Observational Study

Medicine®

OPEN

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

Shih-Wei Huang (MD)[a,b], Wei-Te Wang (MD)[c], Li-Fong Lin (PhD)[a,d], Chun-De Liao (MSc)[a], Tsan-Hon Liou (MD, PhD)[a,b,e], Hui-Wen Lin (PhD)[f,g,*]

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.[1–3] 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.[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.[4] In an international review, the average lifetime prevalence of schizophrenia was reported to be 0.4%.[5] 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.[6] 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%).[5,7] 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

Editor: Mirko Manchia.

This study is supported by the National Science Council of Taiwan.

This study is partly based on data obtained from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health, managed by National Health Research Institutes in Taiwan.

The authors have no conflicts of interest to disclose.

[a] Department of Physical Medicine and Rehabilitation, Shuang Ho Hospital, Taipei Medical University, [b] Department of Physical Medicine and Rehabilitation, School of Medicine, College of Medicine, Taipei Medical University, Taipei, [c] Department of Physical Medicine and Rehabilitation, Changhua Christian Hospital, Changhua, [d] Institute of Gerontology and Health Management, Taipei Medical University, [e] Graduate Institute of Injury Prevention, Taipei Medical University, [f] Department of Mathematics, Soochow University, [g] Evidence-Based Medicine Center, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan.

[*] Correspondence: Hui-Wen Lin, Department of Mathematics, Soochow University, 70 Linhsi Road, Shihlin, Taipei, Taiwan (e-mail: linhw@tmu.edu.tw).

Medicine (2016) 95:26(e4016)

Received: 4 February 2016 / Received in final form: 14 May 2016 / Accepted: 1 June 2016

http://dx.doi.org/10.1097/MD.0000000000004016

morbidity 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 23 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

