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Research report

Association of asthma and bipolar disorder: A nationwide population-based study in Taiwan

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ABSTRACT

Background: The relationship between asthma and bipolar disorder has received little research. We sought to investigate this in a large national sample. Previous studies have found mood changes after prednisone use in asthma patients, and we therefore also investigated this exposure in relation to bipolar disorder.

Methods: Cases were identified from Taiwan's National Health Insurance Research Database with a new primary diagnosis of asthma (ICD-9:493) between 2000 and 2007. Case status required the presence of any inpatient diagnosis of asthma and/or at least one year diagnosis of asthma in outpatient service. These 46,558 cases were compared to 46,558 sex-, age-, residence- and insurance premium-matched controls and both groups were followed until the end of 2008 for first diagnosis of bipolar disorder (ICD-9 codes 296.0 to 296.16, 296.4 to 296.81 and 296.89). Competing risk adjusted Cox regression analyses were applied, adjusting for sex, age, residence, insurance premium, prednisone, hyperthyroidism, COPD (chronic obstructive pulmonary disease), Charlson comorbidity index, and hospital admission days for any disorder.

Results: Of the 93,116 subjects, 161 were ascertained as having bipolar disorder during a mean (SD) follow-up period of 5.7 (2.2) years. Asthma was an independent risk for bipolar disorder in the fully adjusted model. Higher daily dose of prednisone was a risk factor in asthma cases.

Limitations: The severity of asthma and bipolar disorder, and the route/duration of prednisone treatment were not evaluated.

Conclusions: Asthma was associated with increased risk of bipolar disorder. Higher daily dose of prednisone was associated with a further increased risk.

1. Introduction

Asthma is a disease presenting episodic stressful symptoms. A previous study found an association between asthma and several mental disorders, including bipolar disorder, which was especially strong for severe and lifetime asthma (Goodwin et al., 2003). Asthma has also been found to be one of the most common comorbidities with bipolar disorder in epidemiologic studies of community (Hirschfeld et al., 2003, Calabrese et al., 2003, McIntyre et al., 2006), outpatient (Beyer et al., 2005), emergency department (Castilla-Puentes et al., 2011), and pediatric (Jerrell et al., 2010) samples. A study in Taiwan also identified asthma as one of the risk factors for the development of bipolar disorders in hyperthyroidism patients(Hu et al., 2013). Two recent studies also tried to explore the risk of developing bipolar disorder later in life among adolescent asthma patients(Chen et al., 2014a, 2014b.)

These two conditions also share some common features. Biologically, asthma is a disease of inflammation, which has also been studied in the pathophysiology of bipolar disorder (Goldstein et al., 2009). Besides, the symptoms of asthma are evident stressors for these patients psychologically and socially, which might also be predisposing factors for the development of bipolar disorder.

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In addition to these associations between the two conditions, several clinical studies have found mood changes after the use of prednisone in asthma. Among outpatients treated for asthma, Brown found that use of prednisone was associated with increased manic, but not depressive symptoms (Brown et al., 2002). In a large cohort study by Fardet, the risk of mania increased over fivefold following glucocorticoid therapy (Fardet et al., 2012). The use of prednisone might account for the significant association between bipolar disorder and severe rather than non-severe asthma in the study by Goodwin (Goodwin et al., 2003), but this was not explored.

Given these findings, the relationship between these two conditions deserves further investigation. However, most studies to date have been cross-sectional (Calabrese et al., 2003, Goodwin et al., 2003, Hirschfeld et al., 2003, Beyer et al., 2005, McIntyre et al., 2006, Jerrell et al., 2010, Castilla-Puentes et al., 2011) and/or reliant on questionnaires or self-report for ascertaining one or both of the conditions (Calabrese et al., 2003, Hirschfeld et al., 2003, Castilla-Puentes et al., 2011).

In the study described here, we used a nationwide, population-based dataset in Taiwan, with physician diagnoses, to investigate the association between asthma and bipolar disorder and to test if there was any further association between prednisone use and bipolar disorder in asthma cases.

