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Association between severity of depressive symptoms and chronic knee pain in Korean adults aged 50+; a cross-sectional study using nationally representative data

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Abstract

Objectives: This study aims to identify the association between the presence and severity of depressive symptoms and the presence and severity of knee pain.

Design: Retrospective cross-sectional study

Participants: We used data from the 6th Korea National Health and Nutrition Examination Survey (KNHANES VI-2) performed in 2014. A total of 7,550 patients were included in the KNHANES VI-2.

Outcome measures: Participants were asked whether they had knee pain, and each answer was either 'yes' or 'no'. Patient Health Questionnaire-9 (PHQ-9) was used as screening tool for depressive symptoms, and PHQ-9 scores of 10 or higher was classified as 'depressed' group. A total of 527 patients reported that they had pain in their knee, and 91 of them also had depressive symptoms.

Results: The prevalence of knee pain in the Korean population aged 50+ was 19.8%. Multiple Logistic Regression was conducted after adjustment for sex, age, smoking, alcohol drinking, education level, household income, physical activity, sleep duration and comorbidity. The analysis revealed a significant association between depression and knee pain (OR=2.333, P<0.001). On the other hand, the severity of depression was linearly correlated with the intensity of knee pain (P for trend<0.001). In the subjects with no knee pain (NRS=0) or mild knee pain (NRS=1-4), the prevalence of moderate and severe depression was 3.4% and 0.6%, respectively. However, in the subjects with severe knee pain (NRS=8-10), the prevalence of moderate and severe depression was much high (10.1% and 5.8%, respectively) (P<0.001).

Conclusions: A strong association was observed between the presence and severity of depressive symptoms and the presence of knee pain. The association became stronger with higher levels of depression, indicating a positive correlation between depression severity and chronic knee pain (NRS).

Keywords: Knee pain, depressive symptom, PHQ-9, KNHANES VI-2, Korea National Health and Nutrition Examination Survey

Strengths and limitations of this study

- This study is based on highly reliable data from the national survey using the Korean population-based questionnaire.
- This study found a strong association between the severity of depressive symptoms and the presence and intensity of knee pain.
- This is the first study to describe the correlation between the severity of depressive symptoms and the intensity of knee pain, defined according to NRS scores.
- This study is a cross-sectional study. Therefore, it assessed depression and chronic knee pain using odds ratio without the analysis on the cause-effect relationship between the variables.
- Self- report questionnaires were used to assess NRS and PHQ-9 for knee pain and depression, respectively. Therefore, response biases cannot be ruled out.

Introduction

Depression is one of the most common mental illnesses. An earlier systematic review and meta-analysis reported that a lifetime prevalence of psychotic depression range from 0.35% to 1% and that rates of psychotic depression increase with age [1]. According to a Chinese systematic review, a lifetime prevalence of major depressive disorder (MDD) varies between 1.1 and 3.3% [2]. However, the prevalence of major depressive symptom (MDE), which indicates the relatively mild symptoms of depression, is markedly higher. A cohort study using a sample of 29,621 people representing the general U.S. population found 8% of 3-year prevalence rate for MDE [3]. In addition, a Canadian longitudinal study reported that the prevalence of depressive episode at baseline was 7.5% [4]. Based on World Mental Health Survey data, a cross-sectional study identified diabetes, arthritis, asthma, chronic pulmonary disease, angina symptoms, and stroke, advanced age, women, underweight and lower levels of income and education as risk factors in relation to depression [5].

The prevalence of knee pain has been found to be one of the most common symptoms in the aging population around the world. According to an Italian cross-sectional study, 22.4% of the population aged 65+ complained about pain in the knee [6]. In a study involving the British population aged 65+, 32.6% of subjects reported knee pain [7]. As risk factors for knee pain, advanced age, low education, high BMI are known to have a cause-effect relationship with knee pain [8].

Emotional distress is also known to worsen physical pain, and many studies are underway in this context. The TMD patients with anxiety and depression are more likely to develop migraine and primary headache [9]. According to a systematic review, depression and anxiety symptoms are associated with high morbidity neck pain [10].

The relationship between depression and knee pain has been investigated through literature. A systematic review revealed strong evidence supporting such a relationship between depression and knee pain, confirming a clear association between depression and knee pain in reference to five high-quality studies [11]. A cohort study involving the Japanese population aged 65+ found that the development of depressive symptoms was associated with the presence of knee pain [12]. Among previous studies, a cross-sectional study described the relationship between depression and severity of knee pain assessed by the NRS and Kellgren–Lawrence scale [13]. However, few studies have been conducted to identify the association of depression severity with the presence and intensity of knee pain, measured by NRS. Accordingly, this study aims to identify the association of depression severity with chronic knee pain.

Methods

Study population

This study is based on the results of the nationally representative survey (KHANES VI-2),

which was first launched in 1998 and conducted every year with population-based random samples using standardized questionnaires. This survey is intended to identify socio-demographic characteristics and health and nutritional status of the general Korean population and households, and survey responses are not tracked when the survey is completed each year. KHANES VI-2 used the Patient Health Questionnaire-9 (PHQ-9) as a screening instrument to diagnose depressive disorder. This questionnaire was administered to 7,550 respondents. Of those administered questionnaires, 2,658 questionnaires completed by Korean adults aged 50+ were analyzed with respect to relationship between depressive symptom and knee pain (Figure 1).

Definition of depressive symptom and chronic knee pain

Total score of 10 or higher on the PHQ-9 was used to define the presence of depressive symptom [14]. In previous studies, the PHQ-9 questionnaire was often used to monitor depressive symptoms in patients with chronic pain [15, 16, 17]. The PHQ-9 items are based on the 4th edition of diagnostic and statistical manual of mental disorders (DSM-IV) and designed to ask symptoms that relate to depression over the last two weeks. Each item is scored from 0 (not at all) to 3 (nearly every day)[18, 19]. The PHQ-9, consisting of nine questions, is a reliable and valid depression scale. As a severe measure, its score ranges from 0 to 27 with higher scores indicating higher severity of depression [18, 19].

In previous studies, PHQ-9 score ≥10 was used to determine the presence of depressive symptom, and the reliability of this questionnaire has been proven. In this study, PHQ-9 score ≥10 was also used as an indication of the presence of depressive symptoms. The severity of depression was divided into ‘not depressed’ (0-4 scores), ‘mild’ (5-9 scores), ‘moderate’ (10-14), ‘moderately severe’ (15-19) and ‘severe’ (20-27), according to previous studies [18, 19, 20].

The questionnaire used to identify the presence of knee pain in the respondents aged 50+ included the question "Have you had knee pain at least 30 days during the last three months? Those who answered "yes" to this question were classified as the knee pain group, and their knee pain intensity was assessed using the NRS.

Description of Demographic and Characteristics of the study population

Patient information including demographic characteristics, socioeconomic background, medical history, and life habits was analyzed. BMI was calculated by dividing body weight in kilograms by the square of height in meters and categorized into three groups: underweight (<18.5kg/m), normal weight (18.5-24.9kg/m2) and overweight (≥ 25.0kg/m2). Smoking status was classified into nonsmoker, ex-smoker and current smoker. The frequency of alcohol consumption was grouped into ‘none’, ‘once a month or less ’, ‘2 drinks/month to 3 drinks/week’ and 'more than four times a month‘. Occupation was classified into four groups:

'unemployed (student, housewife, etc.)', 'office work/sales and services', 'agriculture, forestry and fishery' and 'machine fitting and simple labor'. Household income was classified into quartiles: low, low-moderate and moderate-high/high. Education level was also grouped into three groups: ≤ 6 years, 7-9 years and ≥ 10 years. Physical activity was grouped into three groups: moderate activity at least 2 and half hours a week, vigorous activity at least 1 hour and 15 minutes a week and combination of moderate and vigorous activity for longer hours (1-minute vigorous activity was considered equal to 2-minute moderate activity). This study also investigated the presence of comorbidities such as hypertension, dyslipidemia, stroke, myocardial infarction, angina, arthritis, asthma and diabetes mellitus.

Statistical Analysis

The KHANES is a survey of nationwide sample of Koreans selected through stratified clustered sampling, and sampling weights are used for survey data. Accordingly, complex sample survey data were analyzed using parameters for strata, clusters and weights, which comprise the sample design. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis and $P<0.05$ was used as the threshold for statistical significance. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%). Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without knee pain. To assess the effects of depressive symptom on chronic knee pain, logistic regression analysis with complex sampling design was performed by adjusting for covariates. As a result, odd ratios as well as 95% confidence intervals for the odds ratios were generated. Additionally, this study investigated if there is an underlying trend from different levels of depression in each model. (P for trend).

Patient and Public Involvement

We did not involve patients or the public in our work

Results

Characteristics of the study population according to chronic knee pain

This study found that the overall prevalence of chronic knee pain in the Korean population aged 50+ was 19.8%. Of those, females (77.8%) far outpaced males (22.2%). The presence of depressive symptoms, determined by PHQ-9 score ≥ 10, was significantly higher in the subjects with knee pain (17.3%), compared with those without knee pain (5.2%) ($P<0.001$, Table 1). When compared with the subjects without knee pain, the subjects with knee pain showed greater frequency of depressive symptoms, more advanced age, higher percentages of

females and unemployment, lower household income, lower levels of education and physical activity, more comorbidities (hypertension, dyslipidemia, stroke, arthritis, asthma) and shorter sleep duration (Table 1).

Clinical Characteristics of Participants With chronic depression According to the Presence of Depression

When compared with non-depressed patients with chronic knee pain, depressed patients with chronic knee pain had lower household income, lower levels of education and aerobic physical activity and shorter sleep duration. However, no difference between the two groups was found with respect to age, sex, BMI, obesity, alcohol consumption and occupation. In case of smoking status, the percentage of non-smokers was high in the group with co-existing depression and chronic knee pain (Table 2).

Associations between Depression and chronic knee pain

Multiple logistic regression models were used to analyze the effects of depression on chronic knee pain. Univariate analyses revealed a strong association between depressive symptoms and chronic knee pain (Model 1, OR=3.553, P<0.0001). After adjusting for sex and age, a clear association between depression and knee pain was present (Model 2, OR=2.722, P<0.0001). After adjusting for sex, age, smoking status, alcohol use, education level, household income, physical activity, sleep duration and comorbidities, there was still a clear association between depression and knee pain (Model3, OR=2.333, P<0.0001). The odds ratio of depression levels also indicated an association between the severity of depressive symptoms and knee pain. When compared to the absence of depressive symptoms, the probability of having knee pain increased with depression severity: mild (OR=3.715), moderate (OR=4.525), moderately severe (OR=4.124) and severe depression (Model 1, OR=6.93, P for trend <0.0001). In the fully adjusted logistic regression model (Model 3), the association between severe depression and chronic knee pain was strongly significant. When compared to the absence of depressive symptoms, the probability of having knee pain increased with depression severity showing mild depression (OR=2.944) and severe depression (OR=4.552, Model 3, 95% CI 1.489-13.92, P for trend <0.0001, Table 3).

Association between depression state and knee pain intensity

The comparison between severity of depression and intensity of knee pain, measured by NRS, showed a positive linear association. When the knee pain NRS score ranged from 0 to 4, the prevalence of moderate depression was 3.4%, and the prevalence of severe depression was 0.6%. In the presence of severe knee pain (NRS=8-10), the prevalence of moderate and severe depression was high (10.1% and 5.6%, respectively) (Table 4, P<0.001, Fig 2).

Discussion

This study analyzed the association between the severity of depressive symptoms and chronic knee pain by examining a sample of 7,550 Koreans representing the general population from the reliable nationwide survey data. All the subjects selected for this study were aged 50 or older and had information about their knee pain, for which NRS were conducted to measure pain intensity. In the Korean population aged 50+, a significant correlation was observed between depressive symptoms and chronic knee pain. The positive association became stronger in the group with severe depression, when compared with that of those having the symptoms of mild to moderate depression.

The strong linear correlation between depression and chronic knee pain was still present after adjusting for variables such as socioeconomic indicators and comorbidity (adjusted OR: 2.333, 95%CI: 1.605–3.391, P<.0001). In the PHQ-9 survey, a significantly strong association was observed in the severely depressed group, identified with PHQ-9 score of 20 or above (OR: 6.93, 95% CI: 2.519-19.068, P= 0.0002). Such a highly significant association persisted even after adjusting for variables such as sex, age, socioeconomic indicators, smoking status and alcohol use (4.552, 95% CI: 1.489-13.92, P= 0.0082) (Table 3).

A positive linear relationship existed between knee pain and depressive symptoms. In the subjects with no knee pain or light pain (NRS=0-4), the prevalence of severe depression was 0.6. However, it increased to 5.8% in the subjects with more intense knee pain (NRS=8-10) (P<0.001, Table 4).

Significant differences between the groups with and without knee pain were found with respect to socio-demographic factors other than BMI, obesity and certain comorbidities. In particular, the rate of knee pain was linearly correlated with non-smoking and inversely correlated with alcohol consumption (Table 1). This result is attributable to a high percentage (77.8%) of women in the study population with knee pain.

