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A predisposition for allergies predicts subsequent hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder: A nationwide longitudinal study

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ABSTRACT

Background: Previous studies have shown that both severe mental disorders (schizophrenia and bipolar disorder) and atopic diseases were associated with an increased risk of metabolic syndrome. However, the role of atopy/the predisposition for allergies in the development of metabolic syndrome is still unknown among those with severe mental disorders.
Methods: Using the Taiwan National Health Insurance Research Database, 5826 patients with schizophrenia or bipolar disorder (1908 with a predisposition for allergies and 3918 without) were enrolled between 1998 and 2008. Those who developed hypertension, dyslipidemia, and/or diabetes mellitus were identified during the follow-up to the end of 2011.
Results: A predisposition for allergies increased the risk of developing hypertension (HR: 1.67), dyslipidemia (HR: 1.82), and diabetes mellitus (HR: 1.37) in later life among those with severe mental disorders. A dose-dependent relationship was noted between having more atopic comorbidities and a greater likelihood of hypertension (1 atopic disease: HR: 1.60; ≧2 atopic comorbidities: HR: 1.87), dyslipidemia (HR: 1.73; HR: 2.12), and diabetes mellitus (HR: 1.26; HR: 1.69).
Conclusion: A predisposition for allergies was an independent risk factor for hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder. Further studies would be required to elucidate the underlying pathophysiology among atopy, schizophrenia, bipolar disorder, and metabolic syndrome.

1. Introduction

The increased risk of metabolic syndrome/disorders in those with severe mental disorders, including schizophrenia and bipolar disorder, has gained much attention in both psychiatry and public health during the past decade because metabolic syndrome has been reported to elevate the risk of subsequent cardiovascular diseases that may contribute to excess mortality or premature mortality in these patients (Brown et al., 2000; Osby et al., 2001; Angst et al., 2002; Laursen et al., 2011). Previous evidence has shown that patients with severe mental disorders (schizophrenia or bipolar disorder) had a higher prevalence, ranging from 32% to 50%, of metabolic syndrome than the general population (Birkenaes et al., 2007; Malhotra et al., 2013; Vancampfort et al., 2013). The causes of increased metabolic syndrome/disorders are multifactorial, and include an unhealthy lifestyle, the adverse effects of pharmacological treatments, and poorer access to and quality of physical health care (Mitchell et al., 2009; M et al., 2011; Vancampfort et al., 2013).

Previous studies have reported the relationship of atopy or a predisposition for allergies with schizophrenia and bipolar disorder (Goodwin et al., 2003; Chen et al., 2009; Jerrell et al., 2010; Pedersen et al., 2012). Chen et al. surveyed the prevalence of atopic diseases among 44,187 patients with schizophrenia and found that

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more than 20% of them had experienced concurrent atopic diseases (Y. H. Chen et al., 2009). A Danish population-based study showed that atopic diseases, especially asthma, increased the rate ratio of schizophrenia by 1.45 (95% confidence interval [CI]: 1.31–1.90) (Pedersen et al., 2012). Jerrell et al. demonstrated a significantly higher prevalence of asthma among 1841 patients with bipolar disorder than among 4500 controls (25.7% vs. 22.7%, $p < 0.01$) (Jerrell et al., 2010). Goodwin et al. also revealed that lifetime severe asthma was associated with an increased likelihood of bipolar disorder (odds ratio [OR]: 5.64; 95%CI: 1.95–16.35) (Goodwin et al., 2003). Furthermore, some evidence has suggested an association between atopic diseases and metabolic syndrome/disorders (Del-Rio-Navarro et al., 2010; Agrawal et al., 2011; Singh et al., 2013; Garmendia et al., 2014). Assessing the prevalence of metabolic syndrome among 111 patients with asthma and 198 without, Del-Rio-Navarro et al. found that patients with asthma had a higher prevalence of metabolic syndrome than those without (Del-Rio-Navarro et al., 2010). In a study of 3609 adults, Husemoen et al. found an association between insulin resistance and asthma (OR: 1.52, 95%CI: 1.14–2.03) (Husemoen et al., 2008). An animal study further suggested that atopic dermatitis caused abnormal lipid accumulation in the liver of NC/Nga mice (Seino et al., 2012). Overall, some research evidence has suggested that both schizophrenia and bipolar disorder were associated with more atopic diseases, and other studies have suggested that atopic diseases were associated with a higher risk of metabolic syndrome in the general population. However, there has been no study investigating the role of atopic diseases in the development of metabolic syndrome/disorders among patients with schizophrenia and bipolar disorder.

In this study, using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal follow-up study design, we investigated the association among atopic diseases/the predisposition for allergies and metabolic disorders (hypertension, dyslipidemia, and diabetes mellitus) among patients with schizophrenia or bipolar disorder. We hypothesized that atopic diseases/the predisposition for allergies increased the risk of developing metabolic disorders in later life among patients with schizophrenia or bipolar disorder.

