Depression and the Risk of Peptic Ulcer Disease
A Nationwide Population-Based Study

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Abstract: The risk of peptic ulcer disease (PUD) among patients with depression has raised concern. This study determined the association between depression and the subsequent development of PUD using claims data.

Patients newly diagnosed with depression in 2000 to 2010 were identified as depression cohort from the Taiwan National Health Insurance Research Database. The comparison cohort was randomly selected from subjects without depression, frequency matched by age and gender and diagnosis date, with a size 2-fold of the size of the depression cohort. The incidence of PUD was evaluated for both cohorts by the end of 2011. We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) of PUD using the Cox proportional hazards regression model.

The depression cohort consisted of 23,536 subjects (129,751 person-years), and the comparison cohort consisted of 47,069 subjects (285,592 person-years). The incidence of PUD was 2-fold higher in the depression cohort than in the comparison cohort (33.2 vs 16.8 per 1000 person-years) with an age adjusted HR of 1.97 (95% CI = 1.89–2.06) or a multivariable adjusted HR of 1.35 (95% CI = 1.29–1.42).

Depression might increase the risk of developing PUD. Prospective clinical studies of the relationship between depression and PUD are warranted.

INTRODUCTION
Depression, a type of mood disorder, is characterized by emotional dysregulation and depressive cognition, which induces distress in patients.1 In patients with depression, stress not only plays a major role in pathogenesis but also is associated with the disturbance of the hypothalamus-pituitary-adrenal (HPA) axis.2 Additionally, patients with depression have been reported to experience somatic consequences associated with HPA axis dysregulation.3 Regarding the gastrointestinal (GI) system, evidences have shown that depression is associated with irritable bowel syndrome, ulcerative colitis, dyspepsia, and gastroesophageal reflux disease.4–6 However, few studies have reported evidence regarding the relationship between peptic ulcer disease (PUD) and depression.

PUD, including gastric and peptic ulcers, is a prevalent GI disease with a high mortality.7 Evidence has shown that both physical stress and psychological stress are closely related to PUD.8,9 Notably, PUD risk among schizophrenia or anxiety disorder patients has been documented.10,11 but not for depression patients. To make the diagnosis of unipolar depression, patient should not have mania or hypomania, or their diagnosis should be bipolar disorders (BD) instead.12 However, evidence had shown that some patients with BD have unipolar depression as their initial presentation, before mania or hypomania.13 Even

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though the differential diagnosis between BD and unipolar depression was challenging, they shared the common manifestation of having depressive episode.14 Particularly, we have previously demonstrated a positive association between BD and PUD.15 However, we could not identify whether the depression, mania, or hypomania predisposed the patients having subsequent PUD. Therefore, we investigated the association between depression and PUD. We hypothesized that if depression was associated with subsequent PUD, more concern would be raised among patients with unipolar depression or depressive episode of BD.

To test the study hypothesis, we designed a nationwide population-based study to compare the incidence rates of PUD between cohorts with and without depression using longitudinal insurance data.

**METHODS**

**Data Source**

Outpatient and inpatient claims data documented in the Longitudinal Health Insurance Database (LHID) of Taiwan were used in this study. The LHID containing annual claims data from 1 million randomly selected insurants based on the Taiwan National Health Insurance (NHI) program established in 1996 and updated annually by the National Health Research Institutes (NHRI) thereafter. The NHI program is a universal single-payer system that covers >99% of the 23.74 million residents of Taiwan. The NHRI provided scrambled identification numbers that were used to connect each person’s relevant claims information, including sex and date of birth, registry for medical services, and medication prescriptions. Disease definition in the LHID is based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

In accordance with the Personal Information Protection Act, identification of beneficiaries was recoded by a computer. This study was approved to follow the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB had specifically waived the consent requirement.