2. Material and methods

2.1. Sample

A retrospective cohort study was assembled using data from the Taiwan National Health Insurance Research Database (NHIRD) provided by that country's National Health Research Institute (NHRI) which included outpatient, ambulatory, hospital inpatient care, as well as dental services. The National Health Insurance (NHI) program provides compulsory universal health insurance, implemented from March 1995, covering all delivery of health care in 98% of the national population. In cooperation with the Bureau of NHI, the NHRI extracted a randomly sampled representative database of 1,000,000 people from the registry of all NHI enrollees using a systematic sampling method for research purposes, forming the Longitudinal Health Insurance Database (LHID). There are no statistically significant differences in age, sex, or health care costs between this sample and all enrollees (Institutes, 2013).

Asthma cases were identified based on recorded International Classification of Disease, Ninth revision (ICD-9) codes of 493. All medical claims made under this diagnostic code between 1997 and 2007 were collected from NHIRD for further analysis. The definition of asthma for this analysis required an inpatient diagnosis and/or at least one year's worth of diagnosed asthma from outpatient services, a definition consistent with other research using this database (Cazzola et al., 2012). To define new cases, people who had received any asthma diagnosis in medical claim data from 1997 to 1999 were excluded from the analysis. In this way, 46,588 new asthma cases were defined between 2000 and 2007. For assessing the association between asthma and risk of bipolar disorder, one control per case was randomly sampled from the remaining sample, matching on sex, age within 1 year, residence (urban/rural) and insurance premium category (see below). Both cases and controls were followed for bipolar disorder as an outcome. Bipolar disorder was defined on the basis of recorded ICD-9 codes 296.0 to 296.16, 296.4 to 296.81 and 296.89 (WHO, 1975). In our study, the bipolar disorder is defined on the basis of recorded ICD-9 codes 296.0 to 296.16, 296.4 to 296.81 and 296.89. To define new diagnoses of bipolar disorder, people who had received any bipolar disorder diagnosis in medical claim data from 1997 to 1999 were excluded from the analysis. Bipolar disorder required the presence of any inpatient diagnosis and/or at least one year diagnosis in an outpatient service. We also exclude patients with a first diagnosis of bipolar disorder occurring prior to the first diagnosis of asthma. The process for deriving the analyzed samples is shown in Fig. 1.

Covariates considered in this analysis were chosen a priori on the basis of hypothetical associations with the exposure and outcome of interest. These comprised age, sex, area of residence (urban/rural), insurance premium (as a proxy marker of family income), prednisone use, hyperthyroidism, chronic obstructive pulmonary disease (COPD), Charlson comorbidity index and hospital admission days for any disorder. Hyperthyroidism was defined on the basis of recorded ICD-9 codes 242. COPD was defined on the basis of recorded ICD-9 codes 2491, 492, 494 and 496. Both hyperthyroidism and COPD, as defined for this analysis, required an inpatient diagnosis and/or at least one year's duration of diagnosis from outpatient services. The insurance premium served as an indicator of economic status and was classified into one of four categories: fixed premium and dependent, less than New Taiwan Dollars (NTD) 20,000, NTD 20,000 (income per month) to 40,000 and NTD 40,000 or more (1US $=32.1 NTD in 2008). The fixed premium group was the group that required social welfare support, which included low-income citizens and veterans. The 'dependent' insurance group referred to family members that did not have fixed salary income. Only prednisone use for at least one year was classified as use. The annual average cumulative defined daily dose (DDD) of prednisone was calculated and divided into 3 groups (0–30, 31–60, 60+). The defined daily dose recommended by the WHO is a unit for assessing the standard dose of drug. Cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDDs of a drug within a time period. The annual average cumulative DDD was used to access the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index which comprises a summation of diseases weighted on the basis of their association with mortality (D'Hoore et al., 1993). "Hospital admission days" for any disorder was also included as an indicator of

