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Elevated hs-CRP level is associated with depression in younger adults: Results from the Korean National Health and Nutrition Examination Survey (KNHANES 2016)

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ABSTRACT

Introduction: Reports on the association between the level of circulating high-sensitivity C-reactive protein (hs-CRP) and depression have been inconsistent. The aim of this study was to examine the association between hs-CRP and depression in a large sample.

Methods: This study used data obtained from a representative Korean sample of 5447 people who participated in the first (2016) year of the seventh Korean National Health and Nutrition Examination Survey (KNHNES VII-1). Depression was identified using a cutoff of 5 on the Patient Health Questionnaire-9 (PHQ-9), and high hs-CPR level was defined as ≥ 3.0 mg/L.

Findings: Participants with a high CRP levels had a significantly higher rate of depression than did those with a low hs-CRP levels (25.1% vs. 19.8%, p = 0.007). Serum hs-CRP was independently associated with the PHQ-9 total score after adjusting for potentially confounding factors (B = 0.014; 95% CI = 0.008–0.020). After controlling for body mass index (BMI), smoking, alcohol use problems, hypertension, diabetes, dyslipidemia, chronic illness related hs-CRP, and metabolic syndrome. Furthermore, elevated hs-CRP level was significantly associated with an increased risk of depression (adjusted OR = 1.44; 95% CI = 1.01–2.07) in younger adults, but no significant association was observed among older adults.

Conclusion: These findings suggest a significant correlation between high hs-CRP levels and depression in younger adults. Further studies are necessary to investigate the age-specific association and the biological mechanism involved.

1. Introduction

Depression is a major public problem worldwide and is associated with significant disability, mortality, and healthcare costs (Cuijpers et al., 2012; Smith, 2014). The pathogenesis of depression is thought to involve multiple interacting risk factors including biological, psychological, and environmental factors (Kendler et al., 2006). However, the underlying pathophysiology of depression has not yet been fully elucidated. Recent advances in basic and clinical research highlight the potential role of newly identified biological factors that may link to the pathophysiology of depression in combination with the more traditional neurochemical and neuroendocrine mechanisms.

For instance, it has been hypothesized that depression might be associated with immune dysregulation and activation of the inflammatory response (Miller et al., 2009; Raison and Miller, 2011; Slavich and Irwin, 2014). Inflammatory signaling pathways interact with the brain via complicated direct and indirect pathways, including neuronal, immune-mediated, and neuroendocrine-mediated signaling (Irwin and Cole, 2011; Miller et al., 2013). Depression and inflammation are intertwined, and this bidirectional pathway, in which inflammation plays a key role in depression's pathogenesis and depression also facilitates inflammatory responses, appear to be unequivocal (Kiecolt-Glaser et al., 2015), but the underlying mechanisms are still poorly understood.

Consistent with this premise, there is a growing body of published research about elevated levels of proinflammatory cytokines and the proteins released in response to increased cytokine levels in depression (Rosenblat et al., 2014; Young et al., 2014). The high-sensitivity C-reactive protein (hs-CRP) is commonly used to study low-grade inflammation and future risk for inflammatory disease (Dantzer and

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Kelley, 2007). There are age-related changes in hs-CRP level, and elevated hs-CRP with aging is linked to a range of poor health-related outcomes in old age (Woloshin and Schwartz, 2005). It has been the focus of extensive epidemiologic investigation owing to the association of elevated serum hs-CRP level (≥ 3.0 mg/L) with cardiovascular risk and components of metabolic syndrome (Pearson et al., 2003; Shah et al., 2009; Tamakoshi et al., 2003). However, to date, epidemiological evidence concerning the association of elevated level of hs-CRP and depression in general population samples shows inconsistent results. Several studies identified associations between depression and a high level of hs-CRP (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Lee et al., 2019; Liukkonen et al., 2006; Pikhart et al., 2009; Song et al., 2015; Tabatabaeizadeh et al., 2018; Wium-Andersen et al., 2013), whereas some studies did not (Almeida et al., 2007; Bremmer et al., 2008; Chaiton et al., 2010; de Menezes et al., 2017; Douglas et al.;, 2004; McDade et al., 2013; Tiemeier et al., 2003; Zhang et al., 2018). In addition, in two population-based studies, depression was correlated with decreased, rather than elevated, hs-CRP levels (Camacho et al., 2014; Glaus et al., 2014). These discrepancies might be due to differences in the study populations, such as in age, sex, or race/ethnicity; to methods for measuring depression; or to adjustments for potentially confounding factors (Case and Stewart, 2014).

