Relationship between Handgrip Strength and Low-grade Inflammation in Older Adults with Depression

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Objective: The relationship among physical functional decline, low-grade inflammation, and depression remains unclear. The aim of this study was to examine the association between hand grip strength (HGS) and high-sensitivity C-reactive protein (hs-CRP) in a large sample with depression.

Methods: This study used data obtained from a representative Korean sample of 9,402 people who participated in the seventh Korean National Health and Nutrition Examination Survey. Physical function was assessed using a digital grip strength dynamometer. Depression was identified using a cutoff of 5 on the Patient Health Questionnaire-9 (PHQ-9), and high hs-CRP level was defined as ≥ 3.0 mg/L.

Results: In older adults (≥ 60 years) with depression, 43.8% of those with high hs-CRP levels had low HGS, compared to 21.8% of those with hs-CRP levels < 3.0 mg/L (p = 0.002). Multivariate analysis revealed that, after adjustments for potentially confounding factors, high hs-CRP was independently associated with lower HGS (B = −2.25; 95% confidence interval = −4.49 to −0.02) in older adults with depression, but not in younger or middle-aged adults with depression.

Conclusion: These findings suggest a significant correlation between physical functional decline and low-grade inflammation in older adults with depression.

KEY WORDS: Hand grip strength; C-reactive protein; PHQ-9; Depression; Inflammation; Older adults.

INTRODUCTION

Handgrip strength (HGS) serves as a simple, non-invasive proxy measure for physical functioning/performance [1,2]. Several studies have shown that low HGS, as an indicator of physical functional decline, predicts negative clinical outcomes such as functional impairment and mortality in various populations of different ages [3,4], although the mechanisms linking muscle strength and disease outcomes remain poorly understood. One current hypothesis is that inflammatory processes might explain the association between muscle strength and mortality. Previous studies have reported associations between muscle strength and inflammatory processes; unfavorable levels of inflammatory biomarkers, such as elevated C-reactive protein, are also linked with a physical functional decline and adverse health outcomes [5-8].

Recently, several reports have focused on the relationship between low HGS and depression. Previous cross-sectional and longitudinal studies have shown associations between lower HGS and depressive symptoms [9-14]. However, the causal mechanisms underlying this relationship have not yet been determined. Inflammatory processes or age-associated changes in the immune sys-
tem may underlie the link between low HGS and depression. Low-grade inflammation has been associated with depression and physical functional decline; the literature suggests that this relationship is likely bidirectional [15-17].

The purpose of this study was to examine the relationship between depression and physical functional decline, as evidenced by low HGS. The rate of low HGS was determined among adults with depression by using a representative sample of Korean adults stratified according to age group. In addition, this study examined whether high levels of high-sensitivity C-reactive protein (hs-CRP), an indicator of low-grade inflammation [18], were associated with low HGS in adults with depression, which elucidated potential links among hs-CRP, HGS, and age in adults with depression.

METHODS

Study Participants
The data for this study were extracted from the seventh Korea National Health and Nutrition Examination Survey (KNHANES VII, 2016−2018). The KNHANES has been conducted by the Ministry of Health and Welfare of the Korean Government since 1998 to assess the general health and nutritional statuses of Koreans. It is a 3-year cross-sectional study comprising health examinations, health surveys, and nutritional surveys that is administered to a representative sample of the entire Korean population, identified by means of a stratified cluster-sampling method. The data are collected through household interviews and standardized physical examinations conducted at mobile examination centers [19]. The KNHANES database is publicly available at the KNHANES website (http://knhanes.cdc.go.kr). All the protocols were approved by the Institutional Review Board of the Korean Centers for Disease Control and Prevention (2013-12EXP-03-5C).

