**ORIGINAL ARTICLE**
https://doi.org/10.4306/pi.2018.15.1.24

Print ISSN 1738-3684 / On-line ISSN 1976-3026
**OPEN ACCESS**

# Is the Relationship between Depression and C Reactive Protein Level Moderated by Social Support in Elderly?-Korean Social Life, Health, and Aging Project (KSHAP)

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**Objective** To investigate the buffering effects of social support as an effects modifier in the association between depression and inflammation in the elderly.

**Methods** We analyzed the Korean Social Life, Health, and Aging Project (KSHAP) for questionnaire, clinical, and laboratory data of 530 older adults living in a rural community. Multivariate regression models were used to investigate the association between depressive symptoms and C-reactive protein level (CRP), a marker of inflammation, at varying levels of social support.

**Results** Social support affected the association between depressive symptoms and CRP level in both sexes. However, the direction of effects modification was different for men and women. In men, a higher CRP level was significantly associated with depressive symptoms only among those with lower support from a spouse or family members. By contrast, in women, the association was significant only among subgroups with higher spousal or family support. Social support from neighbors or friends did not affect the depression-inflammation relationship in men but modestly affected the relationship in women.

**Conclusion** Our findings suggest that social support may have a buffering effect in the relationship between depression and inflammation in elderly Koreans. But the influence of social support may run in different directions for men and women.

**Psychiatry Investig 2018;15(1):24-33**

**Key Words** C-reactive protein, Social support, Aged.

## INTRODUCTION

There is a stress-buffering hypothesis model, which says that stress can be buffered when a high level of social support is provided.[1-6] After Cohen & Wills formulated this concept in 1985,[7] it has been expanded to social isolation,[3] life satisfaction,[8] and depression[2,9] also. It was found in a meta-analysis, as well as in many cross-sectional studies, that inflammatory markers, including C-reactive protein (CRP), interleukin-1 (IL-1), and IL-6, were elevated in depressed persons.[10] This has also been demonstrated in neuroscientific research,[11] which has found that CRP levels in depressed patients were significantly higher than those in non-depressed subjects, and it was related with brain regions with depression. However, conflicting evidence is still reported, as a recent community study did not find this association.[12] Some of the factors that moderate the relationship between depression and CRP level, as well as their buffering effect, have been explored: loneliness,[2] social support,[4,6,8] and social networks.[9,13] There is also research showing that social support can buffer the relationship between stress and CRP level.[3] However, some of these studies are not supported by evidence in multivariate models.[3,13] Some of them have shown sex differences.[3,5,13] Further, in a previous study that used the same data as this study, the positive relationship between CRP level and depressive symptoms was observed only in men, not in women.[5] Moreover, the results of studies on the association between social support and inflammatory indicators and the biological mechanisms underlying this re-

**Received:** November 14, 2016 **Revised:** February 23, 2017
**Accepted:** March 6, 2017 **Available online:** November 21, 2017

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lationship are not yet conclusive.[2,3,5,6,8,13,14] Thus, the main hypothesis of this study is that social support in elderly Koreans acts as an effects modifier in the relationship between depressive symptoms and CRP level and has a buffering effect.

## METHODS

### Study population

We used Korean Social Life, Health and Aging Project (KSHAP) data, designed to examine the social network and health status of the entire population ages 60 years or older and their spouses (age-irrelevant) as a panel study in a small *ris* (the smallest administrative unit) in Township K, located on Ganghwa Island, Republic of Korea. This study was a precursor to the National Social Life, Health, and Aging Project (NSHAP) study in the United States, designed to understand how social networks in the elderly are related to various health conditions. The main differences between the two studies are the following. First, the target populations are different. NSHAP is a sample of 3,005 individuals representing the elderly population in the United States, whereas KSHAP comprises the entire elderly population of a single small *ris* in Korea.[15,16] Second, because of the difference in target populations, KSHAP could assess not only the local network but also the global network, whereas NSHAP investigated the local network only. At baseline (December 2011 to March 2012), we conducted a face-to-face population survey and completed a questionnaire for 814 community-dwelling members among 860 predefined study members (response rate 94.65%), whose mean±standard deviation(SD) age was 81.39±8.10 years, and whose male proportion was 42.0%. Demographic factors, social support, social network, history of morbidity, and other possible risk factors were obtained via questionnaire. Among them, 698 members participated in additional health examinations and consisted of the KSHAP-Health Examination Cohort. The health examination consisted of anthropometry investigation, appendicular skeletal muscle mass measurement, blood pressure measurement, a physical function test, and a blood test using fasting blood samples.[15,17] Participation in the additional health examination was determined entirely by the subject. Age, sex, employment status, depressive symptom based on the Center for Epidemiologic Studies Depression Scale (CES-D) score, and income level were compared between participants and nonparticipants. The mean±SD age of participants in the health screening was 71.7±7.8 years, which was statistically significantly higher than that of nonparticipants (69.6±9.8). However, the other characteristics were not different between the two groups. The study was approved by the Institutional Review Board of Yonsei University (YUIRB-2011-012-01), and informed consent was obtained after explanation of the study from all of the participants.[5,15-19]

