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Prevalence and risk of atopic disorders among schizophrenia patients: A nationwide population based study

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ABSTRACT

Objective: Although a body of evidence indicates a link between psychiatric illnesses and allergies, no one has investigated the association between schizophrenia and atopic disorders. The objective of this nationwide population-based study was to examine the prevalence and risk of atopic disorders (asthma, allergic rhinitis, urticaria, and atopic dermatitis) among schizophrenia patients.

Method: This study used data from the Taiwan National Health Insurance Research Database covering the years 2000 to 2002. A total of 44,187 patients diagnosed with schizophrenia in the year 2000 were included, together with 132,561 matched non-psychiatric controls. Follow up until the end of 2002 identified concurrent diagnoses of atopic disorders. Logistic regression analyses were performed after controlling for the covariates of socio-demographic characteristics.

Results: Findings indicated high comorbidity, with 20.2% of schizophrenia patients (approximately one in five) experiencing concurrent atopic disorders. Moreover, schizophrenia in patients was independently associated with a 1.3-fold increased risk (95%CI = 1.24–1.39) of concurrent asthma, after adjusting for socio-demographic characteristics. Yet the risk of diagnosed allergic rhinitis and urticaria was 23% (95%CI = 0.74–0.81) and 26% (95%CI = 0.72–0.77) lower, respectively, among schizophrenia patients compared to people without any psychiatric disease.

Conclusion: Data suggests an increased risk of asthma and decreased risk of allergic rhinitis and urticaria among schizophrenia patients. Future studies on the identification of common etiologic pathways for schizophrenia and asthma could be significant for developing innovative treatments that target both illnesses concurrently.

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1. Introduction

Schizophrenia is a chronic psychiatric illness with an approximate prevalence of 1% worldwide (Freedman, 2003). A number of studies have demonstrated an excess of mortality among schizophrenia patients, with overall standar-

dized mortality ratios of schizophrenic to general populations ranging approximately from 1.5 to 4.5 (Capasso et al., 2008; Wood et al., 1985). Despite the fact that increased mortality among schizophrenia patients resulted from higher prevalence of physical disease, the somatic wellbeing of such patients has been neglected for decades (Leucht et al., 2007). Physical comorbidities should be a serious concern both scientifically and for effective clinical management of schizophrenia. A review of literature on the co-occurrence of physical illnesses and schizophrenia shows that areas including atopic disorders have not been sufficiently considered.

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Globally, the prevalence of atopic disorders, a familial group of allergic disorders including asthma, allergic rhinitis, urticaria, and atopic dermatitis, has continued to rise in the past few decades (Asher et al., 2006). In developed countries like Taiwan, as many as one in three or four individuals suffer from certain atopic disorders (Asher et al., 2006; Liao et al., 2005). Previous studies have investigated the co-occurrence of psychosocial factors and allergies, proposing a bidirectional relationship. Physiological, behavioral, and socioeconomic factors have all been proposed as playing a role in the reciprocal association between psychiatric symptoms and atopic disorders (Chida et al., 2008). Specifically, stress or psychiatric illness might elicit factors (e.g., inflammatory processes, poor diet, sleep disturbance, unhygienic living environment, and poor medical compliance) that would intensify atopic diseases. Conversely, atopic diseases negatively affect mental health through chronically distressing symptoms, consistently unsuccessful treatment with cumulating medical expenses, and impaired social functioning (Chida et al., 2008; Marshall and Roy, 2007).

Although a body of evidence indicates that allergies are associated with psychosocial factors, most studies have centered on psychiatric disorders such as anxiety disorders, depressive disorders, and attention deficit hyperactivity disorder (Patten and Williams, 2007; Slattery, 2005). To our knowledge, none has investigated the association between schizophrenia and allergies. Since atopic disorders are common and distressing, significantly disrupting social, personal, and domestic life, there is a substantial and immediate need to address allergies among schizophrenia patients.

The objective of this nationwide population-based study was to document the prevalence and risk of atopic disorders among schizophrenia patients. Schizophrenia patients who visited outpatient departments at any time in the year 2000 were followed up till the end of 2002 to identify the extent of comorbid atopic disorders including asthma, allergic rhinitis, urticaria, and atopic dermatitis. Risks for schizophrenics are compared with non-psychiatric matched controls.

2. Methods

2.1. Database

This study used 2000–2002 data from the Taiwan National Health Insurance Research Database (NHIRD). Taiwan implemented a National Health Insurance (NHI) program in March 1995 that is characterized by mandatory enrollment in a government-run, single-payer insurance system, and comprehensive benefits coverage. The program currently has over 21 million enrollees, representing around 97% of the island's population. Therefore, the NHIRD is one of the largest and most comprehensive nationwide population-based data sources currently available. It thus provides a unique opportunity to explore the prevalence and risk of atopic disorders among patients with schizophrenia.