In terms of correlation between depression and knee pain, the non-depressed group with knee pain and the depressed group with knee pain showed somewhat contrasting results. No differences were found between these two groups in age, sex, BMI, obesity, alcohol use and occupation. However, in comparison with the non-depressed group, the group with co-

existing pain and depression showed greater number of non-smokers (p=0.0372), lower household income (P<0.001), education level ≤ 6 years (P=0.0076), lower levels of physical activity (0.0162) and shorter sleep duration (P=0.0325) (Table 2).

Although there is no clear evidence that depressive symptoms can cause knee pain, many potential hypotheses have been suggested. Depression can interfere with the mechanism of inflammatory cytokine [21], and the regulation of autonomic nervous system [22, 23]. It can also destabilize the hypothalamic-pituitary-adrenal axis [24]. Depression-induced pathological conditions act as the catalyst for chronic pain syndrome [25, 26]. It is also known that neurotransmitters of noradrenalin and serotonin are associated with the pathological mechanism of depression [22]. These neurotransmitters also play an important role in pain inhibitory pathways [27, 28]. Taken together, these findings suggest the effects of depressive symptoms on the pathogenic mechanism of chronic pain. The association between depression and knee pain can be explained by reduced physical activity, which may be associated with depression, consequently decrease muscle strength and joint stability whereby negative outcomes such as osteoarthritis can be induced [29, 30, 31]

Strength and Limitations

This study has the following strengths: First, this study is based on highly reliable data from the national survey using the Korean population-based questionnaire.
Secondly, this study found a strong association between the severity of depressive symptoms and the presence and intensity of knee pain.
Third, to our knowledge, this is the first study to describe the correlation between the severity of depressive symptoms and the intensity of knee pain, defined according to NRS scores.

However, the findings of this study are limited to the following: First, this study is a cross-sectional study. Therefore, it assessed depression and chronic knee pain using odds ratio without the analysis on the cause-effect relationship between the variables.
Second, self- report questionnaires were used to assess NRS and PHQ-9 for knee pain and depression, respectively. Therefore, response biases cannot be ruled out.

Conclusions

This study identified a strong association between the presence and severity of depressive symptoms and the presence and intensity of knee pain. Furthermore, the association became stronger with higher levels of depression, showing greater NRS score for chronic knee pain. This study suggests depression as an independent risk factor that is important when screening for chronic knee pain.

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Author Contributions

Conceptualization: Su-Bin Han, Sook-Hyun Lee

Data curation: Sook-Hyun Lee, In-Hyuk Ha, Eun-Jung Kim

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Competing interests

None declared.

Ethics approval

The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board (approval no. 2013–12EXP-03–5C). Informed consent was obtained from all participants when the surveys were conducted. Approval of IRB was not required because the study did not deal with any sensitive information, but rather accessed only publicly available data from the KNHANES (JASENG IRB File No. 2018-11-017).

Data sharing statement

The data are available from the corresponding author upon reasonable request.

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409 **Table 1. Characteristics of the study population according to chronic knee pain**

Variable	Without Knee Pain(n=2131)	Knee Pain (n=527)	P-Value
PHQ-9 n (%)			
< 10	2021 (94.8)	436 (82.7)	<.0001
≥ 10	110 (5.2)	91 (17.3)	
Levels of depression, n (%)			
None(PHQ-9 ≤ 4)	1780 (83.5)	303 (57.5)	<.0001
Mild (5–9)	241 (11.3)	133 (25.2)	
Moderate (10–14)	66 (3.1)	51 (9.7)	
Moderately Severe (15-19)	33 (1.6)	28 (5.3)	
Severe (≥20)	11 (0.5)	12 (2.3)	
Age, y (mean±SD)	61.2±8.6	66.1±9.1	<.0001
Age, n (%)			
50-59	845 (39.7)	111 (21.1)	<.0001
60-69	698 (32.8)	182 (34.5)	
≥80	588 (27.6)	234 (44.4)	
Sex, n(%)			
Male	1002 (47)	117 (22.2)	<.0001
Female	1129 (53)	410 (77.8)	
BMI, kg/m2 (mean±SD)	23.9±3.1	24.3±3.3	0.0533
Obesity, n (%)			
Underweight (≤18.5)	55 (2.6)	13 (2.5)	0.2473
Normal (18.5-24.9)	1365 (64.1)	300 (57)	
Obese (≥25)	711 (33.4)	213 (40.5)	
Smoking status, n (%)			
Nonsmoker	1265 (60.4)	383 (75)	<.0001
Ex-smoker	496 (23.7)	78 (15.3)	
Current smoker	334 (15.9)	50 (9.8)	
Alcohol consumption, n (%)			
None	805 (38.4)	235 (45.7)	<.0001
1 drinks/month or less	516 (24.6)	156 (30.4)	
2 drinks/ month to 3 drinks/week	585 (27.9)	93 (18.1)	
4 drinks/ week or more	193 (9.2)	30 (5.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	1003 (47.1)	328 (62.2)	<.0001
Office work / Sales and services	463 (21.8)	53 (10.1)	
Agriculture, forestry and fishery	186 (8.7)	50 (9.5)	
Machine fitting and simple labor	477 (22.4)	96 (18.2)	
Household income, n (%)			
Low	546 (25.7)	232 (44.3)	<.0001
Low–moderate	589 (27.7)	136 (26)	
Moderate–high / High	989 (46.6)	156 (29.8)	
Educational level, n (%)			
≤ 6	805 (37.8)	345 (65.5)	<.0001
7–9 y	396 (18.6)	73 (13.9)	
≥10	928 (43.6)	109 (20.7)	
Aerobic physical activity, n (%)			
No	1100 (52.0)	313 (60.5)	0.0005
Yes	1016 (48.0)	204 (39.5)	
Duration of sleep, h	6.7±1.4	6.4±1.7	0.0026
Comorbidities, n (%)			
Hypertension	765 (35.9)	262 (49.7)	<.0001
Dyslipidemia	413 (19.4)	145 (27.5)	0.0002
Stroke	77 (3.6)	38 (7.2)	0.0002

Myocardial infarction	31 (1.5)	13 (2.5)	0.2165
Angina	64 (3)	17 (3.2)	0.698
Arthritis	252 (11.8)	285 (54.1)	<.0001
Asthma	56 (2.6)	33 (6.3)	<.0001
Diabetes mellitus	304 (14.3)	86 (16.3)	0.7091

Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without knee pain. Missing values/nonresponses were excluded from analysis. BMI; Body mass index PHQ; Patient Health Questionnaire. Individuals with over 10 score of PHQ-9 was regarded to have depressive symptom. Levels of depression was divided into 5 quartiles; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to PHQ-9 score. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%).

Table 2. Characteristics of Knee pain Population According to Presence of Depression

Variables	Non-depression (n=436)	Depression (n=91)	P-Value
Age, y(mean±SD)	65.9±9.2	67±8.8	0.4956
Age, n (%)			
50–59	94 (21.6)	17 (18.7)	0.8051
60–69	152 (34.9)	30 (33)	
≥70	190 (43.6)	44 (48.4)	
Sex, n (%)			
Male	104 (23.9)	13 (14.3)	0.1181
Female	332 (76.2)	78 (85.7)	
BMI, kg/m2, (mean±SD)	24.4±3.3	23.8±3.1	0.1927
Obesity, n (%)			
Underweight (<18.5)	9 (2.1)	4 (4.4)	0.1711
Normal (18.5–24.9)	246 (56.4)	54 (60)	
Obese (≥25)	181 (41.5)	32 (35.6)	
Smoking status, n (%)			
Nonsmoker	312 (73.8)	71 (80.7)	0.0372
Ex-smoker	71 (16.8)	7 (8)	
Current smoker	40 (9.5)	10 (11.4)	
Alcohol consumption, n (%)			
None	183 (43)	52 (59.1)	0.2782
1 drinks/month or less	136 (31.9)	20 (22.7)	
2 drinks/month to 3 drinks/week	83 (19.5)	10 (11.4)	
4 drinks/week or more	24 (5.6)	6 (6.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	262 (60.1)	66 (72.5)	0.0561
Office work/Sales and services	48 (11)	5 (5.5)	
Agriculture, forestry and fishery	42 (9.6)	8 (8.8)	
Machine fitting and simple labor	84 (19.3)	12 (13.2)	
Household income, n (%)			
Low	171 (39.5)	61 (67)	<.0001
Low–moderate	112 (25.9)	24 (26.4)	
Moderate–high/high	150 (34.6)	6 (6.6)	
Educational level, n (%)			
≤6	278 (63.8)	67 (73.6)	0.0076
7–9 y	58 (13.3)	15 (16.5)	
≥10	100 (22.9)	9 (9.9)	
Aerobic physical activity, n (%)			
No	254 (59.1)	59 (67.8)	0.0162
Yes	176 (40.9)	28 (32.2)	
Duration of sleep, h(mean)	6.5±1.7	5.9±1.9	0.0325

Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without knee pain. Missing values/nonresponses were excluded from analysis. BMI; Body mass index, PHQ; Patient Health Questionnaire. Individuals with over 10 score of PHQ-9 was regarded to have depressive symptom. Levels of depression was divided into 5 quartiles; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to PHQ-9 score.

Table 3. Association between severity of depressive symptom and chronic knee pain

	Model 1 OR(95% CL)	P-Value	Model 2 OR(95% CL)	P-Value	Model 3 OR(95% CL)	P-Value
Diagnosis of depressive symptom						
No	1		1		1	
Yes	3.553 (2.558,4.935)	<.0001	2.722 (1.844,4.017)	<.0001	2.333 (1.605,3.391)	<.0001
Levels of depressive symptom						
None (0–4)	1		1		1	
Mild (5–9)	3.715 (2.687,5.138)	<.0001	3.266 (2.35,4.541)	<.0001	2.944 (2.112,4.103)	<.0001
Moderate (10–14)	4.525 (2.964,6.909)	<.0001	3.619 (2.233,5.865)	<.0001	3.211 (1.977,5.217)	<.0001
Moderately severe (15–19)	4.124 (2.256,7.539)	<.0001	2.805 (1.553,5.066)	0.0007	2.43 (1.355,4.359)	0.0031
Severe (20–27)	6.93 (2.519,19.068)	0.0002	5.109 (1.606,16.257)	0.006	4.552 (1.489,13.92)	0.0082
p for trend		<.0001		<.0001		<.0001

Logistic regression analysis with complex sampling design was performed by adjusting for covariates. OR indicates odds ratio; 95% CI, 95% confidence interval. Individuals with over 10 score of PHQ-9 was regarded to have depressive symptom. Levels of depression was divided into 5 quartiles; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to PHQ-9 score. Model 1 was unadjusted odds ratio. Model 2 was adjusted by age, and sex. Model 3 was fully adjusted by age, sex, and other environmental factors such as smoking, alcohol consumption, educational level, household income, physical activity, duration of sleep and comorbidities.

Table 4. Association between severity of knee pain NRS and severity of depressive symptom

	Depressive symptom					
	None (0–4)	**Mild (5–9)**	**Moderate (10–14)**	**Moderately severe(15–19)**	**Severe (20–27)**	**P-Value**
Knee pain NRS (0-4) (%)	1872 (82.4)	272 (12)	77 (3.4)	38 (1.7)	13 (0.6)	<.0001
Knee pain NRS (5-7) (%)	136 (58.1)	63 (26.9)	25 (10.7)	8 (3.4)	2 (0.9)	
Knee pain NRS (8-10) (%)	65 (46.8)	37 (26.6)	14 (10.1)	15 (10.8)	8 (5.8)	

Rao-Scott Chi-Square test was performed to compare severity of depressive symptom according to Knee pain NRS. Individuals without knee pain were regarded as 'NRS 0'.

Figure Legends

Figure 1. Flow chart diagram of inclusion and exclusion of participants

Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

Figure 2. Severity of depressive symptom according to knee pain NRS

Severity of depressive symptom according to knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptom according to PHQ-9 score; none (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), severe (20-27). Individuals without knee pain were regarded as NRS 0.

