

# Effects of depression and antidepressant medications on hip fracture

## A population-based cohort study in Taiwan

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### Abstract

This study was conducted to investigate the effects of depression and antidepressant medications on hip fracture. The database of the Taiwan National Health Insurance with medical records of more than 1,000,000 individuals was searched for patients who had hip fracture with or without depression from 1998 to 2009. Patients with the following conditions were excluded: hip fracture due to cancer or traffic accidents, hip fracture that occurred before the diagnosis of depression, and use of antidepressants before the diagnosis of depression. A matched cohort of 139,110 patients was investigated, including 27,822 (17,309 females; 10,513 males) with depression and 111,288 (69,236 females; 42,052 males) without depression (1:4 randomly matched with age, sex, and index date). Among these patients, 232 (158 females and 74 males) had both hip fracture and depression, and 690 (473 females and 217 males) had hip fracture only. The Cox proportional-hazards regression method was used to determine the effect of depression on hip fracture. The hazard ratio (HR) for each clinical parameter was calculated after adjusting for confounders including sex, age, Charlson comorbidity index, urbanization, osteoporosis, and antidepressants. Results showed that patients with major depressive disorder had a 61% higher incidence of hip fracture than those without depression (HR 1.61, 95% confidence interval [CI] 1.19–2.18,  $P=0.002$ ). The risk of hip fracture for patients with less severe depressive disorder (dysthymia or depressive disorder, not otherwise specified) was not statistically higher than that of patients with no depression (HR 1.10, 95% CI=0.91–1.34,  $P=0.327$ ). Among the patients with depression, females had a 49% higher incidence for hip fracture than males (HR 1.49, 95% CI 1.30–1.72,  $P<0.001$ ). The incidence of hip fracture also increased with age and Charlson comorbidity index scores. Analyses of both all (139,110) patients and only patients (27,822) with depression revealed that antidepressants had no negative impact on the incidence of hip fracture. In conclusion, major depression was found to be a risk factor for hip fracture and that use of antidepressants had no adverse effect on hip fracture in the Taiwanese population.

**Abbreviations:** aOR = adjusted odds ratio, BMD = bone mineral density, CCI = Charlson comorbidity index, CI = confidence interval, DDD = defined daily dose, DP = depression, HF = hip fracture, HR = hazard ratio, ICD = International Classification of Diseases, MAOIs = monoamine oxidase inhibitors, MDD = major depressive disorder, NHI = National Health Insurance, NHRI = National Health Research Institute, ODD = other depressive disorder, SARI = serotonin antagonist and reuptake inhibitor, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressants.

**Keywords:** Charlson comorbidity index, defined daily dose, depression, hazard ratio, hip fracture, SNRI, SSRI

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### 1. Introduction

Hip fracture (HF) is a devastating disease with an acute mortality rate of approximately 5% and 1-year mortality rate of 15% to 25%.<sup>[1]</sup> It has been estimated that 20% of patients who suffer a HF completely lose the ability to walk.<sup>[1]</sup> Osteoporosis is a major cause of HF. Risk factors for osteoporosis-related HF include age, osteoarthritis, disability before fracture, malnutrition, muscle weakness, arthritis, cognitive deficit, and impaired balance, visual ability, or activity of daily living. Osteoporosis is usually diagnosed by determining bone mineral density (BMD) that is closely related to dietary intake of calcium and protein, serum vitamin D level, and weight-bearing physical activity.<sup>[2,3]</sup> Many diseases such as those affecting bone mineral homeostasis, imbalance of bone remodeling, and collagen synthesis may also affect BMD.<sup>[4]</sup>

Similar to osteoporosis, depression (DP) is a common disorder and is a leading cause of disability, affecting at least 120 million people worldwide.<sup>[5]</sup> Approximately 10% of adults in the United States are prescribed with an antidepressant for more than 6 months.<sup>[6]</sup> Selective serotonin reuptake inhibitors (SSRIs) are the most widely prescribed antidepressants. On average, antidepressant prescriptions are increased by 10% per year.<sup>[7]</sup> DP has been implicated as a risk factor for low BMD<sup>[8–17]</sup> and

fracture.<sup>[11,18–23]</sup> Some studies found that the relationship between DP and low BMD is more pronounced in men,<sup>[12,13,24]</sup> but another study found such relationship occurs more significantly in women.<sup>[14]</sup> However, some studies found no association between DP and BMD<sup>[25–28]</sup> or HF.<sup>[28]</sup> It is possible that the relationship between DP and BMD or fracture varies with sex or race.

