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Depression and incident hip fracture

A longitudinal follow-up study using a national sample cohort

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Abstract

The aim of the present study was to evaluate the risk of hip fracture in depression patients using a nationwide cohort population.

Data from the Korean National Health Insurance Service-National Sample Cohort for a population ≥50 years of age from 2002 to 2013 were collected. The 25,197 individuals with depression were matched for age, sex, income, region of residence, hypertension, diabetes, and dyslipidemia, with 100,788 individuals comprising the control group. In both the depression and control groups, history of hip fracture was evaluated. Using the International Classification of Disease-10 (ICD-10) codes, depression (F31–F39), and hip fracture (S720, S721, and S722) were investigated. The crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of hip fracture in depression patients were analyzed using a Cox proportional hazard model. Subgroup analyses were conducted according to age and sex.

In the depression group, 1.1% (277/25,197) of the subjects had hip fracture, and 0.7% (693/100,095) in the control group had hip fracture ($P < .001$). The depression group demonstrated a higher adjusted HR for hip fracture than the control group (adjusted HR = 1.46, 95% CI = 1.27–1.68, $P < .001$). This result was consistent in the ≥65 years old subgroups.

The risk of hip fracture was elevated in depression patients.

Abbreviations: CIs = confidence intervals, NHIS-NSC = Korean National Health Insurance Service-National Sample Cohort.

Keywords: cohort studies, depression, epidemiology, fracture, hip, risk factors

1. Introduction

The hip is one of the most common involved sites of osteoporotic fracture.[1] With the aging population, the incidence of hip fracture has increased in recent years. Its incidence was reported as approximately 1.5 million people per year, which was predicted to be approximately 2.6 million people per year by 2025 worldwide.[2] In Korea, approximately 15,000 women and 5000 men per year suffer from hip fracture.[3] Moreover, the mortality and morbidity following hip fracture are considerable. The excess mortality within 1 year after hip fracture is increased 4.6 times in men and 2.8 times in women.[4] These increasing incidences together with the high mortality and morbidity of hip fracture warrant early detection and the management of risk factors. In addition to osteoporosis, several comorbidities such as hypertension, diabetes mellitus, and cerebrovascular disease are suggested to be related to the risk of hip fracture.[5]

Depression is a prevalent mental disorder that accounts for approximately 8.2% (5.9–10.8%) of people globally living with a disability.[6] The aging population and industrialized society promote the burden of depression. In addition to the negative psychiatric impacts, depression was suggested to increase the risk of various chronic diseases, such as osteoporosis, stroke, diabetes, and dementia.[7]

Several previous studies reported the association between depression and hip fractures. A population cohort study demonstrated that the incidence of hip fracture was 1.34 times higher in depression patients than that in an age- and sex-matched control group (95% confidence interval [CI] = 1.08–1.66, $P = .008$).[5] Because both depression and hip fracture are related to various diseases and influenced by demographic factors, these confounders should be considered for the control group. Moreover, the impacts of depression on hip fracture could be different according to age or sex. Because major depressive disorder is about twice more common and has more severe symptomatology in women than men, the impacts of depression could have higher statistical power in women.[8] Indeed, prior studies have demonstrated a higher risk of hip fracture with depression in women than that in men.

The running hypothesis of the present study was that depression might elevate the risk of hip fracture in an adult population. Control groups were matched for age, sex, income,

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region of residence, and past medical histories of hypertension, diabetes, and dyslipidemia. Additional comorbidities of ischemic heart disease, stroke, and osteoporosis were adjusted with these matched variables. In addition, the present study fills the gap of previous findings by subgroup analyses for age and sex.

2. Materials and methods

2.1. Study population and data collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. The requirement for written informed consent was waived by the Institutional Review Board.

This national cohort study relied on data from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC).[9] The approval number of the NHIS-NSC data was NHIS-2015–025. The detailed description of this data was described in our previous studies.[10,11]

2.2. Participant selection

Out of 1,125,691 cases with 114,369,638 medical claim codes, we included participants who were diagnosed with depression. Depression was defined using ICD-10 codes F31 (bipolar affective disorder) through F39 (unspecified mood [affective] disorder) by a psychiatrist from 2002 through 2013. Among them, we selected the participants who were seen by a provider using these codes ≥2 times (n = 68,019).

