Association between psychiatric disorders and osteoarthritis: a nationwide longitudinal population-based study

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Abstract
Although the association between depressive disorders and osteoarthritis (OA) has been studied, the association of other psychiatric disorders with OA remains unclear. Here, we investigated whether psychiatric disorders are risk factors for OA.

The data were obtained from the Longitudinal Health Insurance Database 2005 of Taiwan. We collected the ambulatory care claim records of patients who were diagnosed with psychiatric disorders according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes between January 1, 2004 and December 31, 2008. The prevalence and adjusted hazard ratios (HRs) of osteoarthritis among patients with psychiatric disorders and the control cohort were estimated.

Of 74,393 patients with psychiatric disorders, 16,261 developed OA during the 7-year follow-up period. The crude HR for OA was 1.44 (95% confidence interval [CI], 1.39–1.49), which was higher than that of the control cohort. The adjusted HR for OA was 1.42 (95% CI, 1.39–1.42) among patients with psychiatric disorders during the 7-year follow-up period. Further analysis revealed that affective psychoses, neurotic illnesses or personality disorders, alcohol and drug dependence or abuse, and other mental disorders were risk factors for OA.

This large-scale longitudinal population-based study revealed that affective psychoses, personality disorders, and alcohol and drug dependence or abuse are risk factors for OA.

Abbreviation: CCI = Charlson comorbidity index, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, HRs = adjusted hazard ratios, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, LHID2005 = Longitudinal Health Insurance Database 2005, NHI = National Health Insurance, OA = Osteoarthritis.

Keywords: osteoarthritis, population-based study, psychiatric disorder, risk factor

1. Introduction
Osteoarthritis (OA), a slowly progressive degenerative arthritis or degenerative joint disease, includes a group of mechanical abnormalities involving subchondral bone and articular cartilage degradation of joints. OA can affect various joints such as the knee, hip, hand, and spine joints.\cite{1,2} Symptoms of OA include pain and stiffness of the affected joints; lower limb OA is associated with considerable physical disability and an increased economic burden on healthcare services.\cite{3,4}

Psychiatric disorders commonly occur worldwide, with their lifetime prevalence varying from 20% and 12% in Mexico and Turkey, respectively, to >40% in the Netherlands and the United States.\cite{5,6} In an international review, the average lifetime prevalence of schizophrenia was reported to be 0.4%.\cite{7} Regarding mood disorders, a survey study examining several countries demonstrated that the lifetime prevalence of major depressive and bipolar I disorders was 6.7% and 0.8%, respectively.\cite{8} A large-scale 5-year Norwegian survey study reported that the prevalence of personality disorders was 13.4%, which is in agreement with the results of an American survey study (14.79%).\cite{9,10} In clinical practice, psychiatrists, who frequently treat psychiatric disorders, generally focus on providing psychological therapy and prescribing antipsychotic medication.

The association between OA and psychiatric disorders has not been analyzed comprehensively. A previous study reported that patients with arthritis are predisposed to increased psychiatric
morbidit and that this morbidity is observed in various mental disorders.[8] Another study reported that OA is strongly correlated with mental health on the basis of the high prevalence of anxiety and depression (40.7%) among patients with OA.[9] The report also suggested that psychological evaluation and intervention should be included in the multidisciplinary clinical management of patients with OA. Other than the aforementioned studies, no study has analyzed whether psychiatric disorders are risk factors for OA; furthermore, the temporal association between psychiatric disorders and OA remains unknown. Therefore, in this large-scale longitudinal population-based cohort study, we investigated the association between a broad range of psychiatric disorders and OA risk.