### Measurements

#### Anthropometry

According to a predetermined manual, standing height and body weight were measured using a stadiometer, and a digital scale, respectively. Using these measures, body mass index (BMI) was calculated as kg/m$^2$. Systolic and diastolic blood pressure was measured after at least five minutes in a seated position, and the measurements were performed at least twice for each participant, with the average of the last two measurements included in the analysis. An oscilloscopic automatic sphygmomanometer was used to measure blood pressure.[5,16,18]

#### CRP level

As a marker of acute systemic inflammation, CRP level was analyzed, in blood samples collected from the antecubital vein of the participants after a fasting period of at least 8 hours. It was analyzed using turbidimetric immunoassay with an ADVIA1800 autoanalyzer (Siemens, Tarrytown, NY, USA) and expressed as mg/L. The interassay coefficient of variation was from 0.38% to 1.53%.[5]

#### Depressive symptoms

Depressive symptoms were measured using the Korean version of the CES-D. Since the CES-D scale was created in 1977, it has been adapted for use in various types of surveys, such as by self-report or interview, and its usability has been extended to different populations, including the elderly.[20-22] The CES-D was designed to measure depressive symptoms by 20 items that ask about symptoms experienced during the last week.[23] The response values for each question are 0 to 4, with the total range of the scale being 0 to 60. Depression was defined, to estimate the prevalence in a community, as a score of more than 16 in this study.[24,25] However, it was used as a continuous variable when we assessed the impact of social support on the relationship between depressive symptoms and CRP level.

#### Social support

Social support was assessed using the same items as those used in the NSHAP.[26,27] Participants were asked about their social relationships as different sources of contacts, divided into 3 types, which are their spouse, family/relatives, and friends/neighbors. For each of their social contacts, social support was measured using 4 questions: 1) How often can you open up to (NAME) if you need to talk about your worries (spouse or family/relatives or friends/neighbors)? Would you say hardly ever, some of the time, or often? 2) How often can you rely on (NAME) for help if you have a problem? Would you

say hardly ever, some of the time, or often? 3) How often does (NAME) make too many demands of you? Would you say hardly ever, some of the time, or often? 4) How often does (NAME) criticize you? Would you say hardly ever, some of the time, or often?

Response categories were divided into four ordinal scales (never, hardly ever, sometimes, and often). To summarize social support as a total score, the responses were coded as 1 for never and 4 for often. Note that the latter two questions are reverse-coded items, so their values are reverse-coded. If the social support total score from the spouse was higher, it was assumed that someone literally received more social support from the spouse. For the analysis, social support total scores were categorized as low or high according to the mean scores.