The depression participants were matched 1:4 with the participants (control group) who were never diagnosed with depression from 2003 through 2013 among this cohort. The control groups were selected from the entire population (n = 1,091,119) and matched for age group, sex, income group, region of residence, and past medical histories (hypertension, diabetes, and dyslipidemia). To prevent selection bias when selecting the matched participants, the control group participants were sorted using a random number order, and they were then selected from top to bottom. The matched control participants were assumed to be involved at the same time as each matched depression participant (index date). Therefore, the control group participants who died before the index date were excluded. The occurrence of hip fracture after the index date was investigated in both the depression and control groups. Hip fracture was diagnosed as ICD-10 codes S720 (fracture of head and neck of femur), S721 (pertrochanteric fracture), or S722 (subtrochanteric fracture of femur). From 2002 through 2013, 7113 hip fracture patients were selected. We searched the hip surgery histories of the patients using claim codes N0601 (open reduction and internal fixation, femur), N0611 (open reduction and internal fixation, femur, complex), N0711 (total hip arthroplasty), N0715 (hemiarthroplasty, hip), N0731 (arthrodesis, hip), and N2710 (hemiarthroplasty, hip, complex). We excluded patients who did not undergo surgery, because these patients either had minimal fractures, such as greater trochanter tip fractures, that did not require surgery or had major comorbidities that prevented them from undergoing hip surgery, which could mislead study results. After excluding these patients, 3555 patients were included in this study. In both the depression and control groups, the participants who had a history of hip fracture before the index date were excluded. In the depression group, 184 participants were excluded. The depression participants for whom we could not identify enough matching participants were excluded (n = 612). We excluded the participants under 50 years old (n = 38,522). In addition, the participants who were diagnosed depression before 2003 years were excluded (n = 3504). Finally, 1:4 matching resulted in the inclusion of 25,197 depression participants and 100,788 control participants. However, they were not matched for ischemic heart disease, stroke, or osteoporosis histories because strict matching increases the drop out of participants due to a lack of control participants (Fig. 1.).

2.3. Variables

The age groups were classified using 5-year intervals: 20 to 24, 25 to 29, 30 to 34 . . . , and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 11 classes (class 1, lowest income; class 11, highest income). The regions of residence were divided into 16 areas according to administrative district. These regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas.

The past medical histories of participants were evaluated using ICD-10 codes. For the accuracy of diagnosis, hypertension (I10 and I15), diabetes (E10-E49), and dyslipidemia (E78) were diagnosed if the participants were treated ≥2 times. Ischemic heart disease (I24 and I25) and stroke (I60-I66) were diagnosed if the participants were treated ≥1 time. Osteoporosis was defined using the ICD-10 codes M80 (osteoporosis with pathological fracture), M81 (osteoporosis without pathological fracture), and M82 (osteoporosis in diseases classified elsewhere) from 2002 through 2013. Among the participants diagnosed with osteoporosis, we selected the participants who were treated ≥ 2 times or the participants who were diagnosed by a bone density test using X-ray or CT (claim code: E7001-E7004, HC341-HC345).

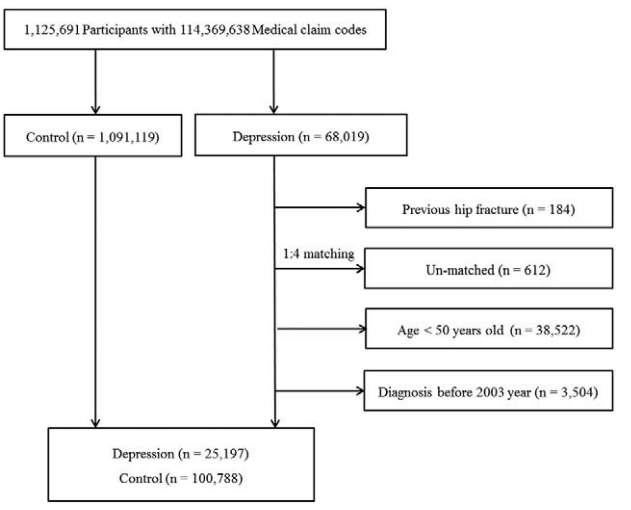

Figure 1. A schematic illustration of the participant selection process used in the present study. Out of a total of 1,125,691 participants, 25,197 depression participants were matched with 100,788 control participants for age group, sex, income group, region of residence, and past medical histories.

