a bioelectrical impedance analysis (BIA) with eight-point tactile electrodes (InBody 720, Biospace, South Korea). The BIA was calibrated every morning prior to the test and validated for reproducibility and accuracy for analysis of skeletal muscle mass.

Measurement of hs-CRP

Low-grade inflammation was assessed according to serum hs-CRP level, which was analysed using a nephelometric assay with a BN II nephelometer (Dade Behring, Deerfield, Illinois, USA). Participants were grouped into low (<1.0 mg/L) and high (≥1.0 mg/L) hs-CRP groups. Serum hs-CRP below 1 mg/L was considered a healthy level due to its lowest risk for cardiovascular diseases,[22 23] and this cut-off value has been widely used in previous studies.[24–27] Values of hs-CRP exceeding 10 mg/L were excluded.

Sarcopenia and SO

Skeletal Muscle Mass Index (SMI) was estimated using the following formula: SMI (%)=skeletal muscle mass (kg)/bodywt (kg) x 100, according to the established method by Janssen *et al*.[28] Sarcopenia was defined as SMI less than 2 SD below the sex-specific mean of a young adult (20–39 years old).[28] The cut-off levels for sarcopenia were 36.7% in men and 32.2% in women, respectively. Obesity was defined as WC ≥90 cm for males and ≥85 cm for females, based on the cut-off points for central obesity in Korean population.[29] Thus, SO was defined as sarcopenia combined with WC ≥90 cm in men and ≥85 cm in women, respectively.[30 31]

Statistical analysis

Baseline demographic characteristics among the study groups of body composition were compared using one-way analysis of variance (ANOVA) for continuous variables and X^2 test for categorical variables. Additionally, after adjustments for age, sex, comorbidities (HTN, DM, stroke and heart disease), LDL-C, HOMA-IR, ALT,

eGFR, health behavioural (smoking, alcohol drinking, physical and energy intake) and demographic factors (marital status and education level), the adjusted means were compared between the study groups using analysis of covariance.

Multivariate logistic regression analyses were conducted to determine the association between high hs-CRP (≥1.0 mg/L) and the study groups with varying body composition. ORs were calculated as the risks for subjects with high hs-CRP values in obesity only, sarcopenia only and SO compared with normal (reference), respectively. We performed two different models with multivariate adjustments for confounding variables. The first model (model 1) was adjusted for age, sex, comorbidities (HTN, DM, stroke, heart disease), LDL-C, HOMA-IR, ALT and eGFR. The second model (model 2) was additionally adjusted for health behavioural (smoking, alcohol drinking, physical, energy intake) and demographic factors (marital status and education level). Furthermore, hs-CRP was introduced as a continuous variable. Multivariate-adjusted coefficients (95% CI) were estimated according to multivariate general linear models using natural log (hs-CRP +1) as the outcome for increasing hs-CRP in the study groups. We repeated multivariate general linear models for subgroup analyses in study subjects stratified by gender (male and female) and age (<60 years vs ≥60 years). Interactions by subgroup were conducted using likelihood ratio tests comparing models with and without multiplicative interaction terms. The level of statistical significance was set at p<0.05. All analyses were conducted using IBM SPSS V.18.0 (IBM).

RESULTS

Baseline demographic characteristics of study participants

The baseline characteristics of the 237 838 eligible participants according to four different groups of body composition are reported in table 1. The mean age of all participants was 39.0 (SD 8.9) years, and the proportion of males was 53.9%. The proportions of the normal, obesity only, sarcopenia only and SO groups were 77.1%, 19.9%, 0.3% and 2.7%, respectively. The group differences in baseline characteristics according to the body composition were significant for all variables (all p<0.001).

Comparison of hs-CRP according to body composition

Significant group differences existed in continuous level of hs-CRP (online supplementary table S1; p for one-way ANOVA <0.001; figure 1). Among the four groups, the level of hs-CRP was highest in SO. The level of hs-CRP gradually increased from normal to obesity only group, obesity only to sarcopenia only group and sarcopenia only to SO group, even after adjustment for various confounders (figure 1; adjusted p<0.001; p for trend <0.001). The proportions of subjects with high levels of hs-CRP (≥1.0 mg/L) were 1.2%, 1.5%, 2.4% and 4.0% in normal, obesity only, sarcopenia only and SO groups, respectively, and showed a positive trend along the study groups (p for trend <0.001).