2. Methods

We used the Longitudinal Health Insurance Database 2005 (LHID2005) of the National Health Insurance (NHI) Institutes of Taiwan to obtain data. This database contains 1 million randomly sampled beneficiaries[10] from a total of 2.3 million participants in the Taiwan NHI program, which covers 99% of the population of Taiwan. In our study cohort, psychiatric disorders were diagnosed between January 1, 2004 and December 31, 2008; the psychiatric disorders were schizophrenia (ICD-9-CM code: 295), affective psychoses (ICD-9-CM code: 296; including depression and bipolar disorders), a paranoid state and other nonorganic psychoses (ICD-9-CM codes: 297–298), neurotic illnesses or personality disorders (ICD-9-CM codes: 300–301), alcohol and drug dependence or misuse (ICD-9-CM codes: 303–305), and other mental disorders (ICD-9-CM codes: 306–316). We included patients with at least 2 consecutive ambulatory visits to the clinic in which psychiatric disorders were determined by a psychiatrist according to the diagnosis criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV); patients with >2 categories of psychiatric disorders were excluded. We also excluded patients who had OA (ICD-9-CM code: 715) before the diagnosis of psychiatric disorders. The patients in the control cohort (3:1 ratio relative to the study cohort) were selected from the LHID2005 and matched to the study cohort patients according to age and sex. Moreover, patients who had been diagnosed with a psychiatric disorder at least once according to the same criteria as those for the study cohort between 2004 and 2008 or had been diagnosed with OA before 2004 were excluded from the control cohort (Fig. 1). We obtained baseline variables, namely age, sex, and urbanization...
level (stratified into three levels: urban, suburban, and rural). We also obtained information on the following confounding factors for all patients: myocardial infarction (ICD-9-CM codes: 410 and 412), congestive heart failure (ICD-9-CM code: 428), cerebral vascular disease (ICD-9-CM codes: 430–438), rheumatic diseases (rheumatoid arthritis, ICD-9-CM code: 714.0; systemic lupus erythematosus, ICD-9-CM code: 710.0), diabetes mellitus with or without complications (ICD-9-CM code: 250), and the Charlson comorbidity index (CCI) score based on the 17 CCI variables recorded in the NHI database before the index date. The primary outcome was 2 consecutive OA diagnoses (according to clinical symptoms upon physical examination and/or radiographic study) and served as the study endpoint. Patients in both the study and control cohorts were followed from the index date to the endpoint (OA occurrence) or December 31, 2011. The NHIRD deidentifies and encrypts data, thus ensuring patient privacy and that researchers cannot trace individual patients or health service providers by using the data. Thus, this study was exempted from a complete review by any institutional review board.

3. Statistical analysis

Demographic characteristics and comorbidities were compared between the study and control cohorts by using the Fisher exact test or Pearson chi-square test. The Cox proportional hazard model was applied for calculating the hazard ratios (HRs) of OA between the study and control cohorts after separately adjusting for sex, age, urbanization level, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, liver disease, diabetes, paraplegia and hemiplegia, renal disease, cancer, acquired immunodeficiency syndrome (AIDS)/HIV, and the CCI. Because the traditional contributory risk factor of OA such as body weight and lifestyle cannot be controlled in this study, hence, we tried to control these possible covariates, which could be associated to these confounding factors (such as body weight, smoking, and drinking could be related to AMI, DM, CVA and lifestyle style could be related to dementia). Furthermore, we plotted the hazard curves of OA for the study and control cohorts according to the Kaplan-Meier method. In addition, we analyzed each psychiatric disorder (schizophrenia, affective psychoses, a paranoid state and other nonorganic psychoses, neurotic illnesses or personality disorders, alcohol and drug dependence or misuse, and other mental disorders) separately after adjusting for sex, age, urbanization level, and comorbidities by using the adjusted HR through the bootstrap method. The number of OA diagnosis codes at hospitals had a similar clustering tendency as long as the hospitals were naturally clustered in the LHID2005. We employed regression parameter estimation in the Cox model by using maximum partial likelihood estimates under an independent working assumption and used a robust sandwich covariance matrix estimate to account for the intracohort dependence and to eliminate the bias caused by clustering. The details of the robust sandwich covariance matrix estimate are presented in the appendix of a previous study. Moreover, we take the age as a confounding factor because of the degenerative character of OA and the model as follows: $H(t;X,U) = H_0(t)exp\beta_1X + \beta_2U$, where $X$ be a vector of observed Psychiatric Disorders, and $U$ be a matrix of observed confounding variables such as patient’s age, sex, CCI, and urbanization level. And considering older individual would be expected to have some degenerative changes, we use stratified analysis by patient aged more than 60 years old and younger than 60 years old of psychiatric disorders. The SAS statistical package (SAS System for Windows, Version 9.1.3; SAS Institute Inc., Cary, NC) and SPSS (Version 20) were used for statistical analysis, and $P < 0.001$ was considered statistically significant.