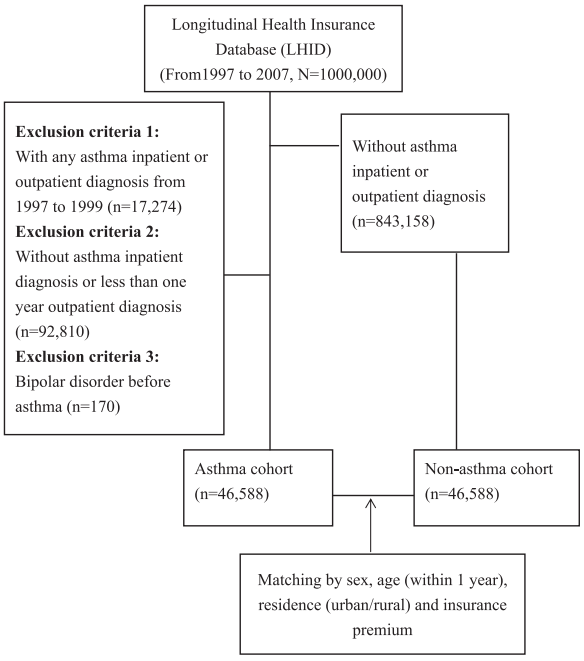

Fig. 1. Flow chart of data collection in this study.

general health. The Charlson comorbidity index and hospital admission days were measured prior to the outcome since 1997.

The NHIRD consists of de-identified secondary data released to the public for research purposes. This study had been reviewed and approved by the Institutional Review Board of Chung Shan Medical University Hospital.

2.2. Statistical analysis

Death prior to bipolar disorder was considered as a competing risk event. The death date was retrieved from the national mortality database. The death-adjusted cumulative incidences of bipolar disorder were calculated using the Fine and Gray method (Fine JP, 1999). Each person's first presentation of bipolar disorder within the study period was used in the calculation of outcome risk over given time intervals. The risks of bipolar disorder during the follow-up period were calculated using survival analysis, with the time function calculated as the number of years from the index date of asthma diagnosis to December 31, 2008 (end of follow-up) or until the date of death or migration if earlier. The index date was the first diagnosis date of asthma and we also assigned this date to their matched controls. Competing risk adjusted Cox regression models (Fine JP, 1999) were fitted to estimate the associations between asthma and bipolar disorder incidence, adjusting for covariates. Hazard ratios with 95% confidence intervals were thus calculated. The model was tested first with all the sample cases included. The subgroups were then divided according to sex, and age group tested next. All data management was performed using SAS 9.3 software (SAS Institute Inc., Cary, NC, USA). Calculations of cumulative incidences and Cox models in the competing risk analysis were carried out using the R package "cmprsk" (Gray, 2010).

3. Result

3.1. Characteristics of subjects

The two cohorts comprised 46,558 people with newly diagnosed asthma and 46,558 matched controls ascertained from the database covering 2000–2007. Cohort characteristics are listed and compared in Table 1. The mean (SD) follow-up interval for all subjects was 5.7 (2.2) years. For the asthma cases, a slight majority was male and most cases were in the youngest age category. Of the total 93,116 subjects, 161 were diagnosed as having bipolar disorder during the surveillance period: 115 (0.25%) in the asthma cohort and 46 (0.10%) in the non-asthma cohort. In the asthma cohort, 2639 (5.66%) used prednisone during the follow-up period more than 30 annual cumulative defined daily dose (DDD) compared to 273 (0.59%) in the non-asthma cohort. The proportion of hyperthyroidism or COPD before the end of follow-up was higher in asthma cohort than non-asthma cohort (both $p < 0.001$). Both the mean Charlson comorbidity indices and hospital admission days were higher in asthma cohort than non-asthma cohort.

Table 1
Characteristics of asthma cases and their matched[a] controls.