The present study was based on participants in the first (2016) and third (2018) years of the seventh KNHANES. Notably, 2017 data were excluded in this study because the Patient Health Questionnaire-9 (PHQ-9) was not included in the survey items during that year. KNHANES VII-1 and VII-3 (2016 and 2018) examinations and health surveys were completed by 8,150 and 7,992 participants, respectively. The study’s flow diagram is presented in Figure 1. The following individuals were included in this analysis: those aged ≥ 19 years (n = 12,875) who completed the PHQ-9 (n = 11,085). Of the individuals with PHQ-9 data, only those with available serum hs-CRP data were eligible for inclusion (n = 10,820). The following individuals were excluded: those who had been diagnosed with rheumatoid arthritis by a doctor (n = 215); those with limited physical activity (n = 797); and those who did not complete an assessment of HGS (n = 406). The remaining 9,402 individuals (4,312 males and 5,090 females) were included in this study.

Assessment and Evaluation

Depression
The presence of depression was identified using the PHQ-9, a reliable and valid screening tool for measuring depression severity over the prior 2 weeks. The PHQ-9 is composed of nine items rated from 0 (not at all) to 3 (symptoms present nearly every day); the scores for each item are summed to produce a total depression severity score (range, 0–27) [20]. The Korean version of the PHQ-9 has high internal consistency (Cronbach’s α = 0.86), and the optimal cut-off total score indicating the presence of depression is 5. Thus, participants were con-

Fig. 1. Selection of study participants. KNHANES, Korea National Health and Nutrition Examination Survey; hs-CRP, high sensitivity C-reactive protein; PHQ-9, Patient Health Questionnaire-9.
considered to have depression if their total PHQ-9 score was \( \geq 5 \) [21].

**HGS**

HGS was measured using a digital grip strength dynamometer (TKK 5401 GRIPD; Takei, Niigata, Japan), which measures force between 5.0 and 100.0 kg and has an adjustable grip span. The minimum measurement unit is 0.1 kg. During the assessment, participants were asked to stand upright with their feet hip-width apart and to look straight ahead with their elbow fully extended. The dynamometer was held with the testing hand in a comfortable neutral position (not flexed or extended) with 90° flexion at the index finger. Participants were instructed to squeeze the grip continuously with full force for at least 3 seconds. They were asked not to swing the grip dynamometer during the test and not to hold their breath. The time between trials was approximately 60 seconds. Each hand was tested three times; the highest reading from the dominant hand was used as maximum grip strength, expressed in kg [22]. Low HGS values were defined as \(< 26\) kg for males and \(< 18\) kg for females [23].

**hs-CRP levels**

Blood samples were collected in 3-ml EDTA-coated tubes (BD Vacutainer, Franklin Lakes, NJ, USA). Serum samples used for the analysis of hs-CRP were stored at 2−8°C in refrigerated containers after blood had been collected. All laboratory analyses were performed within 24 hours of sample collection. Serum hs-CRP levels were measured using an immunoturbidimetric apparatus (Cobas, Roche, Germany), which was calibrated daily with reference standards between 0.15 and 20.0 mg/L. To compare the prevalences of depression among individuals with different levels of hs-CRP, an hs-CRP level of 3.0 mg/L was used. High hs-CRP was defined as \( \geq 3.0 \) mg/L, the cutoff stipulated by the American Heart Association and Centers for Disease Control and Prevention to indicate “high risk” for cardiovascular disorders [24].

**Study variables**

Age, sex, weight, height, smoking status, alcohol use problems, household income, physical activity, and protein intake were recorded. Weight and height were collected in accordance with standardized procedures; 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 alcohol use problems, the Alcohol Use Disorder Identification Test-Alcohol Consumption instrument was administered. A cutoff score of 8 was used to indicate alcohol use problems in this study [25]. Household income was categorized in quartiles.

Physical activity was assessed using the International Physical Activity Questionnaire-short form, which estimates overall physical activity in metabolic equivalent of task (MET)-min/week by determining the duration (in minutes) and number of days (per week) of engagement in three specific types of activity (walking, moderate-intensity activity, and high-intensity activity) across a comprehensive set of domains (leisure time, work-related activity, transport-related physical activity, and domestic and gardening activity) in the prior 7 days [26]. The MET is a unit for estimation of the amount of oxygen used by the body during physical activity. Participants were classified into three physical activity levels (low, moderate, high) based on the cutoff total MET-min/week for each category [27]. Protein intake was assessed with a 24-hour dietary recall questionnaire administered by a trained dietitian. The results were generated using the Food Composition Table developed by the National Rural Resources Development Institute [28]. Inadequate protein intake was defined as protein intake below the recommended dietary reference intake for Koreans in 2015, according to the Korean Nutrition Society.