4. Results

Our study cohort comprised 82,218 patients with psychiatric disorders, whereas the control cohort comprised 246,654 age- and sex-matched patients without psychiatric disorders. The data in Table 1 show that compared with the control cohort, the patients with psychiatric disorders were more likely to exhibit comorbidities, namely myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, liver disease, diabetes, paraplegia and hemiplegia, renal disease, benign cancer, metastatic cancer, and AIDS/HIV, and high CCI scores with $P < 0.001$.

Table 2 lists the incidence, HRs, and adjusted HRs for OA in patients with psychiatric disorders and that in the control cohort after adjustment for patient age, sex, comorbidities (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, liver disease, diabetes, paraplegia and hemiplegia, renal disease, cancer, and AIDS/HIV), urbanization level, and the CCI. In patients with schizophrenia or a paranoid state or other nonorganic psychoses, the risk of developing OA did not increase significantly [adjusted HR of schizophrenia for OA was 0.89 [95% CI, 0.81–1.01, $P = 0.053$]; paranoid state or other nonorganic psychoses for OA was 1.00 [95% CI, 0.85–1.16, $P = 0.699$]]. For patients with affective psychoses such as depression and bipolar disorders, the adjusted HR for OA was 1.45 (95% CI, 1.38–1.53, $P < 0.001$). Moreover, during the 7-year follow-up period, the adjusted HRs for OA were 1.49 in patients with neurotic illnesses or personality disorders (95% CI, 1.45–1.53, $P < 0.001$); 1.30 in patients with alcohol and drug dependence or misuse (95% CI, 1.21–1.40, $P < 0.001$); and 1.45 in patients with other mental disorders (95% CI, 1.40–1.51, $P < 0.001$).

Table 4 showed both aged more than 60 years old and less than 60 years old psychiatric disorder patients had higher HR (≥60 years old: 1.56, 95% CI, 1.53–1.60, $P < 0.001$; ≤60 years old: 1.47, 95% CI, 1.45–1.48, $P < 0.001$) and adjusted HR (≥60 years old: 1.39, 95% CI, 1.35–1.43, $P < 0.001$; ≤60 years old: 1.33, 95% CI, 1.29–1.37, $P < 0.001$) for getting OA with comparison group with up to 7 years follow-up period.

5. Discussion

This large-scale population-based longitudinal study involving a 7-year follow-up period identified psychiatric disorders as risk factors for OA. We analyzed several psychiatric disorders. Our results indicated that affective psychoses, personality disorders, alcohol and drug dependence or misuse, and other mental disorders were risk factors for developing OA; conversely,
### Table 1
Demographic characteristics and comorbid medical disorders for patients with psychiatric diagnoses and patients in the non-psychiatric cohort, 2004–2008.