2.4. Statistical analyses

Chi-square tests were used to compare the rates of general characteristics between the depression and control groups.

To analyze the hazard ratio (HR) of depression on hip fracture, a Cox proportional hazard model was used. In this analysis, crude (simple) and adjusted (age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and osteoporosis) models were used.

For the subgroup analysis, we divided the participants by age and sex (50–64 years old and 65+ years old and men and women).

Two-tailed analyses were conducted, and *P* values less than .05 were considered to indicate significance. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

3. Results

The rates of hip fracture were 1.1% (277/25,197) in the depression group and 0.7% (693/100,788) in the control group ($P<.001$, Table 1). The rates of hip fracture were increased with aging (supplementary table S1, http://links.lww.com/MD/D74). Age, sex, income level, region of residence, hypertension, diabetes, and dyslipidemia were matched between the depression and control groups. The rates of ischemic heart disease, stroke, and osteoporosis were higher in the depression group than those in the control group ($P<.001$). Depression, age, sex, hypertension, diabetes, stroke, and osteoporosis showed high crude HR for hip fracture (Supplementary table S2, http://links.lww.com/MD/D74).

The adjusted HR for hip fracture was 1.46 times higher in the depression group than that in the control group (adjusted HR = 1.46, 95% CI = 1.27–1.68, $P<.001$, Table 2).

According to age and sex, both old male, and old female subgroups demonstrated higher adjusted HRs for hip fracture with depression (adjusted HR = 1.40, 95% CI = 1.01–1.94, $P=.047$ for old men; adjusted HR = 1.60, 95% CI = 1.35–1.90, $P<.001$ for old women; Table 3). Other subgroups of middle-aged men, and middle-aged women did not show higher adjusted HRs for hip fracture with depression.

4. Discussion

The risk of hip fracture was increased in depression patients compared to that in the control group in the present study. These results are consistent with those of previous studies. However, prior studies showed inconsistent results depending on the study group characteristics of age and sex. In this study, both men and women participants demonstrated an elevated risk of hip fracture with depression. In addition, matching and adjustments for potential confounders of age, sex, income, region of residence, and past medical histories of hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and osteoporosis improved the reliability of analyzed results.

Several previous studies demonstrated the association between depression and fracture, although there were some conflicting results. A recent meta-analysis study reported that depression was related to a 1.26-fold increased risk of fracture (95% CI = 1.10–1.43, $P<.001$).[12] However, there were significant heterogeneities in the study population and analyzed strategies. Similar to the present study, a population-based cohort study demonstrated an elevated risk of hip fracture in major depressive disorder patients (HR = 1.61, 95% = 1.19–2.18, $P=.002$).[13]

Table 1

General characteristics of participants.