Relationship between hs-CRP and body composition

Table 2 presents the results of univariate and multivariate logistic regression analyses between the high levels of hs-CRP (≥1.0 mg/L) and the groups with body composition. In the first model (model 1), adjusted for possible confounders (age, sex, HTN, DM, heart disease, stroke, LDL-C, HOMA-IR, ALT and eGFR), adjusted ORs (95% CI) for subjects with high hs-CRP for obesity only, sarcopenia only and SO groups compared with normal group (reference) were 1.19 (1.08 to 1.31), 2.34 (1.43 to 3.79) and 3.39 (2.95 to 3.89) (p for trend <0.001). The second model (model 2) was additionally adjusted for health-related behaviour and demographic factors including smoking, heavy drinking, physical activity, total energy intake, marital status and educational level. Adjusted ORs (95% CI) for subjects with high hs-CRP for obesity only, sarcopenia only and SO groups compared with normal group (reference) were 1.17 (1.05 to 1.31), 2.23 (1.21 to4.07) and 3.23 (2.71 to 3.83) (p for trend <0.001).

When hs-CRP was introduced as a continuous variable, multivariate (model 2) linear regression analyses between hs-CRP and the study groups were performed (online supplementary figure S1). In the model 2 analyses, the coefficients for obesity only, sarcopenia only and SO groups compared with normal group (reference) were 1.48 (1.45 to 1.52), 1.98 (1.81 to 2.17) and 2.74 (2.60 to 2.90), respectively (p for trend <0.001).

Sex differences in the relationship between hs-CRP and body composition

Based on sex subgroup analyses, the associations between hs-CRP and body composition are presented in figure 2A and table 3. In both male and female groups, there was a positive trend in adjusted ORs for the subjects with high hs-CRP (≥1.0) in obesity only, sarcopenia only and SO groups compared with the normal group (all p for trend <0.001). Interestingly, the associations of high hs-CRP (≥1.0) with obesity only, sarcopenia only and SO groups were stronger in females than in male participants (table 3; p for interaction <0.001). When using hs-CRP as a continuous variable, these associations were sustained showing higher coefficients in females than in male groups (figure 2A; p for interaction <0.001).

Age differences in relationship between hs-CRP and body composition

In age subgroup analyses, the associations between hs-CRP and body composition are presented in figure 2B and table 3. In multivariate logistic regression models, the associations of high hs-CRP (≥1.0) with obesity only, sarcopenia only and SO groups were stronger in younger (<60 years) participants than in older (≥60 years) participants (table 3; p for interaction <0.001). When hs-CRP was introduced as a continuous variable, these associations

Table 1 Baseline characteristics of study subjects according to body composition (n=237 838)