To investigate the effects of DP and use of antidepressants on HF in the Taiwanese population, we analyzed the information extracted from the database of the National Health Insurance (NHI) of Taiwan. This national insurance program was initiated in 1995.<sup>[29]</sup> Currently, it covers more than 99.5% of the total population of approximately 23 million in Taiwan. The NHI database was established in 1997 by the National Health Research Institute (NHRI) and is updated regularly.<sup>[29]</sup> This large sample size would minimize the bias in selection of study participants. As this database contains detailed demographic and clinical information of patients, it allows a more accurate assessment of the correlation between diseases and their risk factors. Since results of previous studies on the relationship between DP and HF are inconsistent, we took advantage of this database and conducted 2 prospective cohort studies to clarify the matter. The first one investigated effect of DP on HF rates. The second one investigated whether the use of antidepressants leads to increased incidence of HF.

## 2. Materials and methods

### 2.1. Subjects

The NHRI research database of the NHI of Taiwan was searched for patients who were diagnosed with DP (International Classification of Diseases [ICD]-9-CM 296.2 and 296.3 for major depressive disorder [MDD], 300.4 for dysthymia, and 311 for depressive disorder, not otherwise specified [depressive disorder, NOS]) and those who had HF (ICD-9-CM 820) from 1998 to 2009. The ICD-9 coding system was used in this study because the ICD-10 system was not adopted in Taiwan until 2015. Patients with DP were defined as those who had at least 2 clinical visits or 1 hospital admission for DP within 1 year. Major and other depressive disorders were diagnosed as described previously.<sup>[30,31]</sup> Briefly, patients with at least 5 of the following 9 symptoms were considered as having an MDD: depressed mood or irritable most of the day, decreased interest or pleasure in most activities, significant weight change (5%) or change in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of worthlessness, or excessive or inappropriate guilt, diminished ability to think or concentrate, and thoughts of death or suicide. Other depressive disorders (dysthymia or depressive disorder, NOS) with fewer symptoms than MDD were considered as less severe forms of DP. Patients with the following conditions were excluded: HF due to cancer or traffic accidents, HF that occurred before or within 6 months after the diagnosis of DP, and use of antidepressants before the index date. The diagnosis date of DP was set as the index date. Each patient with DP was compared with at least 4 randomly selected individuals without DP by matching their age and sex. All patients were followed from the index date up to the date of HF or the end of 2009. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number: CGMHIRB 103–3585B).

### 2.2. Charlson comorbidity index

The Charlson comorbidity index (CCI) was determined as described by Charlson et al and Quan et al.<sup>[32,33]</sup> Patients with the

following conditions were given a CCI of 1: myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease, or diabetes. Patients with a CCI of 2 included those with hemiplegia, moderate or severe kidney disease, diabetes with end-organ damage, tumor, leukemia, or lymphoma. Patients with moderate or severe liver disease were assigned a CCI of 3, and those with malignant tumor, metastasis, or AIDS were given a CCI of 6.

### 2.3. Drug evaluation

The use of the following drugs was investigated: selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin antagonist and reuptake inhibitors (SARIs, such as trazodone) mirtazapine, bupropion, and monoamine oxidase inhibitors (MAOI). SSRI drugs evaluated in this study included fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram. Evaluation of drug usage was based on defined daily dose (DDD). A DDD value less than 28 was considered nonuse (level 0). Drug doses were classified into the following 4 levels: level 1, 28 to 83 DDD; level 2, 84 to 167 DDD, level 3, 168 to 335 DDD, and level 4,  $\geq 336$  DDD. Only patients who were on any of the aforementioned drugs for more than 180 days were investigated.

### 2.4. Classification of urbanization

Townships and cities in Taiwan had been classified into 7 urbanization groups, including highly urbanized, moderately urbanized, emerging, ordinary, aging, agricultural, and rural cities.<sup>[34]</sup> This classification was based on the data of the 2000 Taiwan census, Survey of Health Maintenance Organization, and Health Service Utilization. Variables used for the classification included population density, number of physicians per 100,000 people, and population ratio of farmers, people with college or higher educational levels, and people over 65 years old. In this study, we combined some of these groups together and classified urbanization as very high (highly urbanized), high (moderately urbanized and emerging), moderate (ordinary and aging), and low (agriculture and rural).

### 2.5. Statistical analyses

Comparisons of differences in demographic characteristics, CCI, osteoporosis, and antidepressants between the cohorts with and without DP were conducted using the Pearson chi-square test and *t* test. To measure the effect of DP on HF, the multivariate Cox proportional-hazards analysis was performed after adjusting for sex, age, urbanization, CCI, osteoporosis, and antidepressants. Hazard ratios (HRs) of antidepressants on HF were also calculated by the multivariate Cox proportional-hazards method. Cumulative incidence of HF during the entire follow-up period was estimated by the Kaplan–Meier method and compared by the log-rank test. The period for evaluation of CCI was within 1 year before the index date. All analyses were performed with the SAS statistical software (version 9.4).