**Other factors**

For current marital status, the possibilities investigated were living together with a spouse, separated, widowed, divorced, and never married; however, for the analysis, only living together with a spouse was defined as married, and others were defined as non-married. The education-level possibilities investigated were none, elementary school, middle school, high school, and college or higher. Current cigarette smokers were defined as those who answered "now smoking," irrespective of smoking duration. Drinkers were defined as those who answered "I'm drinking alcohol more than one time per week." Participants were asked if they had been diagnosed by a doctor for hypertension, metabolic syndrome, diabetes mellitus, dyslipidemia, cancer, osteoporosis, stroke, myocardial infarction, angina, arthritis, tuberculosis, asthma, cataract, glaucoma, hepatitis B, depression, urinary incontinence, or prostatic hypertrophy. If participants answered that they had been diagnosed with angina, stroke, or myocardial infarction, then they were excluded from the analyzes. For the other cases, we counted the number of comorbidities for them. To measure social integration, we used the social network size as an ecocentric network measure in this study. Social network sizes were calculated by asking participants to name up to five people with whom they discussed important things over the past 12 months, and a spouse, if applicable, so the total number of members could be up to six. Respondents were asked to characterize their relationship, such as spouse, parent, sibling, etc., and network members' sex and cohabitation statuses. Using this, various relationship types were identified. In addition, in the course of constructing a global network, the quality of the social network was examined more closely. Social network members were identified based on four criteria to evaluate duplicates, such as matched character in the name, less than five-year age differences, same address, and same sex. After that, 1,012 nodes and 1,799 social relations were identified. Eliminating those who were not residents of the *ris* and were found not to be spouses, a matrix of 1,012 by 1,012 was created. A more detailed description of the study design and data collection is available.[15]

**Statistical analysis**

For analysis, missing data was deleted for BMI, education level, CES-D, social network size, social support, and angina, stroke, MI, and CRP level >20 mg/dL. Finally, a total of 530 subjects (215 men and 315 women) were used for analysis. Because of missing values for social support, analyzed subjects differed in the kind of social support they received, with spousal social support for 408 subjects, support from family/relatives for 521 subjects, and support from neighbors/friends for 515 subjects. Differences between male and female participants were analyzed using a chi-square test for categorical variables and a two-sample t-test or Wilcoxon's rank sum test for continuous variables in accordance with normality. All of the analyzes were separated by sex, as the proportions or means of demographic factors or social integration were differentiated. Correlations of related variables were evaluated by Pearson's or Spearman's correlation analysis, in accordance with the normality of the variables. However, the statistical significance did not differ between the two methods in this data. To qualify and evaluate the relationship between depression and inflammation (CRP) according to the level of the social support of one's spouse, family/relatives, and friends/neighbors, we conducted multiple regression analyzes, adjusted for age, BMI, current smoking and drinking, marital status, number of comorbidities, total cholesterol, and social network size. We conducted regression analysis with other variables controlled gradationally. Sensitivity analysis was performed only for the comorbidities cardiovascular disease, depression, and cancer. All statistical analyzes were performed using SAS (version 9.4; SAS Inc., Cary, NC, USA).

## RESULTS

In our data analysis of these participants, we found higher levels of smoking, drinking, social networking, and education, compared to women. Women were more obese, highly lipid, and likely to live alone than men. Using the CES-D score over 16 as a cutoff, depressive symptoms were more prevalent in women as the borderline (p=0.0519). The mean±SD age of participants was 71.0±7.5 years (71.9±6.9 years in men and 70.4±7.8 years in women). The prevalence of depressive symptoms was 19.1% for men and 26.4% for women. In men, 2.8% lived alone, whereas 19.4% of the women lived alone. No educational experience was reported by 39.7% of women, compared to 11.6% of men (Table 1). In the CES-D validation study

**Table 1.** General and health related characteristics of the study subjects (N=530). Differences between men and women were compared using t-test or chi-square test, according to the types of the variables

