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The relationship between the presence of depressive symptoms and the severity of self-reported knee pain in the middle aged and elderly

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Abstract
Purpose Knee pain is a very common symptom of knee osteoarthritis (OA), and identification of the major contributors to knee pain is important to establish management plans for patients with knee OA. Among the potential contributors, we hypothesized that coexisting depressive symptoms might increase the severity of knee pain because the increased cytokine levels and neurotransmitter changes related to depression are known to influence the threshold of physical pain perception. Therefore, a possible relationship between self-reported depressive symptoms and self-reported knee pain has been explored. Additionally, we sought to determine factors influencing the severity of knee pain in a middle-aged and elderly Korean population using data from the fifth Korean National Health and Nutrition Examination Survey.

Methods In total, 6599 persons aged ≥50 years were evaluated in terms of the radiographic severity of OA and pain severity using 10-point numerical rating scales. Depressive mood was assessed using a polar question: "Had the subject felt despair or depression every day for more than 2 weeks during the past year?"

Results The Kellgren–Lawrence knee OA grade, depression, gender, educational level, household income, smoking status, marital status, living place, comorbidity status, BMI, and age were identified by multiple linear regression as variables affecting knee pain severity. The presence of depressive symptoms was associated with an increased risk of severe knee pain (odds ratio 2.55 [95 % confidence interval 1.77–3.66]). After stratifying the group in terms of the radiographic severity of knee OA, the relationship with depression persisted in the minimal (2.89 [1.90–4.32]) and moderate OA subgroups (2.29 [1.33–3.94]), but not in the severe OA subgroup.

Conclusions Severe knee pain was independently associated with the presence of depressive symptoms in middle-aged and elderly Korean subjects. This suggests that screening for and treatment of depression may help improve knee pain in elderly individuals.

Level of evidence II.

Keywords Knee pain · Depression · Knee osteoarthritis · KNHANES

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Introduction

Knee osteoarthritis (OA) is one of the most common chronic conditions among middle-aged and elderly adults [6, 7] and is a leading cause of disability in such populations [42]. As life expectancy increases, particularly in

Asian countries, the prevalence of knee OA is expected to increase rapidly [15].

Both self-reported knee pain and radiographic findings are used to diagnose knee OA and determine its severity [1]. Several studies have found that the severity of knee pain and the radiographic severity of knee OA are not well-correlated; patients frequently report significant knee pain when no or mild radiographic OA is evident in the knee, and vice versa [8, 11, 17]. Therefore, it is important to identify other contributors to knee pain to prepare management plans for such patients. Although several factors including socio-economic, demographic, clinical, and psychological variables collectively contribute to the severity of knee pain [10, 12, 35, 38, 41], the precise reason for the difference in pain perception among patients with knee OA remains unclear.

Depression, which is also common in elderly populations [28], can significantly affect physical functioning and quality of life [16]. Furthermore, depression is associated with aggravation of certain chronic medical conditions, including diabetes and cardiometabolic diseases [25, 34]. Although the precise mechanism is poorly understood, the increases in inflammatory cytokines and alterations in neurotransmitter levels [13] caused by depression may contribute to the aggravation of such diseases. Because increased cytokine levels and neurotransmitter changes both influence the threshold of physical pain perception [12, 37], depression may play an important role in aggravating knee pain, even in patients with minimal/mild knee OA. In this context, several studies have sought to identify relationships between depression and the extent of pain in patients with knee OA, but the results have been controversial. Recent studies have found that comorbid depression significantly influences the extent of knee symptoms in patients with knee OA, particularly mild to moderate radiographic OA [11, 22, 30, 33, 43], whereas other studies have failed to detect significant relationships [8, 9, 31]. For example, Kim et al. [22] reported that the presence of depressive symptoms was associated with an increased risk of symptomatic knee OA among 660 elderly Korean patients with minimal to moderate radiographic knee OA. Davis et al. [11] also showed that psychological well-being is associated with knee pain in patients with and without radiographic knee OA. A nested case–control analysis of older adults in a community setting also found a significant relationship between knee pain and depressive symptoms [30]. However, in contrast, another study [9] found no significant relationship between depression and knee pain in 374 community volunteers. Furthermore, Creamer et al. [8] found a significant relationship between depression and knee pain score using the McGill Pain Questionnaire, but no relationship between depression and knee pain quantitated using a visual analogue scale or the WOMAC OA index. Therefore, the association between knee pain and depressive symptoms remains poorly characterized. Although explanations for the differences among studies are elusive, the limitations of some studies may contribute to these conflicting results. Many studies had relatively small sample sizes that did not allow for generalization of data to the population at large [8, 9, 22, 30, 31]. Furthermore, knee and hip OA were evaluated in combination in one study [33], and many studies did not consider the radiographic severity of knee OA [8, 30, 31, 33]. Furthermore, insufficient adjustments of potential confounding factors are evident in many previous studies [8, 11, 43]. Finally, very few studies evaluated large numbers of nationally representative subjects. Hence, although many previous studies have investigated the relationship between the severity of knee pain and depressive symptoms, the associations between these two factors remain unclear; precise associations remain to be determined given the many previous limitations.