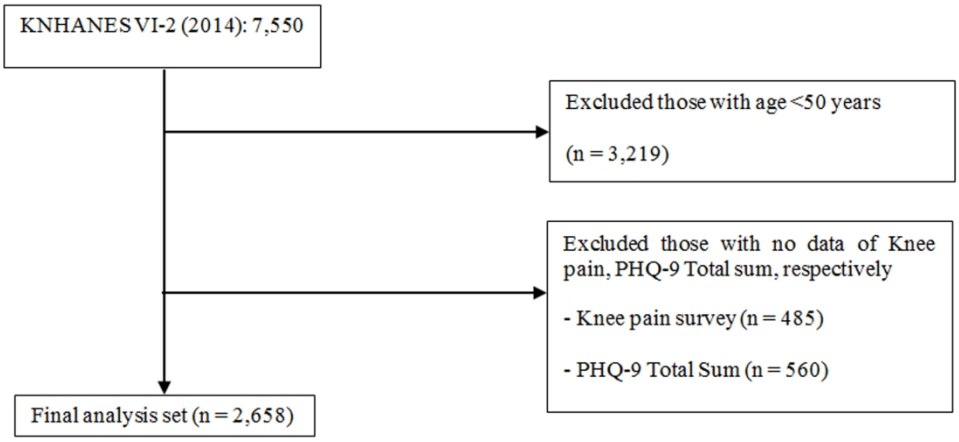
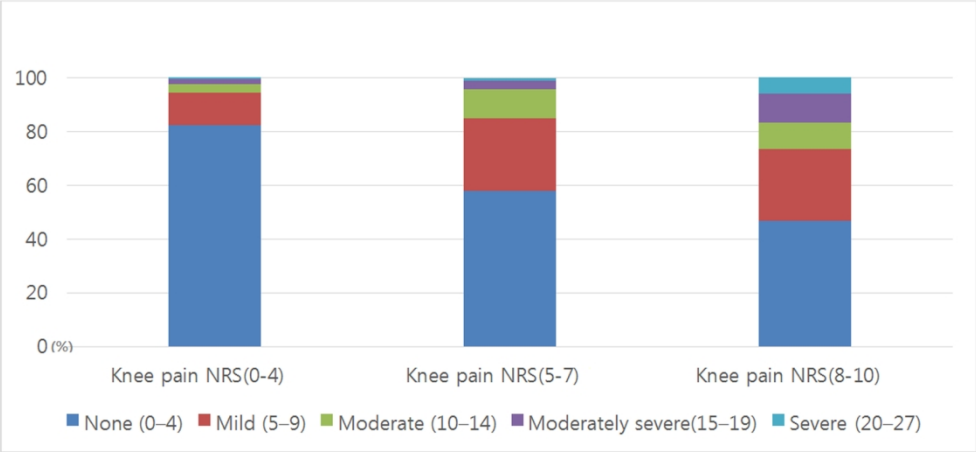


Figure 1. Flow chart diagram of inclusion and exclusion of participants
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

220x104mm (300 x 300 DPI)



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Association between severity of depressive symptoms and chronic knee pain in Korean adults aged over 50 years: a cross-sectional study using nationally representative data

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Abstract

Objectives: To identify the association between the presence and severity of depressive symptoms and those of chronic knee pain.

Design: A retrospective cross-sectional study

Participants: We used data from the 6th Korea National Health and Nutrition Examination Survey (KNHANES VI-2) performed in 2014. Overall, 7,550 patients were included in the KNHANES VI-2.

Outcome measures: Participants were asked whether they had chronic knee pain, and each answer was either "yes" or "no." Patient Health Questionnaire-9 (PHQ-9) was used as a screening tool for depressive symptoms, and PHQ-9 scores of 10 or higher were classified as the depressed group. In total, 527 patients reported that they had pain in their knee, of whom 91 also had depressive symptoms.

Results: The prevalence of chronic knee pain in the Korean population aged over 50 years was 19.8%. Multiple logistic regression was conducted after adjustment for sex, age, smoking, alcohol drinking, education level, household income, physical activity, sleep duration, and comorbidity. The analysis revealed a significant association between depressive symptoms and chronic knee pain (adjusted odds ratio =2.333, P<0.001). In contrast, the severity of depressive symptoms was linearly correlated with the intensity of chronic knee pain (P for trend<0.001). In participants with no chronic knee pain (numerical rating scale; NRS=0) or mild chronic knee pain (NRS=1–4), the prevalence of moderate and severe depressive symptoms was 3.4% and 0.6%, respectively. However, in those with severe chronic knee pain (NRS=8–10), there was a higher prevalence of moderate and severe depressive symptoms (10.1% and 5.8%, respectively) (P<0.001).

Conclusions: A strong association was observed between the presence and severity of depressive symptoms and the presence of chronic knee pain. The association became stronger with higher levels of depressive symptoms, indicating a positive correlation between depressive symptoms severity and chronic knee pain.

Keywords: chronic knee pain, depressive symptoms, Patient Health Questionnaire-9, Korea National Health and Nutrition Examination Survey VI-2

Strengths and limitations of this study

- This study is based on highly reliable data from the national survey using the Korean population-based questionnaire.
- We found a strong association between the severity of depressive symptoms and the presence and intensity of chronic knee pain.
- Because the questionnaire regarding chronic knee pain was only asked to a population aged over 50 years, the younger population with chronic knee pain was excluded in the analysis.
- As this was a retrospective cross-sectional study, it assessed depressive symptoms and chronic knee pain using odds ratios without analyzing the cause-effect relationship between the variables.
- Response biases cannot be ruled out because self-report questionnaires, NRS and PHQ-9, were used to assess chronic knee pain and depressive symptoms, respectively.

Introduction

Depressive symptoms are one of the most common mental illnesses. An earlier systematic review and meta-analysis reported that a lifetime prevalence of psychotic depressive symptoms ranges from 0.35% to 1% and that the rates of psychotic depressive symptoms increase with age.[1] According to a Chinese systematic review, a lifetime prevalence of major depressive disorder (MDD) varies between 1.1 and 3.3%.[2] However, the prevalence of major depressive episode (MDE), which indicates the relatively mild symptoms of depression, is markedly higher. A cohort study using a sample of 29,621 people representing the general United States population found that the 3-year prevalence rate was 8% for MDE.[3] Additionally, a Canadian longitudinal study reported that the prevalence of depressive episode at baseline was 7.5%.[4] Based on World Mental Health Survey data, a cross-sectional study identified diabetes, arthritis, asthma, chronic pulmonary disease, angina symptoms, and stroke, advanced age, women, underweight, and lower levels of income and education as risk factors related to depressive symptoms.[5]

The prevalence of knee pain is one of the most common symptoms in the aging population around the world. According to an Italian cross-sectional study, 22.4% of the population aged over 65 years complained about pain in the knee.[6] In a study involving the British population aged over 65 years, 32.6% of participants reported knee pain.[7] As risk factors for chronic knee pain, advanced age, low education, and high BMI have a cause-effect relationship with chronic knee pain.[8]

Emotional distress is also known to worsen physical pain, and many studies are underway in this context. The patients with temporomandibular disorders who have anxiety and depressive symptoms are more likely to develop migraine and primary headache.[9] According to a systematic review, depressive symptoms and anxiety symptoms are associated with high morbidity neck pain.[10]

The relationship between depressive symptoms and chronic knee pain has been investigated in previous literature. A systematic review revealed strong evidence supporting such a relationship between depressive symptoms and chronic knee pain, confirming a clear association between depressive symptoms and chronic knee pain with reference to five high-quality studies.[11] A cohort study involving the Japanese population aged over 65 years found that the development of depressive symptoms was associated with the presence of chronic knee pain.[12] Among previous studies, a cross-sectional study described the relationship between depressive symptoms and severity of chronic knee pain assessed by the numerical rating scale (NRS) and the Kellgren-Lawrence scale.[13] Moreover, a recent study revealed a relationship between depressive symptoms subtypes and risk for symptomatic knee pain.[14] However, few studies have been conducted to identify the association between the severity of depressive symptoms and the presence and intensity of knee pain. Recently, one study revealed that participants with physical pain symptoms were significantly associated with

depressive symptoms severity. According to this study, participants with pain showed higher scores of Montgomery-Asberg depressive symptoms rating scales. However, results of these studies are limited to showing the mean of depressive symptoms severity score depending on the presence of pain symptoms.[15] Moreover, a longitudinal analysis revealed that pain severity was a strong predictor of subsequent depressive symptoms severity, and conversely, depressive symptoms severity was a strong predictor of subsequent pain severity.[16]

This study aimed to identify the association between the presence and severity of depressive symptoms and those of chronic knee pain. To our knowledge, our study is the first to explore both aspects of the severity of depressive symptoms and severity of chronic knee pain measured by Patient Health Questionnaire-9 (PHQ-9) and NRS.

Methods

Study population

This study was based on the results of the nationally representative survey, the 6th Korea National Health and Nutrition Examination Survey (KHANES VI-2), which was first launched in 1998 and conducted every year with population-based random samples using standardized questionnaires. This survey is intended to identify socio-demographic characteristics and health and nutritional status of the general Korean population and households, and survey responses are not tracked when the survey is completed each year. KHANES VI-2 used the PHQ-9 as a screening instrument to diagnose depressive disorder. This questionnaire was provided to 7,550 respondents. Of those administered questionnaires, 2,658 questionnaires completed by Korean adults aged over 50 years were analyzed with respect to the relationsh210ip between depressive symptoms and chronic knee pain (Figure 1).

Definition of depressive symptoms and chronic knee pain

A total score of 10 or higher on the PHQ-9 was used to define the presence of depressive symptoms.[17] In previous studies, the PHQ-9 questionnaire was often used to monitor depressive symptoms in patients with chronic pain.[18-20] The PHQ-9 items are based on the 4th edition of the diagnostic and statistical manual of mental disorders (DSM-IV) and designed to ask about symptoms that relate to depression over the last 2 weeks. Each item is scored from 0 (not at all) to 3 (nearly every day).[21-22] The PHQ-9, consisting of nine questions, is a reliable and valid depressive symptoms scale. As a severity measure, its score ranges from 0 to 27, with higher scores indicating higher severity of depressive symptoms.[21-22]

In previous studies, a PHQ-9 score ≥10 was used to determine the presence of depressive symptoms, and the reliability of this questionnaire has been proven. In this study, a PHQ-9 score ≥10 was also used to indicate the presence of depressive symptoms. The severity of depressive symptoms was divided into not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–19), and severe (20–27), according to previous studies.[21-23]

The questionnaire used to identify the presence of chronic knee pain in the respondents aged over 50 years included the question "Have you had knee pain for at least 30 days during the last 3 months? Those who answered "yes" to this question were classified as the chronic knee pain group, and their knee pain intensity was assessed using the NRS. Because the questionnaire regarding chronic knee pain was only asked to respondents aged over 50 years in KHANES VI-2, the analyzed data was limited to a population aged over 50 years.

Description of demographic and characteristics of the study population

Patient information, including demographic characteristics, socioeconomic background, medical history, and life habits was analyzed. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters and categorized into three groups: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight (≥25.0 kg/m^2). Smoking status was classified into nonsmoker, ex-smoker, and current smoker. The frequency of alcohol consumption was grouped into none, once a month or less, 2 drinks/month to 3 drinks/week, and more than four times a month. Occupation was classified into four groups: unemployed (student, housewife, etc.); office work/sales and services; agriculture, forestry, and fishery; and machine fitting and simple labor. Household income was classified into quartiles: low, low-moderate, and moderate-high/high. Education level was also categorized into three groups: ≤6 years, 7–9 years, and ≥10 years. Physical activity was categorized into three groups: moderate activity at least 2 hours and 30 minutes a week, vigorous activity at least 1 hour and 15 minutes a week, and combination of moderate and vigorous activity for longer hours (1-minute vigorous activity was considered equal to 2-minute moderate activity). This study also investigated the presence of comorbidities, such as hypertension, dyslipidemia, stroke, myocardial infarction, angina, arthritis, asthma, and diabetes mellitus.

Statistical analysis

The KHANES is a survey of nationwide sample of Koreans selected through stratified clustered sampling, and sampling weights are used for survey data. Accordingly, complex sample survey data were analyzed using parameters for strata, clusters, and weights, which

comprise the sample design. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, and P<0.05 was used as the threshold for statistical significance. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%). The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without chronic knee pain. To assess the effects of depressive symptoms on chronic knee pain, logistic regression analysis with complex sampling design was performed by adjusting for covariates. As a result, odd ratios, as well as 95% confidence intervals for the odds ratios, were generated. Additionally, this study investigated if there was an underlying trend from different levels of depressive symptoms in each model (P for trend). To verify a linear relationship between the intensity of chronic knee pain and depressive symptoms, we used the Cochran-Armitage trend test and complex samples logistic regression.

Patient and public involvement

We did not involve patients or the public in our work.

Results

Characteristics of the study population according to chronic knee pain

This study found that the overall prevalence of chronic knee pain in the Korean population aged over 50 years was 19.8%. Of those, women (77.8%) far outpaced men (22.2%). The presence of depressive symptoms, determined by PHQ-9 score ≥10, was significantly higher in the participants with chronic knee pain (17.3%), compared with those without chronic knee pain (5.2%) (P<0.001, Table 1). When compared with the participants without chronic knee pain, those with chronic knee pain showed greater frequency of depressive symptoms, higher percentages of older women and unemployment, lower household income, lower levels of education and physical activity, more comorbidities (hypertension, dyslipidemia, stroke, arthritis, asthma), and shorter sleep duration (Table 1).

Clinical characteristics of participants with chronic knee pain according to the presence of depressive symptoms

When compared with non-depressed patients with chronic knee pain, depressed patients with chronic knee pain had lower household income, lower levels of education and aerobic physical activity, and shorter sleep duration. However, no difference between the two groups was found with respect to age, sex, BMI, obesity, alcohol consumption, and occupation. In

case of smoking status, the percentage of non-smokers was high in the group with co-existing depressive symptoms and chronic knee pain (Table 2).