Characteristic	Asthma		Non-asthma[a]		Chi-square test p value
	N	%	*N*	%	
Sex					
Female	22,104	47.48	22,104	47.48	1.000
Male	24,454	52.52	24,454	52.52	
Age group					
1–24	23,251	49.94	23,251	49.94	0.994
25–44	6618	14.21	6617	14.21	
45–64	8674	18.63	8700	18.69	
65+	8015	17.22	7990	17.16	
Residence					
Urban	34,569	74.25	34,569	74.25	1.000
Rural	11,989	25.75	11,989	25.75	
Insurance premium					
Fixed premium and dependent	27,619	59.32	27,619	59.32	1.000
Less than NTD [b] 20,000	6651	14.29	6651	14.29	
NTD20,000–400,000	9835	21.12	9835	21.12	
NTD400,000 or more	2453	5.27	2453	5.27	
Prednisone (DDD [c])					
0–30	43,919	94.33	46,285	99.41	< 0.001
31–60	1473	3.16	144	0.31	
60+	1166	2.50	129	0.28	
Hyperthyroidism					
No	46,001	98.80	46,245	99.33	< 0.001
Yes	557	1.20	313	0.67	
COPD [d]					
No	35,487	76.22	44,069	94.65	< 0.001
Yes	11,071	23.78	2489	5.35	
Bipolar disorder					
No	46,443	99.75	46,512	99.9	< 0.001
Yes	115	0.25	46	0.10	
Charlson index [e]	2.89 ± 2.79		1.54 ± 2.49		< 0.001
Hospital days [e]	25.93 ± 104.48		12.52 ± 76.58		< 0.001

[a] Matched by sex and age (±1 years old), residence, and insurance premium.
[b] 1US $=32.1 NTD in 2008.
[c] DDD: defined daily dose (mg).
[d] COPD: chronic obstructive pulmonary disease.
[e] Mean ± SD.

3.2. Association between asthma and risk of bipolar disorder

Analyses of associations of interest are summarized in Table 2 and shown in Fig. 2. In the fully adjusted Cox regression model for competing risk analysis which included adjustment for sex, age group, residence, insurance premium, prednisone, hyperthyroidism, COPD, Charlson comorbidity index and hospital admission days, asthma was positively associated with bipolar disorder. Additional factors associated with the incidence of bipolar disorder were female sex, younger age, lower economic status, higher dose of prednisone use, and higher hospital admission days for any disorder.

In secondary analyses within the asthma cohort, factors associated with the incidence of bipolar disorder were female sex, younger age, lower economic status, higher dose of prednisone use, and higher hospital admission days which were similar with main analysis (Table 3). In stratified analyses, the association of interest was similar between men and women, and strongest in the 45–64 year age group (Table 4).

4. Discussion

In this large retrospective cohort study using national data from Taiwan, the cumulative incidence of bipolar disorder in a cohort with newly diagnosed asthma remained higher than in a non-asthma comparison group over a mean follow-up period of 5.7 years (Fig. 1) with an unadjusted hazard ratio of 2.48 (1.76–3.49). After adjustment for a range of potential confounding factors, including sex, age group, residence, insurance premium, prednisone use, Charlson comorbidity index and hospital admission days for any disorder, the adjusted hazard ratio was only modestly diminished to 1.90 (1.32–2.73). Asthma therefore was associated with an approximately two-fold increased risk of bipolar disorder.

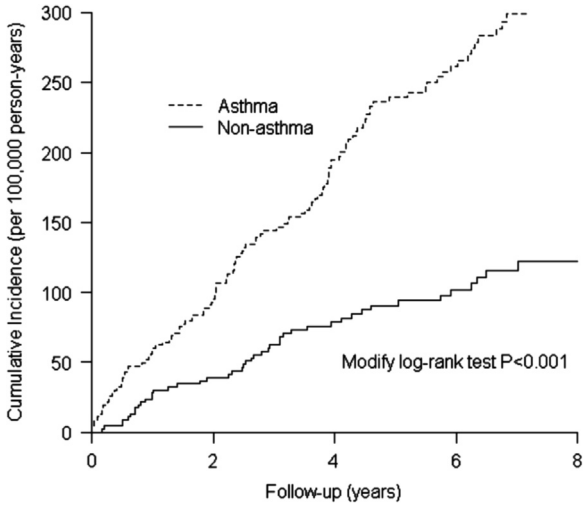

Fig. 2. Cumulative incidence of bipolar disorder in cohorts with/without asthma.

