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# BMJ Open

## 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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Complete List of Authors:	HAN, SUBIN; Jaseng Hospital of Korean Medicine Lee, Sook-Hyun; Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation Ha, In-Hyuk; Jaseng Medical Foundation, Jaseng Spine and Joint Research Institute Kim, Eun-jung; Dongguk University, Dept. of Acupuncture & Moxibustion, College of Oriental Medicin
Keywords:	knee pain, depressive symptom, PHQ-9, KNHANES VI-2, Korea National Health and Nutrition Examination Survey

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5 2 **pain in Korean adults aged 50+; a cross-sectional study using nationally**  
6 3 **representative data**  
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12 5 Su-Bin Han([suebin100@jaseng.co.kr](mailto:suebin100@jaseng.co.kr))<sup>1</sup>, Sook-Hyun Lee([sh00god@jaseng.org](mailto:sh00god@jaseng.org))<sup>2</sup>, In-Hyuk  
13 6 Ha([hanihata@gmail.com](mailto:hanihata@gmail.com))<sup>2</sup>, Eun-Jung Kim ([hanijjung@naver.com](mailto:hanijjung@naver.com))<sup>3\*</sup>  
14  
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16 7  
17  
18 8 <sup>1</sup> Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea  
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20 9 <sup>2</sup> Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, Seoul, Republic of  
21 10 Korea  
22

23 11 <sup>3</sup> Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental  
24 12 Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea  
25  
26

27 13  
28  
29 14 **\*Correspondence should be addressed to:**  
30

31 15 Eun-Jung Kim  
32

33 16 Department of Acupuncture & Moxibustion,  
34

35 17 Dongguk University Bundang Oriental Hospital,  
36

37 18 Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea.  
38

39 19 Phone: +82-31-710-3751  
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41 20 Fax: +82-31-710-3780  
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43 21 E-mail: [hanijjung@naver.com](mailto:hanijjung@naver.com)  
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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*

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4 63  
56 64 **Strengths and limitations of this study**

- 8 65 ● This study is based on highly reliable data from the national survey using the Korean  
9 66 population-based questionnaire.
- 10 67 ● This study found a strong association between the severity of depressive symptoms  
11 68 and the presence and intensity of knee pain.
- 12 69 ● This is the first study to describe the correlation between the severity of depressive  
13 70 symptoms and the intensity of knee pain, defined according to NRS scores.
- 14 71 ● This study is a cross-sectional study. Therefore, it assessed depression and chronic  
15 72 knee pain using odds ratio without the analysis on the cause-effect relationship  
16 73 between the variables.
- 17 74 ● Self- report questionnaires were used to assess NRS and PHQ-9 for knee pain and  
18 75 depression, respectively. Therefore, response biases cannot be ruled out.  
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## 79 Introduction

80 Depression is one of the most common mental illnesses. An earlier systematic review and  
81 meta-analysis reported that a lifetime prevalence of psychotic depression range from 0.35%  
82 to 1% and that rates of psychotic depression increase with age [1]. According to a Chinese  
83 systematic review, a lifetime prevalence of major depressive disorder (MDD) varies between  
84 1.1 and 3.3% [2]. However, the prevalence of major depressive symptom (MDE), which  
85 indicates the relatively mild symptoms of depression, is markedly higher. A cohort study  
86 using a sample of 29,621 people representing the general U.S. population found 8% of 3-year  
87 prevalence rate for MDE [3]. In addition, a Canadian longitudinal study reported that the  
88 prevalence of depressive episode at baseline was 7.5% [4]. Based on World Mental Health  
89 Survey data, a cross-sectional study identified diabetes, arthritis, asthma, chronic pulmonary  
90 disease, angina symptoms, and stroke, advanced age, women, underweight and lower levels  
91 of income and education as risk factors in relation to depression [5].

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

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

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

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## 114 Methods

### 115 *Study population*

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

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4 117 which was first launched in 1998 and conducted every year with population-based random  
5 118 samples using standardized questionnaires. This survey is intended to identify socio-  
6 119 demographic characteristics and health and nutritional status of the general Korean  
7 120 population and households, and survey responses are not tracked when the survey is  
8 121 completed each year. KHANES VI-2 used the Patient Health Questionnaire-9 (PHQ-9) as a  
9 122 screening instrument to diagnose depressive disorder. This questionnaire was administered to  
10 123 7,550 respondents. Of those administered questionnaires, 2,658 questionnaires completed by  
11 124 Korean adults aged 50+ were analyzed with respect to relationship between depressive  
12 125 symptom and knee pain (Figure 1).  
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### 19 127 *Definition of depressive symptom and chronic knee pain*

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21 128 Total score of 10 or higher on the PHQ-9 was used to define the presence of depressive  
22 129 symptom [14]. In previous studies, the PHQ-9 questionnaire was often used to monitor  
23 130 depressive symptoms in patients with chronic pain [15, 16, 17]. The PHQ-9 items are based  
24 131 on the 4th edition of diagnostic and statistical manual of mental disorders (DSM-IV) and  
25 132 designed to ask symptoms that relate to depression over the last two weeks. Each item is  
26 133 scored from 0 (not at all) to 3 (nearly every day)[18, 19]. The PHQ-9, consisting of nine  
27 134 questions, is a reliable and valid depression scale. As a severe measure, its score ranges from  
28 135 0 to 27 with higher scores indicating higher severity of depression [18, 19].  
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33 136 In previous studies, PHQ-9 score  $\geq 10$  was used to determine the presence of depressive  
34 137 symptom, and the reliability of this questionnaire has been proven. In this study, PHQ-9 score  
35 138  $\geq 10$  was also used as an indication of the presence of depressive symptoms. The severity of  
36 139 depression was divided into 'not depressed' (0-4 scores), 'mild' (5-9 scores), 'moderate' (10-  
37 140 14), 'moderately severe' (15-19) and 'severe' (20-27), according to previous studies [18, 19,  
38 141 20].  
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41 142 The questionnaire used to identify the presence of knee pain in the respondents aged 50+  
42 143 included the question "Have you had knee pain at least 30 days during the last three months?  
43 144 Those who answered "yes" to this question were classified as the knee pain group, and their  
44 145 knee pain intensity was assessed using the NRS.  
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### 49 147 *Description of Demographic and Characteristics of the study population*

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51 148 Patient information including demographic characteristics, socioeconomic background,  
52 149 medical history, and life habits was analyzed. BMI was calculated by dividing body weight in  
53 150 kilograms by the square of height in meters and categorized into three groups: underweight  
54 151 ( $<18.5\text{kg/m}^2$ ), normal weight ( $18.5\text{-}24.9\text{kg/m}^2$ ) and overweight ( $\geq 25.0\text{kg/m}^2$ ). Smoking  
55 152 status was classified into nonsmoker, ex-smoker and current smoker. The frequency of  
56 153 alcohol consumption was grouped into 'none', 'once a month or less', '2 drinks/month to 3  
57 154 drinks/week' and 'more than four times a month'. Occupation was classified into four groups:  
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4 155 'unemployed (student, housewife, etc.)', 'office work/sales and services', 'agriculture,  
5 156 forestry and fishery' and 'machine fitting and simple labor'. Household income was  
6 157 classified into quartiles: low, low-moderate and moderate-high/high. Education level was also  
7 158 grouped into three groups:  $\leq 6$  years, 7-9 years and  $\geq 10$  years. Physical activity was grouped  
8 159 into three groups: moderate activity at least 2 and half hours a week, vigorous activity at least  
9 160 1 hour and 15 minutes a week and combination of moderate and vigorous activity for longer  
10 161 hours (1-minute vigorous activity was considered equal to 2-minute moderate activity). This  
11 162 study also investigated the presence of comorbidities such as hypertension, dyslipidemia,  
12 163 stroke, myocardial infarction, angina, arthritis, asthma and diabetes mellitus.

### 164 165 *Statistical Analysis*

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

### 179 180 *Patient and Public Involvement*

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

## 182 183 **Results**

### 184 *Characteristics of the study population according to chronic knee pain*

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



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4 191 females and unemployment, lower household income, lower levels of education and physical  
5 192 activity, more comorbidities (hypertension, dyslipidemia, stroke, arthritis, asthma) and  
6 193 shorter sleep duration (Table 1).  
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11 195 *Clinical Characteristics of Participants With chronic depression According to the Presence*  
12 *of Depression*  
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15 197 When compared with non-depressed patients with chronic knee pain, depressed patients  
16 198 with chronic knee pain had lower household income, lower levels of education and aerobic  
17 199 physical activity and shorter sleep duration. However, no difference between the two groups  
18 200 was found with respect to age, sex, BMI, obesity, alcohol consumption and occupation. In  
19 201 case of smoking status, the percentage of non-smokers was high in the group with co-existing  
20 202 depression and chronic knee pain (Table 2).  
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24 204 *Associations between Depression and chronic knee pain*