Therefore, a possible relationship between depression and self-reported knee pain after careful adjustment for the limitations of previous studies has been explored using data from the fifth Korean National Health and Nutrition Examination Survey (KNHANES). Because no prior study has investigated factors influencing the severity of knee pain in a nationally representative Asian population, we additionally sought differences in socio-economic, demographic, clinical, and psychological factors in middle-aged and elderly Korean subjects with and without severe knee pain. We hypothesized that the presence of a depressive mood might be associated with the severity of knee pain in middle-aged and elderly Korean populations.

Materials and methods

This study constitutes a secondary analysis of data obtained by the KNHANES conducted in 2010 and 2011. The KNHANES is a nationally representative cross-sectional study performed by the Korean Ministry of Health and Welfare. The target population was non-institutionalized civilians over 1 year of age living in Korea. Households (sampling units) were selected using a stratified, multistage, probability sampling method based on gender, age, and geographical area. To ensure that the entire Korean population was represented, a sampling weight was assigned to each participant. Participants were informed that their household had been randomly selected to participate in a survey performed by the Korean Ministry of Health and Welfare. They were given the right to refuse to participate in accordance with the National Health Enhancement Act supported by the National Statistics Law of Korea. Written informed consent was obtained from each participant. Each participant completed a four-part questionnaire exploring

health history, health behaviour, health examinations, and nutrition; a standardized protocol was followed [4]. The Health Interview Survey, Health Behaviour Survey, and Nutrition Survey were conducted using self-administered questionnaires. Interviewers assisted participants who experienced difficulty in self-administration. The Health Interview Survey included questions on medical history, education level, economic status, and occupation. The Health Behaviour Survey included questions on lifestyle behaviours, including cigarette smoking, alcohol consumption, and exercise status. The Health Examination Survey involved anthropometric, biochemical, and radiographic measurements performed by trained medical staff following standard procedures. Dietary intake was assessed via 24-h recall. Before testing, all subjects were told to maintain their normal dietary habits. Nutritional analysis was performed using Can-Pro 2.0; this nutrient intake assessment software was developed by the Korean Nutrition Society. Of all subjects included in the KNHANES, we excluded those lacking radiographic knee images or those who had not completed the health-related behaviour and nutrition questionnaires. Because bilateral knee radiographic images were obtained only in those aged 50 years or older, younger participants were excluded automatically. Those diagnosed with neuromuscular or major psychiatric disorders or who had undergone bilateral knee joint replacement surgery were also excluded. Ultimately, 6588 participants were included in the analysis.

Survey of health-related behaviour

Participants were asked about lifestyle behaviour, including cigarette smoking, alcohol consumption, and dietary habits. Smoking status was classified as current smoker, ex-smoker, or never-smoker. Alcohol consumption status was considered positive if a subject drank ≥70 g of alcohol/day or drank more than once a week. The Korean version of the International Physical Activity Questionnaire (IPAQ) short form was adopted to measure the frequency of physical activity. The Korean version of the IPAQ short form has been shown to be both valid and reliable [29]. Regular physical activity was defined as activity greater than a moderate degree of physical activity (vigorous-intensity physical exercise or work performed more than three times a week for 20 min, or as moderate-intensity physical exercise or work performed more than five times a day for 30 min, or as walking more than five times a week for 30 min) according to the guidelines of the IPAQ Research Committee [5]. Average monthly household income was documented for each participant; the figures were categorized into four groups by interquartile range: low (<25th percentile, <733.30 USD), low to medium (25th to 50th percentile, 733.30–428.57 USD), medium to high (50th to 75th percentile, 1428.57–2380.95 USD), and high (≥75th percentile, ≥3214.00 USD). Living places were defined as either urban or rural. Daily total caloric intake was calculated using Can-Pro 2.0. If a subject was being treated for any disease, he or she was asked for the diagnosis and a list of medications used. Those with a history of hypertension, diabetes mellitus, dyslipidemia, cardiovascular disorders, chronic liver disease, chronic kidney disease, pulmonary disease, or cancer were considered to have a chronic medical condition. Completed questionnaires were reviewed by trained staff, and the responses were entered into a database.