Previous epidemiological studies on the association between hs-CRP levels and depression have mainly focused on Western populations (Bremmer et al., 2008; Chaiton et al., 2010; Danner et al., 2003; Douglas et al.;, 2004; Elovainio et al., 2009; Ford and Erlinger, 2004; Liukkonen et al., 2006; Pikhart et al., 2009; Tiemeier et al., 2003), with only a few targeting Asian populations (Lee et al., 2019; McDade et al., 2013; Song et al., 2015; Zhang et al., 2018). Furthermore, most studies have employed global models that did not account for socio-demographic features that might influence depression and the inflammatory response. Therefore, we aimed to examine how depression is related to hs-CRP levels after controlling for potentially confounding factors in a representative sample of Korean adults. In addition, we also aimed to investigate the potential links among depression, hs-CRP, and age.

2. Methods

2.1. Study participants

The Korean National Health and Nutrition Examination Survey (KNHANES) is a nationwide, population-based, cross-sectional health examination and survey that has been conducted every year since 1998 by the Division of Chronic Disease Surveillance of the Korea Centers for Disease Control and Prevention in the Ministry of Health and Welfare. It was designed to monitor the general health and nutrition status of the non-institutionalized civilian population of South Korea (Kweon et al., 2014). Every year, 8000–10,000 individuals from 4600 households are selected as representative of Koreans. This selection is performed through a multi-stage clustered and stratified random sampling method based on national census data. The survey is composed of three individual surveys: a health interview, a nutrition survey, and a health examination survey. The data are collected through household interviews and standardized physical examinations conducted at mobile examination centers. The KNHANES database is publicly available at the KNHANES website (http://knhanes.cdc.go.kr, available in Korean). The present study was based on data of participants in 2016, the first year of the seventh KNHANES (KNHANES VII-1).

The KNHANES VII-1 was completed by 8150 participants. The following participants were included in this analysis: subjects aged > 20 years (n = 6315) who completed Patient Health Questionnaire-9 (PHQ-9) (n = 5702). Of the 5702 subjects with PHQ-9 data, only those whose serum CRP level data were collected were included (n = 5508). Pregnant or breast-feeding women were excluded (N = 61). The remaining 5447 subjects (2383 men and 3064 women) were eligible for this study.

All procedures involving human subjects were in accordance with the ethical standards of the institutional and/or national research committee as well as the tenets of the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. All the protocols were approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention, and written informed consent was secured from all participants before the survey began. The present study did not require additional Institutional Review Board approval because the KNHANES data are publicly available.

2.2. Assessment of depression

Depression was identified using the PHQ-9, which is a reliable screening tool for measuring depressive symptoms and severity over the past 2 weeks (Kroenke et al., 2001). The PHQ-9 is composed of nine items rated from 0 (not at all) to 3 (having the symptoms nearly every day), and the scores for each item are summed to produce a total depression severity score (range: 0–27). The Korean version of the PHQ-9 has high internal consistency (Cronbach's $\alpha = 0.86$) and the optimal cutoff total score for the presence of depression is 5 (Han et al., 2008). Participants in this study were identified as having depression if their total score of the PHQ-9 score was ≥ 5. The two-dimensional structure of depressive symptoms (i.e., cognitive/affective symptoms and somatic symptoms) was evaluated using the PHQ-9, as was done in previous studies (de Jonge et al., 2007; Hwang et al., 2015). Five items related to feeling depressed, loss of interest, feeling of worthlessness trouble concentrating, and suicidal thoughts were classified as cognitive/affective symptoms, while four items related to change in appetite, sleep problems, psychomotor agitation or retardation, and fatigue were classified as somatic symptoms.