## 3. Results

### 3.1. Patients

In all, 139,110 patients were investigated in this study, including 27,822 (17,309 females; 10,513 males) with DP and 111,288

**Table 1**  
**Number and percent of patients in various categories.**

Depression	With	Without	Total	$\chi^2$ test
Total	27,822 (100.0%)	111,288 (100.0%)	139,110	P
Sex				1.000
F	17,309 (62.2%)	69,236 (62.2%)	86,545	
M	10,513 (37.8%)	42,052 (37.8%)	52,565	
Age				1.000
00–34	9301 (33.4%)	37,204 (33.4%)	46,505	
35–49	8561 (30.8%)	34,244 (30.8%)	42,805	
50–64	5847 (21.0%)	23,388 (21.0%)	29,235	
65–79	3453 (12.4%)	13,812 (12.4%)	17,265	
$\geq 80$	660 (2.4%)	2640 (2.4%)	3300	
Mean age $\pm$ SD	46.5 $\pm$ 17.8	46.5 $\pm$ 17.8		1.000
Urbanization				<0.001
Very high	8265 (29.7%)	33,716 (30.3%)	41,981	
High	13,036 (46.9%)	52,304 (47.0%)	65,340	
Moderate	4376 (15.7%)	17,478 (15.7%)	21,854	
Low	2145 (7.7%)	7790 (7.0%)	9935	
CCI				<0.001
0	16,970 (61.0%)	91,284 (82.0%)	108,254	
1	6243 (22.4%)	12,444 (11.2%)	18,687	
2	2312 (8.3%)	4375 (3.9%)	6687	
$\geq 3$	2297 (8.3%)	3185 (2.9%)	5482	
Osteoporosis	665 (2.4%)	1504 (1.4%)	2169	<0.001
Antidepressants				
SSRI	12,669 (45.5%)	683 (0.6%)	13,352	<0.001
TCA	2012 (7.2%)	889 (0.8%)	2901	<0.001
SNRI	2498 (9.0%)	53 (0.0%)*	2551	<0.001
Others <sup>†</sup>	5465 (19.6%)	395 (0.4%)	5860	<0.001

\* Less than 0.05%.

<sup>†</sup> Others include mirtazapine, burpropion, trazodone, and MAOI.

(69,236 females; 42,052 males) without DP (Table 1 and Fig. 1). These patients included 232 (158 females and 74 males) with both HF and DP, and 690 (473 females and 217 males) with fracture only. Patients with DP were further classified as having major (MDD) or other depressive disorder (ODD) including dysthymia and depressive disorder, not otherwise specified. The following 6 groups of patients were studied: MDD with HF (77 patients, 27 males and 50 females), MDD without HF (9649 patients), ODD with HF (155 patients, 47 males and 108 females), ODD without HF (17,941 patients), no DP with HF (690 patients), and no DP and no HF (110,598 patients).

### 3.2. Correlation between depression and hip fracture

The cumulative incidence of HF was consistently higher in patients with DP than those with no DP every year during the entire 12 years of follow-up (Fig. 2). Compared with those who had no DP (HR 1), the HR for HF in patients with MDD was 1.61 (95% confidence interval [CI] 1.19–2.18,  $P=0.002$ ) after adjusting for confounders (Table 2 and Fig. 3). ODD was found not to be a significant risk factor for HF (multivariate HR 1.10, 95% CI 0.91–1.34,  $P=0.327$ ) (Table 2 and Fig. 3).

Sex was a risk factor for HF as females had a higher incidence of HF than males (multivariate HR 1.49, 95% CI 1.30–1.72,  $P<0.001$ ) (Tables 2–4). Age was also associated with risk of HF as HF rates were increased with age (Tables 2–4). Compared with that of the 0 to 3 age group (HR 1), the multivariate HRs for age groups 35 to 49, 50 to 64, 65 to 79, and  $>80$  were 3.01, 13.57, 98.98, and 261.79, respectively (Table 2).