**Study Cohorts Selection**

This was a retrospective cohort study using the population-based insurance claims data to establish study cohorts. Patients aged 20 years and older with newly diagnosed with depression (ICD-9 codes 296.2, 296.3, 300.4, 311) from 2000 to 2010 and free of PUD (ICD-9-CM codes 531–533) were identified and selected into the depression cohort (Figure 1). The index date was used and defined as the first date on which depression was diagnosed from the medical records in LHID. The insured population without the history of depression and PUD in the LHID were randomly selected into the comparison cohort frequency matched by age (within 5 years), gender, and index date. The enrollment date for the subject in the comparison cohort was matched with the same year and month of the subject in the depression cohort, whereas the day was randomly assigned. The sample size of the comparison cohort was 2-fold of the depression cohort. Subjects without demographic information at the baseline were excluded from the study cohorts.

**Endpoint of Study**

The major endpoint in this study was the development of PUD (ICD-9-CM codes 531–533). Person-years of follow-up were calculated for each person until PUD was diagnosed or censored for death (119 and 129, respectively) and withdrawing from the insurance system due to the loss of follow-up, moving abroad or imprisonment, and so on, (2170 and 3205, respectively), or the end of 2011.

**Comorbidities and Medications**

Comorbidities and medications were considered as possible confounding factors. The examined comorbidities

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**FIGURE 1.** Flowchart of establishing the study cohorts.
were chronic liver disease and cirrhosis (ICD-9-CM code 571), hypertension (HTN) (ICD-9-CM code 401–405), diabetes mellitus (DM) (ICD-9-CM code 250), asthma (ICD-9-CM code 493), chronic kidney disease (CKD) (ICD-9-CM code 585), coronary artery disease (CAD) (ICD-9-CM codes 410–414), alcoholism (ICD-9-CM codes 291, 303, 305.00, 305.01, 305.02, 305.03, 790.3, and V11.3), tobacco dependency (ICD-9-CM code 305.1), chronic obstructive pulmonary disease (COPD) (ICD-9-CM codes 490, 491, 496), anxiety (ICD-9-CM code 300.0), and helicobacter pylori (ICD-9-CM code 041.86), identified before the index date according to inpatient and outpatient files. And the examined medications were nonsteroidal anti-inflammatory drugs (NSAIDs), anxiolytics, and benzodiazepines (BZDs) that were used before the index date according to inpatient and outpatient files. Available antidepressants were divided into 2 groups, selective serotonin reuptake inhibitors (SSRIs) and non-SSRIs.

**Statistical Analysis**

The distributions of these 2 cohorts were presented by the mean and standard deviation (SD) for age and frequency of medical visits (per year during the study period) and numbers and proportions for gender, occupation, monthly income (NTD), comorbidities, and medication uses. Student’s \( t \) test and chi square test were applied to test differences in the continuous and categorical variables between the depression and comparison cohorts. The cumulative incidence curves of PUD were estimated for the 2 cohorts using the Kaplan–Meier method, and the log-rank test was used to evaluate the difference between the curves. The sex-, age-, tobacco dependency-, NSAID-, and comorbidity-specific incidences of PUD per 1000 person-years of follow-up for each cohort were calculated. We used Cox proportional hazards regression models to examine the hazard ratios (HRs) with 95% confidence intervals (CIs) of depression patients developing PUD relative to the