Variables	Normal (n=1 83 326)	Obesity only (n=47 305)	Sarcopenia only (n=694)	Sarcopenic obesity (n=6513)	P values
Demographic factors					
Age (year)	38.5 (8.6)	40.5 (9.2)	41.6 (12.9)	40.0 (11.3)	<0.001*
Sex					
Male (%)	48.6	75.0	23.6	51.3	<0.001†
Female (%)	51.4	25.0	76.4	48.7	<0.001†
Marital status, married (%)	79.4	82.8	69.2	71.5	<0.001†
College graduate (%)	64.3	63.4	48.3	50.8	<0.001†
Height (cm)	166.4 (8.1)	171.4 (8.2)	158.1 (7.4)	165.6 (9.1)	<0.001*
Weight (kg)	61.2 (9.9)	79.4 (10.3)	62.9 (7.7)	84.7 (14.3)	<0.001*
BMI (kg/m^2)	22.0 (2.4)	26.9 (2.2)	25.1 (2.2)	30.7 (3.4)	<0.001*
Waist circumference (cm)	77.8 (6.9)	93.4 (4.7)	81.9 (4.2)	99.7 (8.3)	<0.001*
Skeletal muscle mass (kg)	25.3 (5.6)	31.7 (5.8)	19.6 (3.0)	27.1 (6.2)	<0.001*
SMI (%)	41.4 (3.6)	39.3 (3.2)	32.2 (2.2)	32.9 (2.8)	<0.001*
Health behavioural factors					
Current smoker (%)	18.8	31.6	8.5	23.0	<0.001†
Heavy drinking (%)	14.5	26.9	7.9	20.0	<0.001†
Regular physical activity (%)	15.9	15.5	10.6	10.6	<0.001†
Daily energy intake (cal/day)	1429.2 (690.0)	1551.2 (753.6)	1348.0 (736.1)	1486.6 (801.8)	<0.001*
Comorbidity					
Hypertension (%)	5.8	16.2	12.3	22.3	<0.001†
Diabetes mellitus (%)	1.9	4.6	3.2	6.0	<0.001†
Heart disease (%)	0.6	1.1	1.6	1.4	<0.001†
Stroke (%)	0.3	0.5	1.0	0.7	<0.001†
Hyperlipidaemia (%)	10.3	21.4	15.3	22.9	<0.001†
Chronic kidney disease (%)	0.2	0.6	1.0	0.7	<0.001†
Laboratory findings					
Total cholesterol (mg/dL)	190.4 (32.8)	203.6 (35.6)	202.1 (36.2)	206.1 (36.7)	<0.001*
LDL-C (mg/dL)	115.4 (30.6)	130.9 (32.1)	125.9 (33.3)	132.6 (33.1)	<0.001*
HDL-C (mg/dL)	60.3 (14.8)	49.9 (12.0)	59.2 (14.7)	50.7 (12.1)	<0.001*
Triglycerides (mg/dL)	98.3 (64.6)	153.6 (97.1)	109.3 (61.1)	149.8 (93.0)	<0.001*
Fasting glucose (mg/dL)	93.3 (12.6)	99.5 (17.6)	95.4 (15.3)	102.2 (22.6)	<0.001*
Fasting insulin (IU/L)	5.2 (4.0)	8.8 (5.7)	7.1 (3.8)	12.1 (7.1)	<0.001*
HbA1c (%)	5.5 (0.4)	5.7 (0.6)	5.6 (0.5)	5.8 (0.7)	<0.001*
HOMA-IR	1.2 (1.1)	2.2 (1.7)	1.7 (1.0)	3.1 (2.3)	<0.001*
ALT (U/L)	19.6 (17.3)	33.7 (27.6)	22.7 (18.1)	39.9 (35.0)	<0.001*
eGFR (mL/min/1.73 m^2)	100.9 (14.0)	96.5 (14.1)	106.6 (15.6)	101.6 (15.3)	<0.001*

Data are presented as means (SD) or percentage.
P values for group difference by *one-way ANOVA in continuous variables or by †χ^2 test in categorical variables.
ANOVA, analysis of variance; ALT, alanine aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homoeostasis model assessment of insulin resistance; LDL-C, low-density lipoprotein cholesterol; SMI, Skeletal Muscle Mass Index.

persisted showing higher coefficients in younger than in older groups (figure 2B; p for interaction <0.001).

Additionally, we performed stratified analyses according to CKD status (present or absent) (online supplementary table S2). In multivariate logistic regression models, only the subgroup without CKD (eGFR ≥60) showed a positive trend in adjusted ORs for the subjects with high hs-CRP (≥1.0) in obesity only, sarcopenia only and SO groups compared with the normal group (p for trend <0.001). Due to a smaller