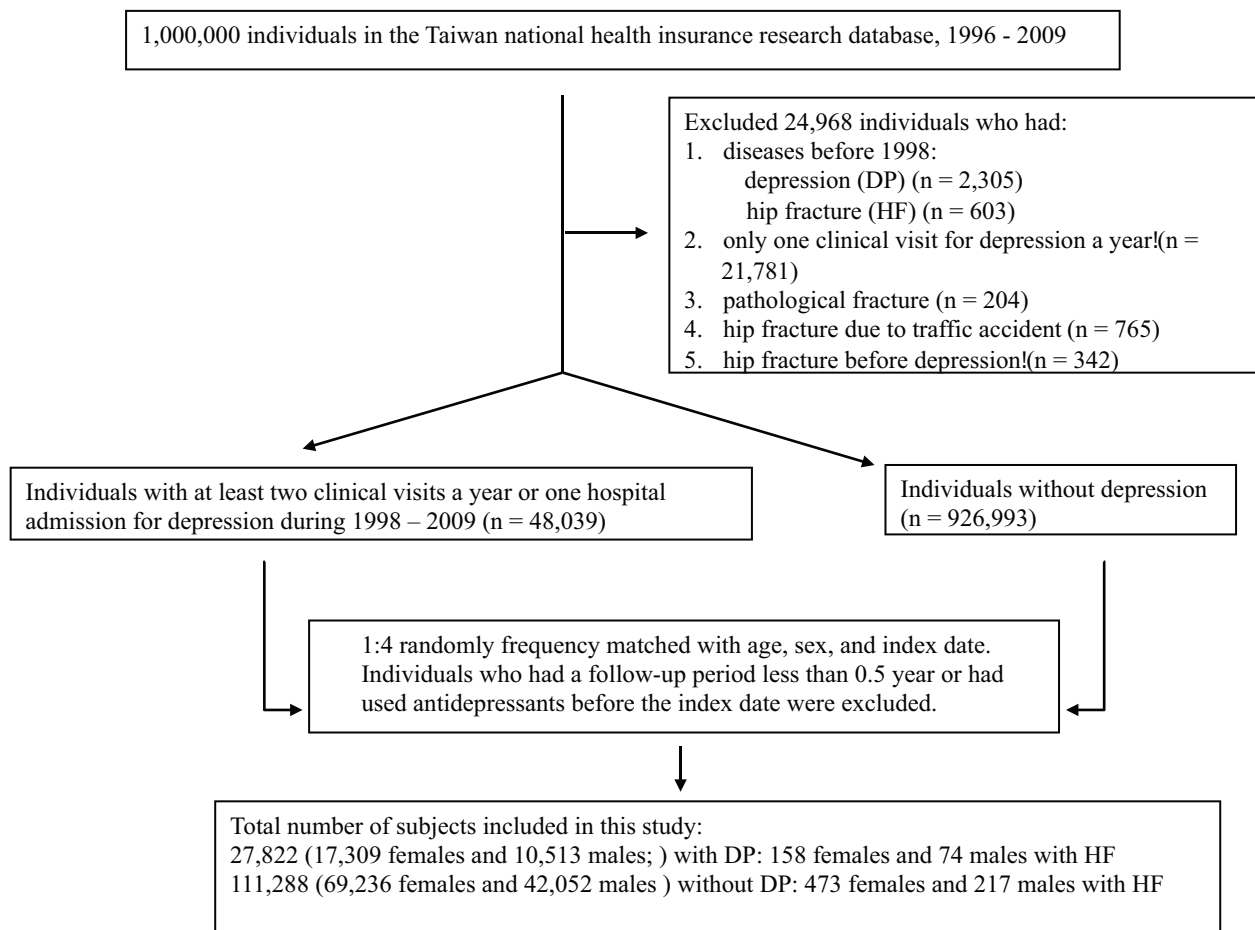
Patients with osteoporosis were found to have a higher risk of HF (multivariate HR 1.32, 95% CI 1.02–1.71,  $P=0.036$ ) (Table 2). Urbanization was found to have no effect on HF (Table 2). Patients with a CCI of 2 or greater were found to have a higher incidence of HF (HR 1.29, 95% CI 1.05–1.60,  $P=0.017$  for CCI=2; HR 1.92, 95% CI 1.59–2.32,  $P<0.001$  for CCI  $\geq 3$ ) (Table 2).

### 3.3. Effects of antidepressants on hip fracture

The following 4 types of antidepressants were investigated for their effect on HF rates in patients with DP: SSRI, TCA, SNRI, and others (mirtazapine, burpropion, trazodone, and MAOI). Numbers of patients who were on various drugs with different DDDs are shown in Table 5. These drugs were analyzed as a whole on all (139,110) patients (Table 5) and on patients (27,822) with DP (Table 6). SSRI drugs including fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram were also analyzed individually on the 27,882 patients with DP (Table 6). None of these drugs were found to significantly increase HF rates in patients with DP (Table 6).