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26 205 Multiple logistic regression models were used to analyze the effects of depression on  
27 206 chronic knee pain. Univariate analyses revealed a strong association between depressive  
28 207 symptoms and chronic knee pain (Model 1, OR=3.553, P<0.0001). After adjusting for sex  
29 208 and age, a clear association between depression and knee pain was present (Model 2,  
30 209 OR=2.722, P<0.0001). After adjusting for sex, age, smoking status, alcohol use, education  
31 210 level, household income, physical activity, sleep duration and comorbidities, there was still a  
32 211 clear association between depression and knee pain (Model3, OR=2.333, P<0.0001). The  
33 212 odds ratio of depression levels also indicated an association between the severity of  
34 213 depressive symptoms and knee pain. When compared to the absence of depressive symptoms,  
35 214 the probability of having knee pain increased with depression severity: mild (OR=3.715),  
36 215 moderate (OR=4.525), moderately severe (OR=4.124) and severe depression (Model 1,  
37 216 OR=6.93, P for trend <0.0001). In the fully adjusted logistic regression model (Model 3), the  
38 217 association between severe depression and chronic knee pain was strongly significant. When  
39 218 compared to the absence of depressive symptoms, the probability of having knee pain  
40 219 increased with depression severity showing mild depression (OR=2.944) and severe  
41 220 depression (OR=4.552, Model 3, 95% CI 1.489-13.92, P for trend <0.0001, Table 3).  
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50 222 *Association between depression state and knee pain intensity*

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53 223 The comparison between severity of depression and intensity of knee pain, measured by  
54 224 NRS, showed a positive linear association. When the knee pain NRS score ranged from 0 to  
55 225 4, the prevalence of moderate depression was 3.4%, and the prevalence of severe depression  
56 226 was 0.6%. In the presence of severe knee pain (NRS=8-10), the prevalence of moderate and  
57 227 severe depression was high (10.1% and 5.6%, respectively) (Table 4, P<0.001, Fig 2).  
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228

**229 Discussion**

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

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239 The strong linear correlation between depression and chronic knee pain was still present  
240 after adjusting for variables such as socioeconomic indicators and comorbidity (adjusted OR:  
241 2.333, 95%CI: 1.605–3.391,  $P<.0001$ ). In the PHQ-9 survey, a significantly strong  
242 association was observed in the severely depressed group, identified with PHQ-9 score of 20  
243 or above (OR: 6.93, 95% CI: 2.519-19.068,  $P= 0.0002$ ). Such a highly significant association  
244 persisted even after adjusting for variables such as sex, age, socioeconomic indicators,  
245 smoking status and alcohol use ( 4.552, 95% CI: 1.489-13.92,  $P= 0.0082$ ) (Table 3).

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247 A positive linear relationship existed between knee pain and depressive symptoms. In the  
248 subjects with no knee pain or light pain (NRS=0-4), the prevalence of severe depression was  
249 0.6. However, it increased to 5.8% in the subjects with more intense knee pain (NRS=8-10)  
250 ( $P<0.001$ , Table 4).

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252 Significant differences between the groups with and without knee pain were found with  
253 respect to socio-demographic factors other than BMI, obesity and certain comorbidities. In  
254 particular, the rate of knee pain was linearly correlated with non-smoking and inversely  
255 correlated with alcohol consumption (Table 1). This result is attributable to a high percentage  
256 (77.8%) of women in the study population with knee pain.

257 In terms of correlation between depression and knee pain, the non-depressed group with knee  
258 pain and the depressed group with knee pain showed somewhat contrasting results. No  
259 differences were found between these two groups in age, sex, BMI, obesity, alcohol use and  
260 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  $\leq 6$  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**

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4 294 This study identified a strong association between the presence and severity of depressive  
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6 295 symptoms and the presence and intensity of knee pain. Furthermore, the association became  
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8 296 stronger with higher levels of depression, showing greater NRS score for chronic knee pain.  
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10 297 This study suggests depression as an independent risk factor that is important when screening  
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12 298 for chronic knee pain.

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16 302

### 17 303 **Author Contributions**

18 304 Conceptualization: Su-Bin Han, Sook-Hyun Lee

19 305 Data curation: Sook-Hyun Lee, In-Hyuk Ha, Eun-Jung Kim

20 306 Formal analysis: Sook-Hyun Lee, In-Hyuk Ha

21 307 Writing-original draft: Su-Bin Han

22 308 Writing-review & editing: In-Hyuk Ha, Eun-Jung Kim

23 309

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26 312 or not-for-profit sectors

27 313

### 28 314 **Competing interests**

29 315 None declared.

30 316

### 31 317 **Ethics approval**

32 318 The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board  
33 319 (approval no. 2013–12EXP-03–5C). Informed consent was obtained from all participants  
34 320 when the surveys were conducted. Approval of IRB was not required because the study did  
35 321 not deal with any sensitive information, but rather accessed only publicly available data from  
36 322 the KNHANES (JASENG IRB File No. 2018-11-017).

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### 38 324 **Data sharing statement**

39 325 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/m <sup>2</sup> (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

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

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416 **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/m <sup>2</sup> , (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

417 Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without knee  
418 pain. Missing values/nonresponses were excluded from analysis. BMI; Body mass index, PHQ; Patient Health  
419 Questionnaire. Individuals with over 10 score of PHQ-9 was regarded to have depressive symptom. Levels of  
420 depression was divided into 5 quartiles; none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19),  
421 and severe (20–27) according to PHQ-9 score.  
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423 **Table 3. Association between severity of depressive symptom and chronic knee pain**

	<b>Model 1</b>		<b>Model 2</b>		<b>Model 3</b>	
	<b>OR(95% CL)</b>	<b>P-Value</b>	<b>OR(95% CL)</b>	<b>P-Value</b>	<b>OR(95% CL)</b>	<b>P-Value</b>
<b>Diagnosis of depressive symptom</b>						
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
<b>Levels of depressive symptom</b>						
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

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

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

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

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

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4 435 **Figure Legends**  
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6 436 **Figure 1. Flow chart diagram of inclusion and exclusion of participants**  
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8 437 Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National  
9 438 Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health  
10 439 Questionnaire.  
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15 441 **Figure 2. Severity of depressive symptom according to knee pain NRS**  
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17 442 Severity of depressive symptom according to knee pain NRS. Individuals without knee pain  
18 443 were regarded as NRS 0. Severity of depressive symptom according to PHQ-9 score; none  
19 444 (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), severe (20-27). Individuals  
20 445 without knee pain were regarded as NRS 0.  
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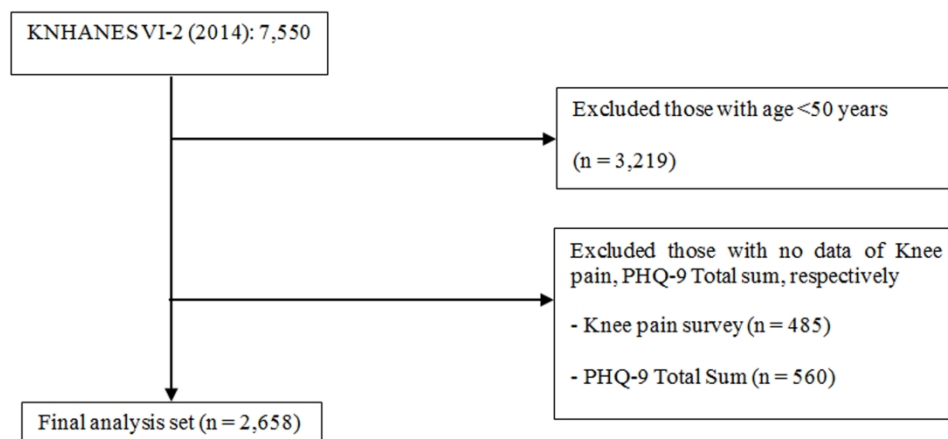
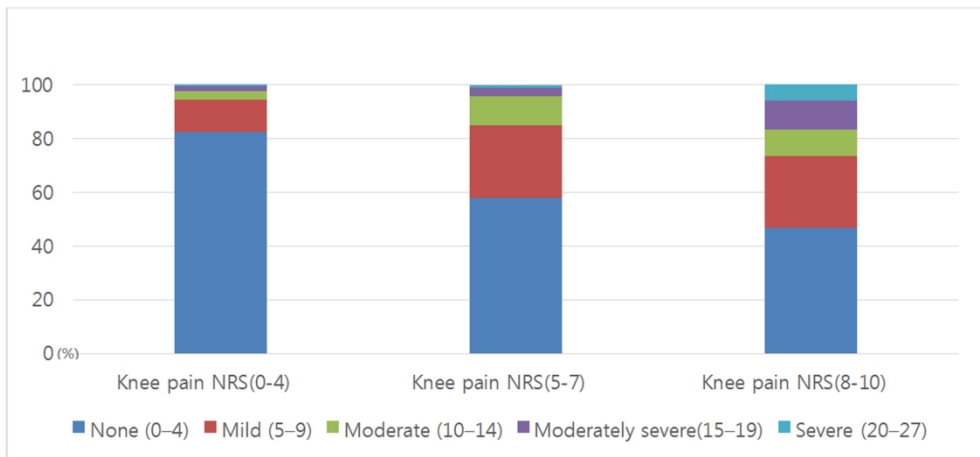


Figure 1. Flow chart diagram of inclusion and exclusion of participants  
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