Table 2
Competing risk adjusted Cox regression analysis of bipolar disorder incidence.

Variable	Unadjusted hazard ratio		Adjusted [a] hazard ratio	
	Estimate (95% CI [b])	*P* value	Estimate (95% CI [a])	*P* value
Asthma				
No	1.00		1.00	
Yes	2.48 (1.76–3.49)	< 0.001	1.82 (1.25–2.65)	0.002
Sex				
Male	1.00	1.00		
Female	1.86 (1.35–2.56)	< 0.001	1.63 (1.15–2.3)	0.006
Age group				
1–24	1.00		1.00	
25–44	2.68 (1.92–3.75)	< 0.001	4.80 (2.37–9.71)	< 0.001
45–64	2.43 (1.76–3.35)	< 0.001	3.64 (1.84–7.19)	< 0.001
65+	0.96 (0.64–1.46)	0.86	1.53 (0.68–3.4)	0.300
Residence				
Urban	1.00		1.00	
Rural	0.97 (0.68–1.37)	0.85	1.15 (0.79–1.67)	0.476
Insurance premium				
Fixed premium and dependent	1.00		1.00	
Less than NTD [c] 20,000	2.79 (2.00–3.87)	< 0.001	1.93 (1.17–3.19)	0.010
NTD20,000–400,000	1.62 (1.16–2.27)	0.005	1.16 (0.70–1.93)	0.571
NTD400,000 or more	0.80 (0.38–1.71)	0.565	0.61 (0.24–1.53)	0.291
Prednisone (DDD [d])				
0–30	1.00		1.00	
31–60	3.00 (1.47–6.11)	0.002	2.31 (1.09–4.89)	0.029
60+	11.81 (7.58–18.43)	< 0.001	7.05 (4.18–11.88)	< 0.001
Hyperthyroidism				
No	1.00		1.00	
Yes	3.30 (1.36–8.03)	0.008	1.51 (0.62–3.68)	0.366
COPD [e]				
No	1.00		1.00	
Yes	2.76 (1.99–3.84)	< 0.001	1.18 (0.77–1.81)	0.436
Charlson comorbidity index	1.13 (1.10–1.16)	< 0.001	1.01 (0.96–1.07)	0.638
Hospital admission days (100 days)	1.11 (1.08–1.13)	< 0.001	1.09 (1.06–1.11)	< 0.001

[a] Competing risk adjusted Cox regression analysis controlling by sex, age, residence, insurance amount, prednisone, hyperthyroidism, COPD, Charlson comorbidity index and hospital days.
[b] CI: Confidence interval.
[c] 1US $=32.1 NTD in 2008.
[d] DDD: Defined daily dose (mg).
[e] COPD: chronic obstructive pulmonary disease.

Table 3
Competing risk adjusted Cox regression analysis of bipolar disorder incidence among asthma patients.