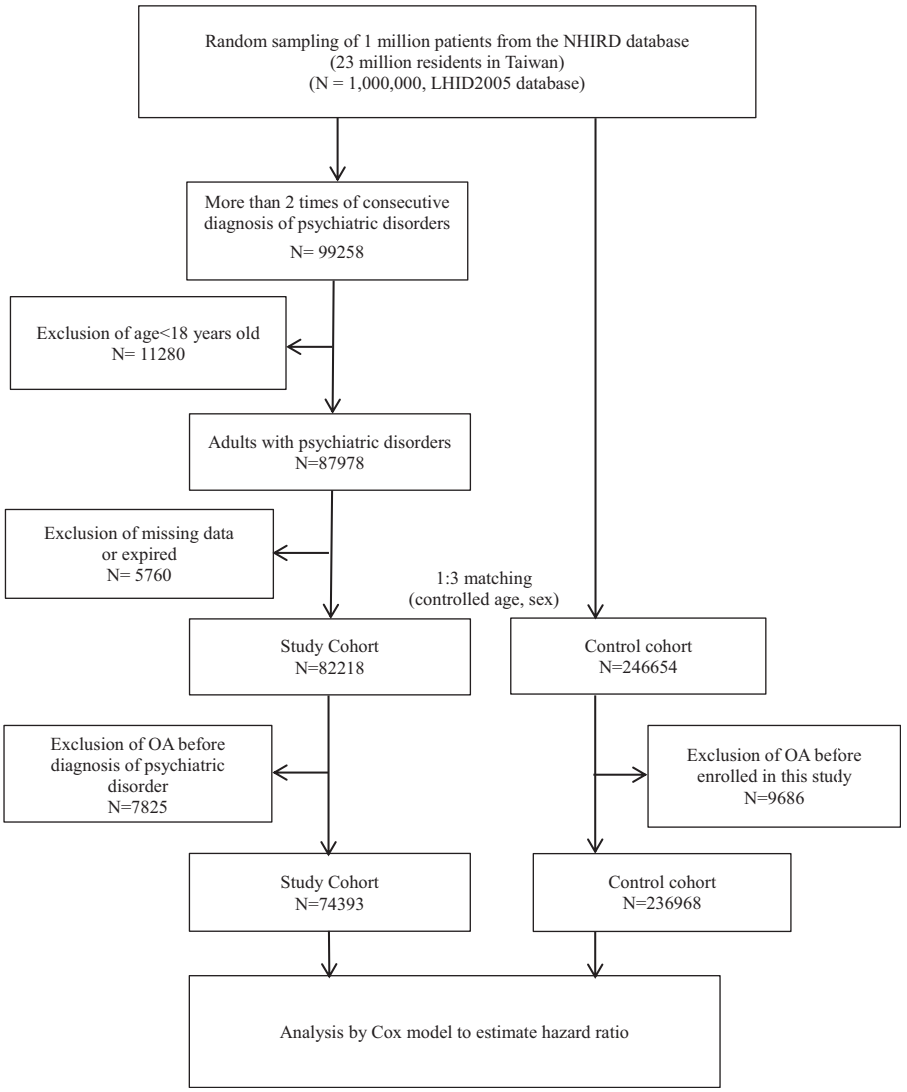

Figure 1. Flowchart diagram of data collection.

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.[11] Because the traditional contributing risk factor of OA such as body weight and life style 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 life 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 intracluster 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.[12] Moreover, we take the age as a confounding factor because of the degenerative character of OA and the model as follows: $H(t|X,U) = H_0(t)\exp\beta_1 X + \beta_2 U$, 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 the study and control cohorts. In 16,261 of the 74,393 patients with psychiatric disorders, OA was diagnosed up to 7 years of follow-up period. In these patients, the HR and adjusted HR for OA were 1.44 (95% confidence interval [CI], 1.39–1.49) and 1.42 (95% CI, 1.39–1.42), respectively, compared with the control cohort (Fig. 2).

Table 3 and Fig. 3 present the 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, $P = 0.99$]). 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*
	No	(%)	No	(%)	
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					<0.001
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					<0.001
Yes	520	0.6	1241	0.5	
No	81,698	99.4	245,413	99.5	
Congestive heart failure					<0.001
Yes	3541	4.3	7730	3.1	
No	78,677	95.7	238,924	96.9	
Peripheral vascular disease					<0.001
Yes	2814	3.4	4452	1.8	
No	79,404	96.6	242,202	98.2	
Cerebrovascular disease					<0.001
Yes	7418	9	13,966	5.7	
No	74,800	91	232,688	94.3	
Dementia					<0.001
Yes	2008	2.4	2849	1.2	
No	80,210	97.6	243,805	98.8	
Chronic pulmonary disease					<0.001
Yes	18,094	22	36,043	14.6	
No	64,124	78	210,611	85.4	
Connective tissue disease-rheumatic disease					<0.001
Yes	3284	4	5539	2.2	
No	78,934	96	241,115	97.8	
Peptic ulcer disease					<0.001
Yes	23,825	29	39,875	16.2	
No	58,393	71	206,779	83.8	
Mild liver disease					<0.001
Yes	17,662	21.5	31,774	12.9	
No	64,556	78.5	214,880	87.1	
Diabetes without complications					<0.001
Yes	10,547	12.8	26,040	10.6	
No	71,671	87.2	220,614	89.4	
Diabetes with complications					<0.001
Yes	2662	3.2	6854	2.8	
No	79,556	96.8	239,800	97.2	
Paraplegia and hemiplegia					<0.001
Yes	1289	1.6	2428	1	
No	80,929	98.6	244,226	99	
Renal disease					<0.001
Yes	2709	3.3	5907	2.4	
No	79,509	96.7	240,747	97.6	
Cancer					<0.001
Yes	3725	4.5	9632	3.9	
No	78,493	95.5	237,022	96.1	
Moderate or severe liver disease					<0.001
Yes	253	0.3	480	0.2	
No	81,965	99.7	246,174	99.8	

Baseline variable	Psychiatric subjects n = 82,218		Non-psychiatric subjects n = 246,654		P
	No	(%)	No	(%)	
Metastatic carcinoma					0.316
Yes	212	0.3	688	0.3	
No	82,006	99.7	245,996	99.7	
AIDS/HIV					<0.001
Yes	118	0.1	109	0.0	
No	82,100	99.9	246,545	100	
CCI score (SD)	1.22	(1.40)	0.79	(1.16)	<0.001

The Charlson comorbidity index (CCI) score was measured by the 17 Charlson comorbidity using the diagnoses recorded in the National Health Insurance database before the index date.
SD = standard deviation.