Anthropometric measurements

Anthropometric measurements were performed by well-trained medical staff following standardized procedures. Body weight (in kg) and height (in cm) were measured to the nearest 0.1 kg and 0.1 cm, respectively. Body mass index (BMI) was calculated as the ratio of weight divided by the height squared (kg/m^2). Waist circumference (cm) (measured at the umbilicus level while the subject was standing) was assessed at the narrowest region of the area between the lower rib cage border and the iliac crest.

Definition of depression

Depressive mood was determined based on the answer to this question: "Have you consistently felt despair or depression every day for more than 2 weeks during the past year?" Subjects who answered "yes" or who had been diagnosed with depressive disorders and were currently under medical treatment were considered to have depression.

Assessment of knee pain

Knee pain was assessed using the following question: "Have you felt pain in the knee joint lasting more than 30 days during the last 3 months?" Subjects who answered "yes" were asked to describe the severity of their pain using a 10-point numerical rating scale (NRS). A score of 0 was equivalent to no pain and 10 reflected the most severe pain. If a subject answered "no" to the first question, the NRS score was recorded as 0. Subjects who reported pain scores from 5 to 10 were considered to have severe knee pain.

Definition of radiographic knee OA

The Kellgren–Lawrence (K–L) grading system was used to assess the extent of radiographic OA of the knee joint [20] (Grade 0, no features of OA; Grade 1, small osteophytes of uncertain significance; Grade 2, definite osteophytes without impairment of joint space; Grade 3,

definite osteophytes with moderate joint space reduction; and Grade 4, definite osteophytes with substantial joint space narrowing and subchondral bone sclerosis). Bilateral anteroposterior, lateral (30° flexion), and weight-bearing anteroposterior plain knee radiographs were taken using an SD 3000 Synchro Stand (Accele Ray, SYFM Co., Seoul, Korea). Radiographic images were stored on a hard disk and reviewed by two radiologists; if a difference of less than one grade between the two radiologists was evident, the higher grade was accepted. If the difference was more than one grade, a third radiologist was consulted and the grade assigned by that radiologist was accepted. The inter-rater agreement (within one grade of difference) between the two radiologists was 92.8 %, and the weighted Cohen's kappa coefficient was 0.65. If secondary OA was suggested on radiographic images, the grading was determined using data from the intact knee.

Ethical approval

This study complied with the Declaration of Helsinki, and the Institutional Review Board (IRB) of the Korean Centers for Disease Control and Prevention approved the work (IRB approval number 2010-02CON-21-C for 2010, 2011-02CON-06-C for 2011, and 2012-01EXP-01-2C for 2012). Additionally, the IRB of the SMG-SNU Medical Center considered that approval was not required because the study did not deal with sensitive information, but rather accessed only publicly available data from the KNHANES (IRB number 07-2014-6).

Statistical analysis

To represent the total Korean population in an unbiased manner, all statistical estimates were weighted.

All data are presented as means (with SEs) or percentages (with SEs). The clinical characteristics were compared between those with severe knee pain and controls using general linear model analysis for continuous variables and Chi-squared tests for categorical data. Estimated mean knee pain scores with reference to the presence of depression were calculated by analysis of covariance (ANCOVA). Multiple linear regression analysis was used to identify factors contributing to knee pain. In this analysis, variables differing between groups at $p < 0.05$ (as determined by Pearson's correlation analysis) and clinically important variables, including age, BMI, alcohol and tobacco use, and exercise habits, were considered. If a significant correlation ($r > 0.8$) was evident between two variables, only one was entered into the model. The odds ratios and 95 % confidence intervals (CIs) for the prevalence of severe knee pain were calculated by multivariate logistic regression analysis, after adjustment for confounding variables, according to the depression status. Clinically important variables (age, BMI, alcohol use, smoking status, regular exercise, and chronic condition status) and variables differing between groups at $p < 0.05$ (as determined by univariate logistic regression analysis) were considered to be confounding factors. All statistical analyses were performed using the Statistical Package for the Social Sciences, version 19\8.0 (SPSS Inc., Chicago, IL, USA).