Participants were considered to have hypertension if they had systolic blood pressure \( \geq 140 \) mmHg, diastolic blood pressure \( \geq 90 \) mmHg, or if they were receiving treatment for hypertension. Participants were considered to have diabetes if they had a fasting blood glucose level \( \geq 126 \) mg/dl that was first detected in this survey, used an antidiabetic medication, or had been previously diagnosed with diabetes by a doctor. Participants were considered to have dyslipidemia if they had total cholesterol level \( \geq 240 \) mg/dl or if they were receiving treatment for dyslipidemia. The National Cholesterol Education Program-Adult Treatment Panel III criteria were used to determine whether metabolic syndrome was present; the cut-offs for the Asia-Pacific region were applied [29]. Participants were considered to have metabolic syndrome if three or more of the following criteria were met: (i) sys-
Table 1. Age-stratified characteristics of participants in KNHANES 2016 and 2018, stratified according to the presence of depression (n = 9,402)

| Variables                        | Age 19−39 years (n = 2,864) | Age 40−59 years (n = 3,685) | Age ≥ 60 years (n = 2,853) |
|----------------------------------|-------------------------------|-------------------------------|----------------------------|
|                                  | Number PHQ-9, < 5 (n = 2,275) | PHQ-9, ≥ 5 (n = 589) p value | Number PHQ-9, < 5 (n = 3,155) | PHQ-9, ≥ 5 (n = 530) p value | Number PHQ-9, < 5 (n = 2,488) | PHQ-9, ≥ 5 (n = 365) p value |
| Handgrip strength (kg)          | 2,864 33.7 ± 10.8 < 0.001     | 3,685 32.4 ± 10.2 29.9 ± 10.1 < 0.001 | 2,853 27.6 ± 9.2 24.6 ± 8.9 < 0.001 |
| Sex, male                       | 1,324 1,142 182 < 0.001       | 1,626 1,444 182 < 0.001      | 1,362 1,233 129 < 0.001       |
| Income level                     |                               |                               |                               |
| 1st quartile                    | 696 534 162 0.005             | 831 665 166 < 0.001          | 642 524 118 0.005             |
| 2nd quartile                    | 729 563 166                   | 944 796 148                  | 697 606 91                    |
| 3rd quartile                    | 719 576 143                   | 956 932 124                  | 729 648 81                    |
| 4th quartile                    | 716 598 118                   | 948 857 91                   | 770 698 72                    |
| Current smoker                  | 675 522 153 0.127             | 799 667 132 0.053            | 320 272 48 0.214              |
| Alcohol use problems            | 712 539 173 0.006             | 813 693 120 0.063            | 322 274 48 0.085              |
| Physical activity               | 0.689                         | 0.014                        | 0.016                        |
| Low                              | 1,251 985 266                 | 1,417 1,239 178              | 1,084 954 130                 |
| Moderate                         | 1,173 936 237                 | 1,141 1,145 199              | 1,086 958 128                 |
| High                             | 440 354 86                    | 425 369 56                   | 232 214 18                    |
| Protein intake (g/d)            | 2,864 81 ± 46 73 ± 42 < 0.001 | 3,137 74 ± 38 69 ± 39 0.017  | 2,853 61 ± 33 55 ± 27 0.002  |
| Body mass index (kg/m²)         |                               | 0.059                        | 0.030                        |
| ≤ 18.5                          | 183 132 50                    | 89 68 21                     | 46 36 10                      |
| 18.5−24.9                       | 1,776 1,420 356               | 2,250 1,940 310              | 1,703 1,478 225               |
| ≥ 25                             | 902 719 183                   | 1,344 1,145 199              | 1,086 958 128                 |
| Hypertension                     | 219 192 27 0.729              | 1,019 873 146 1.000          | 1,636 1,434 202 0.428         |
| Diabetes                         | 52 43 9                      | 369 312 57 0.532            | 697 588 109 0.011             |
| Cardiovascular disease           | 3 2 1                       | 57 50 7 0.849               | 745 244 41 0.400             |
| Metabolic syndrome              | 409 332 77 0.390             | 1,193 1,012 181             | 1,341 1,240 198 0.117         |
| Dyslipidemia                     | 229 169 60 0.033             | 831 702 129 0.286           | 982 832 150 0.005             |
| hs-CRP (mg/L)                    | 2,864 1.1 ± 1.2 ± 2.4 0.138 | 3,685 1.1 ± 1.1 ± 1.1 ± 1.8 0.600 | 2,853 1.3 ± 2.2 1.6 ± 2.8 0.017 |
| High hs-CRP (≥ 3.0 mg/L)         | 228 173 55 0.172             | 259 222 37 1.000            | 284 231 53 0.003             |