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# 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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4 1 **Association between severity of depressive symptoms and chronic knee**  
5 2 **pain in Korean adults aged over 50 years: a cross-sectional study using**  
6 3 **nationally representative data**  
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12 5 Su-Bin Han (suebin100@jaseng.co.kr)<sup>1</sup>, Sook-Hyun Lee (sh00god@jaseng.org)<sup>2</sup>, In-Hyuk  
13 6 Ha (hanihata@gmail.com)<sup>2</sup>, Eun-Jung Kim (hanijjung@naver.com)<sup>3\*</sup>  
14  
15  
16 7

17 8 <sup>1</sup> Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea

18  
19 9 <sup>2</sup> Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, Seoul, Republic of  
20 10 Korea  
21  
22

23 11 <sup>3</sup> Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental  
24 12 Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea  
25  
26  
27 13

28  
29 14 **\*Correspondence should be addressed to:**

30  
31 15 Eun-Jung Kim

32  
33 16 Department of Acupuncture & Moxibustion,

34  
35 17 Dongguk University Bundang Oriental Hospital,

36  
37 18 Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea.  
38

39 19 Phone: +82-31-710-3751

40 20 Fax: +82-31-710-3780

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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

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**Strengths and limitations of this study**

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

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## 78 Introduction

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

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

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

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

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4 116 depressive symptoms severity. According to this study, participants with pain showed higher  
5 117 scores of Montgomery-Asberg depressive symptoms rating scales. However, results of these  
6 118 studies are limited to showing the mean of depressive symptoms severity score depending on  
7 119 the presence of pain symptoms.<sup>15</sup> Moreover, a longitudinal analysis revealed that pain  
8 120 severity was a strong predictor of subsequent depressive symptoms severity, and conversely,  
9 121 depressive symptoms severity was a strong predictor of subsequent pain severity.<sup>16</sup>  
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13 122 This study aimed to identify the association between the presence and severity of depressive  
14 123 symptoms and those of chronic knee pain. To our knowledge, our study is the first to explore  
15 124 both aspects of the severity of depressive symptoms and severity of chronic knee pain  
16 125 measured by Patient Health Questionnaire-9 (PHQ-9) and NRS.  
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## 21 127 **Methods**

### 22 128 *Study population*

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25 129 This study was based on the results of the nationally representative survey, the 6th Korea  
26 130 National Health and Nutrition Examination Survey (KHANES VI-2), which was first  
27 131 launched in 1998 and conducted every year with population-based random samples using  
28 132 standardized questionnaires. This survey is intended to identify socio-demographic  
29 133 characteristics and health and nutritional status of the general Korean population and  
30 134 households, and survey responses are not tracked when the survey is completed each year.  
31 135 KHANES VI-2 used the PHQ-9 as a screening instrument to diagnose depressive disorder.  
32 136 This questionnaire was provided to 7,550 respondents. Of those administered questionnaires,  
33 137 2,658 questionnaires completed by Korean adults aged over 50 years were analyzed with  
34 138 respect to the relationship between depressive symptoms and chronic knee pain (Figure  
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### 43 141 *Definition of depressive symptoms and chronic knee pain*

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45 142 A total score of 10 or higher on the PHQ-9 was used to define the presence of depressive  
46 143 symptoms.<sup>17</sup> In previous studies, the PHQ-9 questionnaire was often used to monitor  
47 144 depressive symptoms in patients with chronic pain.<sup>18-20</sup> The PHQ-9 items are based on the 4th  
48 145 edition of the diagnostic and statistical manual of mental disorders (DSM-IV) and designed to  
49 146 ask about symptoms that relate to depression over the last 2 weeks. Each item is scored from  
50 147 0 (not at all) to 3 (nearly every day).<sup>21-22</sup> The PHQ-9, consisting of nine questions, is a  
51 148 reliable and valid depressive symptoms scale. As a severity measure, its score ranges from 0  
52 149 to 27, with higher scores indicating higher severity of depressive symptoms.<sup>21-22</sup>  
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4 150 In previous studies, a PHQ-9 score  $\geq 10$  was used to determine the presence of depressive  
5 151 symptoms, and the reliability of this questionnaire has been proven. In this study, a PHQ-9  
6 152 score  $\geq 10$  was also used to indicate the presence of depressive symptoms. The severity of  
7 153 depressive symptoms was divided into not depressed (0–4 scores), mild (5–9 scores),  
8 154 moderate (10–14), moderately severe (15–19), and severe (20–27), according to previous  
9 155 studies.<sup>21-23</sup>

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13 156 The questionnaire used to identify the presence of chronic knee pain in the respondents aged  
14 157 over 50 years included the question "Have you had knee pain for at least 30 days during the  
15 158 last 3 months? Those who answered "yes" to this question were classified as the chronic knee  
16 159 pain group, and their knee pain intensity was assessed using the NRS. Because the  
17 160 questionnaire regarding chronic knee pain was only asked to respondents aged over 50 years  
18 161 in KHANES VI-2, the analyzed data was limited to a population aged over 50 years.

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### 23 24 163 *Description of demographic and characteristics of the study population*

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26 164 Patient information, including demographic characteristics, socioeconomic background,  
27 165 medical history, and life habits was analyzed. Body mass index (BMI) was calculated by  
28 166 dividing body weight in kilograms by the square of height in meters and categorized into  
29 167 three groups: underweight ( $< 18.5 \text{ kg/m}^2$ ), normal weight ( $18.5\text{--}24.9 \text{ kg/m}^2$ ), and overweight  
30 168 ( $\geq 25.0 \text{ kg/m}^2$ ). Smoking status was classified into nonsmoker, ex-smoker, and current  
31 169 smoker. The frequency of alcohol consumption was grouped into none, once a month or less,  
32 170 2 drinks/month to 3 drinks/week, and more than four times a month. Occupation was  
33 171 classified into four groups: unemployed (student, housewife, etc.); office work/sales and  
34 172 services; agriculture, forestry, and fishery; and machine fitting and simple labor. Household  
35 173 income was classified into quartiles: low, low-moderate, and moderate-high/high. Education  
36 174 level was also categorized into three groups:  $\leq 6$  years, 7–9 years, and  $\geq 10$  years. Physical  
37 175 activity was categorized into three groups: moderate activity at least 2 hours and 30 minutes a  
38 176 week, vigorous activity at least 1 hour and 15 minutes a week, and combination of moderate  
39 177 and vigorous activity for longer hours (1-minute vigorous activity was considered equal to 2-  
40 178 minute moderate activity). This study also investigated the presence of comorbidities, such as  
41 179 hypertension, dyslipidemia, stroke, myocardial infarction, angina, arthritis, asthma, and  
42 180 diabetes mellitus.

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### 50 51 182 *Statistical analysis*

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54 183 The KHANES is a survey of nationwide sample of Koreans selected through stratified  
55 184 clustered sampling, and sampling weights are used for survey data. Accordingly, complex  
56 185 sample survey data were analyzed using parameters for strata, clusters, and weights, which

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4 186 comprise the sample design. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) was used for  
5 187 statistical analysis, and  $P < 0.05$  was used as the threshold for statistical significance.  
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7 188 Continuous variables are presented as mean and standard deviation, and categorical variables  
8 189 are presented as frequency and percentage (%). The Rao-Scott Chi-Square test or t-test was  
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10 190 performed to determine differences between groups with/without chronic knee pain. To  
11 191 assess the effects of depressive symptoms on chronic knee pain, logistic regression analysis  
12 192 with complex sampling design was performed by adjusting for covariates. As a result, odd  
13 193 ratios, as well as 95% confidence intervals for the odds ratios, were generated. Additionally,  
14 194 this study investigated if there was an underlying trend from different levels of depressive  
15 195 symptoms in each model (P for trend). To verify a linear relationship between the intensity of  
16 196 chronic knee pain and depressive symptoms, we used the Cochran-Armitage trend test and  
17 197 complex samples logistic regression.  
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### 23 199 *Patient and public involvement*

25 200 We did not involve patients or the public in our work.  
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## 30 202 **Results**

### 32 203 *Characteristics of the study population according to chronic knee pain*

34 204 This study found that the overall prevalence of chronic knee pain in the Korean population  
35 205 aged over 50 years was 19.8%. Of those, women (77.8%) far outpaced men (22.2%). The  
36 206 presence of depressive symptoms, determined by PHQ-9 score  $\geq 10$ , was significantly higher  
37 207 in the participants with chronic knee pain (17.3%), compared with those without chronic knee  
38 208 pain (5.2%) ( $P < 0.001$ , Table 1). When compared with the participants without chronic knee  
39 209 pain, those with chronic knee pain showed greater frequency of depressive symptoms, higher  
40 210 percentages of older women and unemployment, lower household income, lower levels of  
41 211 education and physical activity, more comorbidities (hypertension, dyslipidemia, stroke,  
42 212 arthritis, asthma), and shorter sleep duration (Table 1).  
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### 49 214 *Clinical characteristics of participants with chronic knee pain according to the presence of 50 215 depressive symptoms*

52 216 When compared with non-depressed patients with chronic knee pain, depressed patients  
53 217 with chronic knee pain had lower household income, lower levels of education and aerobic  
54 218 physical activity, and shorter sleep duration. However, no difference between the two groups  
55 219 was found with respect to age, sex, BMI, obesity, alcohol consumption, and occupation. In  
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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**