| | Total (N=530) | Men (N=215) | Women (N=315) | p-value |
|---|---|---|---|---|
| Age | 71.01±7.49 | 71.89±6.86 | 70.41±7.84 | 0.0220 |
| Health related factors | | | | |
| Systolic BP (mm Hg) | 134.21±19.52 | 132.80±18.95 | 135.17±19.87 | 0.1709 |
| Diastolic BP (mm Hg) | 72.35±9.67 | 73.15±10.06 | 71.81±9.37 | 0.1163 |
| Total cholesterol (mg/dL) | 183.76±34.83 | 173.75±34.03 | 190.59±33.76 | <0.0001 |
| HDL (mg/dL) | 51.68±12.97 | 51.34±13.97 | 51.91±12.27 | 0.0294 |
| CRP (mg/dL) | 0.82 [0.47, 1.57] | 0.98 [0.52, 2.03] | 0.77 [0.45, 1.36] | 0.0008 |
| No. of comorbidity | 2 [1,3] | 0 [1, 2] | 2 [1, 3] | <0.0001 |
| Body mass index (kg/m$^2$) | 24.08±3.30 | 23.72±3.18 | 24.33±3.36 | 0.0370 |
| CES-D≥16 (%) | 124 (23.4) | 41 (19.1) | 83 (26.4) | 0.0519 |
| Behavioral factors | | | | |
| Smoker (%) | 68 (12.8) | 62 (28.8) | 6 (1.9) | <0.0001 |
| >40 g alcohol/day (%) | 114 (21.5) | 94 (43.7) | 20 (6.4) | <0.0001 |
| Sleep hour/day | 8.44±1.41 | 8.36±1.40 | 8.49±1.42 | 0.3167 |
| Social network | | | | |
| Social network size | 3.32±1.13 | 3.51±1.18 | 3.19±1.07 | 0.0011 |
| Socioeconomic status | | | | |
| Married (%) | 420 (79.4) | 202 (94.0) | 218 (69.4) | <0.0001 |
| Education (%) | | | | |
| None | 150 (28.3) | 25 (11.6) | 125 (39.7) | <0.0001 |
| Elementary school | 230 (43.4) | 94 (43.7) | 136 (43.2) | |
| Middle school | 78 (14.7) | 49 (22.8) | 29 (9.2) | |
| High school | 55 (10.4) | 37 (17.2) | 18 (5.7) | |
| Over college | 17 (3.2) | 10 (4.7) | 7 (2.2) | |

Data were expressed as numbers (percent), mean±standard deviation, or median [inter quartile range]. p value was derived from chi-square test, independent two sample t-test and Wilcoxon's rank sum test. BP: blood pressure, HDL: high density lipoprotein, CRP: C-reactive protein, No: number, CES-D: Centers for Epidemiologic Studies Depression Scale

in Korea, the cutoff value of 21 was proposed in the community setting and 25 in the clinic setting.[28] Using this, 9.3% of males and 12.7% of females had depression by the community standard, and 6.5% and 5.7%, respectively, by the clinical standard. There was no significant difference in depressive symptoms between men and women (p=0.2837 and p=0.8472, respectively).

The correlation analysis revealed that CRP level was positively associated with CES-D score only in men (p=0.0333). In both sexes, CES-D score was inversely statistically significantly associated with social support (p<0.0001). Moreover, the three types of social support were positively correlated with each other and were statistically significant (p<0.0001). However, CRP level and different types of social support were not correlated in either sex (Table 2).

Social support was measured in three types of relationships: spousal, family or relatives, and friend or neighbors. The average of the social support was classified by each item and by sex. The means±SDs of social support in these three categories in men were 12.94±1.98, 12.01±1.68, and 11.70±1.44, respectively, and 12.85±2.10, 12.66±1.87, and 11.85±1.56 for women, respectively. After categorizing the level of social support as low or high, the CES-D scores were higher when the level of social support was low, compared to high. This phenomenon was observed in both sexes regardless of the type of social support, and all of the results were statistically significant. However, CRP level did not differ by level of social support in either sex (Table 3). However, CRP level was positively correlated with BMI and depressive symptoms (CES-D) and negatively correlated with social support and network size (data not shown).

Regression analyses were performed to assess whether social support plays a role as an effects modifier on the relationship between depressive symptoms and CRP level. The analyses of the role of social support as an effects modifier showed sex differences and was different depending on the type of so-

**Table 2.** Correlation of variable factors related inflammation and depression

| | CRP | CES-D | Social supports | | |
|---|---|---|---|---|---|
| | | | Spouse | Family/relatives | Neighbors/friends |
| Men | | | | | |
| CES-D | 0.1425 (0.0333) | | | | |
| Social supports | | | | | |
| Spouse | -0.0334 (0.6462) | -0.3596 (<0.0001) | | | |
| Family/relatives | 0.0617 (0.3735) | -0.2875 (<0.0001) | 0.3998 (<0.0001) | | |
| Neighbors/friends | 0.0003 (0.9963) | -0.1838 (<0.0001) | 0.3375 (<0.0001) | 0.4139 (<0.0001) | 1.000 |
| Women | | | | | |
| CES-D | 0.0292 (0.6052) | | | | |
| Social supports | | | | | |
| Spouse | 0.0234 (0.7313) | -0.3853 (<0.0001) | | | |
| Family/relatives | -0.0291 (0.6091) | -0.1840 (0.0011) | 0.3669 (<0.0001) | | |
| Neighbors/friends | -0.0242 (0.6720) | -0.2829 (<0.0001) | 0.3376 (<0.0001) | 0.4329 (<0.0001) | 1.000 |