| Baseline variable                  | Psychiatric subjects n = 82,218 (%) | Non-psychiatric subjects n = 246,654 (%) | P     |
|-----------------------------------|-------------------------------------|------------------------------------------|-------|
| **Characteristics**               |                                     |                                          |       |
| **Sex**                           |                                     |                                          |       |
| Female                            | 47,637 (57.9)                      | 142,911 (57.9)                          |       |
| Male                              | 34,581 (42.1)                      | 103,743 (42.1)                          |       |
| **Age, y**                        |                                     |                                          |       |
| 18–30                             | 14,436 (17.6)                      | 43,308 (17.6)                           |       |
| 31–40                             | 16,155 (19.6)                      | 48,465 (19.6)                           |       |
| 41–50                             | 18,942 (23)                        | 56,826 (23)                             |       |
| 51–60                             | 14,421 (17.5)                      | 43,263 (17.5)                           |       |
| 61–70                             | 9470 (11.5)                        | 28,410 (11.5)                           |       |
| >70                               | 8794 (10.7)                        | 26,382 (10.7)                           |       |
| **Urbanization level**            |                                     |                                          | <.001 |
| Urban                             | 48,803 (59.4)                      | 148,009 (60.0)                          |       |
| Suburban                          | 23,728 (28.9)                      | 71,766 (29.1)                           |       |
| Rural                             | 9687 (11.8)                        | 26,879 (10.9)                           |       |
| **Comorbid medical disorders**    |                                     |                                          |       |
| **CCI**                           |                                     |                                          |       |
| Myocardial Infarction             | 520 (0.6)                          | 1241 (0.5)                              | <.001 |
| No                                | 81,698 (99.4)                      | 245,413 (99.5)                          |       |
| Congestive heart failure          | 3541 (4.3)                         | 7730 (3.1)                              | <.001 |
| Yes                               | 78,677 (95.7)                      | 238,924 (96.9)                          |       |
| No                                | 2814 (3.4)                         | 4452 (1.8)                              | <.001 |
| Peripheral vascular disease       | 79,404 (96.6)                      | 242,202 (98.2)                          | <.001 |
| Yes                               | 7418 (9)                           | 13,966 (5.7)                            | <.001 |
| No                                | 74,800 (91)                        | 232,688 (94.3)                          |       |
| Dementia                          | 2008 (2.4)                         | 2849 (1.2)                              | <.001 |
| Yes                               | 80,210 (97.6)                      | 243,805 (98.8)                          |       |
| Chronic pulmonary disease         | 18,094 (22)                        | 36,043 (14.6)                           | <.001 |
| Yes                               | 64,124 (78)                        | 210,611 (85.4)                          |       |
| No                                | 3284 (4)                           | 5539 (2.2)                              | <.001 |
| Peptic ulcer disease              | 23,825 (29)                        | 39,875 (16.2)                           | <.001 |
| Yes                               | 58,393 (78)                        | 206,779 (83.8)                          |       |
| No                                | 17,662 (21.5)                      | 31,774 (12.9)                           | <.001 |
| Mild liver disease                | 64,556 (78.5)                      | 214,880 (87.1)                          |       |
| Yes                               | 10,547 (12.8)                      | 26,040 (10.6)                           | <.001 |
| No                                | 71,671 (87.2)                      | 220,614 (89.4)                          |       |
| Diabetes without complications    | 79,556 (96.8)                      | 239,800 (97.2)                          | <.001 |
| Yes                               | 2662 (3.2)                         | 6854 (2.8)                              | <.001 |
| No                                | 1289 (1.6)                         | 2428 (1)                                | <.001 |
| Paraplegia and hemiplegia         | 80,929 (98.6)                      | 244,226 (99)                            |       |
| Yes                               | 2709 (3.3)                         | 5907 (2.4)                              | <.001 |
| No                                | 78,493 (95.5)                      | 237,022 (96.6)                          | <.001 |
| Cancer                            | 3725 (4.5)                         | 9632 (3.9)                              | <.001 |
| Yes                               | 81,965 (99.7)                      | 246,174 (99.8)                          | <.001 |
| No                                | 253 (0.3)                          | 480 (0.2)                               |       |
patients with schizophrenia and a paranoid state were not at risk of OA. The main factors associated with OA development are obesity, the female sex, being elderly, and a previous experience of trauma. Our study suggests that in addition to physical etiology, psychiatric disorders should be considered risk factors for OA.

The adjusted HR for OA was 1.45 in patients with affective psychoses such as depression and bipolar disorders. This outcome corroborates that of a previous study in which the possible risk factors for self-reported arthritis were investigated in patients with >5 depressive symptoms. Several reasons may underlie OA pathogenesis in patients with affective psychoses. Depression and OA are correlated because sensitivity to the pain caused by OA is elevated in patients with depression. A previous study indicated that when radiographic severity was controlled, increased OA joint pain symptoms were reported by patients with affective psychoses. Depression and OA are correlated because sensitivity to the pain caused by OA is elevated in patients with depression.