## 4. Discussion

The present study is the first population-based study in Taiwan to investigate the relationship between the severity of DP and HF, and effect of antidepressants on HF. Two prospective cohort studies were conducted by analyzing medical records in the NHRI research database of the NHI of Taiwan. In the first study, we investigated the effect of DP on HF. To ensure that the

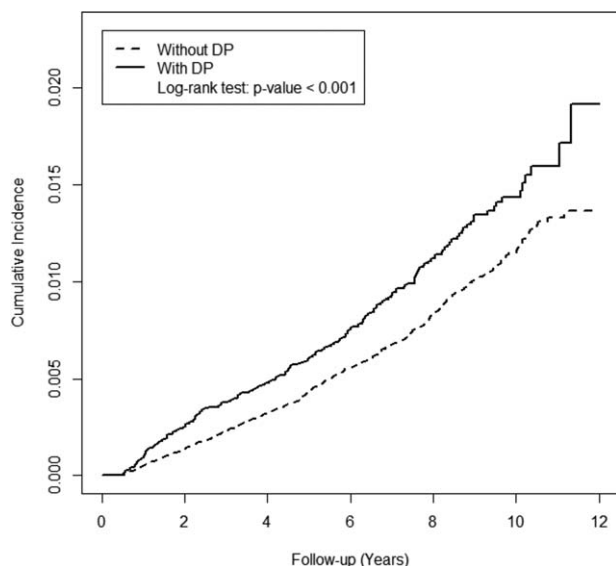


**Figure 1.** Selection of patient cohorts for this study. DP=depression, HF=hip fracture, MDD=major depressive disorder, ODD=other depressive disorder.

cause-and-effect relationship between DP and HF was determined, we included only patients who had HF 180 days after the diagnosis of DP. In addition, patients with HFs due to cancer or traffic accidents were excluded, and the multivariate Cox

proportional-hazards analysis was performed after adjusting for sex, age, urbanization, CCI, osteoporosis, and antidepressants. We found that patients with MDD had a 61% higher incidence of HF than those with no DP (HR 1.61, 95% CI 1.19–2.18) (Table 2 and Fig. 3). This result is highly significant ( $P=0.002$ ) and reliable as the CI is relatively narrow. The severity of depressive disorders was correlated with the risk of HF as the HF rate of patients with ODD was not significantly higher than that of patients with no DP (HR 1.10, 95% CI 0.91–1.34,  $P=0.327$ ) (Table 2 and Fig. 3). The HF incidence was found to increase with age and CCI scores (Table 2). As expected, osteoporosis was found to be a risk factor of HF (Table 2).

Depression has been shown to decrease BMD.<sup>[8,9,12–14,16,35–39]</sup> In a population-based prospective cohort study of 2464 community-dwelling men aged 68 years and older, the mean total hip BMD was found to decrease by 0.70% per year in 136 men with a Geriatric Depression Scale (GDS) score of 6 or higher, compared with 0.39% per year in 2328 men with a GDS score less than 6.<sup>[16]</sup> Similar results were observed in another age-adjusted study of 4177 women aged 69 years and older, in whom the mean total hip BMD was decreased by 0.96% per year in 200 women with a GDS score greater than 6, compared with 0.69% per year in 3977 women with a GDS score less than 6.<sup>[35]</sup> Another study of 1566 Medicare enrollees aged 65 years and older found that the mean BMD was 40 mg/cm<sup>2</sup> lower in those with clinical DP.<sup>[14]</sup> However, there have also been studies that showed no correlation between DP and low BMD.<sup>[11,25,26,28,40]</sup>



**Figure 2.** Kaplan–Meier cumulative incidence curves of hip fracture in patients with or without depression.

**Table 2**  
Unadjusted and adjusted Cox hazard ratios of patients in various categories.

Model	Univariate			Multivariate		
	HR	95% CI	P	HR*	95% CI	P
Depression (ref: without)						
ODD	1.40	1.17–1.66	<0.001	1.10	0.91–1.34	0.327
MDD	1.28	1.01–1.61	0.043	1.61	1.19–2.18	0.002
Sex (ref: male)						
Female	1.27	1.10–1.46	0.001	1.49	1.30–1.72	<0.001
Age (ref: 0–34)						
35–49	3.05	1.59–5.85	0.001	3.01	1.57–5.78	0.001
50–64	14.78	8.17–26.73	<0.001	13.57	7.49–24.59	<0.001
65–79	113.18	63.88–200.54	<0.001	98.98	55.62–176.15	<0.001
≥80	305.03	170.42–545.99	<0.001	261.79	145.46–471.14	<0.001
Urbanization (ref: low)						
Very High	0.42	0.33–0.53	<0.001	0.82	0.65–1.03	0.092
High	0.56	0.45–0.69	<0.001	0.99	0.81–1.22	0.932
Moderate	0.87	0.69–1.09	0.229	1.02	0.81–1.28	0.876
CCI (ref: 0)						
1	2.59	2.19–3.06	<0.001	1.13	0.95–1.34	0.184
2	4.44	3.62–5.45	<0.001	1.29	1.05–1.60	0.017
≥3	8.43	7.05–10.08	<0.001	1.92	1.59–2.32	<0.001
Osteoporosis (ref: without)	4.18	3.23–5.39	<0.001	1.32	1.02–1.71	0.036
Antidepressants (ref: no use)						
SSRI	1.11	0.90–1.38	0.315	0.98	0.75–1.27	0.863
TCA	1.74	1.29–2.36	<0.001	0.85	0.62–1.15	0.291
SNRI	0.88	0.53–1.46	0.607	0.98	0.57–1.68	0.949
Others*	1.36	1.04–1.78	0.025	0.98	0.73–1.32	0.911