Values are presented as mean ± standard deviation or number.

KNHANES, Korea National Health and Nutrition Examination Survey; hs-CRP, high sensitivity C-reactive protein; PHQ-9, Patient Health Questionnaire-9.
HGS and Low-grade Inflammation in Depression

725

Fig. 2. Age-stratified proportion of adults with low handgrip strength, stratified according to depression status, in KNHANES 2016 and 2018 (n = 9,402).

KNHANES, Korea National Health and Nutrition Examination Survey; PHQ-9, Patient Health Questionnaire-9.

*p value < 0.05; **p value < 0.001.

tolic/diastolic blood pressure ≥ 130/85 mmHg or antihypertensive drug treatment; (ii) fasting serum triglyceride level ≥ 150 mg/dl; (iii) low HDL-C level (< 40 mg/dl in males and 50 mg/dl in females); (iv) waist circumference ≥ 90 cm in males and ≥ 80 cm in females; and (v) fasting serum glucose level ≥ 100 mg/dl or use of antidiabetic medication.

Statistical Analysis

Continuous data are expressed as mean (standard deviation [SD]); categorical data are expressed as percentages. Initial analyses explored differences in participant characteristics according to the presence of depression. The chi-square test was used for comparison of categorical variables; the t test was used for comparison of continuous variables.

The association between serum hs-CRP levels and HGS was assessed using multivariate linear regression models with progressive levels of adjustment. In each of these models, the main independent variable was serum hs-CRP level (< 3.0 mg/L vs. ≥ 3.0 mg/L) and the dependent variable was HGS. Model 1 was adjusted for sex and age; model 2 included model 1, with additional adjustments for BMI and income; and model 3 included model 2, with additional adjustments for current smoking, alcohol use problem, physical activity, total protein intake, diabetes mellitus, hypertension, dyslipidemia, cardiovascular disease, and metabolic syndrome. The analyses were stratified according to three pre-defined age groups (19−39, 40−59, and ≥ 60 years) in all three models. A multivariable logistic regression model was used the enter method, to determine whether serum hs-CRP was independently associated with low HGS. All statistical tests were two-tailed; statistical significance was defined as p < 0.05. All statistical analyses were performed using PASW Statistics, version 18 (IBM Co., Armonk, NY, USA).

RESULTS

Sample Characteristics

The sample comprised 9,402 participants; of these, 2,864 were aged 19−39 years, 3,685 were aged 40−59 years, and 2,853 were aged ≥ 60 years. The general characteristics of the study participants according to age group are shown in Table 1. In total, 20.6%, 14.4%, and 12.8% of participants aged 19−39 years, 40−59 years, and ≥ 60 years, respectively, had depression. Females showed significantly higher prevalence of depression than males (19−39 years, 26.4% vs. 13.7%, p < 0.001; 40−59 years, 16.9% vs. 11.2%, p < 0.001; ≥ 60 years, 15.8% vs. 9.47%, p < 0.001). In the younger age group (19−39 years), depression was significantly associated with low income, alcohol use problems, low protein intake, hypertension, and dyslipidemia. In the middle age group (40−59 years), participants with depression had significantly lower income, lower physical activity, lower protein intake, and lower BMI. In the older age group (≥ 60 years), depression was significantly associated with low income, low activity, low protein intake, diabetes, and dyslipidemia.