2.3. Measurement of high sensitivity C-reactive protein (hs-CRP) level

Blood samples were collected in 3-ml EDTA-coated tubes (BD Vacutainer, Franklin Lakes, NJ). Serum samples used for the analysis of hs-CRP were stored at 2–8 °C in refrigerated containers. All laboratory analyses were performed within 24 h of sample collection. Serum hs-CRP levels were measured using the immunoturbidimetric method (Cobas, Roche, Germany), which is calibrated daily with reference standards between 1.0 and 20.0 mg/L. To assess the relative prevalence of depression at different levels of hs-CRP level, we used 3.0 mg/L as a reference, the cutoff stipulated by the American Heart Association and Centers for Disease Control and Prevention to indicate "high risk" for cardiovascular disorder (Pearson et al., 2003). Thus, high hs-CRP was defined as ≥3.0 mg/L, and low hs-CRP as < 3.0 mg/L.

2.4. Study variables

Age, weight, height, smoking status, alcohol use problem, household income, education and marital status (married, living together, divorced/separated/widowed, or not married) were recorded. Younger age was defined as men < 50 years old and premenopausal women, and old age as men ≥50 years old and postmenopausal women. Weight and height were collected according to standardized procedures, and the body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. In terms of smoking status, participants were categorized as current smokers or non-smokers. To obtain information regarding the severity of alcohol consumption problems, we administered the Alcohol Use Disorder Identification Test-Alcohol Consumption (AUDIT-C) instrument (Gordon et al., 2001). For significant alcohol use problems, a cutoff score of 8 was used in this study. Household income was categorized into quartiles. Low income was defined as quartile 1 (≤ 25th percentile). Low education was defined as elementary school and below. Chronic medical illnesses that have been identified as directly associated with hs-CRP levels, namely, coronary heart disease including myocardial infarction and angina

pectoris (Kaptoge et al., 2010), stroke (Di Napoli et al., 2001), rheumatoid arthritis (Dessein et al., 2004), and cancer (Allin and Nordestgaard, 2011), were included as medical comorbidities. Subjects were considered to have hypertension if they had systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or if they were being treated for hypertension. Subjects were deemed to have diabetes if they were previously diagnosed with diabetes by a doctor, used a diabetes medication, or had a fasting blood glucose level ≥126 mg/dL that was detected in this survey. Subject were considered to have high cholesterol if they had total cholesterol ≥240 mg/dL, or if they were being treated for dyslipidemia. We used the National Cholesterol Education Program-Adult Treatment Panel III criteria to determine whether metabolic syndrome was present; cutoffs for the Asia–Pacific region were employed (Grundy et al., 2005). Metabolic syndrome was considered present if three or more of the following conditions were identified: (i) systolic/diastolic blood pressure ≥130/85 mmHg or use of antihypertensive drugs; (ii) fasting serum triglycerides ≥150 mg/dL; (iii) low HDL-C (< 40 mg/dL in men and 50 mg/dL in women); (iv) waist circumference ≥90 cm in men and ≥80 cm in women; or (v) fasting serum glucose ≥100 mg/dL or use of antidiabetic medication.

2.5. Statistical analysis

Continuous data are expressed as mean (SD), and categorical data as percentages. The first analyses explored differences in participant characteristics according to the presence of depression. The chi-square test was used for categorical variables, and the *t*-test for continuous variables.

The association between serum hs-CRP level and PHQ-9 total score was assessed through Poisson regression analysis in all participants. The association between hs-CRP level and PHQ-9 scores according to age group was assessed through four multiple Poisson regression models with progressive levels of adjustment. Model 1 was adjusted for age and gender; model 2 was model 1 plus income, education, and marital status; model 3 was model 1 plus smoking status, alcohol use problems, and BMI; and model 4 was model 3 plus hypertension, diabetes, dyslipidemia, chronic illness-related hs-CRP, and metabolic syndrome. Multivariate regression analysis was performed using the backward method.