Characteristics	Total participants		
	Depression (n, %)	Control (n, %)	*P* value
Age (years old)			1.000
50–54	5491 (21.8)	21,964 (21.8)	
55–59	4380 (17.4)	17,520 (17.4)	
60–64	3996 (15.9)	15,984 (15.9)	
65–69	3960 (15.7)	15,840 (15.7)	
70–74	3422 (13.6)	13,688 (13.6)	
75–79	2182 (8.7)	8728 (8.7)	
80–84	1179 (4.7)	4716 (4.7)	
85+	587 (2.3)	2348 (2.3)	
Sex			1.000
Male	8502 (33.7)	34,008 (33.7)	
Female	16,695 (66.3)	66,780 (66.3)	
Income			1.000
1 (lowest)	462 (1.8)	1848 (1.8)	
2	2104 (8.4)	8416 (8.4)	
3	1586 (6.3)	6344 (6.3)	
4	1528 (6.1)	6112 (6.1)	
5	1749 (6.9)	6996 (6.9)	
6	1853 (7.4)	7412 (7.4)	
7	2047 (8.1)	8188 (8.1)	
8	2326 (9.2)	9304 (9.2)	
9	2835 (11.3)	11,340 (11.3)	
10	3838 (15.2)	15,352 (15.2)	
11 (highest)	4869 (19.3)	19,476 (19.3)	
Region of residence			1.000
Urban	10,963 (43.5)	43,852 (43.5)	
Rural	14,234 (56.5)	56,936 (56.5)	
Hypertension			1.000
Yes	15,224 (60.4)	60,896 (60.4)	
No	9973 (39.6)	39,892 (39.6)	
Diabetes			1.000
Yes	8179 (32.5)	32,716 (32.5)	
No	17,018 (67.5)	68,072 (67.5)	
Dyslipidemia			1.000
Yes	10,848 (43.1)	43,392 (43.1)	
No	14,349 (57.0)	57,396 (57.0)	
Ischemic heart disease			<.001*
Yes	3264 (13.0)	10,285 (10.2)	
No	21,933 (87.1)	90,503 (89.8)	
Stroke			<.001*
Yes	6128 (24.3)	17,258 (17.1)	
No	19,069 (75.7)	83,530 (82.9)	
Osteoporosis			<.001*
Yes	10,321 (41.0)	34,218 (34.0)	
No	14,876 (59.0)	66,570 (66.1)	
Incident hip fracture			<.001*
Yes	277 (1.1)	693 (0.7)	
No	24,920 (98.9)	100,095 (99.3)	

* Chi-square test or Fisher exact test. Significance at $P<.05$.

Although a few prior studies used a control group to compare the risk of hip fracture in depression patients, few studies have considered potential confounders, including past medical histories, when matching control groups. In addition, this study demonstrated the risk of hip fracture in depression patients stratified by age and sex.

The decreased bone mineral density in depression patients may mediate the risk of fracture. A number of previous studies suggested the relation of depression with the decline in bone

Table 2

Crude and adjusted hazard ratios (95% confidence interval) of depression for hip fracture.

Characteristics	Hazard ratio (95% CI)			
	Crude	*P* value	Adjusted†	*P* value
Depression	1.60 (1.40–1.84)	<.001*	1.46 (1.27–1.68)	<.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P<.05$.
† Adjusted model for age, sex, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and osteoporosis histories.

Table 3

Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of depression for hip fracture according to age and sex.

Characteristics	Hazard ratio (95% CI)			
	Crude	*P* value	Adjusted†	*P* value
Middle-aged men (50–64 years old, n=23,000)				
Depression	1.40 (0.76–2.58)	.277	1.23 (0.66–2.27)	.515
Control	1.00		1.00	
Middle-aged women (50–64 years old, n=46,335)				
Depression	1.12 (0.71–1.78)	.624	0.95 (0.60–1.51)	.826
Control	1.00		1.00	
Old men (65+ years old, n=19,510)				
Depression	1.48 (1.07–2.05)	.019*	1.40 (1.01–1.94)	.047*
Control	1.00		1.00	
Old women (65+ years old, n=37,140)				
Depression	1.76 (1.48–2.09)	<.001*	1.60 (1.35–1.90)	<.001*
Control	1.00		1.00	

* Cox-proportional hazard regression model, Significance at $P<.05$.
† Adjusted model for age, income, region of residence, hypertension, diabetes, dyslipidemia, ischemic heart disease, stroke, and osteoporosis histories.