Data were expressed as correlation coefficients (p-value). CRP: C-reactive protein, No: number, CES-D: Centers for Epidemiologic Studies Depression Scale

**Table 3.** Mean differences of the inflammation, depression and body mass index according to the level or kind of the social supports

| | From the spouse | | | From the family except spouse/relatives | | | Neighbors/friends | | |
|---|---|---|---|---|---|---|---|---|---|
| | Low | High | p value | Low | High | p value | Low | High | p value |
| Men | | | | | | | | | |
| CRP | 0.98 [0.51−1.96] | 0.99 [0.57−2.24] | 0.5461 | 0.95 [0.51−2.04] | 1.03 [0.57−1.96] | 0.7086 | 1.19 [0.56−2.24] | 0.90 [0.52−1.96] | 0.5096 |
| CESD-C | 11.53±8.45 | 8.15±6.96 | 0.0016 | 10.84±8.45 | 7.78±6.22 | 0.0030 | 11.42±8.45 | 8.57±7.22 | 0.0098 |
| Women | | | | | | | | | |
| Hs-CRP | 0.75 [0.45−1.52] | 0.80 [0.45−1.25] | 0.5799 | 0.79 [0.45−1.42] | 0.76 [0.45−1.33] | 0.5028 | 0.77 [0.43−1.41] | 0.79 [0.47−1.35] | 0.7851 |
| CESD-C | 12.50±8.27 | 9.33±6.67 | 0.0002 | 12.33±8.47 | 10.13±6.91 | 0.0116 | 13.50±8.77 | 9.61±6.60 | <0.0001 |

Data were expressed as mean±standard deviation, or median [inter quartile range]. p value was derived from independent two sample t-test and Wilcoxon's rank sum test. CRP: C-reactive protein, No: number, CES-D: Centers for Epidemiologic Studies Depression Scale

cial support. In men, only the low social support group showed a correlation between higher CES-D score and higher CRP level. In the high social support group there was no statistically significant relationship between CES-D score and CRP level. In women, only the high social support group showed a positive relationship between CES-D score and CRP level.

The results of the types of social support are as follows. In the spousal social support category, men with high spousal social support benefited from a buffering effect, i.e., CRP level did not increase in accordance with the CES-D score; all models were statistically significant. However, in women the opposite result was seen. Only in women who had high social support from their spouses did the CES-D score show a positive relationship with CRP level, and all of the models showed statistical significance except for the final model, which showed borderline statistical significance.

The influence of the social support of family or relatives other than the spouse was observed only in men. There was no association between depressive symptoms and CRP level in men when they received this type of high social support. However, in the low social support group, there was a positive relationship between depressive symptoms and CRP level, in the unadjusted and final model.

Finally, the social support of friends or neighbors does not seem to act as an effects modifier in either sex. However, women with high social support from friends and neighbors showed a higher CRP level as CES-D scores increased, at the statistically borderline significant level (Table 4).

## DISCUSSION

The Organization for Economic Co-operation and Development (OECD) has reported that age-standardized suicide rates per 100,000 population in 2013 are the highest in South Korea.[29] Suicide is one of the most serious adverse events of depression.[30-32] In addition to depression, low levels of social sup-