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4 256 This study analyzed the association between the severity of depressive symptoms and  
5 257 chronic knee pain by examining a sample of 7,550 Koreans representing the general  
6 258 population from the reliable nationwide survey data. All the participants selected for this  
7 259 study were aged 50 years or older and shared information about their chronic knee pain, for  
8 260 which NRS was used to measure the pain intensity.  
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13 261 The association between depressive symptoms and pain is well established by previous  
14 262 studies.<sup>11, 13</sup> Moreover, a study indicated that persistent depressive symptoms was  
15 263 significantly associated with worsening of osteoarthritis (OA) knee pain.<sup>24</sup> Another previous  
16 264 study also demonstrated that physical pain symptoms were significantly associated with the  
17 265 mean score of depressive symptoms severity.<sup>15</sup> Furthermore, a longitudinal analysis revealed  
18 266 that pain severity was a strong predictor of subsequent depressive symptoms severity, and  
19 267 conversely, depressive symptoms severity was a strong predictor of subsequent pain  
20 268 severity.<sup>16</sup> Further to this, our report is a cross-sectional study which explores the association  
21 269 between severity of depressive symptoms and intensity of chronic knee pain.  
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27 270 In our study, the positive association became stronger in the group with severe depressive  
28 271 symptoms, when compared with that of those having the symptoms of mild to moderate  
29 272 depressive symptoms. The strong linear correlation between depressive symptoms and  
30 273 chronic knee pain was still present after adjusting for variables, such as socioeconomic  
31 274 indicators and comorbidity. In the PHQ-9 survey, a significantly strong association was  
32 275 observed in the severely depressed group, identified with PHQ-9 score of 20 or above. PHQ-  
33 276 9 is a reliable measure of depressive symptoms, and has been used by previous studies to  
34 277 measure severity of depressive symptoms.<sup>17-23</sup> Such a highly significant association persisted  
35 278 even after adjusting for variables, such as sex, age, socioeconomic indicators, smoking status,  
36 279 and alcohol use. Although a previous study using KHANES revealed a relationship between  
37 280 self-reported depressive symptoms and Kellgren-Lawrence knee OA grade, our study is the  
38 281 first to demonstrate the association between depressive symptoms and chronic knee pain  
39 282 using PHQ-9 and NRS in the Korean population.<sup>13</sup>  
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46 283 In our study, a positive linear relationship existed between intensity of chronic knee pain  
47 284 and severity of depressive symptoms in Table 4. We divided severity of depressive symptoms  
48 285 as not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–  
49 286 19) and severe (20–27), and divided severity of chronic knee pain as light (0–4), moderate  
50 287 (5–7), and intense (8–10). In the participants with no chronic knee pain or light pain  
51 288 (NRS=0–4), the prevalence of severe depressive symptoms was 0.6. However, it increased to  
52 289 5.8% in the participants with more intense chronic knee pain (NRS=8–10). To our  
53 290 knowledge, our study is the first to divide and compare both aspects of severity of depressive  
54 291 symptoms and intensity of chronic knee pain. As a result, we found a strong association  
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292 between severity of depressive symptoms and intensity of chronic knee pain. It is a cross-  
293 sectional proof of a previous longitudinal study that suggested severe pain and severe  
294 depressive symptoms can be a predictor of each other.<sup>16</sup>

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

### 308 *Strength and limitations*

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

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

### 320 **Conclusions**

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

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4 323 became stronger with higher levels of depressive symptoms, demonstrating greater NRS  
5 324 scores for chronic knee pain. This study suggests depressive symptoms as an independent risk  
6 325 factor when screening for chronic knee pain.  
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### 23 330 **Author Contributions**

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27 331 Conceptualization: Su-Bin Han, Sook-Hyun Lee  
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30 332 Data curation: Sook-Hyun Lee, In-Hyuk Ha, Eun-Jung Kim  
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33 333 Formal analysis: Sook-Hyun Lee, In-Hyuk Ha  
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37 334 Writing-original draft: Su-Bin Han  
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40 335 Writing-review & editing: In-Hyuk Ha, Eun-Jung Kim  
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4 341 **Competing interests**  
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7 342 None declared.  
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14 344 **Ethics approval**  
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17 345 The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board  
18 346 (approval no. 2013-12EXP-03-5C). Informed consent was obtained from all participants  
19 347 when the surveys were conducted. The approval of IRB was not required because the study  
20 348 did not deal with any sensitive information, but rather accessed only publicly available data  
21 349 from the KNHANES (JASENG IRB File No. 2018-11-017).  
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29 351 **Data sharing statement**  
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33 352 All relevant materials are provided in the manuscript. Survey data are publicly available at  
34 353 (<https://knhanes.cdc.go.kr/knhanes/main.do>). All data from KNHANES VI-2 are coded and  
35 354 freely available.  
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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 <sup>2</sup> (mean±SD)	23.9±3.1	24.3±3.3	0.0533
Obesity, n (%)			
Underweight (≤18.5 kg/m <sup>2</sup> )	55 (2.6)	13 (2.5)	0.2473
Normal (18.5–24.9 kg/m <sup>2</sup> )	1365 (64.1)	300 (57)	
Obese (≥25 kg/m <sup>2</sup> )	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

463 The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without  
 464 chronic knee pain. Missing values/nonresponses were excluded from analysis. BMI, body mass index; PHQ,  
 465 Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive  
 466 symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate  
 467 (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Continuous variables are  
 468 presented as mean and standard deviation, and categorical variables are presented as frequency and percentage  
 469 (%).

470 **Table 2. Characteristics of chronic knee pain population according to presence of depressive**  
 471 **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 <sup>2</sup> , (mean±SD)	24.4±3.3	23.8±3.1	0.1927
Obesity, n (%)			
Underweight (<18.5 kg/m <sup>2</sup> )	9 (2.1)	4 (4.4)	0.1711
Normal (18.5–24.9 kg/m <sup>2</sup> )	246 (56.4)	54 (60)	
Obese (≥25 kg/m <sup>2</sup> )	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

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

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4 475 symptoms. Levels of depressive symptoms were divided into five quartiles: none (0–4), mild (5–9), moderate  
5 476 (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score.  
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478 **Table 3. Association between severity of depressive symptoms and chronic knee pain**

	<b>Model 1</b>		<b>Model 2</b>		<b>Model 3</b>	
	<b>OR (95% CI)</b>	<b>P-value</b>	<b>OR (95% CI)</b>	<b>P-Value</b>	<b>OR (95% CI)</b>	<b>P-value</b>
<b>Diagnosis of depressive symptoms</b>						
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
<b>Levels of depressive symptom</b>						
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

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

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

Chronic knee pain NRS	Depressive symptoms					P-Value
	None (0–4)	Mild (5–9)	Moderate (10–14)	Moderately severe(15–19)	Severe (20–27)	
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)	

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

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4 492 **Figure Legends**

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6 493 **Figure 1. Flow chart diagram of inclusion and exclusion of participants**

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8 494 Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and  
9 495 Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

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13 497 **Figure 2. Severity of depressive symptoms according to chronic knee pain NRS**

14 498 Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were  
15 499 regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0–4), mild (5–9),  
16 500 moderate (10–14), moderately severe (15–19), and severe (20–27). Individuals without knee pain were regarded  
17 501 as NRS 0. NRS, Numerical rating scale.

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21 503 **Supplementary Figure 1. Estimated probability graph of logistic regression according to**  
22 504 **levels of depressive symptom.**

23 505 Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE,  
24 506 PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe  
25 507 (20–27).

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29 509 **Supplementary Figure 2. Logit function graph of logistic regression according to levels**  
30 510 **of depressive symptom.**

31 511 Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-  
32 512 categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–  
33 513 27).

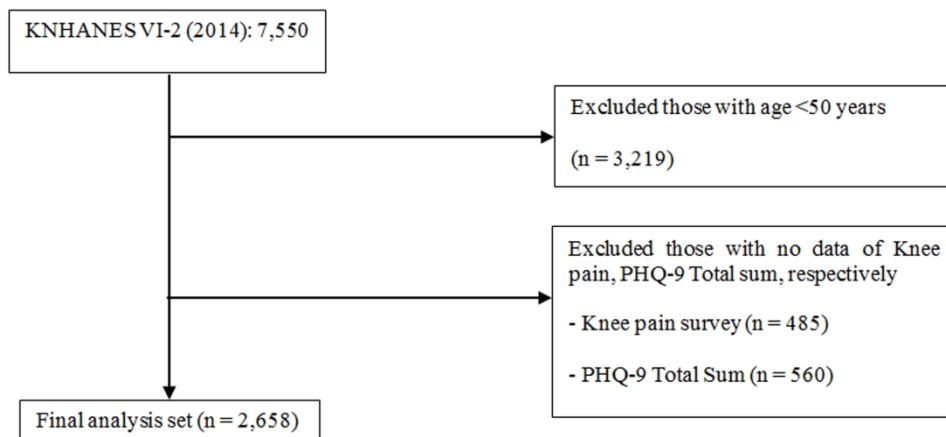


Figure 1. Flow chart diagram of inclusion and exclusion of participants  
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

220x104mm (300 x 300 DPI)



