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Higher risk of developing major depression and bipolar disorder in later life among adolescents with asthma: A nationwide prospective study

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ABSTRACT

Objective: Previous studies have suggested an immunological dysfunction in mood disorders, but rarely have investigated the temporal association between allergic diseases and mood disorders. Using the Taiwan National Health Insurance Research Database, we attempted to investigate the association between asthma in early adolescence and the risk of unipolar depression and bipolar disorder in later life.
Methods: In all, 1453 adolescents with asthma aged between 10 and 15 years and 5812 age-/gender-matched controls were selected in 1998–2000. Subjects with unipolar depression and bipolar disorder that occurred up to the end of follow-up (December 31 2010) were identified.
Results: Adolescents with asthma had a higher incidence of major depression (2.8% vs. 1.1%, $p < 0.001$), any depressive disorder (6.1% vs. 2.6%, $p < 0.001$), and bipolar disorder (1.0% vs. 0.3%, $p < 0.001$) than the control group. Cox regression analysis showed that asthma in early adolescence was associated with an increased risk of developing major depression (hazard ratio [HR]: 1.81, 95% confidence interval [CI]: 1.14–2.89), any depressive disorder (HR: 1.74, 95% CI: 1.27–2.37), and bipolar disorder (HR: 2.27, 95% CI: 1.01–5.07), after adjusting for demographic data and comorbid allergic diseases.
Discussion: Adolescents with asthma had an elevated risk of developing mood disorders in later life. Further studies would be required to investigate the underlying mechanisms for this comorbid association and elucidate whether prompt intervention for asthma would decrease the risk of developing mood disorders.

Asthma in children and adolescents has increased in prevalence in recent decades and has become a major public health issue in developed and developing countries (Eder et al., 2006; Hansen et al., 2013; Moorman et al., 2007; Soriano et al., 2003; Wehrmeister et al., 2012; Yan et al., 2005). In the United States, the prevalence of asthma in children and adolescents has doubled from approximately 3.5% in early 1980 to 8.5% in early 2000 (Moorman et al., 2007), and 5.6 million school-age children and adolescents were reported to have asthma in 2006. In Norway, a questionnaire-based survey among children aged 7–14 years showed a significantly increasing prevalence of asthma, from 7.3% in 1985 to 17.6% in 2008 (Hansen et al., 2013). In Taiwan, the International Study of Asthma and Allergies in Children survey found that the prevalence of asthma increased by 37% within two 12-month periods (5.2% in 1994–1995 to 7.1% in 2001–2002) in a 7-year period (Yan et al., 2005). As a result of this increase in prevalence, asthma-related complications and medical costs per patient have been the focus of greater attention and concern in the area of public health worldwide (Bedouch et al., 2012; Gadenne et al., 2011; Piecoro et al., 2001).

Mood disorders usually occur in late adolescence and early adulthood (Paus et al., 2008). Previous family, twin, and adoption studies have shown that genetic factors play an important role in the etiology of mood disorders, and numerous candidate gene association studies of mood disorders have been carried out, although

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with inconsistent results (Cho et al., 2005; Lee et al., 2012; Munafo, 2012; Seifuddin et al., 2012). Some adverse events in early adolescence, including physical diseases (i.e., arthritis, allergy), negative life events, and substance use, increase the risk of mood disorders in late adolescence and early adulthood (Espejo et al., 2012; Leverich and Post, 2006; Marmorstein, 2009; Nurnberger et al., 2011; Post et al., 2001; Tarakci et al., 2011; Timonen et al., 2002). The interaction between genetic and environmental factors may lead to a neurobiological vulnerability to mood disorders.