Associations between depressive symptoms and chronic knee pain

Multiple logistic regression models were used to analyze the effects of depressive symptoms on chronic knee pain. Univariate analyses revealed a strong association between depressive symptoms and chronic knee pain (Model 1, OR=3.553, 95% CI 2.558–4.935, P<0.0001). After adjusting for sex and age, a clear association between depressive symptoms and chronic knee pain was present (Model 2, OR=2.722, 95% CI 1.844–4.017, P<0.0001). After adjusting for sex, age, smoking status, alcohol use, education level, household income, physical activity, sleep duration and comorbidities, there was still a clear association between depressive symptoms and chronic knee pain (Model 3, OR=2.333, 95% CI 1.605–3.391, P<0.0001). The odds ratio of depressive symptom levels also indicated an association between the severity of depressive symptoms and chronic knee pain. When compared to the absence of depressive symptoms, the probability of having chronic knee pain increased with the severity of depressive symptoms: mild (OR=3.715, 95% CI 2.687–5.138, P<0.0001), moderate (OR=4.525, 95% CI 2.964–6.909, P<0.0001), moderately severe (OR=4.124, 95% CI 2.256–7.539, P=0.0002), and severe depressive symptoms (Model 1, OR=6.93, 95% CI 2.519–19.068, P for trend<0.0001). In the fully adjusted logistic regression model (Model 3), the association between severe depressive symptom and chronic knee pain was strongly significant. When compared to the absence of depressive symptoms, the probability of having chronic knee pain increased with depressive symptoms severity showing mild depressive symptoms (OR=2.944, 95% CI 2.112–4.103, P<0.0001) and severe depressive symptoms (OR=4.552, Model 3, 95% CI 1.489–13.92, P for trend <0.0001, Table 3). Driven by the Cochran-Armitage trend test and complex samples logistic regression, a linear relationship was found between chronic knee pain and depressive symptoms (Supplementary Table 1, Supplementary fig.1 and Supplementary fig. 2).

Association between depressive symptoms state and chronic knee pain intensity

The comparison between severity of depressive symptoms and intensity of chronic knee pain, measured by NRS, showed a positive linear association. When the chronic knee pain NRS score ranged from 0 to 4, the prevalence of moderate depressive symptom was 3.4%, and the prevalence of severe depressive symptoms was 0.6%. In the presence of severe chronic knee pain (NRS=8–10), the prevalence of moderate and severe depressive symptoms was high (10.1% and 5.6%, respectively) (Table 4, P<0.001, Fig 2).

Discussion

This study analyzed the association between the severity of depressive symptoms and chronic knee pain by examining a sample of 7,550 Koreans representing the general population from the reliable nationwide survey data. All the participants selected for this study were aged 50 years or older and shared information about their chronic knee pain, for which NRS was used to measure the pain intensity.

The association between depressive symptoms and pain is well established by previous studies.[11, 13] Moreover, a study indicated that persistent depressive symptoms was significantly associated with worsening of osteoarthritis (OA) knee pain.[24] Another previous study also demonstrated that physical pain symptoms were significantly associated with the mean score of depressive symptoms severity.[15] Furthermore, a longitudinal analysis revealed that pain severity was a strong predictor of subsequent depressive symptoms severity, and conversely, depressive symptoms severity was a strong predictor of subsequent pain severity.[16] Further to this, our report is a cross-sectional study which explores the association between severity of depressive symptoms and intensity of chronic knee pain.

In our study, the positive association became stronger in the group with severe depressive symptoms, when compared with that of those having the symptoms of mild to moderate depressive symptoms. The strong linear correlation between depressive symptoms and chronic knee pain was still present after adjusting for variables, such as socioeconomic indicators and comorbidity. In the PHQ-9 survey, a significantly strong association was observed in the severely depressed group, identified with PHQ-9 score of 20 or above. PHQ-9 is a reliable measure of depressive symptoms, and has been used by previous studies to measure severity of depressive symptoms.[17-23] Such a highly significant association persisted even after adjusting for variables, such as sex, age, socioeconomic indicators, smoking status, and alcohol use. Although a previous study using KHANES revealed a relationship between self-reported depressive symptoms and Kellgren-Lawrence knee OA grade, our study is the first to demonstrate the association between depressive symptoms and chronic knee pain using PHQ-9 and NRS in the Korean population.[13]

In our study, a positive linear relationship existed between intensity of chronic knee pain and severity of depressive symptoms in Table 4. We divided severity of depressive symptoms as not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–19) and severe (20–27), and divided severity of chronic knee pain as light (0–4), moderate (5–7), and intense (8–10). In the participants with no chronic knee pain or light pain (NRS=0–4), the prevalence of severe depressive symptoms was 0.6. However, it increased to 5.8% in the participants with more intense chronic knee pain (NRS=8–10). To our knowledge, our study is the first to divide and compare both aspects of severity of depressive symptoms and intensity of chronic knee pain. As a result, we found a strong association

between severity of depressive symptoms and intensity of chronic knee pain. It is a cross-sectional proof of a previous longitudinal study that suggested severe pain and severe depressive symptoms can be a predictor of each other.[16]

Although there is no clear evidence that depressive symptoms can cause chronic knee pain, many potential hypotheses have been suggested. Depressive symptom can interfere with the mechanism of inflammatory cytokines and the regulation of autonomic nervous system.[25- 27] It can also destabilize the hypothalamic-pituitary-adrenal axis.[28] Depressive symptom-induced pathological conditions act as the catalyst for chronic pain syndrome.[29- 30] Furthermore, neurotransmitters of noradrenalin and serotonin are associated with the pathological mechanism of depressive symptom.[26] These neurotransmitters also play an important role in pain inhibitory pathways.[31-32] Taken together, these findings suggest the effects of depressive symptoms on the pathogenic mechanism of chronic pain. The association between depressive symptoms and chronic knee pain can be explained by reduced physical activity, which may be associated with depressive symptoms, consequently decreasing muscle strength and joint stability, whereby negative outcomes, such as osteoarthritis, can be induced. [33-35]

Strength and limitations

This study has the following strengths. First, this study was based on highly reliable data from the national survey using the Korean population-based questionnaire. Second, to our knowledge, this is the first study to describe the correlation between the severity of depressive symptoms and the intensity of chronic knee pain.

However, this study had certain limitations. First, this study was a cross-sectional study. Therefore, it assessed depressive symptoms and chronic knee pain using odds ratios without the analysis of the cause-effect relationship between the variables. Second, because the questionnaire regarding chronic knee pain was only asked to a population aged over 50 years, the younger population with chronic knee pain was excluded in the analysis. Third, self-reporting questionnaires were used to assess the NRS and PHQ-9 scores for chronic knee pain and depressive symptoms, respectively. Therefore, response biases cannot be ruled out.

Conclusions

This study identified a strong association between the presence and severity of depressive symptoms and the presence and intensity of chronic knee pain. Furthermore, the association

became stronger with higher levels of depressive symptoms, demonstrating greater NRS scores for chronic knee pain. This study suggests depressive symptoms as an independent risk factor when screening for chronic knee pain.

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Author Contributions

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Competing interests

None declared.

Ethics approval

The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board (approval no. 2013-12EXP-03-5C). Informed consent was obtained from all participants when the surveys were conducted. The approval of IRB was not required because the study did not deal with any sensitive information, but rather accessed only publicly available data from the KNHANES (JASENG IRB File No. 2018-11-017).

Data sharing statement

All relevant materials are provided in the manuscript. Survey data are publicly available at (https://knhanes.cdc.go.kr/knhanes/main.do). All data from KNHANES VI-2 are coded and freely available.

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35. Guilak F. Biomechanical factors in osteoarthritis. Best Practice & Research. Clinical Rheumatology. 2011;25(6):815-23.

462 **Table 1. Characteristics of the study population according to chronic knee pain**

Variable	Without chronic knee Pain (n=2131)	Chronic knee pain (n=527)	P-value
PHQ-9, n (%)			
<10	2021 (94.8)	436 (82.7)	<0.0001
≥10	110 (5.2)	91 (17.3)	
Levels of depressive symptom, n (%)			
None(PHQ-9≤4)	1780 (83.5)	303 (57.5)	<0.0001
Mild (5–9)	241 (11.3)	133 (25.2)	
Moderate (10–14)	66 (3.1)	51 (9.7)	
Moderately severe (15–19)	33 (1.6)	28 (5.3)	
Severe (≥20)	11 (0.5)	12 (2.3)	
Age, y (mean±SD)	61.2±8.6	66.1±9.1	<0.0001
Age, n (%)			
50–59 y	845 (39.7)	111 (21.1)	<0.0001
60–69 y	698 (32.8)	182 (34.5)	
≥80 y	588 (27.6)	234 (44.4)	
Sex, n(%)			
Male	1002 (47)	117 (22.2)	<0.0001
Female	1129 (53)	410 (77.8)	
BMI, kg/m^2 (mean±SD)	23.9±3.1	24.3±3.3	0.0533
Obesity, n (%)			
Underweight (≤18.5 kg/m^2)	55 (2.6)	13 (2.5)	0.2473
Normal (18.5–24.9 kg/m^2)	1365 (64.1)	300 (57)	
Obese (≥25 kg/m^2)	711 (33.4)	213 (40.5)	
Smoking status, n (%)			
Nonsmoker	1265 (60.4)	383 (75)	<0.0001
Ex-smoker	496 (23.7)	78 (15.3)	
Current smoker	334 (15.9)	50 (9.8)	
Alcohol consumption, n (%)			
None	805 (38.4)	235 (45.7)	<0.0001
1 drinks/month or less	516 (24.6)	156 (30.4)	
2 drinks/ month to 3 drinks/week	585 (27.9)	93 (18.1)	
4 drinks/ week or more	193 (9.2)	30 (5.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	1003 (47.1)	328 (62.2)	<0.0001
Office work / Sales and services	463 (21.8)	53 (10.1)	
Agriculture, forestry and fishery	186 (8.7)	50 (9.5)	
Machine fitting and simple labor	477 (22.4)	96 (18.2)	
Household income, n (%)			
Low	546 (25.7)	232 (44.3)	<0.0001
Low–moderate	589 (27.7)	136 (26)	
Moderate–high / High	989 (46.6)	156 (29.8)	
Educational level, n (%)			
≤6 y	805 (37.8)	345 (65.5)	<0.0001
7–9 y	396 (18.6)	73 (13.9)	
≥10 y	928 (43.6)	109 (20.7)	
Aerobic physical activity, n (%)			
No	1100 (52.0)	313 (60.5)	0.0005
Yes	1016 (48.0)	204 (39.5)	
Duration of sleep, h	6.7±1.4	6.4±1.7	0.0026

Comorbidities, n (%)			
Hypertension	765 (35.9)	262 (49.7)	<0.0001
Dyslipidemia	413 (19.4)	145 (27.5)	0.0002
Stroke	77 (3.6)	38 (7.2)	0.0002
Myocardial infarction	31 (1.5)	13 (2.5)	0.2165
Angina	64 (3)	17 (3.2)	0.698
Arthritis	252 (11.8)	285 (54.1)	<0.0001
Asthma	56 (2.6)	33 (6.3)	<0.0001
Diabetes mellitus	304 (14.3)	86 (16.3)	0.7091

The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without chronic knee pain. Missing values/nonresponses were excluded from analysis. BMI, body mass index; PHQ, Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%).

Table 2. Characteristics of chronic knee pain population according to presence of depressive symptoms

Variables	Non-depressive (n=436)	Depressive (n=91)	P-Value
Age, y (mean±SD)	65.9±9.2	67±8.8	0.4956
Age, n (%)			
50–59 y	94 (21.6)	17 (18.7)	0.8051
60–69 y	152 (34.9)	30 (33)	
≥70 y	190 (43.6)	44 (48.4)	
Sex, n (%)			
Male	104 (23.9)	13 (14.3)	0.1181
Female	332 (76.2)	78 (85.7)	
BMI, kg/m^2, (mean±SD)	24.4±3.3	23.8±3.1	0.1927
Obesity, n (%)			
Underweight (<18.5 kg/m^2)	9 (2.1)	4 (4.4)	0.1711
Normal (18.5–24.9 kg/m^2)	246 (56.4)	54 (60)	
Obese (≥25 kg/m^2)	181 (41.5)	32 (35.6)	
Smoking status, n (%)			
Nonsmoker	312 (73.8)	71 (80.7)	0.0372
Ex-smoker	71 (16.8)	7 (8)	
Current smoker	40 (9.5)	10 (11.4)	
Alcohol consumption, n (%)			
None	183 (43)	52 (59.1)	0.2782
1 drinks/month or less	136 (31.9)	20 (22.7)	
2 drinks/month to 3 drinks/week	83 (19.5)	10 (11.4)	
4 drinks/week or more	24 (5.6)	6 (6.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	262 (60.1)	66 (72.5)	0.0561
Office work/Sales and services	48 (11)	5 (5.5)	
Agriculture, forestry and fishery	42 (9.6)	8 (8.8)	
Machine fitting and simple labor	84 (19.3)	12 (13.2)	
Household income, n (%)			
Low	171 (39.5)	61 (67)	<.0001
Low–moderate	112 (25.9)	24 (26.4)	
Moderate–high/high	150 (34.6)	6 (6.6)	
Educational level, n (%)			
≤6 y	278 (63.8)	67 (73.6)	0.0076
7–9 y	58 (13.3)	15 (16.5)	
≥10 y	100 (22.9)	9 (9.9)	
Aerobic physical activity, n (%)			
No	254 (59.1)	59 (67.8)	0.0162
Yes	176 (40.9)	28 (32.2)	
Duration of sleep, h (mean)	6.5±1.7	5.9±1.9	0.0325

The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without depressive symptoms. Missing values/nonresponses were excluded from analysis. BMI, Body mass index; PHQ, Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive

symptoms. Levels of depressive symptoms were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score.