2.2. Study sample

This study features a study cohort and a comparison cohort, with the study cohort consisting of all patients under age 45 who visited an outpatient department for the treatment of

schizophrenia (any ICD-9-CM 295 code other than 295.7-schizoaffective disorder) between January and December 2000. Since diagnostic validity is usually a concern with administrative data, to ensure the validity of the schizophrenia diagnoses, we selected only those patients who had at least two consensus schizophrenia diagnoses that year. Ultimately, there were 44,187 schizophrenia patients in the study cohort.

The comparison cohort was selected from a NHIRD sub-dataset consisting of 5% of all enrollees in the NHI program, including 1,073,891 randomly selected subjects. The Bureau of the NHI reported that there were no statistically significant differences in age, gender, and cost between the sample in this sub-dataset and all enrollees. We excluded subjects from the sub-dataset if they had been previously diagnosed with any psychiatric disorder (ICD-9-CM codes 290–319) during 2000–2002. We then randomly selected 132,561 enrollees (three for every schizophrenia patient) from this sub-dataset, matched with the study group in terms of gender and age (<18, 18–24, 25–34 and ≥35 years). The method of age categorization is based on a study by Lin et al. (2008b).

We used NHIRD administrative data to assess atopic disorders. Follow-up of each individual patient from 2000 until the end of 2002 identified all patients who visited outpatient departments for the treatment of asthma (ICD-9-CM code 493), allergic rhinitis (ICD-9-CM code 477), urticaria (ICD-9-CM code 708) or atopic dermatitis (ICD-9-CM codes 691).

3. Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the statistical analyses. Chi-square tests were used to examine demographic differences between the two cohorts. Demographic characteristics included age, gender, urbanization and geographical region (Northern, Central, Eastern and Southern Taiwan) as well as monthly income (0, NT\$1–NT\$15,840, NT\$15,841–NT\$25,000, ≥NT\$25,001 (NT = New Taiwan Dollar, with an exchange rate in the year 2000 of 1 USD = 31.2 NT)). The reason for selecting NT\$15,840 as a cutoff point was that the Taiwan government stipulates this value as the minimum wage for full-time employees. As prior studies have consistently reported the association between atopic disorders and geographical regions and urbanization, possibly due to factors such as air pollution (Ramos et al., 2006; Sole et al., 2007; Yu et al., 2005); these two variables are therefore also taken into account in the regression modeling. We stratified all communities in Taiwan into five levels based on prior studies (Lin et al., 2008a,b), with level one referring to the 'most urbanized' communities and level five referring to the 'least urbanized' communities.

Separate logistic regression analyses were then performed to assess the independent associations between schizophrenia and asthma, allergic rhinitis, urticaria and atopic dermatitis (1=present and 0=absent) after controlling for the covariates of patients' gender, age, income, level of urbanization and geographic region. A two-sided *p* value of less than or equal to .05 was considered statistically significant.

4. Results

Table 1 describes the demographic distributions for the two cohorts. The χ^2 tests show significant differences in

Table 1Demographic characteristics of schizophrenia and comparison cohort patients in Taiwan in the year 2000 ($n=176,748$)

Variable	Schizophrenia patients ($n=44,187$)		Comparison cohort ($n=132,561$)		<i>p</i> value
	Total no.	%	Total no.	%	
Gender					1.000
Male	25,361	57.4	76,083	57.4	
Female	18,826	42.6	56,478	42.6	
Age					1.000
<18	2251	5.1	6573	5.1	
18–24	6355	14.4	19,065	14.4	
25–34	16,099	36.4	48,297	36.4	
>34	19,482	44.1	58,446	44.1	
Monthly income					<0.001
0	7733	17.5	20,414	15.4	
NT\$1–15,840	22,182	50.2	15,126	11.4	
NT\$15,841–25,000	12,284	27.8	66,943	50.5	
≥NT\$25,001	1988	4.5	16,844	12.7	
Urbanization level					<0.001
1	12,196	27.6	32,212	24.2	
2	11,577	26.2	36,189	27.3	
3	8440	19.1	22,800	17.2	
4	5965	13.5	23,994	18.1	
5	6009	13.6	17,366	13.2	
Geographical region					<0.001
Northern	19,973	45.2	92,352	69.7	
Central	9854	22.3	18,117	13.7	
Southern	12,593	28.5	20,510	15.5	
Eastern	1767	4.0	1582	1.2	

monthly income ($p<0.001$), urbanization level ($p<0.001$) and geographic region ($p<0.001$) between these two cohorts. Compared to the comparison cohort, schizophrenia patients were more likely to have lower monthly incomes, to reside in the most urbanized areas and in the central and southern parts of Taiwan.

