Journal of Affective Disorders 168 (2014) 30–36

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

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

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ARTICLE INFO

Article history:
Received 7 May 2014
Received in revised form
20 June 2014
Accepted 24 June 2014
Available online 2 July 2014

Keywords:
Bipolar disorder
Asthma
Prednisone

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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http://dx.doi.org/10.1016/j.jad.2014.06.033
0165-0327/

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

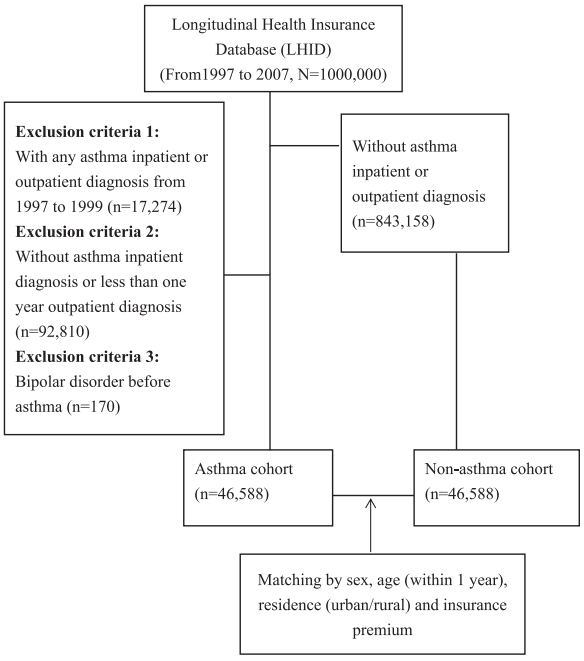

Fig. 1. Flow chart of data collection in this study.