Variable	Unadjusted hazard ratio		Adjusted [a] hazard ratio	
	Estimate (95% CI [b])	*P* value	Estimate (95% CI [b])	*P* value
Sex				
Male	1.00		1.00	
Female	1.78 (1.23–2.6)	0.003	0.020	1.63 (1.08–2.46)
Age group				
1–24	1.00		1.00	
25–44	2.73 (1.84–4.04)	< 0.001	4.18 (1.82–9.6)	0.001
45–64	2.42 (1.65–3.54)	< 0.001	3.05 (1.3–7.11)	0.010
65+	0.93 (0.57–1.51)	0.76	1.2 (0.44–3.27)	0.724
Residence				
Urban	1.00		1.00	
Rural	0.96 (0.63–1.44)	0.831	1.17 (0.75–1.84)	0.488
Insurance amount				
Fixed premium and dependent	1.00		1.00	
Less than NTD [c] 20,000	3.21 (2.19–4.70)	< 0.001	2.33 (1.28–4.25)	0.006
NTD20,000～400,000	1.65 (1.11–2.44)	0.013	1.34 (0.72–2.47)	0.355
NTD40,0000 or more	0.64 (0.24–1.73)	0.375	0.56 (0.17–1.86)	0.344
Prednisone (DDD [d])				
0–30	1.00		1.00	
31–60	2.02 (0.94–4.34)	0.071	2.14 (0.96–4.75)	0.062
60+	9.21 (5.77–14.71)	< 0.001	7.15 (4.14–12.36)	< 0.001
Hyperthyroidism				
No	1.00		1.00	
Yes	2.92 (1.08–7.9)	0.035	1.43 (0.53–3.86)	0.483
COPD [e]				
No	1.00		1.00	
Yes	2.27 (1.57–3.29)	< 0.001	1.24 (0.78–1.97)	0.373
Charlson comorbidity index	1.11 (1.07–1.15)	< 0.001	1.01 (0.94–1.08)	0.817
Hospital admission days (100 days)	1.10 (1.08–1.13)	< 0.001	1.08 (1.06–1.11)	< 0.001

[a] Competing risk adjusted Cox regression analysis controlling by sex, age, residence, insurance amount, prednisone, hyperthyroidism, COPD, Charlson comorbidity index and hospital days.
[b] CI: Confidence interval.
[c] 1US $=32.1 NTD in 2008.
[d] DDD: Defined daily dose (mg).
[e] COPD: chronic obstructive pulmonary disease.

Table 4
Association between asthma and bipolar disorder incidence by sex and age group.

Subgroup	Adjusted hazard ratio for bipolar disorder[a]	
	Estimate (95% CI[b])	*P* value
Total sample	1.82 (1.25–2.65)	0.002
Sex		
Male	1.98 (1.03–3.80)	0.042
Female	1.74 (1.10–2.78)	0.019
Age group		
1–24	1.73 (0.65–4.60)	0.272
25–44	1.77 (0.91–3.47)	0.095
45–64	1.86 (1.11–3.65)	0.019
65+	1.68 (0.61–4.65)	0.320

[a] Competing risk adjusted Cox regression analysis controlling by sex, age, residence, insurance amount, prednisone, hyperthyroidism, COPD, Charlson comorbidity index and hospital days.
[b] CI: Confidence interval.

Previous investigations of the association between asthma and bipolar disorder have almost all been cross-sectional in design (Calabrese et al., 2003, Goodwin et al., 2003, Hirschfeld et al., 2003, Beyer et al., 2005, McIntyre et al., 2006, Jerrell et al., 2010, Castilla-Puentes et al., 2011). They only demonstrated a co-occurrence of these two disorders. As far as we are aware, our study is the first longitudinal cohort study demonstrating a temporal relationship between asthma and bipolar disorder. The study by Goodwin found a significant positive correlation between bipolar disorder and severe asthma, but not non-severe asthma (Goodwin et al., 2003). In our study, we did not evaluate the severity of asthma. However, those hospitalized for longer than 100 days had a higher risk of developing bipolar disorder (Table 3). This might in part reflect asthma severity, although data were not available on the cause of the hospitalization.

On the other hand, the use of higher dose of prednisone also increased the risk on bipolar disorder: both in the whole cohort after adjustment, and in those with asthma. This association was especially evident when the defined daily dose exceeded 60 mg.

The potential psychogenic effects of prednisone are well-recognized, and have been studied previously (Brown et al., 2007, Fardet et al., 2012). Steroid-induced mania has been reported (Couturier et al., 2001) and Brown observed significant mood changes, primarily manic, during brief courses of prednisone among outpatients with asthma (Brown et al., 2002). Another study by Brown evaluated the effects of chronic prednisone therapy (Brown et al., 2007) and concluded an association with initial changes in mood and memory which stabilized over time. However, these studies focused on the association between prednisone use and mood symptoms, rather than mood disorders. Our findings suggest that higher doses of prednisone use do increase the risk of developing bipolar disorder, an effect which we found to be evident in the whole cohort, independent of asthma status, as well as in the asthma group specifically.

