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Research report

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

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ABSTRACT

Background: Few studies have investigated the bidirectional relationship between asthma and anxiety; we sought to investigate asthma and anxiety in a large national sample.
Methods: Cases were identified from Taiwan's National Health Insurance Research Database with a new primary diagnosis of asthma (ICD-9:493) aged more than 15 years 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 22,797 cases were compared to 22,797 sex-, age-, residence- and insurance premium-matched controls and both groups were followed until the end of 2008 for instances of anxiety, defined as ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23, 300.3. Competing risk adjusted Cox regression analyses were applied, adjusting for sex, age, residence, insurance premium, prednisone use, Charlson comorbidity index, cardiovascular disease, diabetes, depression disorder, and hospital admission days for any disorder. The effect of asthma on the risk of panic disorder and the effect of anxiety disorder on the risk of later asthma were also examined as competing risk adjusted Cox regression analyses
Results: Of the 45,594 subjects, 2792 were ascertained as having anxiety during a mean (SD) follow-up period of 5.3 (2.5) years. Asthma, females, older age, rural residence, depression disorder, and prednisone use were independent risks on anxiety in the fully adjusted model. Anxiety, older age, rural residence, and prednisone use were independent risks on asthma in the fully adjusted model.
Limitations: The severity of asthma and anxiety disorder, the duration of prednisone treatment and adherence, stressful life events, smoking, family history and relationship were not evaluated.
Conclusions: Bidirectional relationship between asthma and anxiety disorder was confirmed in this population, in dependent of a number of potential confounding factors.

1. Introduction

Asthma is a common and complex disease that impacts over 300 million people worldwide (Marco et al., 2011). Asthma is associated not only with high medical co-morbidity, mortality, and health care use (Mrazek, 2003), but also has adverse personal and social consequences (Fernandes et al., 2010; Jonas et al., 1999; Wijnhoven et al., 2003), including impaired quality of life, insomnia, school absences and difficulties, as well as physical and psychological distress (Bussing et al., 1996; Fernandes et al., 2010; Jonas et al., 1999). Childhood asthma also has parental impacts including work absences, infra-familial stress and emotional problems (Bussing et al., 1996; Jonas et al., 1999; Oraka et al., 2010).

High prevalence of comorbid anxiety disorders are found in people with asthma: up to 30% in children and adolescents and 34% in adults (Katon et al., 2004; Weiser, 2007). Recent reviews conclude that asthma is a complex multifactorial illness with

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attacks that may result from an interaction between behavioral, psychological, functional, neural, endocrine and immune processes (Marco et al., 2011; Mrazek, 2003). Increasing evidence supports a bidirectional relationship (Hasler et al., 2005; Jonas et al., 1999; Jones et al., 1976; Katon et al., 2004; Marco et al., 2011), with asthma increasing the risk of comorbid psychiatric problems such as anxiety disorder (Hasler et al., 2005; Katon et al., 2007; Lavoie et al., 2006), and anxiety disorders leading to higher asthma incidence and/or deterioration and/or functional impact (Hasler et al., 2005; Jonas et al., 1999; Marco et al., 2011). However, the high correlation between anxiety and asthma may simply reflect a broader relationship between chronic disease and reduced psychological well-being (Marco et al., 2006). Longitudinal studies are needed to examine the sequence of onset and the role of environmental factors in the association between asthma and anxiety to further clarify causative mechanisms (Goodwin et al., 2003).

Corticosteroids are the mainstay of therapy for asthma (O'byrne and Pendersen, 1998). Though efficacious, these drugs are well known to cause somatic side effects such as disturbed growth in children and deficient bone mineral density (Agertoft and Pedersen, 2000; Bonala et al., 2000; Wong et al., 2000). However, the psychiatric complications remain poorly characterized (Dubovsky et al., 2012). Anxiety was one of the most common psychiatric symptoms after corticosteroid medication (Sirois, 2003), but received relatively little attention. One study (Bonala et al., 2003) found that higher doses of corticosteroids correlated directly with higher anxiety symptoms in patients with asthma. However, the cross-sectional design and small size are potentially important limitations for this study.

Most studies of comorbid anxiety in people with asthma are limited by small and non-representative samples, self-reported asthma status, lack of consideration of confounders such as asthma medications, and cross-sectional designs that do not examine the temporal relationship between anxiety and asthma (Dubovsky et al., 2012; Katon et al., 2007; McCauley et al., 2007; Oraka et al., 2010). The prevalence and longitudinal impact of anxiety comorbidity need to be examined within a large population-based sample with asthma and thoroughly clarify the influence of participants' characteristics and clinical variables. In the study reported here, we used a nationwide, population-based cohort in Taiwan to investigate the role of asthma in the subsequent development of anxiety disorder and explored the risk factors.

2. 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 includes information on outpatient, ambulatory, and 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 (National Health Research Institute, 2013).

Asthma cases were identified based on a recorded International Classification of Disease, Ninth revision (ICD-9) code 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. Therefore, asthma patients were required not to have any asthma diagnosis for at least three years prior to their first diagnosis date in our database. In this way, 22,797 new asthma cases aged 16 or above were defined between 2000 and 2007. For assessing the association between asthma and risk of anxiety disorder, one control per case was randomly sampled from the remaining sample, matching for sex, age within 1 year, residence (urban/rural) and insurance premium category (see below). Both cases and controls were followed for anxiety disorder as an outcome. Anxiety disorders were defined in this study on the basis of ICD-9 codes 300.0, 300.01, 300.02, 300.2, 300.21, 300.23, 300.3 (WHO, 1975).To define incident anxiety disorder, people who had received any anxiety diagnosis in medical claim data from 1997 to 1999 were excluded from the analysis. Anxiety disorder required the presence of any inpatient diagnosis of anxiety disorder and/or at least one year diagnosis of anxiety disorder in an outpatient service. We also excluded an anxiety disorder first diagnosis before asthma. The sampling process is summarized in Fig. 1.

Covariates considered in this analysis comprised age, sex, area of residence (urban/rural), insurance premium, cardiovascular disease, diabetes, depression disorder, prednisone use, Charlson comorbidity index and hospital admission days for any disorder. The insurance premium served as an indicator of economic status and was classified into one of four categories: (i) fixed premium and dependent, (ii) monthly income less than New Taiwan Dollars (NTD) 20,000, (iii) NTD 20,000–40,000, and (iv) 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, and the 'dependent' insurance group referred to family members that did not have a fixed salary income. 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, and cumulative DDD, which indicates the exposed duration of drug use for a period, was estimated as the sum of dispensed DDD of drug within a time period. The annual average cumulative DDD was used to measure the dose usage of prednisone in the follow-up time period. General physical health was quantified using the Charlson comorbidity index (D'hoore et al., 1993). Hospital admission days for any disorder served as an indicator of asthma severity.

The NHIRD consists of robustly de-identified secondary data released to the public for research purposes. This study was thus exempt from Institutional Review Board review.

2.2. Statistical analysis

Death prior to anxiety disorder onset was considered as a competing risk event. The death-adjusted cumulative incidences of anxiety disorder were calculated using the Fine and Gray method (Fine and Gray, 1999). Each person's first presentation of anxiety disorder within the study period was used in the calculation of outcome risk over given time intervals. The risks of anxiety disorder during the follow-up period were calculated using survival analysis, with the time function represented 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.