2. Methods

2.1. Data source

The National Health Insurance (NHI) program was implemented in 1995 and covers up to 99% of the 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, such as demographic data, dates of clinical visits, and disease diagnoses, is included in the database. To guarantee privacy, all subjects included in the NHIRD are anonymous. 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 (Wu et al., 2012; Bai et al., 2013; Chen et al., 2013a, 2013b; Shen et al., 2013).

2.2. Inclusion criteria for subjects with schizophrenia or bipolar disorder

For the study, 1,000,000 subjects, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects who were newly diagnosed with schizophrenia (ICD-9-CM code: 295) or bipolar disorder (ICD-9-CM codes: 296.X except 296.2X, 296.3X, 296.9X, and 296.82) by psychiatrists between January 1, 1998 and December 31, 2008, and who had no previous history of hypertension (ICD-9-CM codes: 401–405), dyslipidemia (ICD-9-CM codes: 272.0X–272.4X), or diabetes mellitus (ICD-9-CM code: 250) before enrollment, were included in our study. The enrolled subjects were divided into two subgroups based on the presence or absence of atopic diseases/the predisposition for allergies. A predisposition for allergies was defined as the presence of diagnoses of asthma, allergic rhinitis, atopic dermatitis, and allergic conjunctivitis. Asthma (ICD-9-CM codes: 493) was diagnosed by emergency room doctors, internists, pulmonologists, rheumatologists, or pediatricians; allergic rhinitis (ICD-9-CM code: 477) was diagnosed by family medicine physicians, internists, pulmonologists, rheumatologists, otolaryngologists, or pediatricians; atopic dermatitis (ICD-9-CM codes: 691 or 691.8) was diagnosed by dermatologists; allergic conjunctivitis (ICD-9-CM codes: 372.05, 372.10, and 372.14) was diagnosed by ophthalmologists. We also assessed the association of psychiatric comorbidities, including anxiety disorders, substance use disorders, and alcohol-related disorders, with the risk of hypertension, dyslipidemia, and diabetes mellitus in our study. All subjects were followed to December 31 2011, and those who developed hypertension, dyslipidemia, and diabetes mellitus as diagnosed by family medicine physicians, internists, cardiologists, and endocrinologists were identified. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed in our study (Liu et al., 2006).

2.3. Statistical analysis

For between-group comparisons, the independent *t* test was used for continuous variables and Pearson's X^2 test for nominal variables, where appropriate. Two Cox regression models were used to investigate the HR with 95%CI of hypertension, dyslipidemia, and diabetes mellitus. The primary model investigated the presence or absence of the predisposition for allergies as a categorical variable with the risk of hypertension, dyslipidemia, and diabetes mellitus; the secondary model investigated the numbers of atopic comorbidities as a categorical variable with the risk of hypertension, dyslipidemia, and diabetes mellitus. The two models were adjusted by demographic data and psychiatric comorbidities. We further tested the diagnostic effect of schizophrenia or bipolar disorder between a predisposition for allergies and metabolic syndrome (hypertension, dyslipidemia, and diabetes mellitus). 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).

3. Results

Of the 5826 enrolled subjects, 4269 with schizophrenia and 1557 with bipolar disorder, 1908 had a predisposition for allergies and 3918 did not (Table 1). Those with a predisposition for allergies were predominantly female (58.1% vs. 48.7%, $p < 0.001$) and had an earlier age of diagnosis of schizophrenia or bipolar disorder (32.77 ± 13.39 vs. 34.89 ± 12.60 years, $p < 0.001$) than those without a predisposition for allergies (Table 1). Among the atopic subjects, 1385 (72.6%) were diagnosed as having only one atopic disease, 450 (26.3%) had 2 atopic comorbidities, and 73 (3.8%) had 3 or more atopic comorbidities. The mean number of atopic comorbidities was 1.31 ± 0.55 (Table 1). Follow-up from enrollment to the end of 2011 demonstrated that those with a predisposition for allergies had a higher incidence of any hypertension/dyslipidemia/diabetes mellitus (29.60 vs. 19.78/1000 person-years, $p < 0.001$), including hypertension (16.24 vs. 10.88/1000 person-years, $p < 0.001$), dyslipidemia (14.26 vs. 8.24/1000 person-years, $p < 0.001$), and diabetes mellitus (9.71 vs. 7.46/1000 person-years, $p < 0.001$), with an earlier age at any diagnosis of hypertension/dyslipidemia/diabetes mellitus (46.38 ± 12.81 vs. 48.25 ± 12.76 years, $p = 0.018$), an earlier age at any diagnosis of hypertension (49.35 ± 13.29 vs. 51.47 ± 13.38 years, $p = 0.047$),an equal age at any