### TABLE 1. Comparisons in Demographic Characteristics and Comorbidities in Patient With and Without Depression

| Characteristic                              | No (N = 47069) | Yes (N = 23536) | P Value |
|---------------------------------------------|----------------|----------------|---------|
| Gender                                      |                |                | 0.99    |
| Women                                       | 28,846 (61.3)  | 14,424 (61.3)  |         |
| Men                                         | 18,223 (38.7)  | 9112 (38.7)    |         |
| Age stratified                              |                |                | 0.99    |
| ≤49                                         | 19,870 (42.2)  | 9934 (42.2)    |         |
| 50–64                                       | 20,040 (42.6)  | 10,021 (42.6)  |         |
| ≥65                                         | 7159 (15.2)    | 3581 (15.2)    |         |
| Age, mean ± SD*                             | 45.3 (16.7)    | 45.6 (16.6)    | 0.02    |
| Frequency of medical visits/per year in the study period | 14.7 (13.6) | 29.0 (21.3) | <0.001 |
| Occupation                                  |                |                | <0.001  |
| White collar                                | 25,716 (54.6)  | 12,088 (51.4)  |         |
| Blue collar                                 | 15,111 (32.1)  | 7369 (31.3)    |         |
| Others\(^1\)                                | 6242 (13.3)    | 4079 (17.3)    |         |
| Monthly income (NTD)\(^1\)                 |                |                | <0.001  |
| <15,000                                     | 12,026 (25.6)  | 6511 (27.7)    |         |
| 15,000–19,999                               | 21,856 (46.4)  | 11,029 (46.9)  |         |
| ≥20,000                                     | 13,187 (28.0)  | 5396 (25.5)    |         |
| Comorbidity                                 |                |                |         |
| Chronic liver disease and cirrhosis         | 5000 (10.6)    | 4487 (19.1)    | <0.001  |
| Hypertension                                | 8797 (18.7)    | 6457 (27.4)    | <0.001  |
| Diabetes mellitus                           | 2391 (5.08)    | 1832 (7.78)    | <0.001  |
| Asthma                                      | 1753 (3.72)    | 1457 (6.19)    | <0.001  |
| Chronic kidney disease                      | 300 (0.64)     | 281 (1.19)     | <0.001  |
| Coronary artery disease                     | 3415 (7.26)    | 3254 (13.8)    | <0.001  |
| Alcoholism                                  | 215 (0.46)     | 857 (3.64)     | <0.001  |
| Tobacco dependency                          | 219 (0.47)     | 296 (1.26)     | <0.001  |
| COPD                                        | 2297 (4.88)    | 1926 (8.18)    | <0.001  |
| Anxiety                                     | 1066 (2.26)    | 4801 (20.4)    | <0.001  |
| Helicobacter pylori                         | 154 (0.33)     | 92 (0.39)      | 0.18    |
| Medication                                  |                |                | <0.001  |
| NSAID                                       | 41,167 (87.5)  | 22,208 (94.4)  | <0.001  |
| Anxiolytics                                 | 29,576 (62.8)  | 22,875 (97.2)  | <0.001  |
| Benzodiazepine                              | 25,362 (53.9)  | 22,094 (93.9)  | <0.001  |

\(^1\) Chi square test, \( t \) test.
\(^2\) NTD: New Taiwan Dollars per month. One New Taiwan Dollar equals 0.03 US Dollar.
\(^3\) Other occupations included primarily retired, unemployed, or low-income populations.

COPD = chronic obstructive pulmonary disease; NSAIDs = nonsteroidal anti-inflammatory drugs; SD = standard deviation.
comparison cohort. We first adjusted for age in the Cox model. The multivariable Cox model was then used controlling for age, sex, and comorbidities of cirrhosis, HTN, DM, asthma, CKD, CAD, alcoholism, COPD, and anxiety as well as the use of NSAIDs, anxiolytics, and BZDs. The proportional hazard model assumption was also examined using a test of scaled Schoenfeld residuals. In the model evaluating the PUD risk throughout overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for depression and follow-up time, suggesting that the proportionality assumption was violated ($P$ value $= 0.002$). In the subsequent analyses, we stratified the follow-up duration to deal with the violation of proportional hazard assumption. Data management and statistical analysis were performed using SAS 9.3 (SAS Institute, Cary, NC). The statistical significance was defined as a (2-sided) $P$ value $< 0.05$.

**RESULTS**

The depression cohort consisted of 23,536 subjects (129,751 person-years), and the control cohort consisted of 47,069 subjects without depression (285,592 person-years). (Table 1). The distributions of gender and age were similar in both cohorts. Of the study patients, 61.3% were women, with 42.2% being $\leq$ 49 years old. The mean age of the depression cohort was 45.6 ($SD = 16.6$) years, and the mean age of the comparison cohort was 45.3 ($SD = 16.8$) years. The prevalence rates of comorbidities and medications were greater in the depression cohort than in the comparison cohort (all $P$ values $< 0.001$). The mean follow-up time was 5.51 ($SD = 3.31$) years for the depression cohort and 6.07 ($SD = 3.23$) years for the comparison cohort.