**Table 4.** Differential relationships between depressive symptom and inflammatory marker (CRP) according to the level of the social support of one's spouse, family except spouse/relatives or friends/neighbors in elderly men and women

| Social support | From the spouse | | | | From the family except spouse/relatives | | | | Neighbors/friends | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Low | | High | | Low | | High | | Low | | High | |
| | β (SE) | p | β (SE) | p | β (SE) | p | β (SE) | p | β (SE) | p | β (SE) | p |
| Men | | | | | | | | | | | | |
| Model 1 | 0.0822 (0.0350) | 0.0207 | 0.0382 (0.0436) | 0.3830 | 0.0655 (0.0297) | 0.0290 | 0.0475 (0.0631) | 0.4537 | 0.0654 (0.0386) | 0.0931 | 0.0477 (0.0389) | 0.2226 |
| Model 2 | 0.0726 (0.0356) | 0.0441 | 0.0159 (0.0479) | 0.7413 | 0.0581 (0.0306) | 0.0601 | -0.0002 (0.0699) | 0.9977 | 0.0573 (0.0374) | 0.1288 | 0.0537 (0.0443) | 0.2280 |
| Model 3 | 0.0745 (0.0354) | 0.0379 | 0.0168 (0.0479) | 0.7267 | 0.0582 (0.0305) | 0.0583 | -0.0056 (0.0694) | 0.9319 | 0.0571 (0.0373) | 0.1295 | 0.0547 (0.0443) | 0.0379 |
| Model 4 | 0.1218 (0.0415) | 0.0042 | 0.0214 (0.0528) | 0.6861 | 0.0862 (0.0350) | 0.0150 | -0.0194 (0.0761) | 0.8000 | 0.0640 (0.0454) | 0.1631 | 0.0602 (0.0490) | 0.2221 |
| Women | | | | | | | | | | | | |
| Model 1 | -0.0150 (0.0164) | 0.3618 | 0.0630 (0.0294) | 0.0343 | 0.0029 (0.0176) | 0.8678 | 0.0133 (0.0250) | 0.5951 | -0.0198 (0.0219) | 0.3683 | 0.0381 (0.0204) | 0.0583 |
| Model 2 | -0.0164 (0.0165) | 0.3227 | 0.0622 (0.0305) | 0.0435 | 0.0031 (0.0179) | 0.8626 | 0.0047 (0.0258) | 0.8557 | -0.0254 (0.0221) | 0.2515 | 0.0418 (0.0212) | 0.0502 |
| Model 3 | -0.0105 (0.0164) | 0.5239 | 0.0668 (0.0309) | 0.0324 | 0.0072 (0.0178) | 0.6863 | 0.0043 (0.0260) | 0.8674 | -0.0217 (0.0218) | 0.3217 | 0.0418 (0.0212) | 0.0508 |
| Model 4 | -0.0085 (0.0176) | 0.6306 | 0.0618 (0.0335) | 0.0675 | 0.0058 (0.0189) | 0.7594 | 0.0005 (0.0276) | 0.9846 | -0.0179 (0.0236) | 0.4510 | 0.0387 (0.0227) | 0.0892 |

Model 1=Unadjusted; Model 2=Age adjusted; Model 3=Model 2+BMI adjusted; Model 4=Model 3+No. of comorbidity, current smoking, current drinking, education level, marital status, total cholesterol and network size. CRP: C-reactive protein, No: number, β: beta coefficient, SE: standard error, BMI: body mass index

port,[33] negative life events,[34] and major public holidays[35] have been suggested as risk factors of suicide. The prevalence of depression among those age 65 years or older in one city in Korea was estimated as 5.37% for major depressive symptoms and 5.52% for minor depressive symptoms in 2005.[36] And it was estimated to have increased by 5.76–7.95% in representative national samples during 2007–2013, in women over age 60 years.[37]

Since multiple epidemiological studies have consistently reported that CRP levels predict the risk of cardiovascular disease, it has been used widely as an inflammatory marker related to many diseases and symptoms, such as obesity, metabolic syndrome, gastrointestinal neoplasia, high-altitude pulmonary edema, and intermediate hepatocellular carcinoma.[38-43] Also, it has been reported that depression and inflammatory markers are related, and the different relationships were observed in men and women.[2,5,6,13,44-46]

We investigated social support providers as three types of social ties, as spousal, family/relatives, and friends/neighbors, to confirm the buffering effect of different types of social support with the relationship between CRP level and depressive symptoms in elderly Koreans in a rural area. As a result, the relationship between CRP level and depressive symptoms differ in accordance with whether the social support received is high or low. However, sex distinction was observed in these relationships.