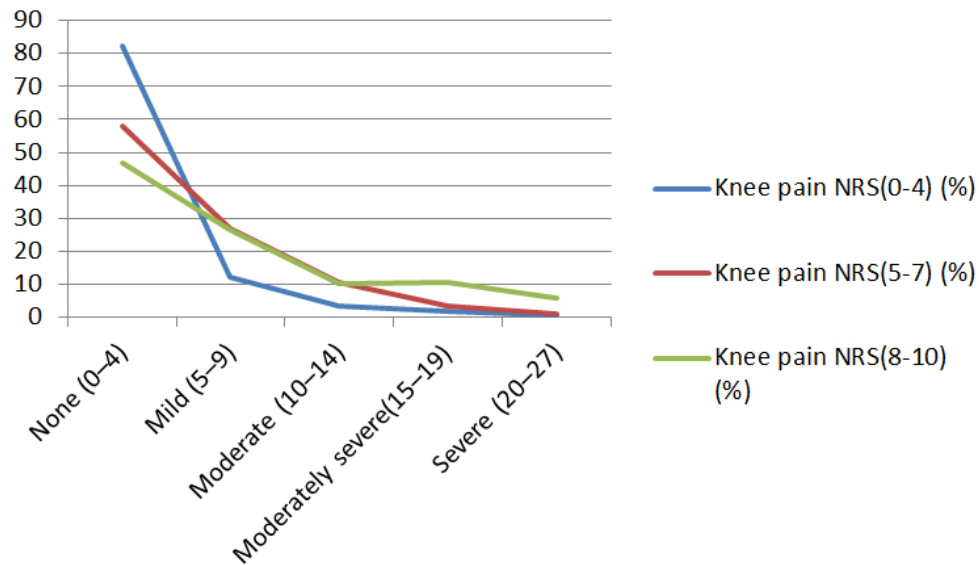
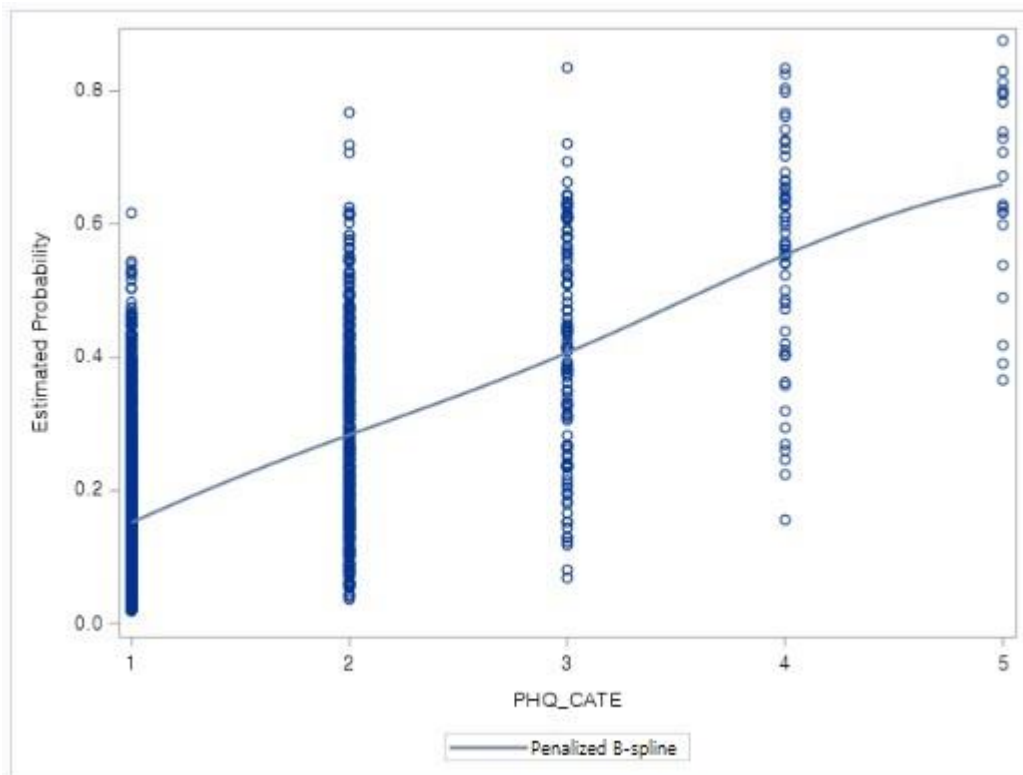


Figure 2. Severity of depressive symptoms according to chronic knee pain NRS

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.

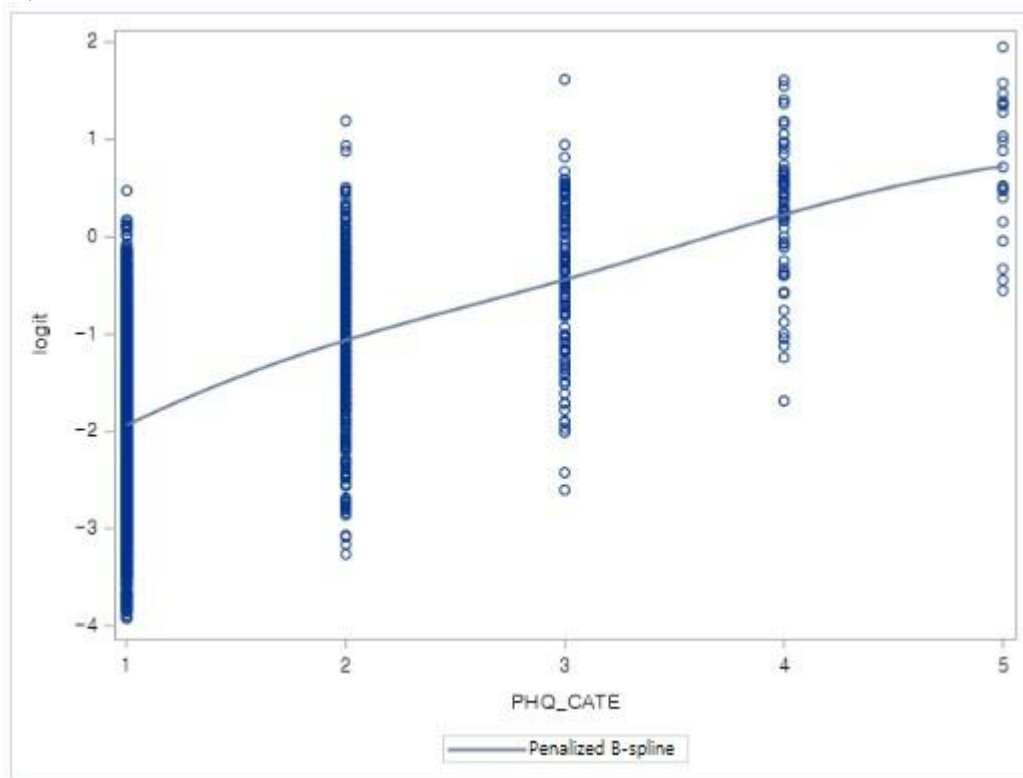
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4 **Supplementary Figure 1. Estimated probability graph of logistic regression according to**  
5 **levels of depressive symptom.**  
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34 Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE,  
35 PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe  
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5 **of depressive symptom.**  
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8 Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-  
9 categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–  
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36 Logit function graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ-  
37 categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–  
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**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 Cochran-Armitage Trend Test in Model 1. Pr, Probability.

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	<b>Item No</b>	<b>Recommendation</b>	
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(p.1-2) (p.1-2)
<b>Introduction</b>			
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)
<b>Methods</b>			
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(p.6, lines 180-185; p.7, lines 186-195)
<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	(p. 7, lines 201-210) (fig 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	(p. 7, lines 201-219) (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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(p.8, lines 221-251) (NA)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	(p.8, lines 241-244)

<b>Discussion</b>		
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)
<b>Other information</b>		
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](http://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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<b>Primary Subject Heading</b>:	Epidemiology
Secondary Subject Heading:	Mental health, Rehabilitation medicine
Keywords:	Epidemiology < THORACIC MEDICINE, Adult psychiatry < PSYCHIATRY, PAIN MANAGEMENT

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Manuscripts

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4 1 **Association between severity of depressive symptoms and chronic knee**  
5 2 **pain in Korean adults aged over 50 years: a cross-sectional study using**  
6 3 **nationally representative data**  
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12 5 Su-Bin Han (suebin100@jaseng.co.kr)<sup>1</sup>, Sook-Hyun Lee (sh00god@jaseng.org)<sup>2</sup>, In-Hyuk  
13 6 Ha (hanihata@gmail.com)<sup>2</sup>, Eun-Jung Kim (hanijjung@naver.com)<sup>3\*</sup>  
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17 8 <sup>1</sup> Jaseng Hospital of Korean Medicine, Seoul, Republic of Korea

18  
19 9 <sup>2</sup> Jaseng Spine and Joint Research Institute, Jaseng Medical Foundation, Seoul, Republic of  
20 10 Korea  
21  
22

23 11 <sup>3</sup> Department of Acupuncture & Moxibustion, Dongguk University Bundang Oriental  
24 12 Hospital, Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea  
25  
26  
27 13