Post hoc power analysis of sample size

Post hoc power analysis of sample sizes affording significance levels (α values) of 0.05 was performed. As a result, sample sizes of 5270 subjects with severe knee pain and 1318 without severe knee pain afforded a >0.999 post hoc power for detection of a between-group difference of −0.1410. Multiple linear regression analysis showed that a sample size of 6588 afforded a >0.999 post hoc power to detect an R^2 value of 0.22 attributable to one independent variable using an F-test with a significance level (α value) of 0.05000. The variables tested were adjusted for 13 independent variables with an R^2 value of 0.19. Additionally, based on multiple logistic regression analysis, logistic regression of a binary response variable (Y) on a binary independent variable (X) using a sample size of 6588 (of which 84 % were in group $X = 0$ and 16 % in group $X = 1$) afforded a >0.999 post hoc power at a 0.05000 significance level when it was desired to detect a change in Prob ($Y = 1$) from the baseline value of 0.200–0.389. This change corresponded to an odds ratio of 2.550.

Results

Comparison of characteristics between groups with and without severe knee pain

Significant differences in socio-economic, demographic, clinical, and psychological characteristics were evident between the groups with and without severe knee pain (Table 1). In terms of demographic characteristics, those with severe knee pain tended to be of older age, female, and non-smokers and exhibited a lower incidence of regular alcohol consumption, less regular exercise, and lower total daily caloric intake. In terms of socio-economic characteristics, those with severe knee pain more frequently lived in rural areas, had a lower education level (<graduate elementary school), had a lower household income, and were unmarried. In terms of clinical characteristics, those with severe knee pain had a higher incidence of chronic medical conditions and K–L Grade 4 status on knee radiographs.

Table 1 Characteristics between participants with and without severe knee pain

Variable	No severe knee pain (NRS < 5)	Severe knee pain (NRS ≥ 5)	*p* value
Subject numbers	5270	1318	
Demographic characteristics			
Age (years)	61.3 ± 0.2	67.4 ± 0.5	0.01
Gender (*n*, %)			<0.01
Male	2506 (50.6 ± 0.9)	290 (24.8 ± 0.2)	
Female	2764 (49.4 ± 0.9)	1028 (75.2 ± 0.2)	
Alcohol use (*n*, %)	2422 (50.5 ± 1.2)	380 (31.1 ± 2.4)	<0.01
Exercise status (*n*, %)	2420 (46.7 ± 1.3)	505 (34.8 ± 2.4)	<0.01
Smoking (*n*, %)			<0.01
None	2909 (52.4 ± 1.1)	966 (69.5 ± 2.3)	
Past	1436 (26.8 ± 1.1)	177 (16.5 ± 1.7)	
Current	925 (20.8 ± 1.1)	175 (14.0 ± 1.7)	
Total caloric intake (kcal)	1920.9 ± 21.8	1626.8 ± 39.7	<0.01
Socio-economic characteristics			
Living place (*n*, %)			0.01
Urban area	3918 (75.1 ± 3.8)	832 (64.7 ± 5.2)	
Rural area	1352 (24.9 ± 3.8)	486 (35.3 ± 5.2)	
Education level (*n*, %)			<0.01
≤Graduate elementary school	2012 (36.3 ± 1.6)	909 (66.8 ± 2.8)	
>Graduate elementary	3258 (63.7 ± 1.6)	409 (33.2 ± 2.8)	
Household income (*n*, %)			<0.01
Low (<733 USD)	1463 (25.3 ± 1.3)	670 (50.6 ± 3.2)	
Low–medium (733–1429 USD)	1344 (26.6 ± 1.4)	293 (23.5 ± 2.3)	
Medium–high (1429–2381 USD)	1162 (23.3 ± 1.3)	174 (15.3 ± 2.0)	
High (≥2380.95 USD)	1261 (24.8 ± 1.6)	161 (10.5 ± 1.6)	
Marital status (*n*, %)			<0.01
Married	4319 (82.3 ± 1.0)	839 (63.1 ± 3.0)	
Unmarried	951 (17.7 ± 1.0)	479 (36.9 ± 3.0)	
Clinical characteristics			
Chronic disease status (*n*, %)	2715 (47.4 ± 1.4)	873 (64.1 ± 2.5)	<0.01
K–L grade (*n*, %)			<0.01
0	2435 (51.4 ± 1.6)	243 (20.5 ± 2.3)	
1	1264 (22.5 ± 0.9)	209 (15.8 ± 2.0)	
2	854 (14.9 ± 0.9)	194 (15.0 ± 1.8)	
3	537 (9.1 ± 0.8)	322 (23.9 ± 2.1)	
4	124 (2.1 ± 0.3)	342 (24.8 ± 2.0)	
BMI (kg/m^2)	23.9 ± 0.1	24.5 ± 0.2	<0.01
WC (cm)	83.4 ± 0.3	84.7 ± 0.6	0.03
Depressive mood (*n*, %)	683 (12.9 ± 0.8)	357 (26.8 ± 2.4)	<0.01