Table 3. Association between severity of depressive symptoms and chronic knee pain

	Model 1 OR (95% CI)	P-value	Model 2 OR (95% CI)	P-Value	Model 3 OR (95% CI)	P-value
Diagnosis of depressive symptoms						
No	1		1		1	
Yes	3.553 (2.558,4.935)	<0.0001	2.722 (1.844,4.017)	<0.0001	2.333 (1.605,3.391)	<0.0001
Levels of depressive symptom						
None (0–4)	1		1		1	
Mild (5–9)	3.715 (2.687,5.138)	<0.0001	3.266 (2.35,4.541)	<0.0001	2.944 (2.112,4.103)	<0.0001
Moderate (10–14)	4.525 (2.964,6.909)	<0.0001	3.619 (2.233,5.865)	<0.0001	3.211 (1.977,5.217)	<0.0001
Moderately severe (15–19)	4.124 (2.256,7.539)	<0.0001	2.805 (1.553,5.066)	0.0007	2.43 (1.355,4.359)	0.0031
Severe (20–27)	6.93 (2.519,19.068)	0.0002	5.109 (1.606,16.257)	0.006	4.552 (1.489,13.92)	0.0082
p for trend		<0.0001		<0.0001		<0.0001

Logistic regression analysis with complex sampling design was performed by adjusting for covariates. OR indicates odds ratio; 95% CI, 95% confidence interval. Individuals with PHQ-9 scores >10 were considered to have depressive symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Model 1 was unadjusted odds ratio. Model 2 was adjusted by age and sex. Model 3 was fully adjusted by age, sex, and other environmental factors, such as smoking, alcohol consumption, educational level, household income, physical activity, duration of sleep, and comorbidities.

Table 4. Association between severity of chronic knee pain NRS and severity of depressive symptoms

Chronic knee pain NRS	Depressive symptoms					
	None (0–4)	Mild (5–9)	Moderate (10–14)	Moderately severe(15–19)	Severe (20–27)	P-Value
NRS (0–4) (%)	1872 (82.4)	272 (12)	77 (3.4)	38 (1.7)	13 (0.6)	<.0001
NRS (5–7) (%)	136 (58.1)	63 (26.9)	25 (10.7)	8 (3.4)	2 (0.9)	
NRS (8–10) (%)	65 (46.8)	37 (26.6)	14 (10.1)	15 (10.8)	8 (5.8)	

The Rao-Scott Chi-Square test was performed to compare severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

Figure Legends

Figure 1. Flow chart diagram of inclusion and exclusion of participants

Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

Figure 2. Severity of depressive symptoms according to chronic knee pain NRS

Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

Supplementary Figure 1. Estimated probability graph of logistic regression according to levels of depressive symptom.

Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

Supplementary Figure 2. Logit function graph of logistic regression according to levels of depressive symptom.

Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

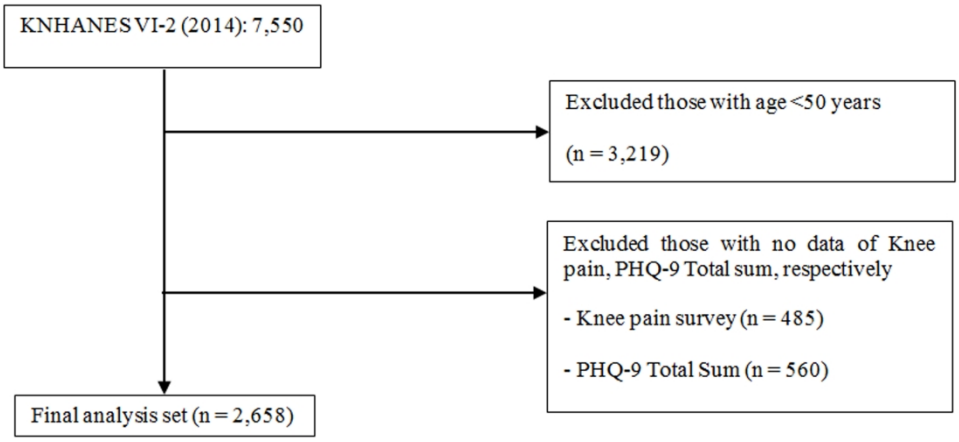

Figure 1. Flow chart diagram of inclusion and exclusion of participants
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

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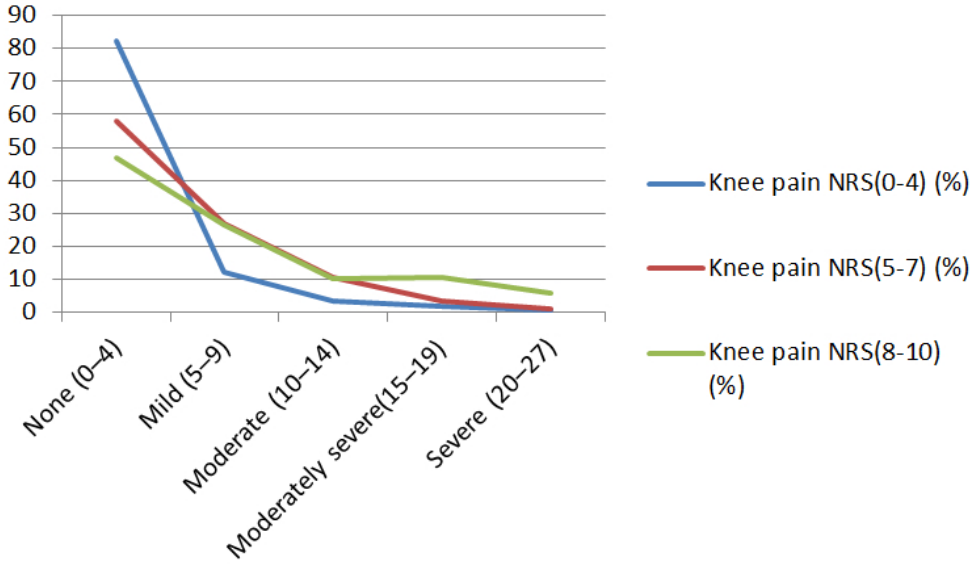
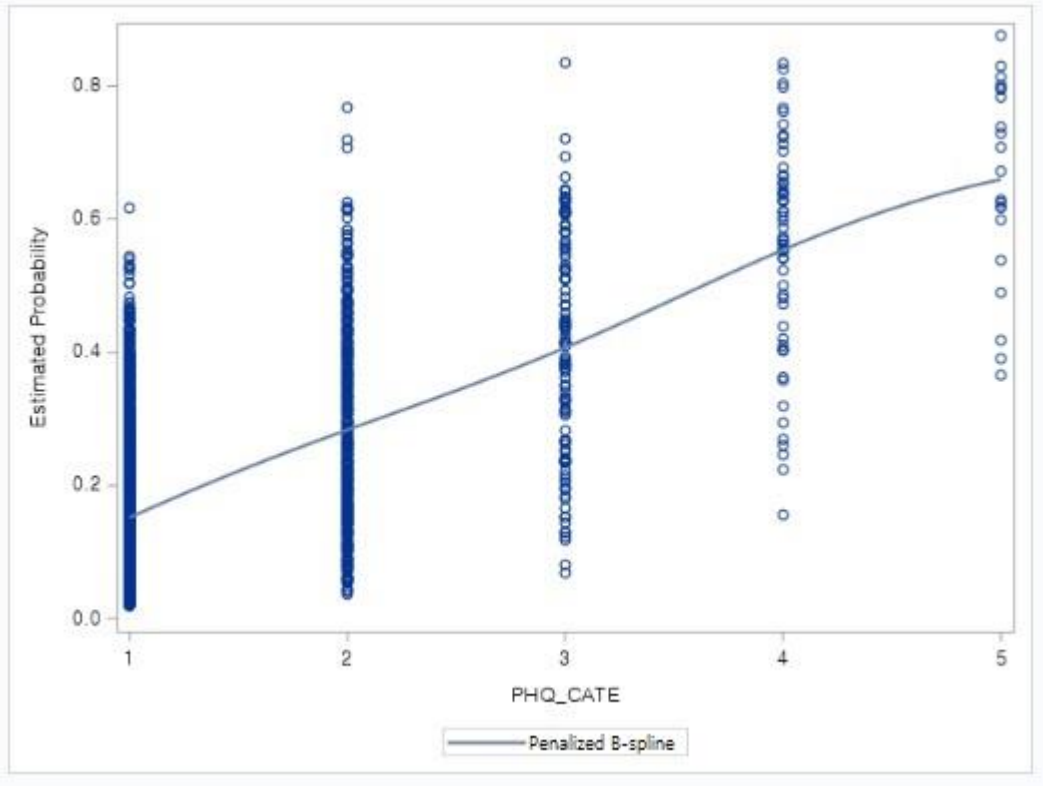


Figure 2. Severity of depressive symptoms according to chronic knee pain NRS
Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

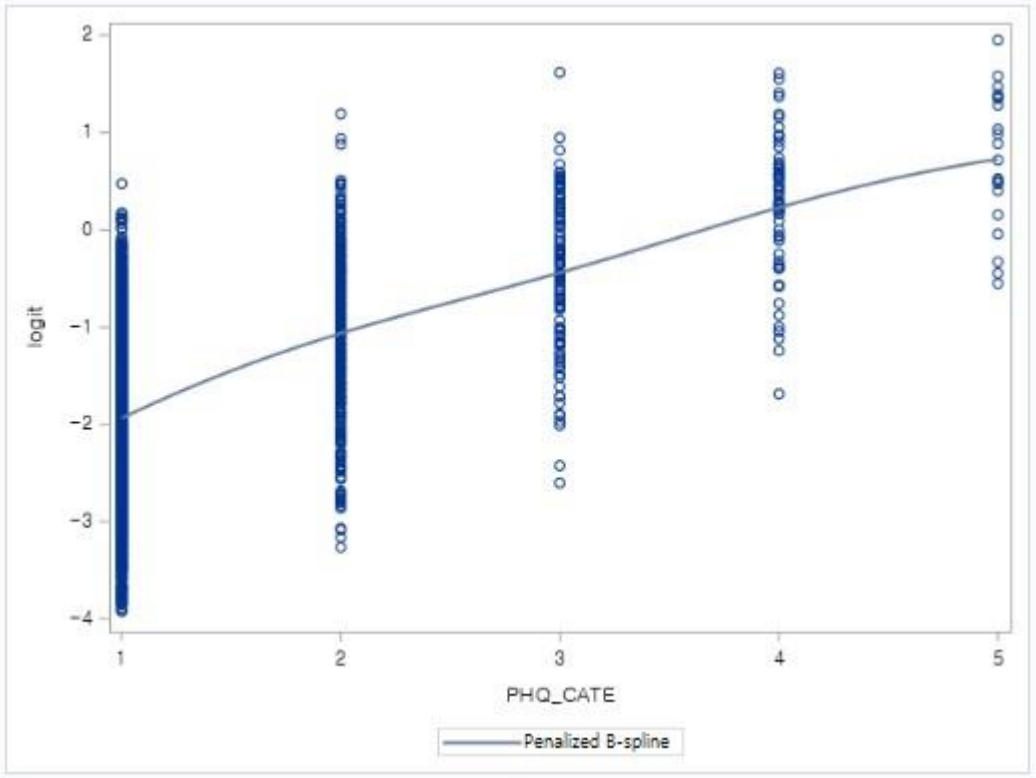
Supplementary Figure 1. Estimated probability graph of logistic regression according to levels of depressive symptom.



Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

Supplementary Figure 2. Logit function graph of logistic regression according to levels of depressive symptom.

Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).



Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

Supplementary Table 1. Cochran-Armitage Trend Test

Cochran-Armitage Trend Test	
Statistics (Z)	-903.3422
Single sides Pr < Z	<.0001
Both sides Pr > |Z|	<.0001

Test results for linear relationship between pain and depressive symptoms can be found to be significant by the Cochrane-Armitage Trend Test in Model 1. Pr, Probability.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p.1-2)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p.1-2)	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	(p. 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses (p. 5, lines 121-124)	
Methods			
Study design	4	Present key elements of study design early in the paper (p. 5, lines 126-137)	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 5, lines 126-137)	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (p. 5, lines 126-137)	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p. 5-6)	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (NA)	
Bias	9	Describe any efforts to address potential sources of bias (NA)	
Study size	10	Explain how the study size was arrived at (p. 5, lines 126-137)	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (NA)	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	(p.6, lines 180-185; p.7, lines 186-195)
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed (NA)	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (NA)	
		(*e*) Describe any sensitivity analyses (NA)	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p. 7, lines 201-210)	
		(b) Give reasons for non-participation at each stage (fig 1)	
		(c) Consider use of a flow diagram (fig 1)	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p. 7, lines 201-219)	
		(b) Indicate number of participants with missing data for each variable of interest (NA)	
Outcome data	15*	Report numbers of outcome events or summary measures (p. 7, lines 201-219)	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p.8, lines 221-251)	
		(*b*) Report category boundaries when continuous variables were categorized (NA)	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (NA)	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p.8, lines 241-244)	

Discussion		
Key results	18	Summarise key results with reference to study objectives (p.8, lines 254-255; p.9, lines 256-258)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p.10, lines 306-317)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p.9, lines 259-290; p.10, lines 291-305)
Generalisability	21	Discuss the generalisability (external validity) of the study results (p.10, lines 319-321;11, lines 322-323)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p. 11, lines 335-337)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association between severity of depressive symptoms and chronic knee pain in Korean adults aged over 50 years: a cross-sectional study using nationally representative data

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Mental health, Rehabilitation medicine
Keywords:	Epidemiology < THORACIC MEDICINE, Adult psychiatry < PSYCHIATRY, PAIN MANAGEMENT

Association between severity of depressive symptoms and chronic knee pain in Korean adults aged over 50 years: a cross-sectional study using nationally representative data

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Abstract

Objectives: To identify the association between the presence and severity of depressive symptoms and those of chronic knee pain.