28  
29 14 **\*Correspondence should be addressed to:**

30  
31 15 Eun-Jung Kim

32  
33 16 Department of Acupuncture & Moxibustion,

34  
35 17 Dongguk University Bundang Oriental Hospital,

36  
37 18 Bundang-gu, Seongnam-si, Gyeonggi-do, Seoul, Republic of Korea.  
38

39 19 Phone: +82-31-710-3751

40 20 Fax: +82-31-710-3780

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42 21 E-mail: hanijjung@naver.com  
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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

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**Strengths and limitations of this study**

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

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## 78 Introduction

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

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

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

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

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4 114 However, few studies have been conducted to identify the association between the severity  
5 115 of depressive symptoms and the presence and intensity of knee pain. Recently, one study  
6 116 revealed that participants with physical pain symptoms were significantly associated with  
7 117 depressive symptoms severity. According to this study, participants with pain showed higher  
8 118 scores of Montgomery-Asberg depressive symptoms rating scales. However, results of these  
9 119 studies are limited to showing the mean of depressive symptoms severity score depending on  
10 120 the presence of pain symptoms.<sup>17</sup> Moreover, a longitudinal analysis revealed that pain  
11 121 severity was a strong predictor of subsequent depressive symptoms severity, and conversely,  
12 122 depressive symptoms severity was a strong predictor of subsequent pain severity.<sup>18</sup>

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17 123 In addition to previous studies regarding depressive symptoms and chronic knee pain, this  
18 124 study aimed to identify the association between the presence and severity of depressive  
19 125 symptoms and those of chronic knee pain. To our knowledge, our study is the first to explore  
20 126 both aspects of the severity of depressive symptoms and severity of chronic knee pain  
21 127 measured by Patient Health Questionnaire-9 (PHQ-9) and NRS.  
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## 26 128 27 129 **Methods**

### 28 29 130 *Study population*

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31 131 This study was based on the results of the nationally representative survey, the 6th Korea  
32 132 National Health and Nutrition Examination Survey (KNHANES VI-2), which was first  
33 133 launched in 1998 and conducted every year with population-based random samples using  
34 134 standardized questionnaires. This survey is intended to identify socio-demographic  
35 135 characteristics and health and nutritional status of the general Korean population and  
36 136 households, and survey responses are not tracked when the survey is completed each year.  
37 137 KNHANES VI-2 used the PHQ-9 as a screening instrument to diagnose depressive disorder.  
38 138 This questionnaire was provided to 7,550 respondents. Of those administered questionnaires,  
39 139 2,658 questionnaires completed by Korean adults aged over 50 years were analyzed with  
40 140 respect to the relationship between depressive symptoms and chronic knee pain (Figure 1).  
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### 45 141 46 47 142 *Definition of depressive symptoms and chronic knee pain*

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49 143 A total score of 10 or higher on the PHQ-9 was used to define the presence of depressive  
50 144 symptoms.<sup>19</sup> In previous studies, the PHQ-9 questionnaire was often used to monitor  
51 145 depressive symptoms in patients with chronic pain.<sup>20-21</sup> The PHQ-9 items are based on the 4th  
52 146 edition of the diagnostic and statistical manual of mental disorders (DSM-IV) and designed to  
53 147 ask about symptoms that relate to depression over the last 2 weeks. Each item is scored from  
54 148 0 (not at all) to 3 (nearly every day). The PHQ-9, consisting of nine questions, is a reliable  
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4 149 and valid depressive symptoms scale. As a severity measure, its score ranges from 0 to 27,  
5 150 with higher scores indicating higher severity of depressive symptoms.<sup>22-23</sup>

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8 151 In previous studies, a PHQ-9 score  $\geq 10$  was used to determine the presence of depressive  
9 152 symptoms, and the reliability of this questionnaire has been proven. In this study, a PHQ-9  
10 153 score  $\geq 10$  was also used to indicate the presence of depressive symptoms. The severity of  
11 154 depressive symptoms was divided into not depressed (0–4 scores), mild (5–9 scores),  
12 155 moderate (10–14), moderately severe (15–19), and severe (20–27), according to previous  
13 156 studies.<sup>22-24</sup>

16 157 The questionnaire used to identify the presence of chronic knee pain in the respondents aged  
17 158 over 50 years included the question "Have you had knee pain for at least 30 days during the  
18 159 last 3 months? Those who answered "yes" to this question were classified as the chronic knee  
19 160 pain group, and their knee pain intensity was assessed using the NRS. Because the  
20 161 questionnaire regarding chronic knee pain was only asked to respondents aged over 50 years  
21 162 in KNHANES VI-2, the analyzed data was limited to a population aged over 50 years.

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#### 27 164 *Description of demographic and characteristics of the study population*

29 165 Patient information, including demographic characteristics, socioeconomic background,  
30 166 medical history, and life habits was analyzed. Body mass index (BMI) was calculated by  
31 167 dividing body weight in kilograms by the square of height in meters and categorized into  
32 168 three groups: underweight ( $< 18.5 \text{ kg/m}^2$ ), normal weight ( $18.5\text{--}24.9 \text{ kg/m}^2$ ), and overweight  
33 169 ( $\geq 25.0 \text{ kg/m}^2$ ). Smoking status was classified into nonsmoker, ex-smoker, and current  
34 170 smoker. The frequency of alcohol consumption was grouped into none, once a month or less,  
35 171 2 drinks/month to 3 drinks/week, and more than four times a month. Occupation was  
36 172 classified into four groups: unemployed (student, housewife, etc.); office work/sales and  
37 173 services; agriculture, forestry, and fishery; and machine fitting and simple labor. Household  
38 174 income was classified into quartiles: low, low-moderate, and moderate-high/high. Education  
39 175 level was also categorized into three groups:  $\leq 6$  years, 7–9 years, and  $\geq 10$  years. Physical  
40 176 activity was categorized into three groups: moderate activity at least 2 hours and 30 minutes a  
41 177 week, vigorous activity at least 1 hour and 15 minutes a week, and combination of moderate  
42 178 and vigorous activity for longer hours (1-minute vigorous activity was considered equal to 2-  
43 179 minute moderate activity). This study also investigated the presence of comorbidities, such as  
44 180 hypertension, dyslipidemia, stroke, myocardial infarction, angina, arthritis, asthma, and  
45 181 diabetes mellitus.

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#### 55 183 *Statistical analysis*

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4 184 The KNHANES is a survey of nationwide sample of Koreans selected through stratified  
5 185 clustered sampling, and sampling weights are used for survey data. Accordingly, complex  
6 186 sample survey data were analyzed using parameters for strata, clusters, and weights, which  
7 187 comprise the sample design. SAS V9.4 (SAS Institute Inc., Cary, NC, USA) was used for  
8 188 statistical analysis, and  $P < 0.05$  was used as the threshold for statistical significance.  
9 189 Continuous variables are presented as mean and standard deviation, and categorical variables  
10 190 are presented as frequency and percentage (%). The Rao-Scott Chi-Square test or t-test was  
11 191 performed to determine differences between groups with/without chronic knee pain. To  
12 192 assess the effects of depressive symptoms on chronic knee pain, logistic regression analysis  
13 193 with complex sampling design was performed by adjusting for covariates. As a result, odd  
14 194 ratios, as well as 95% confidence intervals for the odds ratios, were generated. Additionally,  
15 195 this study investigated if there was an underlying trend from different levels of depressive  
16 196 symptoms in each model (P for trend). To verify a linear relationship between the intensity of  
17 197 chronic knee pain and depressive symptoms, we used the Cochran-Armitage trend test and  
18 198 complex samples logistic regression.

199

#### 200 *Patient and public involvement*

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

202

## 203 **Results**

### 204 *Characteristics of the study population according to chronic knee pain*

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

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### 215 *Clinical characteristics of participants with chronic knee pain according to the presence of 216 depressive symptoms*

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4 217 When compared with non-depressed patients with chronic knee pain, depressed patients  
5 218 with chronic knee pain had lower household income, lower levels of education and aerobic  
6 219 physical activity, and shorter sleep duration. However, no difference between the two groups  
7 220 was found with respect to age, sex, BMI, obesity, alcohol consumption, and occupation. In  
8 221 case of smoking status, the percentage of non-smokers was high in the group with co-existing  
9 222 depressive symptoms and chronic knee pain (Table 2).

#### 13 223 14 224 *Associations between depressive symptoms and chronic knee pain*

16 225 Multiple logistic regression models were used to analyze the effects of depressive symptoms  
17 226 on chronic knee pain. Univariate analyses revealed a strong association between depressive  
18 227 symptoms and chronic knee pain (Model 1, OR=3.553, 95% CI 2.558–4.935, P<0.0001).  
19 228 After adjusting for sex and age, a clear association between depressive symptoms and chronic  
20 229 knee pain was present (Model 2, OR=2.722, 95% CI 1.844–4.017, P<0.0001). After adjusting  
21 230 for sex, age, smoking status, alcohol use, education level, household income, physical  
22 231 activity, sleep duration and comorbidities, there was still a clear association between  
23 232 depressive symptoms and chronic knee pain (Model 3, OR=2.333, 95% CI 1.605–3.391,  
24 233 P<0.0001). The odds ratio of depressive symptom levels also indicated an association  
25 234 between the severity of depressive symptoms and chronic knee pain. When compared to the  
26 235 absence of depressive symptoms, the probability of having chronic knee pain increased with  
27 236 the severity of depressive symptoms: mild (OR=3.715, 95% CI 2.687–5.138, P<0.0001),  
28 237 moderate (OR=4.525, 95% CI 2.964–6.909, P<0.0001), moderately severe (OR=4.124, 95%  
29 238 CI 2.256–7.539, P=0.0002), and severe depressive symptoms (Model 1, OR=6.93, 95% CI  
30 239 2.519–19.068, P for trend<0.0001). In the fully adjusted logistic regression model (Model 3),  
31 240 the association between severe depressive symptom and chronic knee pain was strongly  
32 241 significant. When compared to the absence of depressive symptoms, the probability of having  
33 242 chronic knee pain increased with depressive symptoms severity showing mild depressive  
34 243 symptoms (OR=2.944, 95% CI 2.112–4.103, P<0.0001) and severe depressive symptoms  
35 244 (OR=4.552, Model 3, 95% CI 1.489–13.92, P for trend <0.0001, Table 3). Driven by the  
36 245 Cochran-Armitage trend test and complex samples logistic regression, a linear relationship  
37 246 was found between chronic knee pain and depressive symptoms (Supplementary Table 1,  
38 247 Supplementary fig.1 and Supplementary fig. 2).