mineral density or the occurrence of osteoporosis. A meta-analysis study estimated that hip bone mineral density was annually reduced by approximately 0.35% in depression patients (95% CI=0.18–0.53, $P<.001$).[12] Although the underlying pathophysiologic mechanisms are still ambiguous, depression modulates several key hormones of bone metabolism. High levels of cortisol are thought to cause major depression disorder.[14] Depression patients demonstrated both a high basal level of cortisol and a disturbed diurnal rhythm or feedback regulation by glucocorticoid due to the hyperactivity of the hypothalamic-pituitary-adrenal axis.[15] These high cortisol levels are known to induce osteoporosis by involving several possible mechanisms of bone metabolism.[16] For instance, high levels of glucocorticoids may induce apoptosis of osteocytes, thereby stimulating osteoclast activities.[16] In addition to cortisol, the inflammatory cytokines tumor necrosis factor-α, interleukin 1β, interleukin-6, and interleukin-8 are also thought to be elevated in depression patients and to mediate the loss of bone mineral density.[16–18] Depression patients demonstrated a higher level of these proinflammatory cytokines than those in the control group in a recent meta-analysis study.[18] These inflammation and hormonal changes were reported to cause bone loss and fracture.[19] In addition, the use of serotonin reuptake inhibitors (SSRI) in depression patients could impede the osteogenic regeneration and bone healing.[20] A mice study demonstrated the reduced osteoblast differentiation and mineralization after chronic use of SSRI.[20,21]

The elevated risk of falls in depression patients can elevate the risk of fracture. A passive coping style could increase the risk of falls in depression patients. Depressive symptoms were negatively associated with active coping and executive functioning.[22] In addition, unexplained falls that were not related to accidental falls by slips were increased in depression patients.[23] Another cohort study demonstrated that the depressive symptoms were related to both falls and fear of falls in elderly subjects.[24] A prospective cohort study reported a temporal relationship between falls and depression.[25] They showed that depressive symptoms were associated with both decreased physical activity and falls.[25] Thus, a reduced active coping style reduced physical activity, and other undefined factors might influence the risk of falls and subsequent fractures in depression patients. In addition, antidepressant medication could elevate the risk of falls and subsequent fracture in depression patients.[26] To support this, selective serotonin reuptake inhibitors were also related to impaired physical activity without decreased bone mineral density or bone microstructure in a population-based study.[27]

Both men and women showed elevated risk of hip fracture in depression patients in this study. Although other studies reported that women were more influenced by depression for the risk of falls and hip fractures, these results could be caused by the high incidence of depression in women.[13,23] Because the present study was conducted with a large number of populations and used a control group matched for possible confounders, statistical power was reached to show the impact of depression on hip fracture in both sexes. According to age, old men and old women groups demonstrated higher adjusted HRs of depression for hip fractures in this study. To estimate the modifying effects of age on the risk of hip fracture in depression patients, Z test was performed according to age subgroups (Supplementary table S3 and S4, http://links.lww.com/MD/D74).[28] As results, old men group did not show higher adjusted HR of depression for hip fracture than young men group (Supplementary table S3, http://links.lww.com/MD/D74). On the other hands, old women group demonstrated higher adjusted HR of depression for hip fracture than young women group (Supplementary table S4, http://links.lww.com/MD/D74).

In addition to the large study population and matched control group, the present study has several virtues. The NHIS-NSC provides nationwide representative data validated in a previous study.[9] The Korean medical health insurance system registers and manages all Korean citizens without exception. Thus, the NHIS data included all Korean citizens. The control group was randomly selected and matched for age, sex, income, region of residence, and medical history of hypertension, diabetes, and dyslipidemia.

However, there were some limitations mainly due to the restriction of the medical claim code information. Because both depression and hip fracture were based on the ICD-10 codes, the severity of disease and treatment histories, such as medication, could not be considered. To minimize the subclinical minor hip fracture patients, the hip fracture patients who did not undergo surgery were excluded from this study. For depression, only the depression patients with ≥2 instances of diagnosis were included in this study. To minimize the effects of the accessibility of medical care, income, and region of residence were matched between the depression and control groups. In addition, although a number of confounders were considered in this study, the NHIS data lack information on other confounding lifestyle factors including smoking, alcohol consumption, sleep, obesity, diet, and

nutrition. Lastly, the effects of institutionalization and morbidity could not be accounted in this study.

In conclusion, depression increased the risk of hip fracture in a ≥50 years old population. Both men and women demonstrated an elevated risk of hip fracture in the depression group.

Author contributions

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