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.[13] 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.[14] 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 anxiety and depression.[15] Increased awareness of OA symptoms may simplify OA diagnoses in patients with depression disorders. Lithium is commonly administered to patients exhibiting manic episodes for treatment. A recent animal study revealed that lithium chloride can reduce catabolic events in interleukin (IL)-1β-treated human articular chondrocytes and reduce cartilage destruction in IL-1β-treated mouse femoral head explants and in surgically induced OA mouse models.[16] These findings may explain why patients with psychiatric disorders are at a higher risk of developing OA.

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.[17] 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.[18,19] In the present study, patients with alcohol and drug dependence or misuse were also more vulnerable to OA than were those in the control cohort. However, our result disagrees with that of McWilliams et al,[17] 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;[20] 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 on the basis of a recent brief report mentioning that the 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.[21] In addition, patients with OA have high cytokine levels in both blood and synovial fluid.[22] 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	193,858	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 $P < 0.001$.

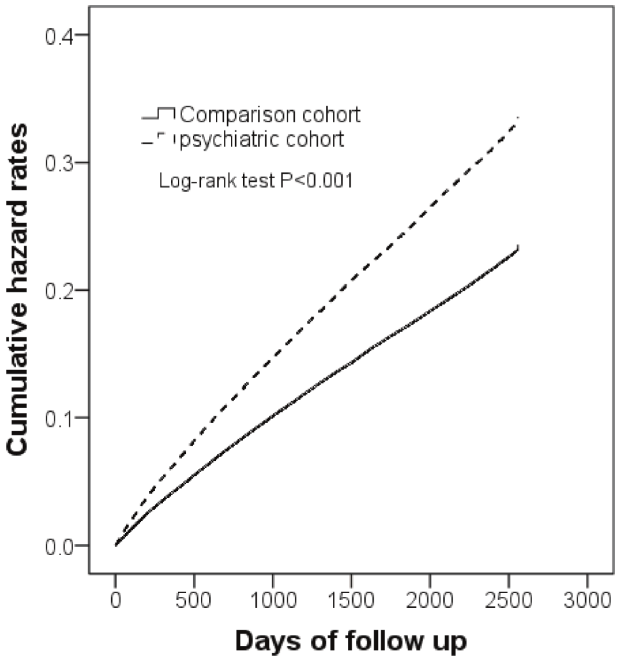

Figure 2. A hazard-rates plot of the Kaplan–Meier method for osteoarthritis in psychiatric disorder patients and the controls during the follow-up period of up to 7 years.

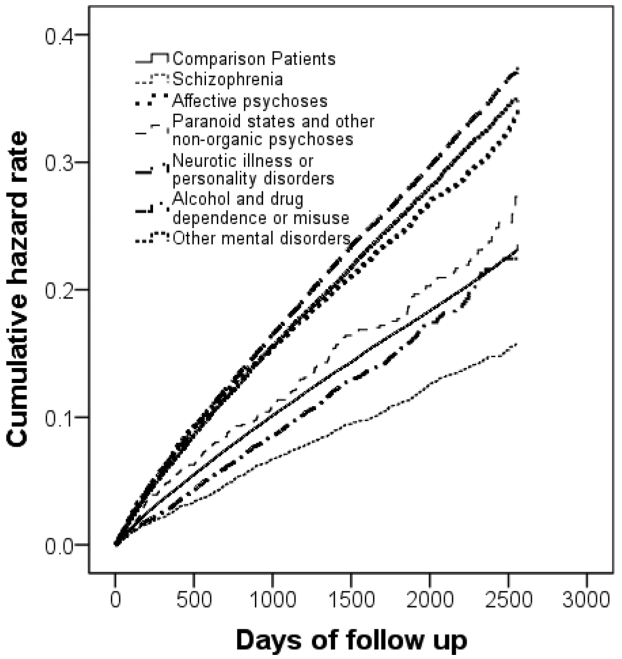

Figure 3. Hazard-rates plot of the Kaplan–Meier method for osteoarthritis in schizophrenia, affective psychosis, paranoid status and nonorganic psychoses, neurotic illness or personality disorders, alcohol and drug dependence or misuse, and other mental disorders patients and the controls during the follow-up period of up to 7 years.

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

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: 300–301)	8151/33876	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 is uses a bootstrap method for the robust BCa 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.

	Patient age (years)			
	≤60		>60	
Presence of OA	Comparison	All psychiatric patients	Comparison	All psychiatric patients
Crude HR (95% CI)	1.00	1.56* (1.53–1.60)	1.00	1.39* (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.