We conducted a multiple logistic regression analysis to evaluate the association between hs-CRP level and depression; odds ratios (ORs) with 95% CIs were calculated. Potential confounding factors were adjusted in the multivariable model, including age, gender, household income, education, marital state, smoking status, alcohol use problem, BMI, hypertension, diabetes, dyslipidemia, chronic illness-related hs-CRP, and metabolic syndrome. Statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA), and $p < 0.05$ was used to indicate statistical significance.

3. Results

The general characteristics of the study participants are presented in Table 1. The study comprised 5447 participants (2383 men, 3064 women). A total of 1104 cases of depression were identified, for a prevalence of 20.3%. Women showed significantly higher depression prevalence than men (24.5% vs. 14.9%, $p < 0.001$). Depression was significantly associated with low income ($p < 0.001$), lower education level ($p < 0.001$), and unmarried status ($p < 0.001$). Participants with depression had significantly higher rates of current smoking ($p < 0.001$), diabetes ($p = 0.005$), dyslipidemia ($p = 0.001$), chronic illness ($p < 0.001$), and metabolic syndrome ($p = 0.048$). Serum hs-CRP levels were significantly higher in participants with depression than in those without [1.43 (SE = 2.64) vs. 1.25 (SE = 2.24) ng/ml, respectively]. Among participants with depression, 11% (n = 120) had high hs-CRP levels (≥3.0 mg/L), compared with 8% (n = 359) of those without depression ($p = 0.007$). Fig. 1 shows the association between PHQ-9 total score and depression according to hs-CRP level. Participants with high hs-CRP tended to have more severe depression [3.3 (SD = 4.4) vs. 2.6 (SD = 4.8) ng/ml, $p = 0.001$)], and had a significantly higher rate of depression than those with a low hs-CRP level (25.1% vs. 19.8%, $p = 0.007$).

Table 1
Participants characteristics (n = 5447).

	Total	Depression[a]		
		No	Yes	p-value
Total, *n*	5447	4343 (80)	1104 (20)	
Gender, *n* (%)				< **0.001**
Male	2383 (44)	2029 (47)	354 (32)	
Female	3064 (56)	2314 (53)	750 (68)	
Age, years, mean (SE)	51 (16)	51 (16)	51 (17)	0.523
Household income, *n* (%)[b]				< **0.001**
Quartile 1 (low)	1023 (19)	712 (16)	311 (28)	
Quartile 2	1335 (25)	1064 (25)	271 (25)	
Quartile 3	1501 (28)	1224 (28)	277 (25)	
Quartile 4 (high)	1575 (29)	1332 (31)	243 (22)	
Education, *n* (%)[C]				< **0.001**
Elementary school and below	1150 (21)	848 (20)	302 (27)	
Middle school	569 (10)	452 (10)	117 (11)	
High school	1723 (32)	1381 (32)	342 (31)	
University or above	1998 (37)	1656 (38)	342 (31)	
Marital status, *n* (%)				< **0.001**
Married, living together	3897 (72)	3235 (75)	662 (60)	
Divorced/separated/ widowed	731 (13)	499 (11)	232 (21)	
Not married	819 (15)	609 (14)	210 (19)	
Alcohol use problems, *n* (%)	983 (18)	770 (18)	213 (19)	0.228
Current smoking, *n* (%)	1024 (19)	2314 (53)	750 (68)	< **0.001**
Hypertension, *n* (%)	1787 (33)	1424 (33)	363 (33)	0.954
Diabetes, *n* (%)	729 (13)	553 (13)	176 (16)	**0.005**
Dyslipidemia, *n* (%)	937 (17)	710 (16)	227 (21)	**0.001**
Chronic illness related with hs-CRP, *n* (%)[d]	614 (11)	438 (10)	176 (16)	< **0.001**
Metabolic syndrome, *n* (%)	1740 (32)	1360 (31)	380 (34)	**0.048**
Body mass index (kg/m^2), mean (SE)	24.0 (3.5)	24.1 (3.5)	23.8 (3.6)	**0.033**
hs-CRP (mg/L), mean (SE)	1.29 (2.33)	1.25 (2.24)	1.43 (2.64)	**0.040**
High hs-CRP (≥ 3.0 mg/L), *n* (%)	479 (9)	359 (8)	120 (11)	**0.007**