After a 12-year follow-up, the Kaplan–Meier method estimated cumulative incidence of PUD was 9.47% higher in the depression cohort than that in the comparison cohort (27.0% vs 17.53%; $P < 0.001$) (Figure 2).

The incidence of PUD was 2-fold higher in the depression cohort than in the comparison cohort (33.2 vs 16.8 per 1000 person-years) with an age adjusted HR of 1.97 (95% CI $= 1.89$, 2.06) or a multivariable adjusted HR of 1.35 (95% CI $= 1.29$–1.42) (Table 2). The incidence rate of PUD was consistently higher in the depression cohort than in the comparison cohort in each stratum by gender, age, NSAID use, comorbidity, and follow-up year, except tobacco dependency. The PUD incidence increased with age and decreased with follow-up year. However, the depression cohort to the comparison cohort relative HR decreased with age and follow-up year. For those with tobacco dependency, the PUD incidence was lower in the depression cohort than in controls, but not significant.

Table 3 shows the PUD associations with socioeconomic status. Subjects of nonwhite collar and middle income were at significantly higher hazard of PUD. Almost all comorbidity and drug use factors were related with greater PUD except tobacco dependency.

Table 4 shows that among 23,536 depression cases, those who did not receive any treatment had the highest incidence of PUD, 55.2 per 1000 person-years with an adjusted HR of 2.27 (95% CI 2.07, 2.48) for PUD compared to the comparison cohort. Treatment reduced the incidence to 31.0 per 1000 person-years for those took SSRI.

Table 5 shows that depression patients were diagnosed mainly in outpatient setting (84.70%) and by general physicians (84.47%). The PUD incidence was higher in those to be diagnosed as inpatients than as outpatients. Patients cared by psychiatrists were associated with a lower risk of PUD.

**DISCUSSION**

This was the first population-based study, which examined depression as a risk factor for PUD by using matched cohorts and a long-term (12-y) follow-up period. As expected, results of this study showed that patients with depression were at an elevated risk of developing PUD. We hypothesized that the possible mechanism may be associated with the HPA axis. The HPA axis is closely related to stress, and a disturbed HPA axis response has been noted in patients with depression, which seems to be a stress-related disorder. In addition, psychological stress has been considered as a risk factor for PUD. As a type of psychological stress, depression is characterized by a high risk of lifelong persistence and chronic course. Animal models have shown that corticosterone may be ulcerogenic under chronic stressful conditions. Consequently, depression may increase the risk of PUD.

In the analyzed of risk factors associated with subsequent PUD in patients with depression, we found that patients with comorbidities, except tobacco dependency, were at a risk of developing PUD. Studies have shown that there is a dose–dependent relationship between chronic illness and depression. In other words, the longer chronic comorbidities persist, the higher the psychological stress patients may experience. Consequently, patients with depression and the aforementioned comorbidities may have an elevated risk of subsequent PUD. On the other hand, patients with depression were reported having positive association with tobacco dependence. Tobacco use was seemed as self-medication for mood disturbance and negative affectivity in patients with depression. Although smoking was a risk factor for PUD, smoking was also reported slowing the progression of depression. Hence, further progression of the association between depression and PUD may be delayed under the concern of this paradoxical effect.

Alcohol use disorders have been reported as major problems in patients with depression, and alcoholism is an
As a result, the course of depression was affected, antidepressants would impair the neurogenesis of hippocampus damage caused by disturbed HPA axis. However, the use of NSAIDs is a known risk factor for PUD. Furthermore, patients with depression at high stress levels are at a higher risk of inappropriate use of anxiolytics and BZDs. Also, in depression, antidepressants were used under the consideration of restoring the level of brain-derived neurotrophic factor and the prevention of further hippocampus damage caused by disturbed HPA axis. However, the animal model was reported that concurrent use of BZDs and antidepressants would impair the neurogenesis of hippocampus. As a result, the course of depression was affected, and the risk of subsequent PUD increased.