Data are presented as mean ± standard error or proportion (%) ±standard deviation in parentheses

NRS numeric rating scale, *K–L grade* Kellgren–Lawrence grade, *BMI* body mass index, *WC* waist circumference

Severity of knee pain according to depression status

When NRS knee pain scores were compared with reference to the presence of depression, the adjusted scores were significantly higher in the depression group after adjustment for age, gender, and knee K–L grade (2.0 ± 0.1 vs. 3.1 ± 0.2, $p < 0.01$) (Fig. 1).

Upon linear multiple regression analysis, knee K–L grade ($\beta = 2.3$, $p < 0.01$), depression ($\beta = 1.1$, $p < 0.01$), gender ($\beta = 0.6$, $p < 0.01$), education level ($\beta = -0.6$,

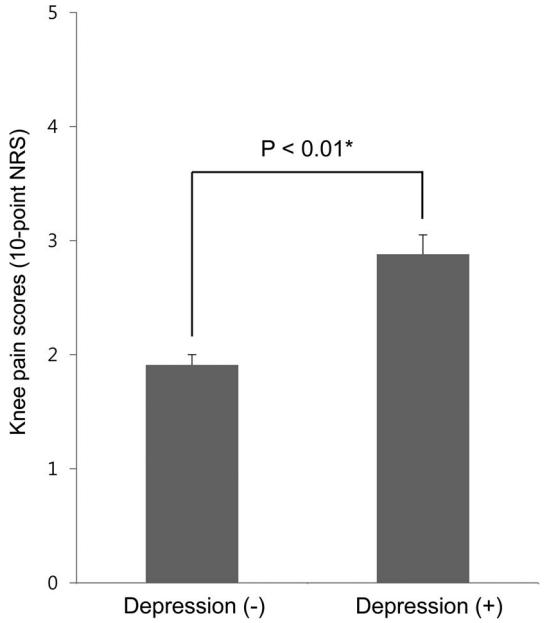

Fig. 1 Mean extents of knee pain scores with reference to the presence of depression. *The *p* value was calculated by analysis of covariance with adjustment for age, gender, and Kellgren–Lawrence knee osteoarthritis grade

$p = 0.03$), household income ($\beta = -0.3$, $p < 0.01$), smoking status ($\beta = 0.2$, $p = 0.04$), marital status ($\beta = -0.2$, $p = 0.03$), living place ($\beta = -0.2$, $p = 0.03$), comorbidity status ($\beta = 0.2$, $p = 0.02$), BMI ($\beta = 0.1$, $p < 0.01$), and age ($\beta = 0.0$, $p < 0.01$) were identified as explanatory variables of knee pain severity, accounting for 22.0 % of the variance (Table 2).

After adjustment for age, gender, living place, BMI, marital status, exercise status, smoking status, alcohol use, household income, educational level, chronic underlying disease status, total daily caloric intake, and severity of radiographic OA (K–L grade), the multivariate-adjusted odds ratio (95 % CI) for the presence of knee pain concomitant with depression was 2.6 (1.8–3.7). Additionally, upon stratification of subjects by the radiographic severity of knee OA [minimal (K–L Grade 0–1), moderate (K–L Grade 2–3), and severe (K–L Grade 4)], the positive relationship persisted in the minimal and moderate OA subgroups (2.9 [1.9–4.3] and 2.3 [1.3–3.9], respectively), but not in the severe OA subgroup (Table 3).