Prednisone was thus independent of asthma as an exposure; however, asthma equally was independent of prednisone – i.e. the association between asthma and higher risk of bipolar disorder could not be accounted for by prednisone use alone. Among those who have not received prednisone, asthma was also associated with bipolar disorder (HR=1.70, 95% CI:1.15–2.51, *P*=0.008).

The independent role of asthma for bipolar disorder is further supported.

Asthma and bipolar disorder share some common clinical features, including an episodic course and the need in some cases for maintenance treatment. However, investigations of shared causative mechanisms have been scarce. One early case report noticed coincidental improvement in asthma during lithium treatment for bipolar disorder, which may imply common pathophysiology (Nasr and Atkins, 1977), and Lieb suggested that substance P may play a role in the regulation of both disorders (Lieb et al., 2002). Inflammation, an important underlying factor in asthma, has also been studied in the pathophysiology of bipolar disorder (Goldstein et al., 2009). Considering the anti-inflammatory and psychogenic effect of prednisone, further immunologic research is warranted to explore the interplay between prednisone, asthma and bipolar disorder.

4.1. Strengths and limitations

To our knowledge, this is the first study using a nationally representative sample and longitudinal dataset to investigate the temporal relationship between asthma and bipolar disorder. As well as their cross-sectional design, previous studies have been also limited to identifying asthma based on self-report (Castilla-Puentes et al., 2011, Jerrell et al., 2010, McIntyre et al., 2006, Beyer et al., 2005, Hirschfeld et al., 2003, Calabrese et al., 2003), whereas in our study we restricted case definitions to physician-assigned diagnoses with further criteria surrounding their application in inpatient or outpatient settings. Nonetheless, there are also important limitations.

First, the dose-effects of prednisone were evaluated by the Defined Daily Dose which does not allow dosage patterns to be examined (e.g. whether the drug was received longer-term on a daily basis or in intermittent, more intensive administrations). Second, more than one third of the asthma patients had their first onset at age 45 or later (Table 1), which is inconsistent with most epidemiological studies (Yunginger et al., 1992). As previously reported, specialists have more confidence in diagnosing asthma than general practitioners in Taiwan, and the diagnosis is mainly based on the clinical history. (Yeh et al., 2008) The validity of asthma diagnosis was uncertain in this cohort, as this was derived from administrative data rather than standardized research interviews. However, we believe that misclassification of exposure will have been non-differential, and will thus have obscured rather than exaggerated associations of interest. Symptoms of bipolar disorder might be coded as 'Substance-Induced Mood Disorder' (ICD-9: 292.84) if these developed during the treatment course of asthma. This diagnosis was not included in this study. Third, it was not possible to evaluate directly the severity of asthma and bipolar disorder in our study and neither was it possible to investigate the route and duration of prednisone treatment. As far as was possible from the data available, we focused on new diagnoses of both asthma and bipolar disorder; however, it should be borne in mind that exclusion of earlier diagnoses could only be achieved over a limited time period. Because a recorded diagnosis is required for all forms of treatment, missed historic cases would only include people who were both in remission and not receiving any maintenance treatment for either condition during the period of 1997–1999; groups which we feel are unlikely to have substantially altered our principal findings.

In summary, our findings from a national health insurance dataset are consistent with a link between asthma and bipolar disorder. Prednisone use was also associated with increased risk for bipolar disorder, especially at higher doses. Given the high, and potentially rising, prevalence of asthma, clinicians need to at least consider mental health issues in general and the risk of bipolar disorder during treatment, including recognition of early signs suggesting a need for intervention and/or specialist referral. Further research is needed to clarify underlying mechanisms linking these two adverse health conditions.

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Conflict of interest

No conflict declared.

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