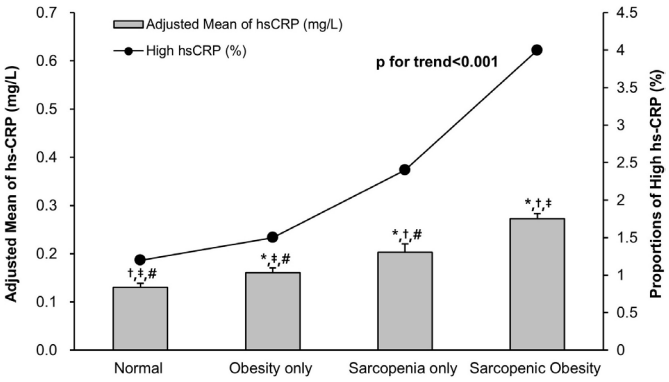

Figure 1 Comparison of hs-CRP between study groups according to body composition. Adjusted means of hs-CRP in the study groups were estimated from ANCOVA after adjustments for age, sex, comorbidities (HTN, DM, heart disease, stroke), LDL-C, HOMA-IR, ALT, eGFR, health behavioural (smoking, heavy drinking, physical activity, energy intake) and demographic factors (marital status, education level). *Adjusted p<0.001 versus normal group in post hoc analysis. †Adjusted p<0.001 versus obesity only group in post hoc analysis. ‡Adjusted p<0.001 versus sarcopenia only group in post hoc analysis. #Adjusted p<0.001 versus sarcopenic obesity group in post hoc analysis. ANCOVA, analysis of covariance; ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HOMA-IR, homoeostasis model assessment of insulin resistance; HTN, hypertension; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

number in the group with CKD, this analysis might be subject to power constraints.

DISCUSSION

The two major findings of the study are as follows. First, the increased level of hs-CRP was independently associated with different groups of body composition, and the association was highest with SO group. Second, in subgroup analyses involving sex and age, we found a considerably strong association between increased hs-CRP and SO among females and younger (<60 years) subjects.

The hs-CRP level was significantly increased with altered body composition compared with normal reference group and was highest in subjects with SO. Furthermore, a positive trend for increased hs-CRP along the study groups from normal to obesity, sarcopenia and SO was observed. To our knowledge, this is the largest population study to show an association between hs-CRP and SO spanning the entire age frame of adulthood. Previous studies demonstrated the close association between obesity and increased CRP.[16 20] Furthermore, a few studies observed that the levels of CRP were elevated in sarcopenia and SO,[32 33] which were consistent with our findings. However, SO is a condition associated with low-grade inflammation. Therefore, a precise measurement tool using hs-CRP rather than standard CRP is useful in determining low-grade inflammation.[13] Furthermore, a large epidemiological study confirming a relationship between SO and hs-CRP was lacking. A recent study by Yang *et al* showed that SO was associated with increased hs-CRP in elderly males but not in elderly females.[34] However, the present study demonstrated that there were significant associations between SO and hs-CRP in both male and female subgroups. Furthermore, the association of high hs-CRP with SO was higher in female participants than in males. There are several differences. First, sample size was much higher in the present study than in the previous one. Second, although the previous study recruited only elderly subjects above 65 years, the present study included all adult ages to generalise the result and further stratified the subjects by age of 60 to find out a sex difference in the association of hs-CRP with SO. Moreover, the present study conducted the multivariate regression analyses with various confounding factors (eg, DM, cholesterol level, HOMA-IR, ALT, alcohol drinking, total energy intake and education level), which were not included in the previous study. Additionally, females of SO in the previous study had too low WC (81.9±6.3 cm), which may have diluted the association of SO with hs-CRP. Lastly, Yang *et al*[34] used dual-energy X-ray absorptiometry (DEXA) for analysing body composition rather than BIA. Although recent studies demonstrated that BIA showed good validity and

Table 2 Multivariate regression analyses showing associations between high hs-CRP (≥1.0) and the groups of body composition

	Crude ORs	Model 1	Model 2
Normal	Reference	Reference	Reference
Obesity only	1.17 (1.07–1.27)	1.19 (1.08–1.31)	1.17 (1.05–1.31)
Sarcopenia only	2.23 (1.37–3.62)	2.34 (1.43–3.79)	2.23 (1.21–4.07)
Sarcopenic obesity	3.41 (2.98–3.89)	3.39 (2.95–3.89)	3.23 (2.71–3.83)
P for trend	<0.001	<0.001	<0.001

Model 1: age, sex, comorbidities (HTN, DM, heart disease, stroke), LDL-C, HOMA-IR, ALT and eGFR.
Model 2: Model 1+ health behavioural (smoking, heavy drinking, physical activity, energy intake) and demographic factors (marital status, education level).
ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HOMA-IR, homoeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol.