The association between allergy and mood disorders has been proposed for a long time. Hurwitz et al. reported that subjects with a history of any allergy (i.e., asthma or allergic rhinitis [AR]) were more likely to be diagnosed with major depression (odds ratio [OR]: 1.58; 95% confidence interval [CI]: 1.13–2.21) (Hurwitz and Morgenstern, 1999). Richardson et al. conducted a telephone survey of 767 adolescents with asthma (aged 11–17 years) and found that 21 (2.5%) met the diagnosis of depressive disorder, and that asthma symptoms were significantly associated with the number of depressive symptoms (Richardson et al., 2006). The 2002 World Health Survey found that asthma and wheezing (OR: 2.37, 95% CI: 2.10–2.66; OR: 3.06, 95% CI: 2.75–3.40) were associated with major depressive episodes (Loerbroks et al., 2012), but some studies failed to support this association (Goodwin and Buka, 2008; Slattery and Essex, 2011). Slattery et al. indicated the lack of a relationship between asthma and depression (Slattery and Essex, 2011). Studies on the association between asthma and bipolar disorder are very limited (Beyer et al., 2005; Goodwin et al., 2003; Jerrell et al., 2010). Jerrell et al. found a significantly higher prevalence of asthma among 1841 children and adolescents with bipolar disorder than that among 4500 controls (25.7% vs. 22.7%, $p < 0.01$), and the onset of asthma temporally preceded the diagnosis of bipolar disorder (Jerrell et al., 2010). Goodwin et al. also found that lifetime severe asthma was associated with an increased likelihood of bipolar disorder (OR: 5.64; 95% CI: 1.95–16.35), but not unipolar disorder (OR: 0.97, 95% CI: 0.59–1.62) (Goodwin et al., 2003). These inconsistent results regarding the association between asthma and mood disorders may be due to the different study methodologies, including cross-sectional but not longitudinal study designs, self-reported asthma and mood symptoms and diagnoses, and the lack of adjusting for other comorbid allergic diseases. In addition, some previous studies suggested the association between corticosteroid use in asthma treatment and the development of manic symptoms/bipolar disorder (Bolanos et al., 2004; Brown et al., 2002). But, most studies regarding the association between asthma and the development of mood disorders did not include this important confounding factor although this association was still controversial (Goodwin et al., 2003; Hurwitz and Morgenstern, 1999; Jerrell et al., 2010; Loerbroks et al., 2012; Richardson et al., 2006).

Using the Taiwan National Health Insurance Research Database (NHIRD) with its large sample size and a case–control prospective study design, we investigated the temporal association between asthma in early adolescence and the risk of mood disorders. We hypothesized that adolescents with asthma were associated with an increased risk of developing mood disorders in their later life after adjusting for other comorbid allergic diseases.

1. Methods

1.1. Data source

The National Health Insurance (NHI) program was implemented in 1995, and covers up to 99% of all 23,000,000 residents of Taiwan (http://www.nhi.gov.tw/). The NHIRD was audited and released by the National Health Research Institute. Comprehensive information on insured subjects is included in the database, including demographic data, dates of clinical visits, and disease diagnoses. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Bai et al., 2013; Chen et al., 2012, 2013a,b; Li et al., 2012; Wu et al., 2012).

1.2. Inclusion criteria for subjects with asthma and the control cohort

For the study, 1,000,000 subjects, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects aged between 10 and 15 years who were identified as having asthma (ICD-9-CM codes: 493) by emergency room doctors, pulmonologists, rheumatologists, or pediatricians between January 1, 1998 and December 31, 2000, and who had no history of any psychiatric disorder before selection, were included as the asthma cohort. The time of the diagnosis of asthma was regarded as the time of selection. The age- and gender-matched control cohort (4 for every patient in the study cohort) was randomly identified from among the 1,000,000 subjects after eliminating the study subjects, children who had been given a diagnosis of asthma at any time, and those with any psychiatric disorder before selection. Diagnoses of major depression (ICD-9-CM codes: 296.2X and 296.3X), any depressive disorder (ICD-9-CM codes: 296.2X, 296.3X, 300.4, and 311), and bipolar disorder (ICD-9-CM codes: 296.X except 296.2X, 296.3X, 296.9X, and 296.82) given by psychiatrists were identified during the follow-up (from selection to December 31, 2010). Due to the high comorbidity of other allergic diseases with asthma, we assessed the comorbid effects of different allergic diseases on the risk of developing mood disorders. Allergic rhinitis (ICD-9-CM code: 477) diagnosed by internists, pulmonologists, rheumatologists, otolaryngologists or pediatricians, atopic dermatitis (ICD-9-CM codes: 691 or 691.8) diagnosed by dermatologists or pediatricians, and allergic conjunctivitis (ICD-9-CM codes: 372.05, 372.10, and 372.14) diagnosed by ophthalmologists were identified. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. Level of urbanization (level 1 to level 4; level 1: most urbanized region; level 4: least urbanized region) was also assessed for our study (Liu et al., 2006). Furthermore, we assessed the average expenditure of mental health consultation between asthma cohort and control group, and investigated the association between the presence of asthma diagnosis and the expenditure of mental healthcare.

1.3. Statistical analysis

For between-group comparisons, the independent t test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate. Two Cox regression models were used to investigate the HR with 95% CI of major depression, any depressive disorder, and bipolar disorder. The first model was adjusted by age, gender, and level of urbanization, and the second model was adjusted by age, gender, level of urbanization, and comorbid allergic diseases. In addition, we further investigated the association between the use of inhaled corticosteroids during the follow-up period and the risk of developing mood disorders among those adolescents with asthma. A two-tailed p-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).