However, when gender-based subgroups were formed further, the aforementioned relationships between the presence of severe knee pain and depression in the context of varying radiological severity of knee OA differed between males and females. In males, the positive relationship was evident with all three degrees of knee OA, whereas in females, the relationship was not evident with severe radiographic OA (Table 4).

Table 2 Multiple regression analysis of independent relationships between the extent of knee pain and clinical variables

Variable	β coefficient	SE	*p*
Knee K–L grade	2.3	0.1	<0.01
Depression	1.1	0.1	<0.01
Gender	0.6	0.1	<0.01
Educational level	−0.6	0.1	0.03
Household income	−0.3	0.1	<0.01
Smoking status	0.2	0.1	0.04
Marital status	−0.2	0.1	0.03
Living place	−0.2	0.1	0.03
Comorbidity status	0.2	0.1	0.02
BMI	0.1	0.0	<0.01
Age	0.0	0.0	<0.01

The variables included in the stepwise model for knee pain were age, gender, smoking status, alcohol use status, exercise status, educational level, household income, living place, marital status, comorbidity status, BMI, K–L grade, depressive mood, and caloric intake. The coefficient of determination (R^2) of the regression model is 0.22

K–L grade Kellgren–Lawrence grade, *BMI* body mass index

Table 3 Results of multiple logistic regressions for the presence of severe knee pain with reference to the presence of depressive mood (weighted data)

	Severe knee pain	
	Absent	Present
Total	1.0	**2.6 (1.8–3.7)**[a]
Severity of radiographic OA		
Minimal	1.0	**2.9 (1.9–4.3)**[b]
Moderate	1.0	**2.3 (1.3–3.9)**[b]
Severe	1.0	**2.3 (0.8–6.5)**[b]

Data are presented as odds ratios and 95 % confidence intervals in parentheses

Odds ratios and 95 % confidence intervals were calculated using multiple logistic regression

The results with statistical significance are in bold font

OA osteoarthritis

[a] Adjusted for age, gender, living place, BMI, marital status, exercise status, smoking status, alcohol use status, household income, educational level, chronic disease status, total daily caloric intake, and severity of radiographic OA (K–L grade)

[b] Adjusted for age, gender, living place, BMI, marital status, exercise status, smoking status, alcohol use status, household income, educational level, chronic disease status, and total daily caloric intake

Discussion

A positive relationship between knee pain and depressive symptoms in the elderly Korean population was evident in our cross-sectional study using nationwide Korean data. Depression was associated with an approximately 2.6-fold

Table 4 Results of multiple logistic regressions for the presence of severe knee pain with reference to the presence of depressive mood, according to gender (weighted data)

	Severe knee pain	
	Absent	Present
Males		
Total	1.0	**2.8 (1.6–5.0)**[a]
Severity of radiographic OA		
Minimal	1.0	**2.4 (1.3–4.6)**[b]
Moderate	1.0	**4.1 (1.3–13.0)**[b]
Severe	1.0	**3.7 (2.4–5.8)**[b]
Females		
Total	1.00	**2.5 (1.7–3.7)**[a]
Severity of radiographic OA		
Minimal	1.00	**3.3 (2.0–5.4)**[b]
Moderate	1.00	**1.9 (1.1–3.2)**[b]
Severe	1.00	3.1 (0.8–12.0)[b]

Data are presented as odds ratios and 95 % confidence intervals in parentheses

The results with statistical significance are in bold font

OA osteoarthritis

higher prevalence of severe knee pain after adjustment for confounding factors. Such a relationship persisted when the subjects were stratified by the radiographic severity of knee OA and was evident in both the mild and moderate OA groups.