Interest in the impact of the social support on health and disease etiology has been ongoing since the early 1970s. Seizing on this interest, Cohen and Wills[7] proposed the stress-buffering hypothesis. Some of the research that followed reported a buffering effect of the social support on psychosocial status or immunological markers,[4,8,24] and some of them did not.[3,13] In our data, the social support of the spouse seems to mediate the psychosocial effect on immunologic markers; however, a buffering effect was observed only in men. That is, in the case of men, the level of CRP and depressive symptoms increased together in contexts of low spousal social support, although this association was not observed in cases of high spousal social support. Even when adjusting for all other variables this phenomenon remained statistically significant. In contrast, in cases of lower spousal social support, CRP level and depressive symptoms were not related to each other in women, but did rise with higher spousal social support. Social support seems to mediate the relationship between CRP level and depressive symptoms in women, but the direction is opposite in men. As an effects mediator, different types of social support had an effect on the relationship between CRP level and depressive symptoms in the other two types of social ties also; however, observed relationships showed distinction by sex here too. Further research on this sex difference is needed. Our

study supported the buffering effects model of the relationship between inflammatory markers and depressive symptoms, but only in men. In an epidemiological sense, social support played a role as an effects modifier. However, this still does not establish a clear mechanism of the buffering effects and the relevance of these sex differences.

There are several possible interpretations of these results. First of all, they may be due to differences in sex roles and marital relations based on Confucianism in Korea.[47] Unlike the younger generation, elderly Koreans have been taught a lot Confucianism, with actions and values based on Confucianism required in their daily lives.[47,48] For most married women of the older generation in Korea, this entailed sacrifice and becoming psychologically submissive to her husband and his family. In the traditional marital relationship, men have a major role as the sole wage earner in the family, and women have to be dedicated to childcare and housework.[47] According to research on Korean-American immigrants, married women were involved in the family business in many cases, but their labor was being taken for granted and being regarded as a natural sacrifice.[47,49] We investigated whether they had worked without pay for the family business or not, and while only 29 participants answered yes, all of them were female. Given these Confucianism values, the observed buffering effect of social support provided by family members other than spouses seen only in men could be explained.

A second, possible explanation for the differential influence of familial social support on women can be found in research by Uchino et al.[6] Relationships among family members have mixed positive and negative aspects. Termed an ambivalent relationship, previous research reported that about 50% of important network members had this type of relationship.[6,50] In Korea, women rather than men are likely to have ambivalent emotions toward their spouse because of their role in the marital relationship, as previously discussed.[6,50] For example, the risk of coronary artery calcium plaque was increased when couples considered each other as ambivalent in 150 elderly couples.[6,51]

It seems that there are impacts on friends or familial social ties in certain health outcomes, such as depression. However, compared with the Western study of the elderly, the Korean population showed a weaker influence from friends' functional and emotional support compared to the family network.[9] Although supportive or ambivalent social support of family could predict the level of CRP, it did not predict the level of social support of friends in the elderly Western subjects,[6] whereas our study showed results similar to previous research, i.e., that in men there is a buffering effect but not in women. In the female subjects, social support of family or relatives did not show buffering effects on the CRP level, but social support of friends or neighbors had a slight effect. For many years, the study area has had a lower migrant rate than the average in Korea. The net number of migrants in other regions in Korea Island (named Jeju Island) were 3.5 times higher in 1995 and 15.2 times higher in 2015 than the area in this study. Also, the net number of migrants was 7.4 times higher in 1995 and 2.6 times higher in 2015, respectively, in another small town (Junggu) in the same administrative area (Incheon City) than this area.[52] Moreover, the study participants reported a long period of residence (mean±SD 47.3±25.5 years; 69.4% had lived there for more than 40 years) in the study area. Thus, in the case of elderly women, it is possible that a neighbor was an old friend and that social networking would change frequently.