Comorbidities of cirrhosis, hypertension, diabetes mellitus, asthma, chronic kidney disease, coronary artery disease, alcoholism, tobacco dependency, COPD, anxiety, and *Helicobacter pylori* were classified as the comorbidity group.

| Comorbidity | No | Yes | Age-adjusted HR* (95% CI) | Adjusted HR† (95% CI) |
|-------------|----|-----|--------------------------|----------------------|
| No          | 4790 | 284,889 | 16.8 | 1.98 (1.90, 2.06)*** | 1.24 (1.18, 1.30)*** |
| Yes         | 18 | 703 | 25.6 | 0.93 (0.49, 1.76) | 0.52 (0.24, 1.12) |
| NSAID       | No | 508 | 42,883 | 11.9 | 1.84 (1.55, 2.17)*** | 1.01 (0.81, 1.25) |
| Yes         | 4300 | 242,709 | 17.7 | 1.93 (1.85, 2.02)*** | 1.25 (1.19, 1.31)*** |
| Years of follow-up | | | | | |
| ≤1          | 889 | 46,262 | 19.2 | 2.12 (1.98, 2.27)*** | 1.19 (1.10, 1.29)*** |
| 2–3         | 1517 | 81,603 | 18.6 | 1.57 (1.48, 1.65)*** | 1.13 (1.07, 1.20)*** |
| 4–5         | 1074 | 64,726 | 16.6 | 2.76 (2.53, 3.01)*** | 1.61 (1.46, 1.78)*** |
| ≥5          | 1328 | 93,000 | 14.3 | 2.07 (1.93, 2.23)*** | 1.43 (1.32, 1.56)*** |

In consideration of this close relationship, this study also showed that patients with depression and alcoholism had a higher risk of subsequent PUD than those without alcoholism. Depression has been associated with a neuroinflammatory mechanism. However, the use of NSAIDs is a known risk factor for PUD. Furthermore, patients with depression at high stress levels are at a higher risk of inappropriate use of anxiolytics and BZDs. Also, in depression, antidepressants were used under the consideration of restoring the level of brain-derived neurotrophic factor and the prevention of further hippocampus damage caused by disturbed HPA axis. However, the animal model was reported that concurrent use of BZDs and antidepressants would impair the neurogenesis of hippocampus. As a result, the course of depression was affected, and the risk of subsequent PUD increased.

Our study is the first longitudinal study using population-based data to examine depression as a risk factor for the subsequent PUD occurrence. The strength of our study is the age- and gender-matched design cohorts with and without depression with a maximum of 12 years follow-up and adequate adjustments for comorbidities and drug uses in data analysis. However, our study has several limitations that are inherent in the use of claims databases. First, the diagnoses of depression in the NHIRD were based on ICD-9-CM codes. Thus, the severity of depression as a risk factor for subsequent PUD was not explored. Second, as mentioned above, unipolar depression still had the possibility to reach the diagnosis of BD, if patients had mania or hypomania after their depression. Hence, we could not exactly confirm this condition, especially beyond our follow-up years. Third, our further data analysis showed that PUD were diagnosed mainly based on clinical symptoms (79.4%) and few were diagnosed with oesophageal-gastro-duodenoscopy (OGD) (20.6%). However, the corresponding adjusted HR of PUD for patients with depression was slightly higher for those diagnosed with OGD than those diagnosed by clinical symptoms. Fourth, the associations were assessed by the chronological order in which these two diseases were diagnosed as the comorbidity group.
### TABLE 3. Hazard Ratios of Peptic Ulcer Disease in Association With Gender, Age, and Comorbidities in Univariable and Multivariable Cox Regression Models