Design: A retrospective cross-sectional study

Participants: We used data from the 6th Korea National Health and Nutrition Examination Survey (KNHANES VI-2) performed in 2014. Overall, 7,550 patients were included in the KNHANES VI-2.

Outcome measures: Participants were asked whether they had chronic knee pain, and each answer was either "yes" or "no." Patient Health Questionnaire-9 (PHQ-9) was used as a screening tool for depressive symptoms, and PHQ-9 scores of 10 or higher was classified as the depressed group. In total, 527 patients reported that they had pain in their knee, of whom 91 also had depressive symptoms.

Results: The prevalence of chronic knee pain in the Korean population aged over 50 years was 19.8%. Multiple logistic regression was conducted after adjustment for sex, age, smoking, alcohol drinking, education level, household income, physical activity, sleep duration, and comorbidity. The analysis revealed a significant association between depressive symptoms and chronic knee pain (adjusted odds ratio =2.333, P<0.001). In contrast, the severity of depressive symptoms was linearly correlated with the intensity of chronic knee pain (P for trend<0.001). In participants with no chronic knee pain (numerical rating scale; NRS=0) or mild chronic knee pain (NRS=1–4), the prevalence of moderate and severe depressive symptoms was 3.4% and 0.6%, respectively. However, in those with severe chronic knee pain (NRS=8–10), there was a higher prevalence of moderate and severe depressive symptoms (10.1% and 5.8%, respectively) (P<0.001).

Conclusions: A strong association was observed between the presence and severity of depressive symptoms and the presence of chronic knee pain. The association became stronger with higher levels of depressive symptoms, indicating a positive correlation between depressive symptoms severity and chronic knee pain.

Keywords: chronic knee pain, depressive symptoms, Patient Health Questionnaire-9, Korea National Health and Nutrition Examination Survey VI-2

Strengths and limitations of this study

- This study is based on highly reliable data from the national survey using the Korean population-based questionnaire.
- We found a strong association between the severity of depressive symptoms and the presence and intensity of chronic knee pain.
- Because the questionnaire regarding chronic knee pain was only asked to a population aged over 50 years, the younger population with chronic knee pain was excluded in the analysis.
- As this was a retrospective cross-sectional study, it assessed depressive symptoms and chronic knee pain using odds ratios without analyzing the cause-effect relationship between the variables.
- Response biases cannot be ruled out because self-report questionnaires, NRS and PHQ-9, were used to assess chronic knee pain and depressive symptoms, respectively.

Introduction

Depressive symptoms are one of the most common mental illnesses. An earlier systematic review and meta-analysis reported that a lifetime prevalence of psychotic depressive symptoms ranges from 0.35% to 1% and that the rates of psychotic depressive symptoms increase with age.[1] According to a Chinese systematic review, a lifetime prevalence of major depressive disorder (MDD) varies between 1.1 and 3.3%.[2] However, the prevalence of major depressive episode (MDE), which indicates the relatively mild symptoms of depression, is markedly higher. A cohort study using a sample of 29,621 people representing the general United States population found that the 3-year prevalence rate was 8% for MDE.[3] Additionally, a Canadian longitudinal study reported that the prevalence of depressive episode at baseline was 7.5%.[4] Based on World Mental Health Survey data, a cross-sectional study identified diabetes, arthritis, asthma, chronic pulmonary disease, angina symptoms, and stroke, advanced age, women, underweight, and lower levels of income and education as risk factors related to depressive symptoms.[5]

The prevalence of knee pain is one of the most common symptoms in the aging population around the world. According to the 6th National Health and Nutrition Survey (KNHANES VI, 2013-2015), 20.8% of Korean population aged over 50 reported chronic knee pain.[6] In an Italian cross-sectional study, 22.4% of the population aged over 65 years complained about pain in the knee.[7] In a study involving the British population aged over 65 years, 32.6% of participants reported knee pain.[8] As risk factors for chronic knee pain, advanced age, low education, and high BMI have a cause-effect relationship with chronic knee pain.[9]

Emotional distress is also known to worsen physical pain, and many studies are underway in this context. The patients with temporomandibular disorders who have anxiety and depressive symptoms are more likely to develop migraine and primary headache.[10] According to a systematic review, depressive symptoms and anxiety symptoms are associated with high morbidity neck pain.[11]

The relationship between depressive symptoms and chronic knee pain has been investigated in previous literature.[12] A systematic review revealed strong evidence supporting such a relationship between depressive symptoms and chronic knee pain, with reference to five high-quality studies.[13] A cohort study involving the Japanese population aged over 65 years found that the development of depressive symptoms was associated with the presence of chronic knee pain.[14] Among previous studies, a cross-sectional study described the relationship between depressive symptoms and severity of chronic knee pain assessed by the numerical rating scale (NRS) and the Kellgren-Lawrence scale.[15] Moreover, a recent study revealed a relationship between depressive symptoms subtypes and risk for symptomatic knee pain.[16]

However, few studies have been conducted to identify the association between the severity of depressive symptoms and the presence and intensity of knee pain. Recently, one study revealed that participants with physical pain symptoms were significantly associated with depressive symptoms severity. According to this study, participants with pain showed higher scores of Montgomery-Asberg depressive symptoms rating scales. However, results of these studies are limited to showing the mean of depressive symptoms severity score depending on the presence of pain symptoms.[17] Moreover, a longitudinal analysis revealed that pain severity was a strong predictor of subsequent depressive symptoms severity, and conversely, depressive symptoms severity was a strong predictor of subsequent pain severity.[18]

In addition to previous studies regarding depressive symptoms and chronic knee pain, this study aimed to identify the association between the presence and severity of depressive symptoms and those of chronic knee pain. To our knowledge, our study is the first to explore both aspects of the severity of depressive symptoms and severity of chronic knee pain measured by Patient Health Questionnaire-9 (PHQ-9) and NRS.

Methods

Study population

This study was based on the results of the nationally representative survey, the 6th Korea National Health and Nutrition Examination Survey (KNHANES VI-2), which was first launched in 1998 and conducted every year with population-based random samples using standardized questionnaires. This survey is intended to identify socio-demographic characteristics and health and nutritional status of the general Korean population and households, and survey responses are not tracked when the survey is completed each year. KNHANES VI-2 used the PHQ-9 as a screening instrument to diagnose depressive disorder. This questionnaire was provided to 7,550 respondents. Of those administered questionnaires, 2,658 questionnaires completed by Korean adults aged over 50 years were analyzed with respect to the relationship between depressive symptoms and chronic knee pain (Figure 1).

Definition of depressive symptoms and chronic knee pain

A total score of 10 or higher on the PHQ-9 was used to define the presence of depressive symptoms.[19] In previous studies, the PHQ-9 questionnaire was often used to monitor depressive symptoms in patients with chronic pain.[20-21] The PHQ-9 items are based on the 4th edition of the diagnostic and statistical manual of mental disorders (DSM-IV) and designed to ask about symptoms that relate to depression over the last 2 weeks. Each item is scored from 0 (not at all) to 3 (nearly every day). The PHQ-9, consisting of nine questions, is a reliable

and valid depressive symptoms scale. As a severity measure, its score ranges from 0 to 27, with higher scores indicating higher severity of depressive symptoms.[22-23]

In previous studies, a PHQ-9 score ≥10 was used to determine the presence of depressive symptoms, and the reliability of this questionnaire has been proven. In this study, a PHQ-9 score ≥10 was also used to indicate the presence of depressive symptoms. The severity of depressive symptoms was divided into not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–19), and severe (20–27), according to previous studies.[22-24]

The questionnaire used to identify the presence of chronic knee pain in the respondents aged over 50 years included the question "Have you had knee pain for at least 30 days during the last 3 months? Those who answered "yes" to this question were classified as the chronic knee pain group, and their knee pain intensity was assessed using the NRS. Because the questionnaire regarding chronic knee pain was only asked to respondents aged over 50 years in KNHANES VI-2, the analyzed data was limited to a population aged over 50 years.

Description of demographic and characteristics of the study population

Patient information, including demographic characteristics, socioeconomic background, medical history, and life habits was analyzed. Body mass index (BMI) was calculated by dividing body weight in kilograms by the square of height in meters and categorized into three groups: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), and overweight (≥25.0 kg/m^2). Smoking status was classified into nonsmoker, ex-smoker, and current smoker. The frequency of alcohol consumption was grouped into none, once a month or less, 2 drinks/month to 3 drinks/week, and more than four times a month. Occupation was classified into four groups: unemployed (student, housewife, etc.); office work/sales and services; agriculture, forestry, and fishery; and machine fitting and simple labor. Household income was classified into quartiles: low, low-moderate, and moderate-high/high. Education level was also categorized into three groups: ≤6 years, 7–9 years, and ≥10 years. Physical activity was categorized into three groups: moderate activity at least 2 hours and 30 minutes a week, vigorous activity at least 1 hour and 15 minutes a week, and combination of moderate and vigorous activity for longer hours (1-minute vigorous activity was considered equal to 2-minute moderate activity). This study also investigated the presence of comorbidities, such as hypertension, dyslipidemia, stroke, myocardial infarction, angina, arthritis, asthma, and diabetes mellitus.

Statistical analysis

The KNHANES is a survey of nationwide sample of Koreans selected through stratified clustered sampling, and sampling weights are used for survey data. Accordingly, complex sample survey data were analyzed using parameters for strata, clusters, and weights, which comprise the sample design. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analysis, and $P<0.05$ was used as the threshold for statistical significance. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%). The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without chronic knee pain. To assess the effects of depressive symptoms on chronic knee pain, logistic regression analysis with complex sampling design was performed by adjusting for covariates. As a result, odd ratios, as well as 95% confidence intervals for the odds ratios, were generated. Additionally, this study investigated if there was an underlying trend from different levels of depressive symptoms in each model (P for trend). To verify a linear relationship between the intensity of chronic knee pain and depressive symptoms, we used the Cochran-Armitage trend test and complex samples logistic regression.

Patient and public involvement

We did not involve patients or the public in our work.

Results

Characteristics of the study population according to chronic knee pain

This study found that the overall prevalence of chronic knee pain in the Korean population aged over 50 years was 19.8%. Of those, women (77.8%) far outpaced men (22.2%). The presence of depressive symptoms, determined by PHQ-9 score ≥10, was significantly higher in the participants with chronic knee pain (17.3%), compared with those without chronic knee pain (5.2%) ($P<0.001$, Table 1). When compared with the participants without chronic knee pain, those with chronic knee pain showed greater frequency of depressive symptoms, higher percentages of older women and unemployment, lower household income, lower levels of education and physical activity, more comorbidities (hypertension, dyslipidemia, stroke, arthritis, asthma), and shorter sleep duration (Table 1).

Clinical characteristics of participants with chronic knee pain according to the presence of depressive symptoms

When compared with non-depressed patients with chronic knee pain, depressed patients with chronic knee pain had lower household income, lower levels of education and aerobic physical activity, and shorter sleep duration. However, no difference between the two groups was found with respect to age, sex, BMI, obesity, alcohol consumption, and occupation. In case of smoking status, the percentage of non-smokers was high in the group with co-existing depressive symptoms and chronic knee pain (Table 2).