[a] The presence of depression was defined as total score on the Patient Health Questionnaire-9 (PHQ-9) ≥ 5.
[b] Available data in 5434.
[c] Available data in 5440.
[d] The presence of cardiovascular disease (myocardial infarct, ischemic pectoris), stroke, or rheumatoid arthritis, or cancer.

We examined the association between serum hs-CRP level and PHQ-9 total score in all subjects using Poisson regression analysis (Table 2). Multivariate analysis revealed that increased serum hs-CRP was independently associated with higher PHQ-9 total scores (B = 0.014; 95% CI = 0.008–0.020) after adjusting for potentially confounding factors. Increased serum hs-CRP was also associated with both higher PHQ-9 cognitive/affective symptoms scores (B = 0.015; 95% CI = 0.007–0.023) and somatic symptoms scores (B = 0.016; 95% CI = 0.006–0.020) after adjusting for potentially confounding factors. The results of our secondary analysis, which stratified subjects by age group, are shown in Tables 3 and 4. In the initial regression analysis, after adjusting for demographic factors, serum hs-CRP level was significantly and positively associated with PHQ-9 total score in both the younger adults and older adults groups. In the fully adjusted model, which included age, gender, income, education, marital status, alcohol use problems, smoking status, BMI, hypertension, diabetes, dyslipidemia, chronic illness, and metabolic syndrome (model 4), the association between serum hs-CRP level and PHQ-9 total score was significant only in younger adults (Table 3). The results of the multiple logistic regression analysis showed this same pattern of association by

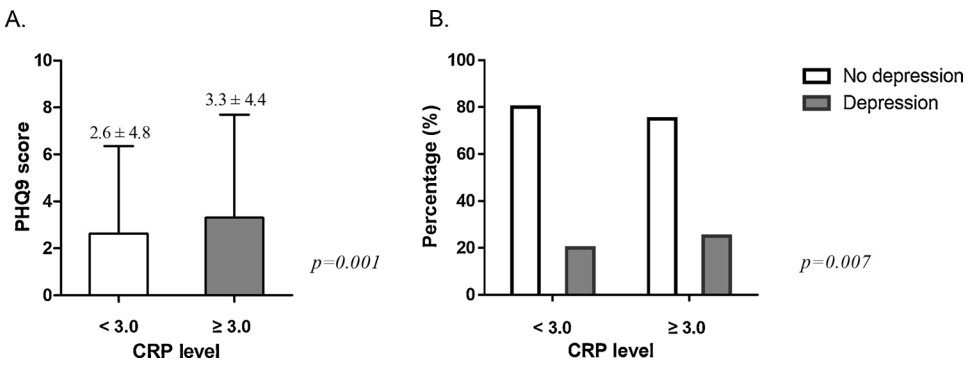

Fig. 1. Comparison of PHQ score and prevalence of depression according to CRP level.
A. Comparison of PHQ-9 total score between low CRP group (< 3.0 mg/L) and high CRP group (≥ 3.0 mg/L). Data was expressed by mean with SD.
B. Prevalence of depression according to CRP level. The presence of depression was defined as total score on the PHQ-9 ≥ 5.

age group (Table 4). In younger adults, the high hs-CRP group was 1.44 times more likely to have depression after adjusting for potential confounding factors (adjusted OR = 1.44, 95% CI = 1.01–2.07). In older adults, however, the association between high hs-CRP level and depression was not significant before or after adjustment.