#### 47 248 *Association between depressive symptoms state and chronic knee pain intensity*

49 249 The comparison between severity of depressive symptoms and intensity of chronic knee  
50 250 pain, measured by NRS, showed a positive linear association. When the chronic knee pain  
51 251 NRS score ranged from 0 to 4, the prevalence of moderate depressive symptom was 3.4%,  
52 252 and the prevalence of severe depressive symptoms was 0.6%. In the presence of severe  
53 253 chronic knee pain (NRS=8–10), the prevalence of moderate and severe depressive symptoms  
54 254 was high (10.1% and 5.6%, respectively) (Table 4, P<0.001, Fig 2).

255

256 **Discussion**

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

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

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

283 In our study, a positive linear relationship existed between intensity of chronic knee pain  
284 and severity of depressive symptoms in Table 4. We divided severity of depressive symptoms  
285 as not depressed (0–4 scores), mild (5–9 scores), moderate (10–14), moderately severe (15–  
286 19) and severe (20–27), and divided severity of chronic knee pain as light (0–4), moderate  
287 (5–7), and intense (8–10). In the participants with no chronic knee pain or light pain  
288 (NRS=0–4), the prevalence of severe depressive symptoms was 0.6. However, it increased to



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4 289 5.8% in the participants with more intense chronic knee pain (NRS=8–10). To our  
5 290 knowledge, our study is the first to divide and compare both aspects of severity of depressive  
6 291 symptoms and intensity of chronic knee pain. As a result, we found a strong association  
7 292 between severity of depressive symptoms and intensity of chronic knee pain. It is a cross-  
8 293 sectional proof of a previous longitudinal study that suggested severe pain and severe  
9 294 depressive symptoms can be a predictor of each other.<sup>18</sup>

14 295 Although there is no clear evidence that depressive symptoms can cause chronic knee pain,  
15 296 many potential hypotheses have been suggested. Depressive symptom can interfere with the  
16 297 mechanism of inflammatory cytokines and the regulation of autonomic nervous system.  
18 298 Moreover, It can also destabilize the hypothalamic-pituitary-adrenal axis.<sup>26-28</sup> Depressive  
19 299 symptom-induced pathological conditions act as the catalyst for chronic pain syndrome.<sup>29-30</sup>  
20 300 Furthermore, neurotransmitters of noradrenalin and serotonin are associated with the  
21 301 pathological mechanism of depressive symptom. These neurotransmitters also play an  
22 302 important role in pain inhibitory pathways.<sup>31-33</sup> The association between depressive symptoms  
23 303 and chronic knee pain can also be explained by reduced physical activity, which may be  
24 304 associated with depressive symptoms, consequently decreasing muscle strength and joint  
25 305 stability, whereby negative outcomes, such as osteoarthritis, can be induced.<sup>34-35</sup> Taken  
26 306 together, these findings suggest the effects of depressive symptoms on the pathogenic  
27 307 mechanism of chronic pain.

### 34 308 *Strength and limitations*

37 309 This study has the following strengths. First, this study was based on highly reliable data  
38 310 from the national survey using the Korean population-based questionnaire. Second, to our  
39 311 knowledge, this is the first study to describe the correlation between the severity of  
40 312 depressive symptoms and the intensity of chronic knee pain.

45 313 However, this study had certain limitations. First, this study was a cross-sectional study.  
46 314 Therefore, it assessed depressive symptoms and chronic knee pain using odds ratios without  
47 315 the analysis of the cause-effect relationship between the variables. Second, because the  
48 316 questionnaire regarding chronic knee pain was only asked to a population aged over 50 years,  
49 317 the younger population with chronic knee pain was excluded in the analysis. Third, self-  
50 318 reporting questionnaires were used to assess the NRS and PHQ-9 scores for chronic knee  
51 319 pain and depressive symptoms, respectively. Therefore, response biases cannot be ruled out.

### 56 320 **Conclusions**

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4 321 This study identified a strong association between the presence and severity of depressive  
5 322 symptoms and the presence and intensity of chronic knee pain. Furthermore, the association  
6 323 became stronger with higher levels of depressive symptoms, demonstrating greater NRS  
7 324 scores for chronic knee pain. This study suggests depressive symptoms as an independent risk  
8 325 factor when screening for chronic knee pain.  
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## 26 330 **Author Contributions**

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29 331 Conceptualization: Su-Bin Han, Sook-Hyun Lee  
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32 332 Data curation: Sook-Hyun Lee, In-Hyuk Ha, Eun-Jung Kim  
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35 333 Formal analysis: Sook-Hyun Lee, In-Hyuk Ha  
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38 334 Writing-original draft: Su-Bin Han  
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41 335 Writing-review & editing: In-Hyuk Ha, Eun-Jung Kim  
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7 341 **Competing interests**8  
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10 342 None declared.11  
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17 344 **Ethics approval**18  
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21 345 The VI-2 version of KNHANES was approved by the KCDC Institutional Review Board  
22 346 (approval no. 2013-12EXP-03-5C). Informed consent was obtained from all participants  
23 347 when the surveys were conducted. The approval of IRB was not required because the study  
24 348 did not deal with any sensitive information, but rather accessed only publicly available data  
25 349 from the KNHANES (JASENG IRB File No. 2018-11-017).26  
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32 351 **Data sharing statement**33  
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36 352 All relevant materials are provided in the manuscript. Survey data are publicly available at  
37 353 (<https://knhanes.cdc.go.kr/knhanes/main.do>). All data from KNHANES VI-2 are coded and  
38 354 freely available.39  
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480 **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 <sup>2</sup> (mean±SD)	23.9±3.1	24.3±3.3	0.0533
Obesity, n (%)			
Underweight (≤18.5 kg/m <sup>2</sup> )	55 (2.6)	13 (2.5)	0.2473
Normal (18.5–24.9 kg/m <sup>2</sup> )	1365 (64.1)	300 (57)	
Obese (≥25 kg/m <sup>2</sup> )	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

481 The Rao-Scott Chi-Square test or t-test was performed to determine differences between groups with/without  
 482 chronic knee pain. Missing values/nonresponses were excluded from analysis. BMI, body mass index; PHQ,  
 483 Patient Health Questionnaire. Individuals with PHQ-9 scores >10 were considered to have depressive  
 484 symptoms. Levels of depressive symptom were divided into five quartiles: none (0–4), mild (5–9), moderate  
 485 (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score. Continuous variables are  
 486 presented as mean and standard deviation, and categorical variables are presented as frequency and percentage  
 487 (%).



488 **Table 2. Characteristics of chronic knee pain population according to presence of depressive**  
 489 **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 <sup>2</sup> , (mean±SD)	24.4±3.3	23.8±3.1	0.1927
Obesity, n (%)			
Underweight (<18.5 kg/m <sup>2</sup> )	9 (2.1)	4 (4.4)	0.1711
Normal (18.5–24.9 kg/m <sup>2</sup> )	246 (56.4)	54 (60)	
Obese (≥25 kg/m <sup>2</sup> )	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

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

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493 symptoms. Levels of depressive symptoms were divided into five quartiles: none (0–4), mild (5–9), moderate  
494 (10–14), moderately severe (15–19), and severe (20–27) according to the PHQ-9 score.  
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496 **Table 3. Association between severity of depressive symptoms and chronic knee pain**

	<b>Model 1</b>		<b>Model 2</b>		<b>Model 3</b>	
	<b>OR (95% CI)</b>	<b>P-value</b>	<b>OR (95% CI)</b>	<b>P-Value</b>	<b>OR (95% CI)</b>	<b>P-value</b>
<b>Diagnosis of depressive symptoms</b>						
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
<b>Levels of depressive symptom</b>						
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

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

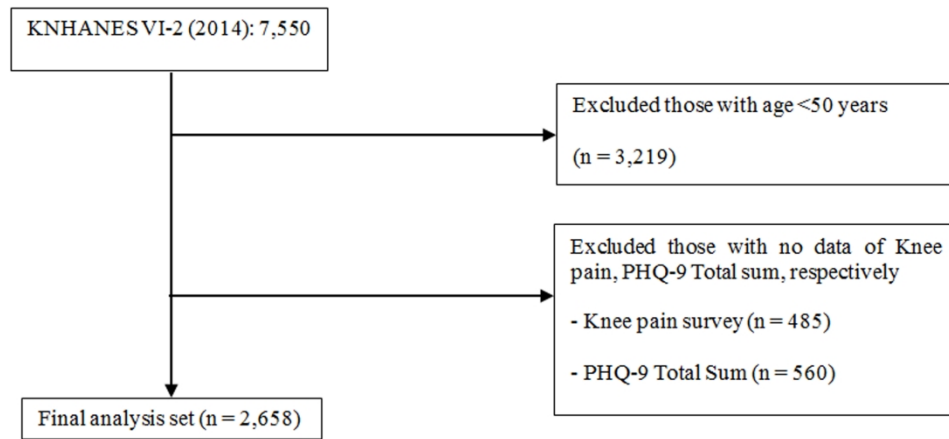


Figure 1. Flow chart diagram of inclusion and exclusion of participants  
Flow chart diagram of inclusion and exclusion of participants from the 2014 Korea National Health and Nutrition Examination Surveys (KNHANES). PHQ-9 indicates Patient Health Questionnaire.