Third, a recent review article on the various effects of emotional intelligence in multiple contexts, including health, could be helpful.[53] Emotional intelligence has been explored as two perspectives broadly; one is emotion-relevant self-control and personal character, and the other is cognitive ability for emotional processing, such as emotional perception. Of these two, the former as an emotional skill has been found to amplify the effects of various stressful events, including depression.[53-55] And the latter seems to be positively related with cortisol reactivity and negatively related to recovery from situational social stress.[53,56] The relationships among social support, emotional intelligence, immunologic markers, and depression have not been investigated fully, and it could be a clue in understanding the impact of social support on health and disease etiology. In addition, a recent article, using the same data as that used in this study, showed sex differences in hypertension awareness and control in relation to social support or social networks. Compared to women, in men there was a correlation between better hypertension awareness and control and the depth of their social network. In women, instrumental support of friends increased hypertension awareness. This result shows that the forms and objects of social support that women and men consider important may be different.[57]

In this study, there was a buffering effect in men from social support from spouses, family members, and relatives. Future research is needed to characterize the underlying pathway, such as paternalistic attitudes that could create dependency on family members among Korean elderly men, or that lots of contact with relatives would make them feel happy. Uchino et al argued that the kind of person who has the strongest social relationships should be considered in a study on social ties and physical health.[6] Thus, we hypothesized that the spouse would be the most important provider of social support to Korean elderly men, but that, for women, networks with neighbors or friends are noticeable in a rural area. This study was designed to create a global data network comprising all of the residents in a small town; therefore, there is an advantage to

investigate the psychosocial effect of neighbors among rural elderly persons. Besides, the social network size was adjusted in the multivariate models in our data. It could be helpful to understand the effect of social support more broadly.

Several limitations should be noted, in addition to the cross-sectional design. First, various inflammatory markers, such as IL-6, fibrinogen, and tumor necrosis factor-α have been compared in other studies, and they have shown differing results.[2,3,10,13] Our study dealt with only one inflammatory marker, CRP. It was selected as the main index for two reasons. One is that this study has focused on the association with cardiovascular disease since the planning stage, and the other is that CRP has shown the most persistent association of the three inflammatory markers examined in previous studies.[3,6,58]

Second, we used the CES-D to measure depressive symptoms, not the Geriatric Depression Scale (GDS), even though the study subjects were elders. There are two main reasons for using the CES-D in the KSHAP study. First, in the NSHAP study, the NSHAP Depressive Symptoms Measure, which consists of 11 items selected from the original 20-item CES-D, was developed. However, in KSHAP, the original 20 CES-D items were all used to focus more on depression and to improve the comparativeness of the results to other studies. Second, while the Korean version of the CES-D has been tested for relevance in a variety of ways, the GDS showed a higher cutoff point in the West than in Korea. It has been pointed out that the translation process of the question item or the item itself are not suitable for Korean culture.[59] The internal consistency of the Korean CES-D questionnaire was 0.893 for Cronbach's alpha, and test-retest reliability was assessed by Pearson's gamma coefficient as 0.68 ($p<0.001$).[28] Moreover, the social support measure item is the same as the NSHAP measure item.[26,60] However, since the target NSHAP and KSHAP populations are different, the support provider has changed slightly in accordance with the research purpose. In the NSHAP, social support categories were divided into spouse, family, and friends. In the KSHAP, the family was extended to include relatives, and friends were extended to include neighbors in the same category.

Third, cognitive disability level or activities of daily living were not considered in our study. Maybe we could adjust these variables in the follow-up data. Last, because of the small magnitude of beta coefficients in the regression analysis, interpretation should be done with caution. Previous research also showed a similarly small magnitude or borderline relationships.[3,13] It necessitates future studies with more conclusive evidence to prove that there is a buffering effect.

Finally, as the study design is cross-sectional, no causal relationships could suggest an actual relationship between the level of social support and inflammatory markers or depressive symptoms. In this study, we confirmed the role of social support as a mediator, with the correlation between immune indicators and depression. However, the buffering effect of social support on the spouse or family was observed only in men. The marginal impact of the social support was different in both sexes. Yet there are clues to understanding sex differences in the effects of social support on the relationship between inflammatory markers and depressive symptoms in Korean rural elderly persons.

## Acknowledgments

This study was supported by a grant from the National Research Foundation of Korea (NRF-2017S1A3A2067165). The authors declare that there are no conflicts of interest regarding this study.

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