4. Discussion

Our results highlight that participants with depression showed significantly greater prevalence of high hs-CRP levels than those without depression (11% vs. 8%) in Korean adults based on a nationally representative survey. Similarly, elevated hs-CRP levels were significantly associated with an increased risk of depression. After controlling for potentially confounding factors, the association remained in younger adults, but not in older adults.

Our results are consistent with previous cross-sectional studies that have shown a positive association between depression and elevated hs-CRP levels (Danner et al., 2003; Elovainio et al., 2009; Ford and Erlinger, 2004; Liukkonen et al., 2006; Pikhart et al., 2009; Song et al., 2015; Tabatabaeizadeh et al., 2018; Wium-Andersen et al., 2013). However, several studies have reported no significant association between serum hs-CRP and depression (Almeida et al., 2007; Bremmer et al., 2008; Chaiton et al., 2010; de Menezes et al., 2017; Douglas et al.;, 2004; McDade et al., 2013; Tiemeier et al., 2003; Zhang et al., 2018). Two recent meta-analyses of cross-sectional studies found that elevated hs-CRP levels showed a small but significant association with

Table 3
Multivariate Poisson regression analysis of association between the level of hs-CRP and PHQ-9 total score according to age group.

	Younger adults (N = 2631)		Older adults (N = 2816)	
	Beta coefficients (95% Cl)	p-value	Beta coefficients (95% Cl)	p-value
Model 1	0.035 (0.024, 0.045)	< 0.001	0.020 (0.013, 0.028)	< 0.001
Model 2	0.035 (0.024, 0.045)	< 0.001	0.012 (0.005, 0.020)	0.002
Model 3	0.031 (0.021, 0.042)	< 0.001	0.009 (0.001, 0.017)	0.019
Model 4	0.030 (0.020, 0.041)	< 0.001	0.006 (-0.001, 0.014)	0.107

Model 1: adjusted for age (per year) and gender.
Model 2: Model 1 + adjusted for income, education, and marital status.
Model 3: Model 2 + adjusted for smoking status, alcohol use problems, and body mass index.
Model 4: Model 3 + adjusted for hypertension, diabetes, dyslipidemia, chronic illness-related hs-CRP, and metabolic syndrome.

Table 2
Poisson regression analysis for PHQ-9 total score.

	Univariate model Beta coefficients (95% Cl)	Multivariate model Beta coefficients (95% Cl)
Female	0.419 (0.384, 0.453)**	0.593 (0.552, 0.634) **
Age per 1 year	0.000 (-0.001, 0.001)	
Household income		
Quartile 1 (low)	Reference	Reference
Quartile 2	−0.356 (-0.401, -0.312) **	−0.254 (-0.302, -0.206) **
Quartile 3	−0.488 (-0.532, -0.443) **	−0.350 (-0.401, -0.299) **
Quartile 4 (high)	−0.628 (-0.674, -0.582) **	−0.481 (-0.535, -0.426) **
Education		
Elementary school and below	Reference	Reference
Middle school	−0.178 (-0.236, -0.120) **	−0.027 (-0.087, 0.033)
High school	−0.271 (-0.314, -0.228) **	−0.057 (-0.108, -0.006)*
University or above	−0.371 (-0.414, -0.329) **	−0.011 (-0.065, 0.043)
Marital status		
Married, living together	Reference	Reference
Divorced/separated/widowed	0.583 (0.542, 0.625) **	0.255 (0.208, 0.302)**
Not married	0.362 (0.319, 0.405) **	0.403 (0.357, 0.449)**
Alcohol use problems	0.051 (0.010, 0.0936) *	0.238 (0.191, 0.285)**
Current smoking	0.197 (0.158, 0.236) **	0.425 (0.379, 0.470)**
Hypertension	0.043 (0.009, 0.077) *	−0.108 (-0.150, 0.066)**
Diabetes	0.212 (0.168, 0.257) **	0.102 (0.052, 0.152)**
Dyslipidemia	0.203 (0.162, 0.243) **	0.140 (0.096, 0.184)**
Chronic illness related with hs-CRP[a]	0.396 (0.352, 0.440) **	0.338 (0.291, 0.385)**
Metabolic syndrome	0.128 (0.094, 0.162) **	0.095 (0.051, 0.139)**
Body mass index (kg/m^2)	−0.008 (-0.013, -0.03) **	−0.012 (-0.017, -0.007)**
hs-CRP (mg/L), mean (SE)	0.022 (0.016, 0.029) **	0.014 (0.008, 0.020)**