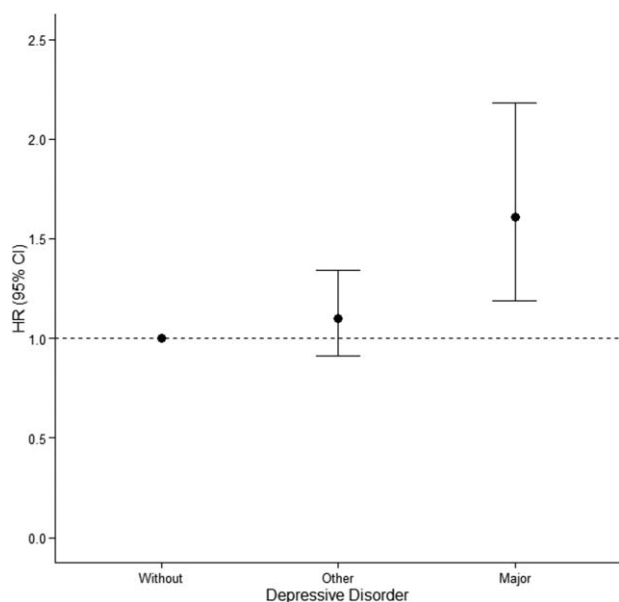
CCI = Charlson comorbidity index, CI = confidence interval, HR = hazard ratio, MDD = major depressive disorder, NOS = depressive disorder, not otherwise specified, ODD = other depressive disorder (dysthymia or depressive disorder), SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.  
\* Multivariate HRs were adjusted for sex, age, urbanization, CCI, osteoporosis, and antidepressants.

Patients with DP usually have elevated plasma cortisol that may decrease bone formation and increase resorption, leading to a lower BMD.<sup>[41,42]</sup> Increased expression of proinflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor

(TNF)-α, which mediates resorption, has also been observed in patients with DP.<sup>[43–45]</sup> DP has also been shown to increase addiction to smoking and alcohol consumption, and decrease physical activity.<sup>[46]</sup> Depressed patients are also more prone to suffer from dietary imbalance or malnutrition, leading to weight loss and development of medical comorbidities that negatively impact BMD. They also have difficulties in taking necessary safety precautions to the environment, and thus have a higher chance of falling, leading to HF.

Our finding that urbanization is not associated with risk of HF in patients with DP is not consistent with that of a meta-study of 15 publications. In that meta-study, rural residents were found to have a 5% higher BMD than urban residents in high-income countries.<sup>[47]</sup> Another meta-study found that residents in rural regions had a lower incidence of HF compared with urban residents.<sup>[48]</sup> A study from China found a higher BMD in urban residents<sup>[49]</sup>; this was postulated to be due to better nutrition. Since the living conditions in rural and urban areas in Taiwan are very similar, it is conceivable that urbanization was found not associated with risk of HF.

In the second prospective cohort study, we investigated HF rates in patients who were on antidepressants with a DDD greater than 28 for more than 180 days. Our results showed that antidepressant medications had no significantly negative impact on HF in patients with DP (Table 2 and Table 4). This result is consistent with that of Diem et al<sup>[15]</sup> and Ensrud et al.<sup>[50]</sup> They also found that the use of antidepressants such as SSRI drugs is not associated with an increased risk of HF. Kinjo et al<sup>[51]</sup> and Spangler et al<sup>[28]</sup> also found no association between low hip BMD and use of antidepressants. Our findings were similar to those of another recent case-control study in Taiwan by Wang et al.<sup>[52]</sup> They also did not find an association between the use of SSRI



**Figure 3.** Hazard ratio and 95% confidence interval of patients with no depression (without); dysthymia/depressive disorder, NOS (other); or major depressive disorder (major). Solid circles represent adjusted hazard ratio. Whiskers indicate 95% confidence interval. The multivariate Cox proportional-hazards analysis was performed after adjusting for sex, age, urbanization, CCI, osteoporosis, and antidepressants.