The distribution of atopic disorders for the two cohorts is provided in Table 2. Overall, approximately 20.2% of schizophrenia patients (approximately one in five) experienced atopic disorders. The percentages of schizophrenia patients diagnosed with asthma, allergic rhinitis, urticaria and atopic dermatitis during 2000–2002 was 3.7%, 6.7%, 8.0% and 2.0%, respectively. By comparison, 2.8%, 8.5%, 10.5% and 2.1% of patients in the comparison cohorts were diagnosed with asthma, allergic rhinitis, urticaria and atopic dermatitis,

respectively. The χ^2 tests show that there were significant differences in the prevalence of asthma, allergic rhinitis and urticaria (all $p<0.001$) between the two cohorts, but not for atopic dermatitis.

The crude odds ratios of atopic disorders for these two cohorts are also presented in Table 2, revealing that for schizophrenia patients, the odds of being diagnosed with asthma were 1.31 times (95% CI=1.24–1.39, $p<0.001$) those of patients in the comparison cohort. In contrast, the crude odds of allergic rhinitis and urticaria were respectively 0.78 (95% CI=0.74–0.81, $p<0.001$) and 0.72 (95% CI=0.72–0.77, $p<0.001$) times less for schizophrenia patients than for the comparison cohort.

Details of the adjusted odds ratios for atopic disorders by cohort are provided in Table 3. After adjusting for patients' gender, age, income, urbanization level and geographic region, the odds of being diagnosed with asthma were 1.30 (95% CI=1.24–1.39, $p<0.001$) times greater for schizophrenia patients than for patients in the comparison cohort. Furthermore, compared with patients in the comparison cohort, schizophrenia patients had a lower likelihood of allergic rhinitis (OR=0.77, 95% CI=0.74–0.81, $p<0.001$) and urticaria (OR=0.74, 95% CI=0.72–0.77, $p<0.001$), after adjusting for other factors.

5. Discussion

To our knowledge, this is the first report on the prevalence and risk of atopic disorders among schizophrenia patients. Results indicate a considerably higher comorbidity of schizophrenia and allergies, with 20.2% of schizophrenia patients (approximately one in five) concurrently having atopic disorders. Moreover, schizophrenia in patients was independently associated with a 1.3-fold increased risk of asthma, after adjusting for sociodemographic characteristics. Yet, their risk of diagnosed allergic rhinitis and urticaria decreased 23% and 26%, respectively, compared to people without any psychiatric disease. Except for the life-threatening illness of asthma, schizophrenia patients may underuse medical care for chronic but milder atopic disorders such as allergic rhinitis and urticaria.

A link between asthma and schizophrenia has been proposed in previous case studies. For example, Lemke (1992) reported a 33-year-old patient who exhibited combined

Table 2Crude odds ratio of atopic disorder among schizophrenia patients and the comparison cohort in Taiwan ($n=176,748$)

Variable	Atopic disorder				Crude odds ratio	95% confidence interval	p value
	Yes		No				
	N	%	N	%			
Schizophrenia patients							
Asthma	1619	3.7	42,568	96.3	1.31	1.24–1.39	<0.001
Allergic rhinitis	2959	6.7	41,228	93.3	0.78	0.74–0.81	<0.001
Urticaria	3551	8.0	40,636	92.0	0.72	0.72–0.77	<0.001
Atopic dermatitis	884	2.0	43,303	98.0	0.93	0.87–1.01	0.078
Comparison patients							
Asthma	3738	2.8	128,823	97.2	1.00	–	
Allergic rhinitis	11,232	8.5	121,329	91.5	1.00	–	
Urticaria	13,938	10.5	118,623	89.5	1.00	–	
Atopic dermatitis	2836	2.1	129,725	97.9	1.00	–	

Table 3Adjusted odds ratio of atopic disorder for schizophrenia and comparison patient samples in Taiwan ($n = 176,748$)