*p-value < 0.05, **p-value < 0.01.
[a] The presence of cardiovascular disease (myocardial infarct, ischemic pectoris), stroke, or rheumatoid arthritis, or cancer.

Table 4
Logistic regression analysis for the association between depression and hs-CRP level.

hs-CRP	Total (n = 5447)		Younger adults (N = 2631)		Older adults (N = 2816)	
	Crude OR (95% CI)	Adjusted OR (95% CI)[a]	Crude OR (95% CI)	Adjusted OR (95% CI)	Crude OR (95% CI)	Adjusted OR (95% CI)
Low level (< 3.0 mg/L)	1	1	1	1	1	1
High level (≥ 3.0 mg/L)	1.35 (1.09, 1.68)*	1.28 (1.02, 1.61)*	1.44 (1.01, 2.07)*	1.44 (1.01, 2.07)*	1.30 (0.98, 1.73)	1.18 (0.88, 3.62)

*$p < 0.05$.
[a]Adjusted by age (per 1 year), gender, low income (Quartile 1, low), low education (elementary school and below), marital status, smoking status, alcohol use problems, body mass index (< 18.5, 18.5–22.9, 23–24.9, ≥ 25 kg/m^2), hypertension, diabetes, dyslipidemia, chronic illness-related hs-CRP, and metabolic syndrome.

depression (Haapakoski et al., 2015; Howren et al., 2009). The first meta-analysis assessing the association between hs-CRP and depression used relatively relaxed inclusion and sampling criteria, which may partially explain the smaller overall effect size estimate (Howren et al., 2009). The meta-analysis conducted by Haapakoski et al. (2015) was based on studies that were conducted in clinical populations, so the results may not be applicable to a community sample. Furthermore, in these meta-analyses, the effect of elevated hs-CRP on depression was present regardless of age (Howren et al., 2009; Haapakoski et al., 2015). This could be explained by methodological issues, such as the relatively small number of studies reporting results separately for each age group. Most previous studies have evaluated the association between hs-CRP level and depression without considering age-specific differences.

Our secondary analysis, which stratified the study population by age group, showed that high hs-CRP levels were associated with increased risk of depression in younger adults, but not in older adults. Some previous studies focusing on older adults reported no association between hs-CRP level and depression (Almeida et al., 2007; Bremmer et al., 2008; McDade et al., 2013; Zhang et al., 2018), which is consistent, in part, with our finding. In contrast, many other studies involving older adults have reported an association between high hs-CRP and depression, suggesting that inflammation's role in depression might be related to age-associated immune system changes (Liukkonen et al., 2006; Penninx et al., 2003; Song et al., 2015). Older adults tend to have higher circulating levels of inflammation than younger adults (Chung et al., 2009). With aging, increased activation of the peripheral immune system produces an exaggerated central inflammatory response (Dilger and Johnson, 2008).As a result, the brain is in a chronic state of neuroinflammation, and this can lead to the development of depression (Alexopoulos and Morimoto, 2011). Chronic conditions such as cardiovascular disease and metabolic abnormalities are also associated with elevated hs-CRP. The prevalence of these conditions increases with age as well, and they may be comorbid with depression in older adults (Almeida et al., 2007; Au et al., 2015). In our study, this association disappeared when we adjusted for potentially confounding factors such as chronic illness, hypertension, diabetes, and dyslipidemia. We suggest that confounding factors that may modify the association between inflammatory processes and depressive symptoms in older adults should be carefully considered, as this may be the reason for inconsistent reports on the association between hs-CRP level and depression. Additionally, in future studies, other related factors that could explain the relationship between inflammation and depression in older adults, such as physical activity (Schuch et al., 2017), frailty (Soysal et al., 2017), physical disability (Reuben et al., 2002), and adiposities (Dowlati et al., 2010), should also be considered.