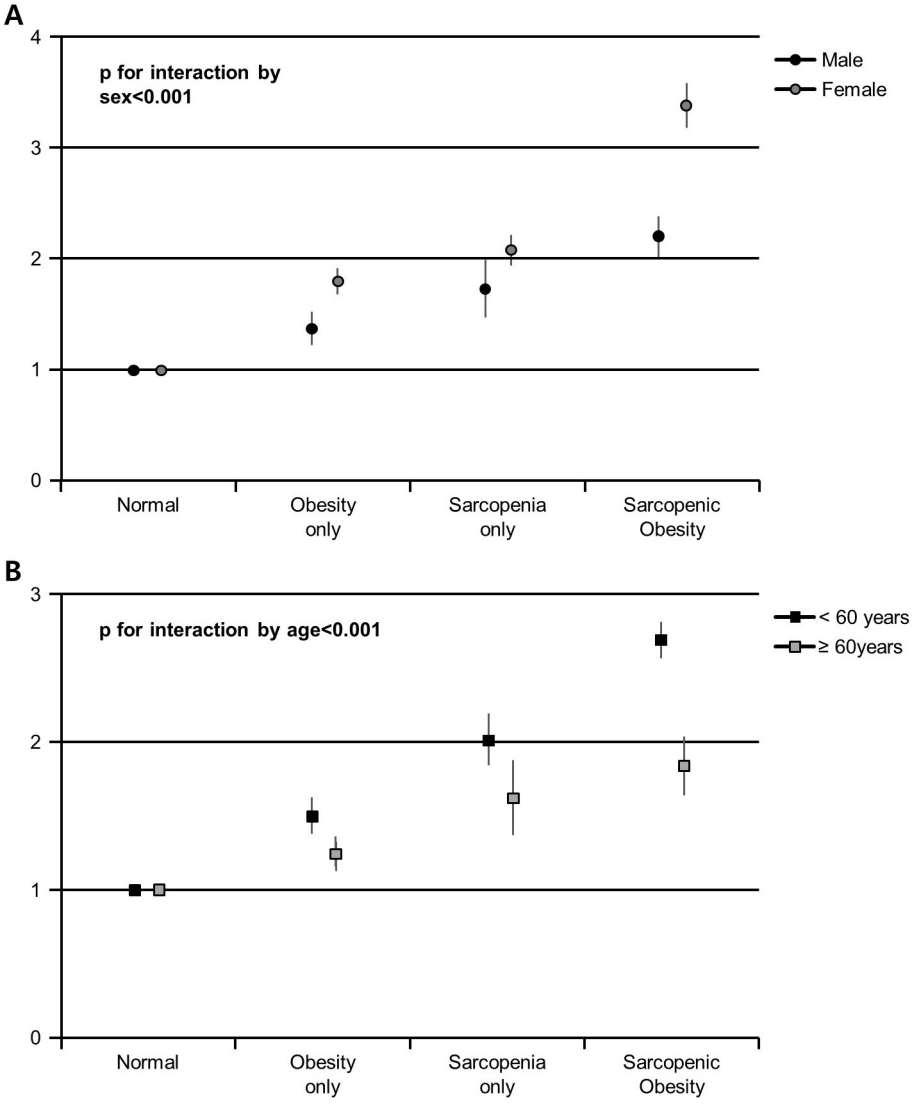

Figure 2 *Multivariate-adjusted coefficients (95% CI) for increasing hs-CRP according to groups of body composition (A) in male and female subjects, and (B) in younger (<60 years) and older subjects (≥60 years). The p value for the interaction by sex or age between body composition and increasing hs-CRP was indicated. *Estimated from multivariate general linear models used with natural log (hs-CRP +1) as the outcome. Multivariate model (model 2) was adjusted for sex, comorbidities (HTN, DM, heart disease, stroke), LDL-C, HOMA-IR, ALT, eGFR, health behavioural (smoking, heavy drinking, physical activity, energy intake) and demographic factors (marital status, education level). ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HOMA-IR, homoeostasis model assessment of insulin resistance; HTN, hypertension; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol.

correlated well with DEXA,[35 36] different methods may have affected the results of association of SO with hs-CRP. Therefore, further studies are needed to compare the results of the associations between SO and hs-CRP using different evaluation tools of body composition.

An inflammatory status would be expected to be highest among the subjects with SO. Kim *et al*[37] reported that serum CRP levels were independently associated with SO among females, which is consistent with the present study. In our study, the level of hs-CRP was sharply increased and the adjusted ORs for elevated hs-CRP were highest in SO, even after adjustment for possible confounding factors such as age, sex, comorbidities, metabolic, heath-related behavioural and demographic factors. Additionally, we have confirmed significant associations between SO and hs-CRP either as a categorical variable or as a continuous variable. Therefore, our results suggest that hs-CRP represents a useful parameter representing the synergistic association of obesity and sarcopenia with inflammation.