Associations between depressive symptoms and chronic knee pain

Multiple logistic regression models were used to analyze the effects of depressive symptoms on chronic knee pain. Univariate analyses revealed a strong association between depressive symptoms and chronic knee pain (Model 1, OR=3.553, 95% CI 2.558–4.935, P<0.0001). After adjusting for sex and age, a clear association between depressive symptoms and chronic knee pain was present (Model 2, OR=2.722, 95% CI 1.844–4.017, P<0.0001). After adjusting for sex, age, smoking status, alcohol use, education level, household income, physical activity, sleep duration and comorbidities, there was still a clear association between depressive symptoms and chronic knee pain (Model 3, OR=2.333, 95% CI 1.605–3.391, P<0.0001). The odds ratio of depressive symptom levels also indicated an association between the severity of depressive symptoms and chronic knee pain. When compared to the absence of depressive symptoms, the probability of having chronic knee pain increased with the severity of depressive symptoms: mild (OR=3.715, 95% CI 2.687–5.138, P<0.0001), moderate (OR=4.525, 95% CI 2.964–6.909, P<0.0001), moderately severe (OR=4.124, 95% CI 2.256–7.539, P=0.0002), and severe depressive symptoms (Model 1, OR=6.93, 95% CI 2.519–19.068, P for trend<0.0001). In the fully adjusted logistic regression model (Model 3), the association between severe depressive symptom and chronic knee pain was strongly significant. When compared to the absence of depressive symptoms, the probability of having chronic knee pain increased with depressive symptoms severity showing mild depressive symptoms (OR=2.944, 95% CI 2.112–4.103, P<0.0001) and severe depressive symptoms (OR=4.552, Model 3, 95% CI 1.489–13.92, P for trend <0.0001, Table 3). Driven by the Cochran-Armitage trend test and complex samples logistic regression, a linear relationship was found between chronic knee pain and depressive symptoms (Supplementary Table 1, Supplementary fig.1 and Supplementary fig. 2).

Association between depressive symptoms state and chronic knee pain intensity

The comparison between severity of depressive symptoms and intensity of chronic knee pain, measured by NRS, showed a positive linear association. When the chronic knee pain NRS score ranged from 0 to 4, the prevalence of moderate depressive symptom was 3.4%, and the prevalence of severe depressive symptoms was 0.6%. In the presence of severe chronic knee pain (NRS=8–10), the prevalence of moderate and severe depressive symptoms was high (10.1% and 5.6%, respectively) (Table 4, P<0.001, Fig 2).

Discussion

This study analyzed the association between the severity of depressive symptoms and chronic knee pain by examining a sample of 7,550 Koreans representing the general population from the reliable nationwide survey data. All the participants selected for this study were aged 50 years or older and shared information about their chronic knee pain, for which NRS was used to measure the pain intensity.

The association between depressive symptoms and pain is well established by previous studies.[13-15] Moreover, a study indicated that persistent depressive symptoms was significantly associated with worsening of osteoarthritis (OA) knee pain.[25] Another previous study also demonstrated that physical pain symptoms were significantly associated with the mean score of depressive symptoms severity.[17] Furthermore, a longitudinal analysis revealed that pain severity was a strong predictor of subsequent depressive symptoms severity, and conversely, depressive symptoms severity was a strong predictor of subsequent pain severity.[18] Further to this, our report is a cross-sectional study which explores the association between severity of depressive symptoms and intensity of chronic knee pain.

In our study, the positive association became stronger in the group with severe depressive symptoms, when compared with that of those having the symptoms of mild to moderate depressive symptoms. The strong linear correlation between depressive symptoms and chronic knee pain was still present after adjusting for variables, such as socioeconomic indicators and comorbidity. In the PHQ-9 survey, a significantly strong association was observed in the severely depressed group, identified with PHQ-9 score of 20 or above. Such a highly significant association persisted even after adjusting for variables, such as sex, age, socioeconomic indicators, smoking status, and alcohol use. Although a previous study using KNHANES revealed a relationship between self-reported depressive symptoms and Kellgren-Lawrence knee OA grade, our study is the first to demonstrate the association between depressive symptoms and chronic knee pain using PHQ-9 and NRS in the Korean population.[15]

In our study, a positive linear relationship existed between intensity of chronic knee pain and severity of depressive symptoms in Table 4. We divided severity of depressive symptoms as not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–19) and severe (20–27), and divided severity of chronic knee pain as light (0–4), moderate (5–7), and intense (8–10). In the participants with no chronic knee pain or light pain (NRS=0–4), the prevalence of severe depressive symptoms was 0.6. However, it increased to

5.8% in the participants with more intense chronic knee pain (NRS=8–10). To our knowledge, our study is the first to divide and compare both aspects of severity of depressive symptoms and intensity of chronic knee pain. As a result, we found a strong association between severity of depressive symptoms and intensity of chronic knee pain. It is a cross-sectional proof of a previous longitudinal study that suggested severe pain and severe depressive symptoms can be a predictor of each other.[18]

Although there is no clear evidence that depressive symptoms can cause chronic knee pain, many potential hypotheses have been suggested. Depressive symptom can interfere with the mechanism of inflammatory cytokines and the regulation of autonomic nervous system. Moreover, It can also destabilize the hypothalamic-pituitary-adrenal axis.[26-28] Depressive symptom-induced pathological conditions act as the catalyst for chronic pain syndrome.[29- 30] Furthermore, neurotransmitters of noradrenalin and serotonin are associated with the pathological mechanism of depressive symptom. These neurotransmitters also play an important role in pain inhibitory pathways.[31-33] The association between depressive symptoms and chronic knee pain can also be explained by reduced physical activity, which may be associated with depressive symptoms, consequently decreasing muscle strength and joint stability, whereby negative outcomes, such as osteoarthritis, can be induced. [34-35] Taken together, these findings suggest the effects of depressive symptoms on the pathogenic mechanism of chronic pain.

Strength and limitations

This study has the following strengths. First, this study was based on highly reliable data from the national survey using the Korean population-based questionnaire. Second, to our knowledge, this is the first study to describe the correlation between the severity of depressive symptoms and the intensity of chronic knee pain.

However, this study had certain limitations. First, this study was a cross-sectional study. Therefore, it assessed depressive symptoms and chronic knee pain using odds ratios without the analysis of the cause-effect relationship between the variables. Second, because the questionnaire regarding chronic knee pain was only asked to a population aged over 50 years, the younger population with chronic knee pain was excluded in the analysis. Third, self-reporting questionnaires were used to assess the NRS and PHQ-9 scores for chronic knee pain and depressive symptoms, respectively. Therefore, response biases cannot be ruled out.

Conclusions

This study identified a strong association between the presence and severity of depressive symptoms and the presence and intensity of chronic knee pain. Furthermore, the association became stronger with higher levels of depressive symptoms, demonstrating greater NRS scores for chronic knee pain. This study suggests depressive symptoms as an independent risk factor when screening for chronic knee pain.

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Author Contributions

Conceptualization: Su-Bin Han, Sook-Hyun Lee

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Competing interests

None declared.

Ethics approval

The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board (approval no. 2013-12EXP-03-5C). Informed consent was obtained from all participants when the surveys were conducted. The approval of IRB was not required because the study did not deal with any sensitive information, but rather accessed only publicly available data from the KNHANES (JASENG IRB File No. 2018-11-017).

Data sharing statement

All relevant materials are provided in the manuscript. Survey data are publicly available at (https://knhanes.cdc.go.kr/knhanes/main.do). All data from KNHANES VI-2 are coded and freely available.

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Table 1. Characteristics of the study population according to chronic knee pain

Variable	Without chronic knee Pain (n=2131)	Chronic knee pain (n=527)	P-value
PHQ-9, n (%)			
<10	2021 (94.8)	436 (82.7)	<0.0001
≥10	110 (5.2)	91 (17.3)	
Levels of depressive symptom, n (%)			
None(PHQ-9≤4)	1780 (83.5)	303 (57.5)	<0.0001
Mild (5–9)	241 (11.3)	133 (25.2)	
Moderate (10–14)	66 (3.1)	51 (9.7)	
Moderately severe (15–19)	33 (1.6)	28 (5.3)	
Severe (≥20)	11 (0.5)	12 (2.3)	
Age, y (mean±SD)	61.2±8.6	66.1±9.1	<0.0001
Age, n (%)			
50–59 y	845 (39.7)	111 (21.1)	<0.0001
60–69 y	698 (32.8)	182 (34.5)	
≥80 y	588 (27.6)	234 (44.4)	
Sex, n(%)			
Male	1002 (47)	117 (22.2)	<0.0001
Female	1129 (53)	410 (77.8)	
BMI, kg/m^2 (mean±SD)	23.9±3.1	24.3±3.3	0.0533
Obesity, n (%)			
Underweight (≤18.5 kg/m^2)	55 (2.6)	13 (2.5)	0.2473
Normal (18.5–24.9 kg/m^2)	1365 (64.1)	300 (57)	
Obese (≥25 kg/m^2)	711 (33.4)	213 (40.5)	
Smoking status, n (%)			
Nonsmoker	1265 (60.4)	383 (75)	<0.0001
Ex-smoker	496 (23.7)	78 (15.3)	
Current smoker	334 (15.9)	50 (9.8)	
Alcohol consumption, n (%)			
None	805 (38.4)	235 (45.7)	<0.0001
1 drinks/month or less	516 (24.6)	156 (30.4)	
2 drinks/ month to 3 drinks/week	585 (27.9)	93 (18.1)	
4 drinks/ week or more	193 (9.2)	30 (5.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	1003 (47.1)	328 (62.2)	<0.0001
Office work / Sales and services	463 (21.8)	53 (10.1)	
Agriculture, forestry and fishery	186 (8.7)	50 (9.5)	
Machine fitting and simple labor	477 (22.4)	96 (18.2)	
Household income, n (%)			
Low	546 (25.7)	232 (44.3)	<0.0001
Low–moderate	589 (27.7)	136 (26)	
Moderate–high / High	989 (46.6)	156 (29.8)	
Educational level, n (%)			
≤6 y	805 (37.8)	345 (65.5)	<0.0001
7–9 y	396 (18.6)	73 (13.9)	
≥10 y	928 (43.6)	109 (20.7)	
Aerobic physical activity, n (%)			
No	1100 (52.0)	313 (60.5)	0.0005
Yes	1016 (48.0)	204 (39.5)	
Duration of sleep, h	6.7±1.4	6.4±1.7	0.0026

Comorbidities, n (%)			
Hypertension	765 (35.9)	262 (49.7)	<0.0001
Dyslipidemia	413 (19.4)	145 (27.5)	0.0002
Stroke	77 (3.6)	38 (7.2)	0.0002
Myocardial infarction	31 (1.5)	13 (2.5)	0.2165
Angina	64 (3)	17 (3.2)	0.698
Arthritis	252 (11.8)	285 (54.1)	<0.0001
Asthma	56 (2.6)	33 (6.3)	<0.0001
Diabetes mellitus	304 (14.3)	86 (16.3)	0.7091

The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without chronic knee pain. Missing values/nonresponses were excluded from analysis. BMI, body mass index; PHQ, Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequency and percentage (%).

Table 2. Characteristics of chronic knee pain population according to presence of depressive symptoms

Variables	Non-depressive (n=436)	Depressive (n=91)	P-Value
Age, y (mean±SD)	65.9±9.2	67±8.8	0.4956
Age, n (%)			
50–59 y	94 (21.6)	17 (18.7)	0.8051
60–69 y	152 (34.9)	30 (33)	
≥70 y	190 (43.6)	44 (48.4)	
Sex, n (%)			
Male	104 (23.9)	13 (14.3)	0.1181
Female	332 (76.2)	78 (85.7)	
BMI, kg/m^2, (mean±SD)	24.4±3.3	23.8±3.1	0.1927
Obesity, n (%)			
Underweight (<18.5 kg/m^2)	9 (2.1)	4 (4.4)	0.1711
Normal (18.5–24.9 kg/m^2)	246 (56.4)	54 (60)	
Obese (≥25 kg/m^2)	181 (41.5)	32 (35.6)	
Smoking status, n (%)			
Nonsmoker	312 (73.8)	71 (80.7)	0.0372
Ex-smoker	71 (16.8)	7 (8)	
Current smoker	40 (9.5)	10 (11.4)	
Alcohol consumption, n (%)			
None	183 (43)	52 (59.1)	0.2782
1 drinks/month or less	136 (31.9)	20 (22.7)	
2 drinks/month to 3 drinks/week	83 (19.5)	10 (11.4)	
4 drinks/week or more	24 (5.6)	6 (6.8)	
Occupation, n (%)			
Unemployed (Student, housewife, etc.)	262 (60.1)	66 (72.5)	0.0561
Office work/Sales and services	48 (11)	5 (5.5)	
Agriculture, forestry and fishery	42 (9.6)	8 (8.8)	
Machine fitting and simple labor	84 (19.3)	12 (13.2)	
Household income, n (%)			
Low	171 (39.5)	61 (67)	<.0001
Low–moderate	112 (25.9)	24 (26.4)	
Moderate–high/high	150 (34.6)	6 (6.6)	
Educational level, n (%)			
≤6 y	278 (63.8)	67 (73.6)	0.0076
7–9 y	58 (13.3)	15 (16.5)	
≥10 y	100 (22.9)	9 (9.9)	
Aerobic physical activity, n (%)			
No	254 (59.1)	59 (67.8)	0.0162
Yes	176 (40.9)	28 (32.2)	
Duration of sleep, h (mean)	6.5±1.7	5.9±1.9	0.0325

The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without depressive symptoms. Missing values/nonresponses were excluded from analysis. BMI, Body mass index; PHQ, Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive

symptoms. Levels of depressive symptoms were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score.