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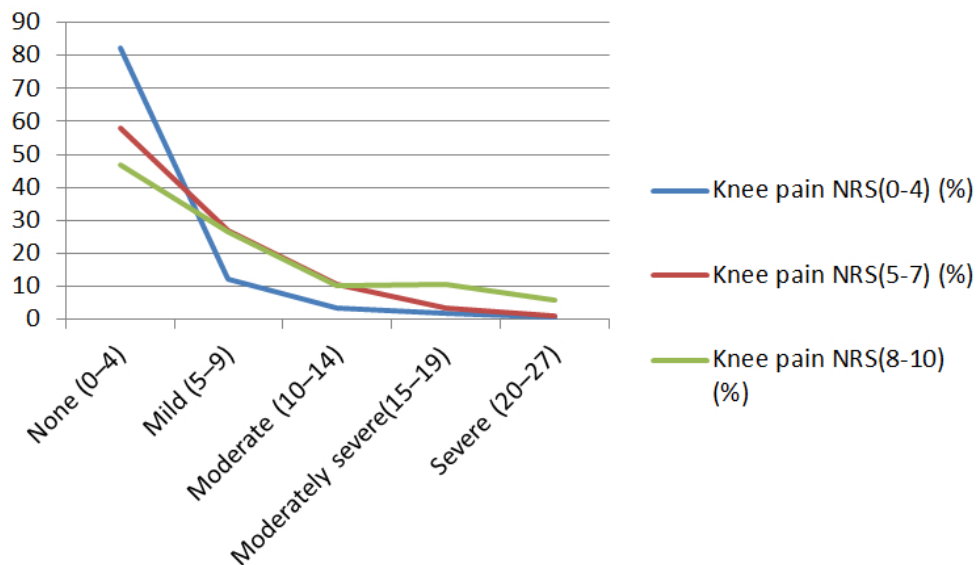
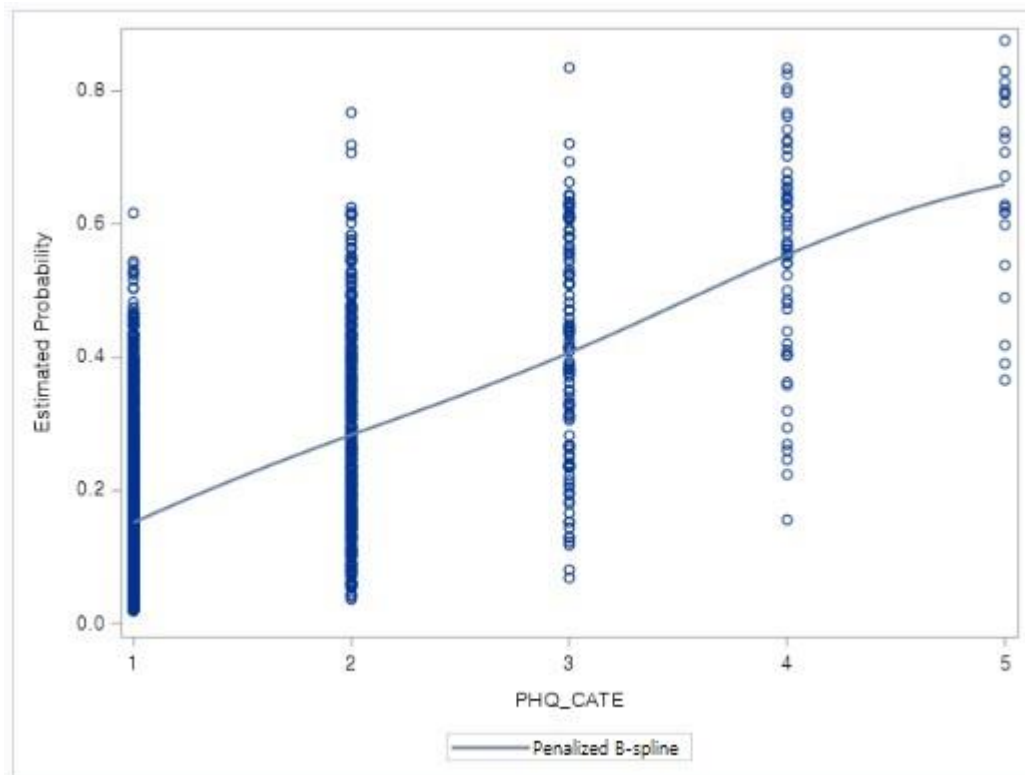


Figure 2. Severity of depressive symptoms according to chronic knee pain NRS  
 Severity of depressive symptoms according to chronic knee pain NRS. Individuals without knee pain were regarded as NRS 0. Severity of depressive symptoms according to PHQ-9 score; none (0-4), mild (5-9), moderate (10-14),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

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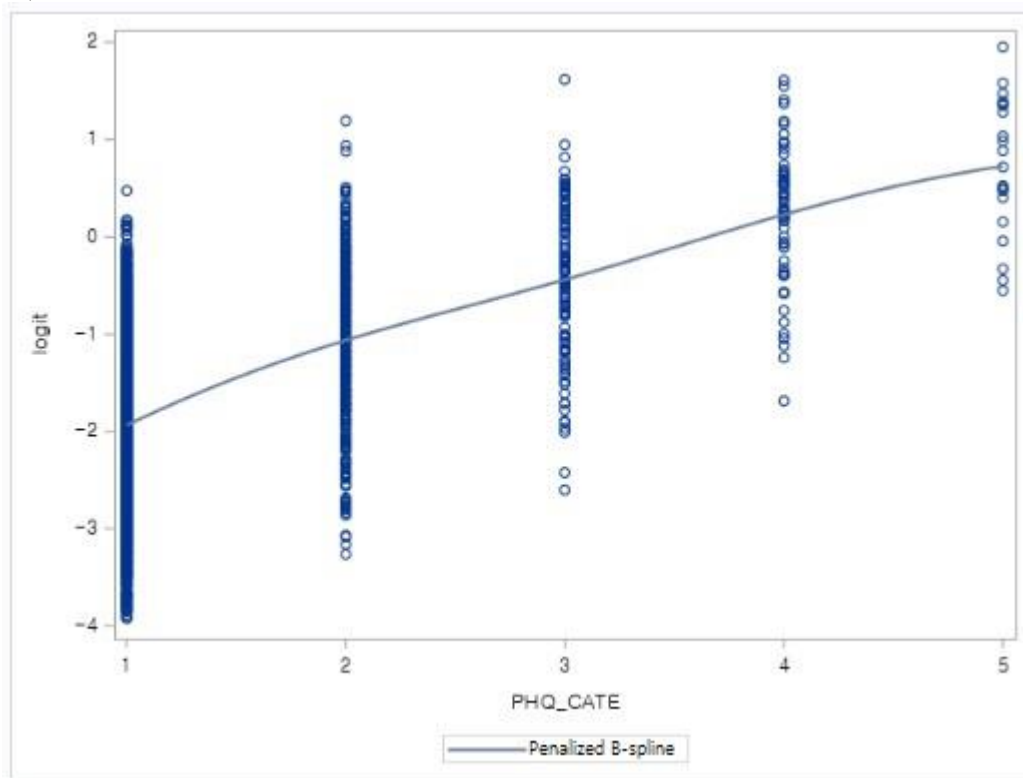


Estimated probability graph of logistic regression demonstrates a linear relationship in Model 3. PHQ-CATE, PHQ- categories 1 : None (0–4); 2 : Mild (5–9); 3 : Moderate (10–14); 4 : Moderately severe (15–19); 5 : Severe (20–27).



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



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

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

	Item No	Recommendation	
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	(p.1-2) (p.1-2)
<b>Introduction</b>			
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)
<b>Methods</b>			
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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	(p.6, lines 180-185; p.7, lines 186-195)
<b>Results</b>			
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 (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	(p. 7, lines 201-210)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest	(p. 7, lines 202-221) (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 (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	(p.8, lines 223-253) (NA)
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	(p.8, lines 247-253)

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<b>Discussion</b>		
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)
<b>Other information</b>		
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](http://www.strobe-statement.org).