In the present study, female subjects showed a stronger association between high hs-CRP and SO than males. This finding is in line with a previous study, which presented a higher association between CRP and obesity in females than in male subjects.[38] However, studies investigating the role of sex differences in the correlation between hs-CRP and SO are unavailable. Although a few reports suggest that hormonal alteration is one of the factors that underlying sarcopenia,[20 38] the pathophysiology of sex

Table 3 Multivariate regression analyses showing associations between high hs-CRP (>1.0) and the study groups by sex and age

Subgroups	Crude ORs	Model 1	Model 2
Male (n=128 117)			
Normal	Reference	Reference	Reference
Obesity only	1.10 (1.00–1.22)	1.14 (1.03–1.26)	1.12 (0.98–1.27)
Sarcopenia only	2.02 (0.83–4.95)	2.08 (0.85–5.05)	1.89 (0.60–5.98)
Sarcopenic obesity	2.15 (1.75–2.63)	2.19 (1.77–2.70)	2.10 (1.63–2.71)
P for trend	<0.001	<0.001	<0.001
Female (n=109 721)			
Normal	Reference	Reference	Reference
Obesity only	1.34 (1.12–1.60)	1.30 (1.08–1.56)	1.41 (1.12–1.78)
Sarcopenia only	2.48 (1.39–4.41)	2.47 (1.38–4.40)	2.41 (1.19–4.91)
Sarcopenic obesity	5.67 (4.76–6.75)	5.04 (4.20–6.16)	5.43 (4.26–6.93)
P for trend	<0.001	<0.001	<0.001
P for interaction by sex	<0.001	<0.001	<0.001
Age <60 (n=230 066)			
Normal	Reference	Reference	Reference
Obesity only	1.16 (1.07–1.28)	1.20 (1.09–1.32)	1.24 (1.10–1.34)
Sarcopenia only	2.13 (1.25–3.63)	2.27 (1.33–3.86)	2.57 (1.21–4.29)
Sarcopenic obesity	3.44 (3.00–3.95)	3.44 (2.98–4.00)	3.41 (2.82–3.98)
P for trend	<0.001	<0.001	<0.001
Age ≥60 (n=7772)			
Normal	Reference	Reference	Reference
Obesity only	1.09 (0.77–1.55)	1.03 (0.72–1.47)	1.07 (0.80–1.19)
Sarcopenia only	2.28 (0.70–7.39)	1.94 (0.60–6.37)	1.84 (0.88–3.21)
Sarcopenic obesity	2.53 (1.57–4.06)	2.19 (1.33–3.60)	2.22 (1.61–2.80)
P for trend	<0.001	<0.001	<0.001
P for interaction by age	<0.001	<0.001	<0.001

Model 1: age, sex, comorbidities (HTN, DM, heart disease, stroke), LDL-C, HOMA-IR, ALT and eGFR.
Model 2: Model 1+ health behavioural (smoking, heavy drinking, physical activity, energy intake) and demographic factors (marital status, education level).
ALT, alanine aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HOMA-IR, homoeostasis model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; HTN, hypertension; LDL-C, low-density lipoprotein cholesterol.

differences in the relationship between hs-CRP and SO is still unknown. A few possible explanations related to the sex-specific differences are as follows. First, the metabolic activity of adipose tissue in females differs from that of males, which may affect the levels of hs-CRP.[39] Second, leptin is an adipocyte-derived hormone, which occurs at a higher level in females than in males. Thus, leptin may be a mediator of sex-specific correlation of hs-CRP with SO.[40 41] Additionally, the distribution of body fat and skeletal muscle is different between females and males, which also may influence the levels of CRP.[20 38] Therefore, SO may be strongly associated with high hs-CRP levels among females than in male subjects.