| Variable                                      | Crude*        | Adjusted†       |
|-----------------------------------------------|---------------|-----------------|
|                                              | HR (95%CI)    | HR (95%CI)      |
| Age, years                                   | 1.03 (1.02, 1.03)*** | 1.02 (1.02, 1.02)*** |
| Sex (female vs male)                         | 1.03 (0.99, 1.07)*** | 1.05 (1.01, 1.10)*** |
| Frequency of medical visits/year             | 1.03 (1.02, 1.03)*** | 1.02 (1.02, 1.02)*** |
| Occupation                                    |               |                 |
| White collar                                  | 1 (Reference) | 1 (Reference)   |
| Blue collar                                   | 1.47 (1.40, 1.54)*** | 1.10 (1.04, 1.16)*** |
| Others                                        | 1.43 (1.35, 1.52)*** | 1.12 (1.05, 1.19)*** |
| Monthly income (NTD)                          |               |                 |
| < 15,000                                      | 1.13 (1.06, 1.19)*** | 0.95 (0.89, 1.01) |
| 15,000–19,999                                 | 1.22 (1.16, 1.28)*** | 1.06 (1.00, 1.12) |
| ≥ 20,000                                      | 1 (Reference) | 1 (Reference)   |
| Baseline comorbidities (yes vs no)           |               |                 |
| Chronic liver disease and cirrhosis          | 1.99 (1.90, 2.10)*** | 1.31 (1.25, 1.38)*** |
| Hypertension                                 | 2.31 (2.21, 2.41)*** | 1.07 (1.01, 1.13) |
| Diabetes mellitus                            | 2.07 (1.93, 2.22)*** | 0.95 (0.88, 1.02) |
| Asthma                                       | 1.78 (1.64, 1.93)*** | 1.01 (0.93, 1.10) |
| Chronic kidney disease                       | 3.02 (2.58, 3.54)*** | 1.18 (1.00, 1.39) |
| Coronary artery disease                      | 2.59 (2.45, 2.73)*** | 1.12 (1.05, 1.19) |
| Alcoholism                                    | 1.56 (1.35, 1.81)*** | 1.26 (1.08, 1.46)*** |
| Tobacco dependency                            | 0.91 (0.67, 1.25) | 0.73 (0.53, 1.00) |
| COPD                                          | 2.32 (2.17, 2.48)*** | 1.04 (0.97, 1.12) |
| Anxiety                                       | 1.72 (1.61, 1.83)*** | 1.03 (0.96, 1.10) |
| *Helicobacter pylori*                         | 2.42 (1.93, 3.03)*** | 2.22 (1.77, 2.77)*** |
| Medicine                                      |               |                 |
| NSAID                                         | 1.66 (1.54, 1.79)*** | 1.10 (1.01, 1.19) |
| Anxiolytics                                   | 2.28 (2.15, 2.42)*** | 1.12 (1.00, 1.25) |
| Benzodiazepine                                | 2.23 (2.12, 2.35)*** | 1.13 (1.02, 1.24) |

CI = confidence interval, COPD = chronic obstructive pulmonary disease, NSAIDs = nonsteroidal anti-inflammatory drugs, NTD = New Taiwan Dollars per month.

*Crude HR: relative hazard ratio.

†Adjusted HR: adjusted hazard ratio, mutually adjusted for age, gender, frequency of medical visits, occupation, monthly income, and comorbidities of cirrhosis, hypertension, diabetes mellitus, asthma, chronic kidney disease, coronary artery disease, alcoholism, tobacco dependency, COPD, anxiety, Helicobacter pylori, and medicine of NSAID, anxiolytics, and benzodiazepine in Cox proportional hazard regression.

* *P < 0.05.