Several previous studies have investigated the factors contributing to the severity of knee pain, and some reports describe significant relationships between depressive symptoms and the extent of knee pain [11, 22, 30, 32, 33, 43]. However, conflicting results have also been reported [8, 9, 31]. Small sample sizes, the confounding effects of different clinical characteristics among participants, insufficient adjustment for various potential risk factors, and the lack of standardized diagnoses for depression and OA have likely contributed to the differences among studies. In the present work, we investigated the relationships between depressive symptoms and the severity of knee pain using nationally representative data. Potential confounding factors associated with knee pain, including socio-economic status, nutritional status, and comorbidities, were carefully investigated to reduce their effects. In addition, the severity of radiographic knee OA was diagnosed by well-educated orthopaedic specialists. These features were strengths of our study. A precise understanding of the relationship between knee pain and depression remains elusive. Neurotransmitters may be involved. Alterations in the levels of neurotransmitters and inflammatory cytokines in those with depressive disorders have been well documented. Secretion of serotonin, dopamine, and norepinephrine is significantly reduced in those with depressive disorders [3, 14]. These neurotransmitters contribute to both pain perception and mood regulation [18, 37]. Therefore, a decline in the pain perception threshold caused by alterations in neurotransmitter levels in those with depression may explain why such subjects report more severe knee pain when the extent of joint damage is similar to that in non-depressed subjects. A second possible explanation involves the actions of proinflammatory cytokines in both depression and OA. The levels of various inflammatory cytokines, including TNF-alpha and interleukin 6, increase in patients with depression [13, 26]. These cytokines mediate peripheral pain sensitization of osteoarthritic joints [19, 21]. Furthermore, inflammatory cytokines aggravate depressive symptoms. For example, the prevalence of depressive disorders is significantly higher in patients with chronic inflammatory conditions such as autoimmune rheumatoid arthritis or inflammatory bowel disease [23, 27], and cytokine therapy increases the extent of depressive symptoms in healthy individuals [40]. Because knee OA is an inflammatory condition and elevations in the levels of several cytokines and C-reactive protein have been reported in patients with knee OA [19], it is possible that a bidirectional relationship exists between pain and depression mediated by inflammatory cytokines.

After all subjects were subcategorized by gender in terms of the severity of radiographic findings, a positive relationship was evident between knee pain and depression in female participants with minimal to moderate knee OA but not in those with severe radiographic knee OA after adjustment for all potential confounders. These results are consistent with those of a previous study [22] and suggest that assessment of mood status may be more accurate in patients with severe knee pain who do not have significant radiographic joint damage, especially females. Among males, however, the positive relationship between severe knee pain and depressive mood was also evident in those with severe radiographic knee OA. This suggests that assessment of mood status may be more important in males with severe knee pain. We do not currently understand the reasons for the differences between males and females. The finding may imply that complex relationships exist among gender, mood status, development of knee OA, and perception of knee pain. However, further study is required to derive definite conclusions.

In the present study, gender, education level, household income, social status, marriage status, living place, comorbidity status, BMI, age, knee radiographic K–L grade, and depressive symptoms were identified as variables affecting the severity of knee pain; these results are consistent with those of previous studies [36, 38, 44]. Furthermore, cigarette smoking increased the severity of knee pain, but the association was not as clear as in previous studies. Amin

et al. [2] also found that cigarette smoking increased the risk of knee cartilage loss and knee pain in males with knee OA, but opposite results have also been reported [24]. Therefore, further studies investigating the potential link between smoking and knee pain are required.

Some limitations of our study are evident. First, identification of any causal relationship was precluded by the cross-sectional nature of our work. Second, depressive symptoms and the extent of knee pain were measured via simple self-report questionnaires. This indicates that information bias may perhaps not be fully excluded. In particular, a single question that seeks to measure the extent of depression is not appropriate for diagnosis of a depressive disorder; thus, the reliability of the answer is lower than that of standardized depression scales. However, in a previous study, the single question used in the present study exhibited high sensitivity (86 %), specificity (78 %), positive predictive value (82 %), and negative predictive value (82 %) compared with a validated depression scale (the Montgomery–Asberg Depression Rating Scale) [39]. Thus, the method of depression assessment used in our study may be considered valid when used to evaluate depression in a nationwide cohort. Nevertheless, further studies using validated systemic instruments would allow for the establishment of more accurate relationships between depressive symptoms and knee pain. Third, although many clinical parameters were adjusted, possible unknown factors may have influenced our findings. Finally, the test–retest reliability of measurements was not explored except for determination of the radiographic K–L knee grade. Despite these limitations, our results collectively suggest that the severity of knee pain may be significantly affected by depressive symptoms. Therefore, detection and/or active management of depression should be performed when knee pain and knee OA are being treated in subjects who complain of severe knee pain although the radiographic severity of knee OA is mild.

Conclusions

The severity of knee pain is independently associated with the level of depressive symptoms in the middle-aged and elderly Korean population. We believe that clinicians will be helped by this finding to manage middle-aged and elderly patients with significant knee pain.

Acknowledgments The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/tN08pw.

Conflict of interest All authors declare that they have no conflict of interest.

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