The present study demonstrated the strongest association between SO and increased hs-CRP in younger (<60 years) than in elderly (≥60 years) subjects. This is the first study of demonstrating age differences in the relationship between SO and hs-CRP. SO is commonly described as an age-related phenomenon, and is a multifactorial condition, which can occur in young-aged and middle-aged populations.[4] Although in the elderly, it is mainly affected by ageing, SO in younger subjects can be triggered by other factors including nutritional deficit, physical activity or endocrine factors rather than ageing.[42 43] Therefore, we suspect that the other factors in younger subjects may differently affect the levels of hs-CRP compared with elderly subjects. Furthermore, a previous study reported that the association of obesity with all-cause mortality was increased in younger-aged subjects.[44] Considering that CRP is a risk factor for all-cause mortality,[45 46] the present finding of strong association of hs-CRP with obesity in younger subjects is in line with a previous report.[44] Moreover, we found the strongest association between hs-CRP and SO in younger than in elderly subjects. Although the

precise pathophysiology of age differences is unknown, these findings are informative for clinicians when measuring hs-CRP in younger populations with SO.

The present study was conducted by defining obesity using WC. There are some reasons for using this method. First, recent studies demonstrated that SO defined by WC was associated with mortality.[47] This is because the mortality associated with sarcopenia is related to increased catabolic metabolism of skeletal muscle in the presence of abdominal obesity.[48] Although higher body mass index (BMI) has been known as a risk factor for cardiovascular diseases,[44] recent studies presented that underweight BMI or weight loss status in late-aged life were associated with increased long-term mortality.[49 50] Thus, whole body obesity by BMI was inversely associated with mortality (called 'obesity paradox'). Moreover, a few studies revealed that abdominal obesity rather than whole body obesity by BMI was associated with both obesity-related mortality and all-cause mortality.[51 52] Second, Batsis *et al*[53] demonstrated that SO defined by per cent body fat mass was not associated with mortality even after adjustments for comorbidities, physical activity, smoking and mobility limitations. This is because per cent body fat mass and BMI could not detect the regional body fat such as visceral fat instead of measuring whole body fat. Additionally, Sanada *et al*[54] investigated the associations between SO and all-cause mortality comparing three different definitions of obesity by BMI, per cent fat mass or WC in a longitudinal cohort study. Sanada *et al* demonstrated that all-cause mortality was significantly increased in men with SO defined by WC but not by BMI or per cent fat mass, suggesting that WC is a good index of SO compared with other obesity definition variables.[54] Therefore, the present study was proceeded by defining obesity by WC.

In the current study, we investigated the independent association of SO with hs-CRP in Korean population. Based on our results, we conclude that increased hs-CRP was associated with the presence of SO. Furthermore, there was a strong relationship between SO and high hs-CRP among females and younger subjects. Previous studies reported a higher prevalence of sarcopenia-related oxidative stress in healthy males and older subjects, which would be related to low-grade inflammation.[55 56] However, our findings suggest that females and younger subjects had stronger associations of increased hs-CRP with SO than males and older subjects. Furthermore, the associations persisted even after adjustment for various confounding factors such as comorbidities, demographic, metabolic and health-related behavioural factors, which supported the significance of the current findings. To the best of our knowledge, this is the first study reporting the role of sex and age differences in the association between SO and hs-CRP using a large study sample. Since the increased level of hs-CRP is considered as a significant risk factor for cardiovascular illness and all-cause mortality, this measurement may be useful to screen for inflammatory markers in female and younger subjects diagnosed with SO.

There are some limitations in this study. First, subjects aged 60 years and above were relatively fewer in number than subjects aged below 60, which may suggest a selection bias. However, we addressed this issue by analysing the data after adjustments for age. Second, because this was a cross-sectional study, cause–effect associations cannot be inferred. Third, the skeletal muscle mass was measured using BIA. Nevertheless, recent studies demonstrated that BIA showed good validity and correlated well with DEXA.[35 36] Additionally, BIA is usefully applied for large-scale health screening purposes due to its speed and simplicity without the need for a specialised radiologist.[57]

In conclusion, we demonstrated that a high level of hs-CRP was associated with SO in Korean adults. Furthermore, SO in female and younger (<60 years) subjects had a stronger association with the high level of hs-CRP than in male and elderly subjects.

Contributors C-HP: manuscript drafting, critical revision and study design. JGD: study supervision and data interpretation. Y-TL: study concepts, design and manuscript revision for important intellectual content. KJY: study concepts, design and critical revision of manuscript. All authors: final version approval.

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