In this study, we observed that patients with personality disorders and neurotic illnesses were also at risk of developing OA. Our results corroborate those of a previous epidemiological association study on personality disorders and arthritis, which showed that compared with controls, patients with arthritis had a considerably higher incidence of each personality disorder examined, even after adjustment for relevant sociodemographic variables and the presence of medical conditions other than arthritis. The authors hypothesized that increased vulnerability of the patients to arthritis may be related to childhood adversities and the diathesis—stress model proposed by Weisberg and Keefe. In the present study, patients with alcohol and drug dependence or misuse were also more vulnerable to OA than those in the control cohort. However, our result disagrees with that of McWilliams et al, who used multivariate analyses and reported a negative association between arthritis and alcohol or substance abuse or dependence; however, they did not adjust the results for the confounding factor of age. In the present large-scale population-based study, we enrolled age- and sex-matched cohorts and conducted longitudinal follow-ups for eliminating age-related bias when examining the causes of OA.

Another possible mechanism of OA pathogenesis is the inflammation process occurring in patients with psychiatric disorders. OA was previously considered noninflammatory. A recent review article indicated that many patients with primary OA had synovitis and joint inflammation during the OA pathogenesis; the authors stated that inflammatory factors including cytokines, chemokines, adipokines, neuropeptides, and lipid inflammatory mediators have been implicated in the pathogenesis. In patients with psychiatric disorders, the involvement of inflammation was considered based on the results of a previous study showing that increased levels of inflammatory cytokines, such as IL-6 and tumor necrosis factor, in blood and cerebral spinal fluid were increased among depression patients regardless of their health condition. In addition, patients with OA have high cytokine levels in both blood and synovial fluid. Therefore, we believe that because psychiatric patients are prone to inflammation, they are at a higher risk of developing OA.

In contrast to other psychiatric disorders examined in this study, schizophrenia and a paranoid state were not risk factors.

### Table 2

Crude and adjusted hazard ratios for OA among the psychiatric sample patients during the 7-year follow-up period starting from the index ambulatory care visit.

| Presence of OA | Comparison | All psychiatric patients |
|----------------|------------|-------------------------|
|                | No.        | %                       | No.        | %                        |
| 7-year follow-up period |           |                         |            |                          |
| Yes            | 43,110     | 18.2                    | 16,261     | 21.9                     |
| No             | 193,658    | 81.8                    | 58,132     | 78.1                     |
| Crude HR (95% CI) | 1.00       |                         | 1.44† (1.39–1.49) |                           |
| Adjusted† HR (95% CI) | 1.00   |                         | 1.42† (1.39–1.42) |                           |

CI = confidence interval, HR = hazard ratio, OA = osteoarthritis.

† Adjustments are made for patients’ age, sex, Charlson comorbidity index (CCI) and urbanization level. In addition, this model uses a clustered method for the robust sandwich covariance matrix estimation to account for hospital clustering.

‡ Indicates P < 0.001.
for OA. In addition, patients with schizophrenia display impaired recognition of their own emotions and pain. Wojakiewicz et al.[23] investigated pain cognition among patients with schizophrenia and demonstrated that these patients failed to completely identify and categorize pain. Another experimental study demonstrated that patients with schizophrenia were more sensitive to acute pain but had decreased sensitivity to chronic pain.[24] Thus, we surmise that patients with schizophrenia report fewer joint pain symptoms.

Our study is the first large-scale longitudinal population-based study on the risk of developing OA among patients with a broad range of psychiatric disorders. However, several limitations of the study should be considered. First, the psychiatric disorders and OA were diagnosed on the basis of the ICD codes of the NHI database. The accuracy of the diagnoses remains poorly investigated. The Bureau of NHI has established various audit committees for verifying the accuracy of diagnoses and proper payment of insurance; these committees randomly sample claims data regularly and verify their diagnostic validity. Moreover, we selected only consecutively coded cases to prevent inaccurate codes in the database records from influencing our results. These methods can facilitate preventing bias in case selection. Second, because a broad range of psychiatric disorders was studied, the effect of psychiatric medications was complicated and could not be analyzed comprehensively. Moreover, even in the same disease classification category (both bipolar disorder and major depression are under the same ICD-9-CM code: 296), patients may have quite different clinical presentations and etiologies. Hence, although many psychiatric disorders were considered in this study, additional studies focusing on specific psychiatric disorders with similar clinical or etiological patterns must be conducted. Third, patients may have increased their frequency of using the medical resources because of somatization; thus, more patients diagnosed with OA may have been listed in the NHI database.