**Table 3**

**Number and percentage of females with hip fracture in various age groups of patients with or without depression.**

Age group	HF/MDD (%) <sup>*</sup>	HF/ODD (%) <sup>†</sup>	HF/no DP (%) <sup>‡</sup>
0–34	0/2571 (0.0%)	1/3290 (0.0%)	0/23,444 (0.0%)
35–49	1/1924 (0.1%)	4/3425 (0.1%)	10/21,396 (0.0%)
50–64	8/1123 (0.7%)	15/2592 (0.6%)	72/14,860 (0.5%)
65–79	30/504 (6.0%)	55/1519 (3.6%)	288/8092 (3.6%)
≥80	11/75 (14.7%)	33/286 (11.5%)	103/1444 (7.1%)

DP = depression, HF = hip fracture, MDD = major depressive disorder, ODD = other depressive disorder (dysthymia or depressive disorder).

<sup>\*</sup> Number of patients with hip fracture / number of patients with major depressive disorder.

<sup>†</sup> Number of patients with hip fracture / number of patients with other depressive disorders.

<sup>‡</sup> Number of patients with hip fracture / number of patients with no depression.

**Table 4**

**Number and percentage of males with hip fracture in various age groups of patients with or without depression.**

Age group	HF/MDD (%) <sup>*</sup>	HF/ODD (%) <sup>†</sup>	HF/no DP (%) <sup>‡</sup>
0–34	2/1445 (0.1%)	2/1995 (0.1%)	7/13,760 (0.1%)
35–49	3/1012 (0.3%)	6/2200 (0.3%)	13/12,848 (0.1%)
50–64	3/600 (0.5%)	4/1532 (0.3%)	21/8528 (0.2%)
65–79	16/389 (4.1%)	29/1041 (2.8%)	127/5720 (2.2%)
≥80	3/83 (3.6%)	6/216 (2.8%)	49/1196 (4.1%)

DP = depression, HF = hip fracture, MDD = major depressive disorder, ODD = other depressive disorder (dysthymia or depressive disorder).

<sup>\*</sup> Number of patients with hip fracture/number of patients with major depressive disorder.

<sup>†</sup> Number of patients with hip fracture/number of patients with other depressive disorders.

<sup>‡</sup> Number of patients with hip fracture/number of patients with no depression.

(adjusted OR [aOR] 1.10, 95% CI 0.90–1.24) or SNRI (aOR 1.16, 95% CI 0.95–1.42) drugs and fracture rates, but they found a positive association between combined use of these 2 classes of antidepressants and fracture rates (aOR 1.16, 95% CI 1.05–1.28). This controversial result may be due to their analysis of drug effects based on medication possession ratio (MPR), which was defined as the total prescribing days divided by the total number of follow-up days. Similar to our study, they also found no adverse effects of individual SSRIs such as fluoxetine, sertraline, or paroxetine on fracture. Our results are consistent with those of another recent cohort study in Taiwan by Lee et al<sup>[53]</sup> in which they found that DP was linked to osteoporosis and that the use of antidepressants lowered the risk of osteoporosis.

Our results regarding the effects of antidepressants on HF differ from some of previous studies from Western countries. These studies showed that antidepressants increased the risk of fracture in patients with DP.<sup>[15,35,52,54–66]</sup> Epidemiological studies have also linked antidepressants to falls,<sup>[67–69]</sup> loss of bone density,<sup>[70]</sup> and fractures.<sup>[50,71,72]</sup> Antidepressants such as SSRI and TCA drugs have been shown to decrease BMD.<sup>[46,73]</sup> In a study of a cohort of 2722 older women (mean age 78.5 years), hip BMD was found to decrease by 0.82% in SSRI users compared with 0.47% per year in nonusers.<sup>[74]</sup> The use of anticonvulsants<sup>[51]</sup> and glucocorticoids<sup>[75,76]</sup> have also been associated with low BMD and 25-hydroxyvitamin D levels in patients with DP.<sup>[77,78]</sup> Therefore, TCA and SSRI drugs are considered as “potentially inappropriate” medications in older adults with a history of falls or fractures in the 2012 American Geriatrics Society Beers Criteria.<sup>[79]</sup>

Our finding of the lack of adverse effects of antidepressants on HF in patients with DP is probably due to our stringent study