Depression and Low HGS

In all age groups, participants with depression tended to have lower HGS (19−39 years, 29.8 [SD = 10.8] vs. 33.7 [SD = 10.8] kg, p < 0.001; 40−59 years, 29.9 [SD = 10.1] vs. 32.4 [SD = 10.2] kg, p < 0.001; ≥ 60 years, 24.6 [SD = 8.9] vs. 27.6 [SD = 9.2] kg, p < 0.001) (Table 1). Moreover, rates of low HGS were significantly higher in participants with depression than in participants without depression (19−39 years, 6.3% vs. 4.0%, p = 0.025; 40−59 years, 6.0% vs. 3.9%, p = 0.034; ≥ 60 years, 24.9% vs. 17.0%, p < 0.001) (Fig. 2).

In older adults (≥ 60 years), serum hs-CRP levels were significantly higher in individuals with depression than in...
Association between Low HGS and Serum hs-CRP Levels in Adults with Depression

In older adults (≥ 60 years) with depression, 43.8% of those with hs-CRP levels ≥ 3.0 mg/L had low HGS, compared to 21.8% of those with hs-CRP levels < 3.0 mg/L (p = 0.002). However, among younger and middle-aged adults with depression, the rate of low HGS did not differ according to CRP level (Fig. 3).

Multivariate analysis revealed that, after adjustments for potentially confounding factors, high hs-CRP was independently associated with lower HGS (B = −2.25;
95% confidence interval = −4.49 to −0.02) in older adults with depression, but not in younger or middle-aged adults with depression (Table 2).

Multiple logistic regression analysis showed this same pattern of associations among age groups (Table 3). In older adults with depression, the high hs-CRP group was 9.3-fold more likely to have low HGS after adjustments for potential confounding factors (adjusted odds ratio = 9.3, 95% confidence interval = 1.8−47.9). Conversely, the associations between high hs-CRP level and low HGS in younger and middle-aged adults with depression were not significant, regardless of adjustments for confounding factors (Table 3). Moreover, among adults without depression or with minimal depressive symptoms, no significant associations between high hs-CRP and low HGS were observed in any age group after adjustments for potential confounding factors.

**DISCUSSION**

These analyses revealed an association between low HGS and depression in a nationally representative sample of the adult Korean population. An association between serum hs-CRP levels and depression was observed in older adults alone. More importantly, high hs-CRP levels were significantly associated with an elevated risk of low HGS in older adults with depression, but not in younger and middle-aged adults with depression.

Our results are consistent with the findings of two previous cross-sectional studies, which showed significant associations between depression and low HGS [9,10]. A large sample study targeting older adults in the USA found that females with moderate to severe depressive symptoms had low HGS; however, no such association was observed in males [11]. Another study found that lower HGS, standardized according to age and sex, was both cross-sectionally and longitudinally associated with depressive symptoms [12].

Furthermore, various studies have reported associations between depression and physical functional decline in adults [13,14,30,31]. A recent meta-analysis revealed that more than one-third of older people with physical frailty had depression, and a similar proportion of older people with depression had physical frailty; the odds of each condition were 4-fold greater, compared with controls [32]. These studies provide evidence of a consistent and bidirectional relationship between depression and declining physical function among adults [31,32]. Depressive symptoms might cause this physical functional decline. For instance, depressive symptoms such as poor oral intake, sleep disturbances, and reductions in physical activity can change body composition and metabolism, thereby promoting physical decline [33,34]. Furthermore, reduced physical function results in diminished ability to undertake activities of daily living, ultimately leading to social isolation and functional impairment, which enhance the risk of depression [35].