Table 3. Association between severity of depressive symptoms and chronic knee pain

	Model 1 OR (95% CI)	P-value	Model 2 OR (95% CI)	P-Value	Model 3 OR (95% CI)	P-value
Diagnosis of depressive symptoms						
No	1		1		1	
Yes	3.553 (2.558,4.935)	<0.0001	2.722 (1.844,4.017)	<0.0001	2.333 (1.605,3.391)	<0.0001
Levels of depressive symptom						
None (0–4)	1		1		1	
Mild (5–9)	3.715 (2.687,5.138)	<0.0001	3.266 (2.35,4.541)	<0.0001	2.944 (2.112,4.103)	<0.0001
Moderate (10–14)	4.525 (2.964,6.909)	<0.0001	3.619 (2.233,5.865)	<0.0001	3.211 (1.977,5.217)	<0.0001
Moderately severe (15–19)	4.124 (2.256,7.539)	<0.0001	2.805 (1.553,5.066)	0.0007	2.43 (1.355,4.359)	0.0031
Severe (20–27)	6.93 (2.519,19.068)	0.0002	5.109 (1.606,16.257)	0.006	4.552 (1.489,13.92)	0.0082
p for trend		<0.0001		<0.0001		<0.0001

Logistic regression analysis with complex sampling design was performed by adjusting for covariates. OR indicates odds ratio; 95% CI, 95% confidence interval. Individuals with PHQ-9 scores >10 were considered to have depressive symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Model 1 was unadjusted odds ratio. Model 2 was adjusted by age and sex. Model 3 was fully adjusted by age, sex, and other environmental factors, such as smoking, alcohol consumption, educational level, household income, physical activity, duration of sleep, and comorbidities.

Table 4. Association between severity of chronic knee pain NRS and severity of depressive symptoms

Chronic knee pain NRS	Depressive symptoms					
	None (0–4)	Mild (5–9)	Moderate (10–14)	Moderately severe(15–19)	Severe (20–27)	P-Value
NRS (0–4) (%)	1872 (82.4)	272 (12)	77 (3.4)	38 (1.7)	13 (0.6)	<.0001
NRS (5–7) (%)	136 (58.1)	63 (26.9)	25 (10.7)	8 (3.4)	2 (0.9)	
NRS (8–10) (%)	65 (46.8)	37 (26.6)	14 (10.1)	15 (10.8)	8 (5.8)	

The Rao-Scott Chi-Square test was performed to compare severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

Figure Legends

Figure 1. Flow chart diagram of inclusion and exclusion of participants

Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

Figure 2. Severity of depressive symptoms according to chronic knee pain NRS

Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

Supplementary Figure 1. Estimated probability graph of logistic regression according to levels of depressive symptom.

Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

Supplementary Figure 2. Logit function graph of logistic regression according to levels of depressive symptom.

Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

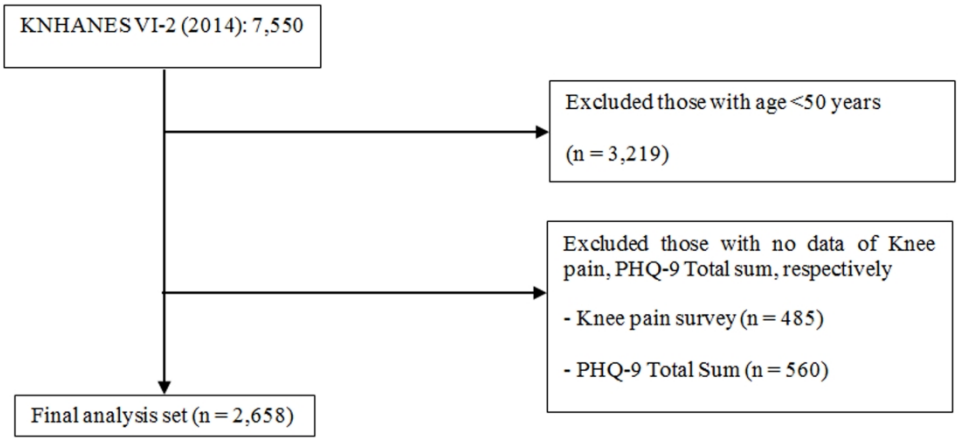

Figure 1. Flow chart diagram of inclusion and exclusion of participants
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

220x104mm (300 x 300 DPI)

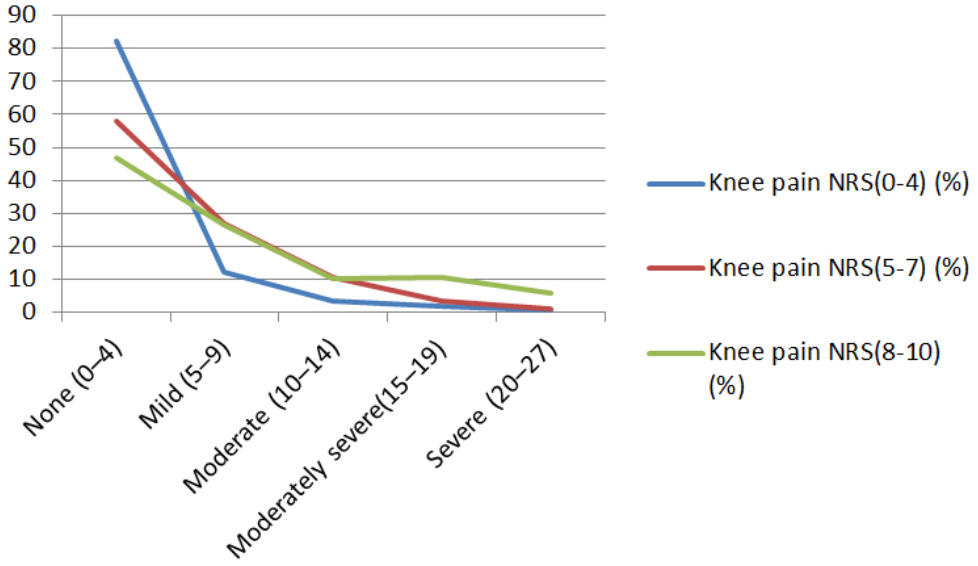

Figure 2. Severity of depressive symptoms according to chronic knee pain NRS
Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27). Individuals without knee pain were regarded as NRS 0. NRS, Numerical rating scale.

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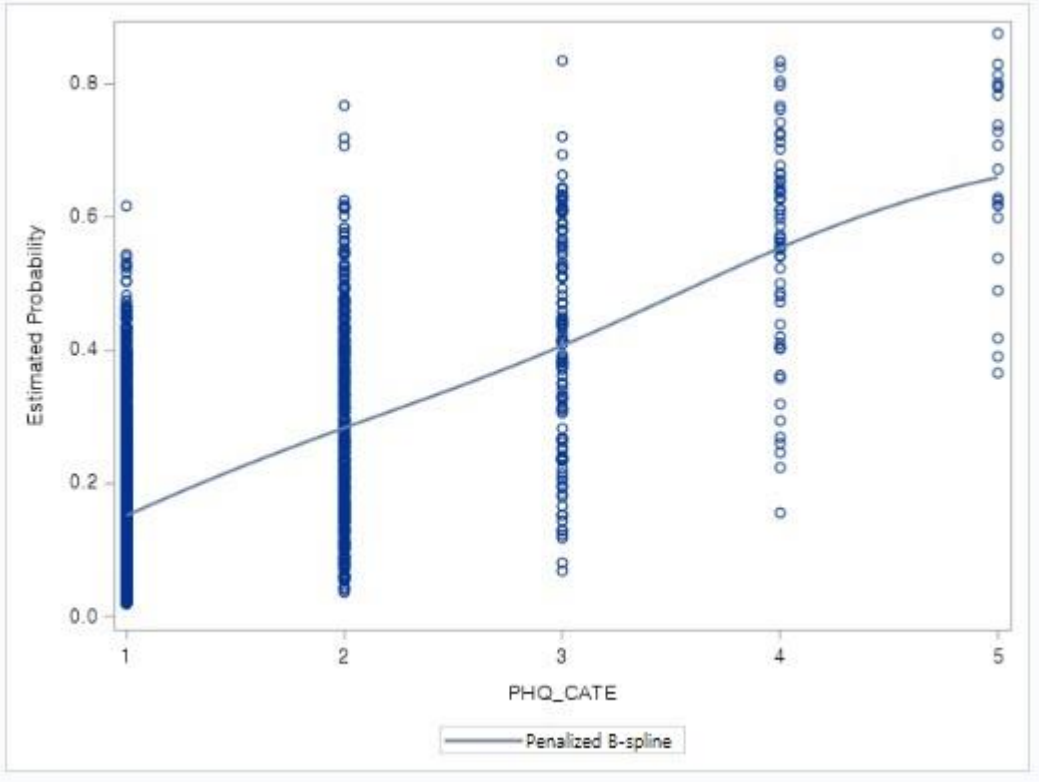

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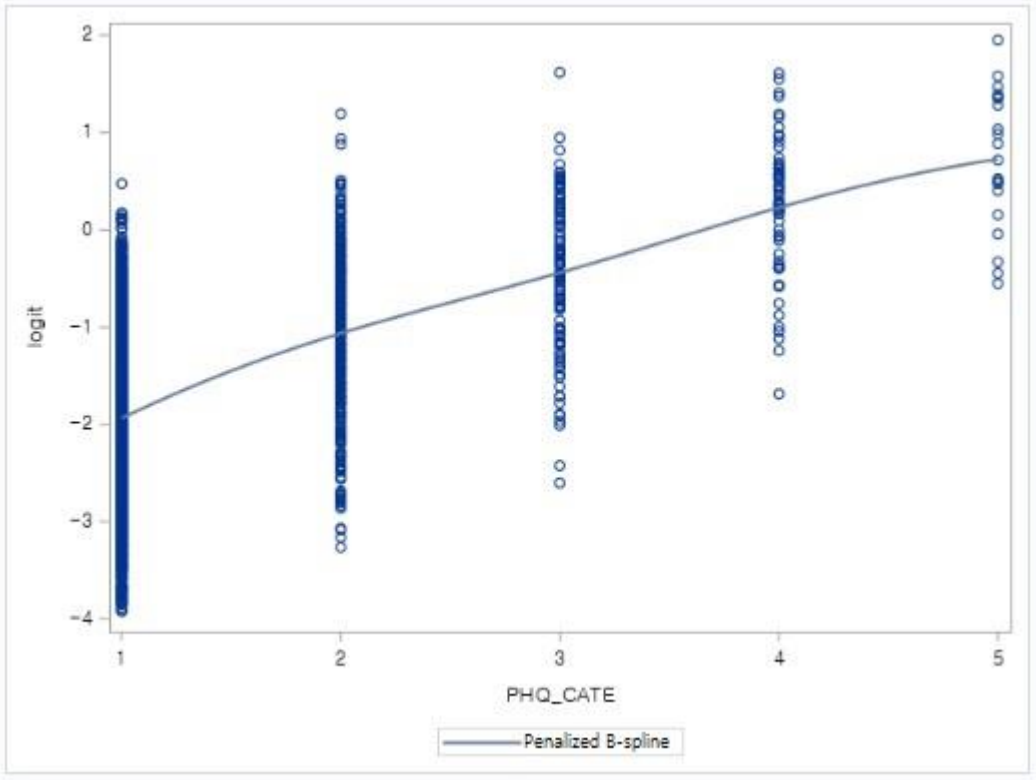
Supplementary Figure 2. Logit function graph of logistic regression according to levels of depressive symptom.

Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).



Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).

Supplementary Table 1. Cochran-Armitage Trend Test

Cochran-Armitage Trend Test	
Statistics (Z)	-903.3422
Single sides Pr < Z	<.0001
Both sides Pr > |Z|	<.0001

Test results for linear relationship between pain and depressive symptoms can be found to be significant by the Cochrane-Armitage Trend Test in Model 1. Pr, Probability.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (p.1-2)	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (p.1-2)	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	(p. 4-5)
Objectives	3	State specific objectives, including any prespecified hypotheses (p. 5, lines 122-126)	
Methods			
Study design	4	Present key elements of study design early in the paper (p. 5, lines 128-139)	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (p. 5, lines 128-139))	
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants (p. 5, lines 128-139))	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (p. 5-6)	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (NA)	
Bias	9	Describe any efforts to address potential sources of bias (NA)	
Study size	10	Explain how the study size was arrived at (p. 5, lines 128-139)	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (NA)	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	(p.6, lines 180-185; p.7, lines 186-195)
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed (NA)	
		(*d*) If applicable, describe analytical methods taking account of sampling strategy (NA)	
		(*e*) Describe any sensitivity analyses (NA)	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (p. 7, lines 201-210)	
		(b) Give reasons for non-participation at each stage (fig 1)	
		(c) Consider use of a flow diagram (fig 1)	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (p. 7, lines 202-221)	
		(b) Indicate number of participants with missing data for each variable of interest (NA)	
Outcome data	15*	Report numbers of outcome events or summary measures (p. 7, lines 202-221)	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (p.8, lines 223-253)	
		(*b*) Report category boundaries when continuous variables were categorized (NA)	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period (NA)	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses (p.8, lines 247-253)	

Discussion		
Key results	18	Summarise key results with reference to study objectives (p.9, lines 256-260)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (p.10, lines 308-318)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (p.9, lines 261-287; p.10, lines 288-306)
Generalisability	21	Discuss the generalisability (external validity) of the study results (11, lines 320-324)
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (p. 11, lines 337-338)

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.