**Table 5**

**Number and per cent of patients with different defined daily dose of various antidepressants\*.**

DP	With	Without	Total
	27,822 (100.0%)	111,288 (100.0%)	
<b>Total</b>	<b>27,822 (100.0%)</b>	<b>111,288 (100.0%)</b>	<b>139,110</b>
<b>SSRI DDD</b>			
0–27	15,153 (54.5%)	110,605 (99.4%)	125,758
28–83	4333 (15.6%)	370 (0.3%)	4703
84–167	2493 (9.0%)	109 (0.1%)	2602
168–335	2198 (7.9%)	100 (0.1%)	2298
≥336	3645 (13.1%)	104 (0.1%)	3749
<b>TCA DDD</b>			
0–27	25,810 (92.8%)	110,399 (99.2%)	136,209
28–83	1013 (3.6%)	548 (0.5%)	1561
84–167	435 (1.6%)	192 (0.2%)	627
168–335	317 (1.1%)	103 (0.1%)	420
≥336	247 (0.9%)	46 (0.0%) <sup>†</sup>	293
<b>SNRI DDD</b>			
0–27	25,324 (91.0%)	111,235 (100.0%)	136,559
28–83	842 (3.0%)	22 (0.0%) <sup>†</sup>	864
84–167	488 (1.8%)	15 (0.0%) <sup>†</sup>	503
168–335	454 (1.6%)	9 (0.0%) <sup>†</sup>	463
≥336	714 (2.6%)	7 (0.0%) <sup>†</sup>	721
<b>Others DDD</b>			
0–27	22,357 (80.4%)	110,893 (99.6%)	133,250
28–83	2366 (8.5%)	248 (0.2%)	2614
84–167	1217 (4.4%)	80 (0.1%)	1297
168–335	914 (3.3%)	39 (0.0%) <sup>†</sup>	953
≥336	968 (3.5%)	28 (0.0%) <sup>†</sup>	996

DDD = defined daily dose, DP = depression, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

\* Others include mirtazapine, burpropion, trazodone, and MAOI.

<sup>†</sup> Less than 0.05.

design. Since the effect of antidepressants on HF is not immediate, we only examined patients with DP who were on antidepressants with a dose greater than 28 DDD for more than 6 months. Hubbard et al<sup>[66]</sup> found negative impact of both TCA and SSRI drugs on HF only during the first week of treatment. Another report of similar finding was that of van den Brand et al<sup>[55]</sup> who found that current use of both SSRIs and TCAs increased hip or femur fracture risk. Arbouw et al<sup>[56]</sup> also found that current use of dopaminergic drugs (1–30 days before the index date) was associated with an increased risk of hip or femur fractures, but the risk rapidly decreased to baseline levels when treatment was discontinued for more than 1 year. Another reason for the discrepancy in results is that we only examined HF, whereas most of previous studies investigated all fractures.

There were several strengths in our study. We used a large and nationally representative cohort. We determined the relative contribution of both DP and treatment of DP to the incidence of HF. We also explored different classes of antidepressants on HF risk. The cohort study design of our research with a 1:4 case to control match avoided the problem of selection bias. To investigate whether the use of antidepressants increases the risk of HF, we evaluated effects of antidepressants on HF based on DDD not on days of prescription (Table 3), and followed patients up to 12 years (1998–2009). Furthermore, DP in our study was diagnosed by psychiatrists, and not by self-evaluations of patients. A major limitation of our study was that the use of antidepressants was based on prescription records, and not on compliance. This is a common limitation of almost all similar studies as it is very difficult to trace compliance. Another limitation of this study was the lack of information regarding the

**Table 6****Adjusted hazard ratios of antidepressants on hip fracture.**

Variables	HR*	95% CI	P
SSRI (ref: none)			
All SSRIs	1.02	0.78–1.34	0.884
Fluoxetine	1.15	0.82–1.62	0.425
Citalopram	1.18	0.71–1.97	0.519
Paroxetine	1.14	0.72–1.81	0.573
Sertraline	0.80	0.52–1.22	0.303
Fluvoxamine	1.02	0.42–2.48	0.962
Escitalopram	0.60	0.22–1.62	0.317
TCA (ref: none)	0.80	0.52–1.23	0.299
SNRI (ref: none)	1.18	0.70–2.00	0.532

CI=confidence interval, HR=hazard ratio, SNRI=serotonin-norepinephrine reuptake inhibitor, SSRI=selective serotonin reuptake inhibitor, TCA=tricyclic antidepressant.

\*Multivariate HRs were adjusted for sex, age, urbanization, CCI, and osteoporosis.

severity of depressive disorders of patients at the time of fracture. Since the severity of DP is a major confounder in the final outcome, it is not possible to conclude that DP increased HF rates due to apathy, negligence, motor retardation, or adverse effects of antidepressants. As the information on smoking, alcohol consumption, exercise, diet, serum vitamin D levels, and nutrition supplements that may also affect bone health is not in the database, their effects on HF could not be evaluated.

Based on the results of this study, we postulate that it is the disease (i.e., DP)—not treatment of the disease—that predisposes patients to HF. Therefore, we propose that Taiwanese patients with MDD should be effectively treated with antidepressants, so that they can become better in managing their food intake, sleep behavior, and physical activities, thus decreasing the chance of falling and incidence of HF.

## 5. Conclusions

In this study, we found MDD, but not dysthymia or depressive disorder, not otherwise specified, a risk factor for HF. Females and older people had a higher risk of HF. We also found that antidepressants had no effect on HF rates in the Taiwanese population. Since this observation is contrary to those of previous studies in Western countries, additional studies in this regard in the Taiwanese population are needed.

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