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

* Indicates $P < 0.001$.

administrative database. Fourth, our results were obtained through a retrospective cohort study. Hence, information regarding lifestyle, behavior, obesity, smoking, and substance and alcohol consumption could not be obtained. Finally, our study investigated patients diagnosed with psychiatric disorders from only one diagnostic category; patients with diagnoses made by a psychiatrist from more than one category were not considered.

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 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.

References

[1] Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum 1998;41:778–99.

[2] Andrianakos A, Trontzas P, Christoyannis F, et al. Prevalence of rheumatic diseases in Greece: a cross-sectional population based epidemiological study. The ESORDIG Study. J Rheumatol 2003;30: 1589–601.

[3] Andrianakos A, Miyakis S, Trontzas P, et al. The burden of the rheumatic diseases in the general adult population of Greece: the ESORDIG study. Rheumatology 2005;44:932–8.

[4] Dieppe P, Cushnaghan J, Tucker M, et al. The Bristol 'OA500 study': progression and impact of the disease after 8 years. Osteoarthritis Cartilage 2000;8:63–8.

[5] Alonso J, Angermeyer MC, Bernert S, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand 2004;109:21–7.

[6] Consortium WWMHS . Prevalence, severity, and unmet need for treatment of mental disorders in the World Health Organization World Mental Health Surveys. JAMA 2004;291:2581–90.

[7] Kessler RC, Chiu WT, Demler O, et al. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity survey replication. Arch Gen Psychiatry 2005;62:617–27.

[8] Patten SB, Williams JV, Wang J. Mental disorders in a population sample with musculoskeletal disorders. BMC Musculoskelet Disord 2006;7:37.

[9] Axford J, Butt A, Heron C, et al. Prevalence of anxiety and depression in osteoarthritis: use of the Hospital Anxiety and Depression Scale as a screening tool. Clin Rheumatol 2010;29:1277–83.

[10] Leucht S, Burkard T, Henderson J, et al. Physical illness and schizophrenia: a review of the literature. Acta Psychiatr Scand 2007;116:317–33.

[11] Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

[12] Lin SC, Lin HW. Urbanization factors associated with childhood asthma and prematurity: a population-based analysis aged from 0 to 5 years in Taiwan by using Cox regression within a hospital cluster model. J Asthma 2015;52:273–8.

[13] Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage 2010;18:24–33.

[14] Seavey WG, Kurata JH, Cohen RD. Risk factors for incident self-reported arthritis in a 20 year followup of the Alameda County Study Cohort. J Rheumatol 2003;30:2103–11.

[15] Creamer P, Lethbridge-Cejku M, Costa P, et al. The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging. Arthritis Care Res 1999;12:3–7.

[16] Minashima T, Zhang Y, Lee Y, et al. Lithium protects against cartilage degradation in osteoarthritis. Arthritis Rheumatol 2014;66:1228–36.

[17] McWilliams LA, Clara IP, Murphy PD, et al. Associations between arthritis and a broad range of psychiatric disorders: findings from a nationally representative sample. J Pain 2008;9:37–44.

[18] Norman SB, Means-Christensen AJ, Craske MG, et al. Associations between psychological trauma and physical illness in primary care. J Trauma Stress 2006;19:461–70.

[19] Weisberg JN, Keefe FJ. Personality disorders in the chronic pain population: basic concepts, empirical findings, and clinical implications. Paper Presented at: Pain Forum 1997.

[20] Sokolove J, Lepus CM. Role of inflammation in the pathogenesis of osteoarthritis: latest findings and interpretations. Ther Adv Musculoskelet Dis 2013;5:77–94.

[21] Friedrich MJ. Research on psychiatric disorders targets inflammation. JAMA 2014;312:474–6.

[22] Sohn DH, Sokolove J, Sharpe O, et al. Plasma proteins present in osteoarthritic synovial fluid can stimulate cytokine production via Toll-like receptor 4. Arthritis Res Ther 2012;14:R7.

[23] Wojakiewicz A, Januel D, Braha S, et al. Alteration of pain recognition in schizophrenia. Eur J Pain 2013;17:1385–92.

[24] Levesque M, Potvin S, Marchand S, et al. Pain perception in schizophrenia: evidence of a specific pain response profile. Pain Med 2012;13:1571–9.