| Table 3 | Adjusted hazard ratios for OA among psychiatric patients in six diagnostic categories and comparison cohort. |
|---|---|
| Presence of OA during 7-year follow-up period | Yes/Total | Percentage | Adjusted HR (95% CI) | P value |
| Comparison patients | 43110/236968 | 18 | 1.00 (Reference) | – |
| Schizophrenia (ICD-9: 295) | 538/4121 | 13 | 0.89 (0.81–1.01) | 0.053 |
| Affective psychoses (ICD-9: 296) | 1698/7207 | 24 | 1.45 (1.38–1.53) | <0.001 |
| Paranoid states and other non-organic psychoses (ICD-9: 297–298) | 188/1045 | 18 | 1.00 (0.85–1.16) | 0.99 |
| Neurotic illness or personality disorders (ICD-9: 300–310) | 6151/33876 | 24 | 1.49 (1.45–1.53) | <0.001 |
| Alcohol and drug dependence or misuse (ICD-9: 303–305) | 893/6772 | 13 | 1.30 (1.21–1.40) | <0.001 |
| Other mental disorders (ICD-9: 306–316) | 4793/21372 | 22 | 1.45 (1.40–1.51) | <0.001 |

Adjustments are made for patients’ age, sex, Charlson Comorbidity Index (by myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer, liver disease, diabetes, paraplegia and hemiplegia, renal disease, cancer, metastatic cancer, and AIDS/HIV) and urbanization level. In addition, this model uses a bootstrap method for the robust 95% CI.

CI = confidence interval, HR = hazard ratio, ICD-9 = International Classification of Diseases, Ninth Revision, OA = osteoarthritis.
Table 4
Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for OA during up to 7 years follow-up period for patients with psychiatric and comparison group stratified by patient age.

| Presence of OA | Patient age (years) | <60 | >60 |
|----------------|---------------------|-----|-----|
|                | Comparison | All psychiatric patients | Comparison | All psychiatric patients |
| Crude HR (95% CI) | 1.00 | 1.56 (1.53–1.60) | 1.00 | 1.30 (1.35–1.43) |
| Adjusted HR (95% CI) | 1.00 | 1.47 (1.45–1.48) | 1.00 | 1.33 (1.29–1.37) |

Adjustments are made for patients’ sex, Charlson Comorbidity Index (CCI), and urbanization level. In addition, this model uses a clustered method for the robust sandwich covariance matrix estimation to account for hospital clustering.

In this study, we investigated the relationship between psychiatric disorders and the risk of developing OA. Our results indicate that patients with psychiatric disorders are at a risk of developing OA. We also found that the presence of OA was associated with certain psychiatric disorders. However, the mechanism of OA pathogenesis in these patients remains unclear. Factors such as body weight, psychiatric medication use, a sedentary lifestyle, and somatization should be considered in future studies to clarify the mechanism by which the psychiatric disorders separately affect OA.

6. Conclusions
The results of this population-based, longitudinal, case-controlled cohort study indicate that patients with psychiatric disorders are at a risk of developing OA. We analyzed a broad range of psychiatric disorders and determined that affective psychoses, neurotic illnesses or personality disorders, alcohol and drug dependence or misuse, and other mental disorders are risk factors for OA; by contrast, schizophrenia, a paranoid state, and other nonorganic psychoses are not associated with OA risk. However, the mechanism of OA pathogenesis in these psychiatric patients remains unclear. Factors such as body weight, psychiatric medication use, a sedentary lifestyle, and somatization should be considered in future studies to clarify the mechanism by which the psychiatric disorders separately affect OA.

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