Thus far, epidemiological evidence regarding the association between elevated hs-CRP and depression in general population samples has been inconsistent. Several studies have identified associations between depression and high levels of hs-CRP [36-41], whereas other studies have shown no associations [42-44]. Our analysis, which stratified the study population according to age group, showed that hs-CRP levels were higher among older adults with depression, but not in younger adults. Many previous studies involving older adults have shown an association between high hs-CRP and depression, suggesting that the role of inflammation in depression might be related to age-associated changes in immune system function [40,41]. Notably, our second analysis (based on a sub-sample of adults with depression) also showed a positive association between low HGS and high hs-CRP in older adults with depression, but not in younger or middle-age adults. In older adults with depression, a high hs-CRP level enhanced the odds of low HGS by 9.3-fold. This is presumably because the roles of low-grade inflammation in depression and muscle strength may differ between younger and older adults. The physical functional decline accompanied by late-life depression might most strongly depend on such low-grade inflammation.

Some biological mechanisms may underlie the relationships among low-grade inflammation, physical functional decline, and late-life depression. As noted above, depressive symptoms and declining physical function are generally presumed to exhibit a reciprocal relationship [33-35]. In older age, low-grade inflammation is likely involved in both, comprising the underlying link between depression and physical functional decline [8,17]. Various studies have consistently reported a cross-sectional association between systemic inflammation and reduced muscle strength in older adults [5-8]. In a pro-
spective study, higher levels of serum interleukin-6 and 
CRP were associated with a 2–3-fold greater risk of los-
ing > 40% of muscle strength over a 3-year follow-up pe-
period [45]. Physical frailty-associated inflammatory proc-
esses may underlie the pathway between low muscle 
strength and depression by activation of the hypothal-
amus–pituitary–adrenal axis [46,47]. Additionally, de-
pression facilitates the inflammatory response; low-grade 
inflammation may thus contribute to the development and 
acceleration of physical functional decline among 
older people with depression. Furthermore, reduced 
physical activity and protein intake due to late-life depres-
sion may result in further physical functional decline due 
to sarcopenia, which in itself is associated with low-grade 
inflammation [48]. Many studies have suggested that aging 
is associated with immune dysregulation; sustained 
and prolonged inflammation becomes detrimental to 
physical and mental health [49-51]. Inflammatory signal-
ling pathways interact with complicated molecular and 
physiological pathways such as bioactive hormones, nu-
trition, mitochondria, and genes. With aging, these mo-
lecular and physiological changes may contribute to the 
development of depression and acceleration of physical 
functional decline in older adults [50,51].

The present study had some limitations. First, the 
cross-sectional nature of the study design has important 
implications for the bidirectional relationships among de-
pression, HGS, and hs-CRP levels. Although our findings 
support the hypothesized link between depression and 
low HGS, along with the mediating effects of hs-CRP in 
older adults, the cross-sectional design precludes deter-
mination of the causal direction of these associations. 
Therefore, further studies are necessary to elucidate the 
effect of low-grade inflammation on the association be-
tween depression and physical functional decline; investi-
gating this interaction will require interventional or lon-
gitudinal studies. Second, the PHQ-9 [20,21], a self-rated 
depressive symptom scale, was used to categorize depres-
sion in this study, whereas a standardized diagnostic in-
terview would have been more robust. Although the 
PHQ-9 has been validated as a screening tool for depres-
sion, it is not a diagnostic tool. Third, the use of medici-
ations (e.g., antidepressants) [52], the effects of recent in-
fected [53], and other major confounding factors for de-
pression, HGS, and inflammation were not considered 
because the relevant data were unavailable. Despite these

limitations, our study included a large sample size, which 
facilitated the detection of associations between depre-
sion and physical functioning; it also included strat-
ification by age group. To the best of our knowledge, this 
is the first study to evaluate the associations among phys-
ical function (measured using HGS) and serum hs-CRP 
levels in a cohort of adults with depression.

In conclusion, this study revealed a cross-sectional as-
sociation between depression and low HGS in a com-
unity-living Korean adult population. The association 
between low HGS and high hs-CRP level was more prom-
inent in older adults with depression, compared with 
younger and middle-aged adults. Further studies are 
needed to explore the neurobiological mechanisms and 
clinical consequences of the observed relationships 
among HGS, low-grade inflammation, and depression.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was 
reported.

■ Author Contributions

Conceptualization: Kwi Young Kang, Won-Myong 
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