More importantly, our study showed that the association between elevated hs-CRP and depression is stronger in younger adults than in older adults; after adjusting for potentially confounding factors, a high hs-CRP level increased the prevalence of depression in younger adults by 1.44 fold. This is likely because the inflammatory processes involved in depression differ between younger adults and older adults. For instance, some prospective studies in adolescents and young adults have reported that the link between depression and hs-CRP starts with depression then leads to future inflammation, not the reverse (Copeland et al., 2012; Deverts et al., 2010; Duivis et al., 2015). These findings suggest that, in young people, persistent and repeatedly experienced depressive symptoms are most strongly associated with higher levels of inflammation (Duivis et al., 2015), which may be due to glucocorticoid resistance and impairments in hypothalamus–pituitary–adrenal (HPA) axis function (Silverman and Sternberg, 2012). These findings are also clinically relevant. The assessment of inflammatory markers may prove crucial in developing more effective prevention strategies and treatment in young adults. For example, elevated inflammation is associated with poorer treatment response for depression (Miller et al., 2009), and recent researches have evaluated the potential antidepressant benefit of anti-inflammatory treatment strategies in depressive patients with elevated inflammation (Raison et al., 2013; Rethorst et al., 2013). Taken together, stronger association between elevated hs-CRP and depression in younger adults might be indicative of one specific biological "subtype" of depression. To date, the effect of age on the association between hs-CRP level and depression remains unclear; therefore, further studies are necessary to understand how changes in hs-CRP levels affect depression among younger adults and this would need to be tested in intervention studies.

The present study has several limitations. First, the cross-sectional nature of the study design limits the interpretation of results. Although our findings support the hypothesized link between depression and inflammation in younger adults, the cross-sectional design precludes determination of the causal direction of the association. Second, the definition of depression using the PHQ-9 is open to question. The PHQ-9 has been validated as a screening tool with acceptable sensitivity and specificity (Han et al., 2008); however, it is not a diagnostic tool. Furthermore, the information on prior clinical diagnosis for depression was not considered. Meta-analysis evidence suggests that the association of depressive disorders with CRP is stronger than the association of subsyndromal depressive symptoms with CRP (Howren et al., 2009). Though our findings may not precisely reflect portion of individuals with depression who also have high inflammation, our results show that individuals with elevated depressive symptoms also have elevated hs-CRP levels. Third, the use of medications such as antidepressants (Castanon et al., 2002; Szeleyni and Selmmeczy, 2002), recent infections (Sproston and Ashworth, 2018), seasonal variations (Sung, 2006), dietary intakes (Khayyatzadeh et al., 2017), and other major confounding factors for depression and inflammation were not considered. Despite these limitations, our study included a large sample size, which facilitated the detection of the noted associations, and it included stratification by age group, whereas similar studies have only made statistical adjustments for age.

5. Conclusion

Our results suggest that higher hs-CRP levels are independently associated with depressive symptoms in a non-institutionalized Korean population, even after adjusting for potentially confounding factors. The association between a high hs-CRP level and depression was more prominent in younger adults than in older adults. Further investigations are needed to confirm how and why the association differs between young and older people.

Author's contributions

Author KYK designed the study and wrote the protocol. Author KYK and YEJ managed the literature searches and analyses. Authors YEJ undertook the statistical analysis, and wrote the first draft of the manuscript. Author KYK and YEJ contributed to and have approved the final manuscript.

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Declaration of Competing Interest

No conflicts declared.

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