** *P < 0.01.

*** *P < 0.001.

### TABLE 4. Incidence Rate and Hazard Ratio of Peptic Ulcer Disease Between Treatments for Depression

| Variables                      | N     | Event | PY   | IR     | Age-adjusted HR† (95% CI) | Adjusted HR† (95% CI) |
|-------------------------------|-------|-------|------|--------|---------------------------|----------------------|
| Without depression            | 47,069| 4808  | 285,592 | 16.8  | (Reference)               | (Reference)          |
| Depression                    |       |       |       |        |                           |                      |
| Without treatment             | 1919  | 527   | 9541 | 55.2   | 2.89 (2.64, 3.16)***      | 2.27 (2.07, 2.48)***  |
| With treatment                |       |       |       |        |                           |                      |
| Non-SSRI                      | 5130  | 929   | 28,174 | 33.0  | 1.72 (1.61, 1.85)***      | 1.19 (1.11, 1.29)***  |
| SSRI                          | 16,487| 2856  | 92,036 | 31.0  | 1.95 (1.86, 2.04)***      | 1.28 (1.21, 1.35)***  |

CI = confidence interval, IR = incidence rate (per 1000 person-years), SSRI = selective serotonin reuptake inhibitors.

*Age-adjusted HR: adjusted hazard ratio adjusted for age.

†Adjusted HR: adjusted hazard ratio, mutually adjusted for age, gender, frequency of medical visits, occupation, monthly income, and comorbidities of cirrhosis, hypertension, diabetes mellitus, asthma, chronic kidney disease, coronary artery disease, alcoholism, tobacco dependency, COPD, anxiety, Helicobacter pylori, and medicine of NSAID, anxiolytics, and benzodiazepine in Cox proportional hazard regression.

* *P < 0.05.

** *P < 0.01.

*** *P < 0.001.
TABLE 5. Incidence and Hazard Ratios of Peptic Ulcer Disease Measured for Outpatients and Inpatients and Patients Diagnosed by General Physicians and Psychiatrists

| Variables               | N   | Event | Rate\(^a\) | Age-adjusted HR\(^1\) (95% CI) | Adjusted HR\(^1\) (95% CI) |
|-------------------------|-----|-------|------------|--------------------------------|---------------------------|
| Without depression      |     |       |            |                                |                           |
| Depression              |     |       |            |                                |                           |
| Outpatient              | 19,936 | 3562  | 32.1       | 1.91 (1.83,1.99)**            | 1.32 (1.25,1.39)**       |
| Inpatient               | 3600  | 750   | 40.1       | 2.36 (2.19,2.55)**            | 1.52 (1.40,1.65)**       |
| Diagnosed by            |     |       |            |                                |                           |
| General physicians      | 19,882 | 3731  | 33.8       | 1.96 (1.88,2.05)**            | 1.35 (1.29,1.42)**       |
| Psychiatrists           | 3654  | 581   | 30.1       | 2.05 (1.88,2.24)**            | 1.30 (1.19,1.43)**       |

CI = confidence interval.
\(^a\)Rate, incidence rate, per 1000 person-years.
\(^1\)Adjusted HR, hazard ratio adjusted for age.

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diagnosed. However, the possibility that PUD causes depression cannot be entirely excluded. Finally, information regarding many demographic variables, such as education, lifestyle, and family history, was unavailable. We used alcoholism, tobacco dependency, and COPD to substitute the drinking and smoking behavior. Our results show that those with COPD were also at a higher hazard of PUD.

Depression is a disorder often unrecognized and untreated. The depression cohort identified in this study may not represent the average mild “depressive” persons and may reflect a group of persons with more severe depressive illness perhaps, or with some personal characteristics that make them more likely to seek medical attention and make claims. The findings thus may not be readily generalized to people with milder depression, depression uncomplicated by medical comorbidities, or the healthy population of smaller size. However, this study compares between 2 matched cohorts based on the same database and adjusts related factors, and the real relationship between depression and PUD risk is supposed to be revealed to a certain degree even though the generalization is limited.

In conclusion, this study suggests that depression increases the risk of developing PUD. On the basis of our data, we suggest that greater attention should be focused on female and aging patients, particularly those with comorbidities. Additional prospective clinical studies on the relationship between depression and PUD are warranted.

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