Variables	Atopic disorders							
	Asthma		Allergic rhinitis		Urticaria		Atopic dermatitis	
	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Cohort								
Schizophrenia	1.30***	1.24–1.39	0.77***	0.74–0.81	0.74***	0.72–0.77	0.92	0.84–1.02
Comparison (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
Gender								
Male	0.98	0.93–1.03	0.82***	0.79–0.82	0.68***	0.66–0.70	0.74***	0.69–0.79
Female (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
Age								
<18 (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
18–24	0.38***	0.34–0.43	0.60***	0.56–0.65	0.86***	0.80–0.93	0.55***	0.48–0.62
25–34	0.38***	0.35–0.42	0.52***	0.48–0.55	0.84***	0.79–0.91	0.48***	0.42–0.54
>34	0.44***	0.40–0.48	0.45***	0.42–0.48	0.82***	0.77–0.88	0.48***	0.43–0.54
Monthly income								
0 (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
NT\$1–15,840	0.65***	0.64–0.67	0.54***	0.53–0.56	1.21***	1.18–1.25	0.90	0.78–1.04
NT\$15,841–25,000	0.78***	0.76–0.79	0.48***	0.47–0.48	1.17***	1.15–1.19	0.82**	0.72–0.93
≥NT\$25,001	0.61***	0.59–0.63	0.63***	0.62–0.64	1.11***	1.07–1.14	0.83*	0.71–0.97
Urbanization level								
1 (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
2	1.11***	1.09–1.13	1.08***	1.06–1.10	1.09***	1.06–1.12	0.81***	0.71–0.92
3	1.13***	1.10–1.15	0.96***	0.94–0.98	1.11***	1.08–1.14	0.75***	0.64–0.87
4	1.19***	1.15–1.22	0.91***	0.89–0.93	1.13***	1.10–1.16	0.76**	0.63–0.90
5	0.90***	0.89–0.92	0.67***	0.66–0.69	1.11***	1.08–1.13	0.92	0.80–1.04
Geographic region								
Northern (reference group)	1.00	–	1.00	–	1.00	–	1.00	–
Central	0.87***	0.86–0.89	0.85***	0.84–0.87	0.93***	0.91–0.95	1.02	0.89–1.17
Southern	0.74***	0.72–0.75	0.76***	0.75–0.77	0.89***	0.88–0.91	1.62	1.46–1.80
Eastern	1.13***	1.08–1.19	0.77***	0.73–0.82	1.03	0.97–1.09	1.08	0.75–1.56

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

allergic-asthmatic and paranoid-catatonic symptoms in an anticyclic pattern. Addressing an issue not examined by any prior large-scale study, our findings indicate a slightly increased risk of asthma among schizophrenia patients. Besides the connection with schizophrenia found by our study, previously literature has also linked asthma with neurotic disorders. For example, anxiety and depression are associated with the occurrence of asthma, with estimated risk ranging approximately from 1.4 to 2.5 (Jonas et al., 1999; Wainwright et al., 2007).

Comorbidity of schizophrenia and atopic disorders such as asthma suggests the possibility of shared biologic or environmental risk factors and underlying pathways that contributing to the etiopathogenesis of both diseases. The basis of this comorbidity is very probable multifactorial, including potentially shared inflammatory and stress-response mechanisms as well as psychobehavioral elements. For example, alterations of proinflammatory cytokine levels (e.g., interleukin-6, tumor necrosis factor alpha) have been described and connected with the pathophysiology of schizophrenia (Schmitt et al., 2005) and of inflammatory medical diseases such as atopic allergies (Infante et al., 2007). Of increasing interest physiologically is the role of the hypothalamic-pituitary-adrenal (HPA) axis, a major part of the neuroendocrine system that is triggered by stress and that regulates many body processes, including the immune system, mood and emotions. Schizophrenic symptoms are related to elevated baseline and challenge-induced HPA activity as well as diminishing stress hormone (cortisol) release (Walker et al., 2008). On the other hand, a blunted cortisol response to

stress, reflecting the dysregulation of the HPA axis, might represent a common feature of chronic allergic inflammatory processes that are associated with atopic disorders (Buske-Kirschbaum et al., 2003). Finally, psychobehavioral factors should also be considered when accounting for the co-occurrence of schizophrenia and atopic disorders. For example, schizophrenia may contribute to asthma-exacerbating behaviors such as tobacco smoking, unhygienic living environments with more allergens, and poor treatment compliance (de Leon and Diaz, 2005; Kilian et al., 2006; Rummel-Kluge et al., 2008).

Based upon these findings, we anticipated similar trends and mechanisms would link schizophrenia with allergic rhinitis and dermatologic disorders. In one prior study, fifty-nine outpatients with urticaria were investigated using the Minnesota Multiphasic Personality Inventory (MMPI). Compared with healthy controls, patients with urticaria demonstrated significantly higher scores for schizophrenia, paranoia, and psychopathic deviance (Pasaoglu et al., 2006). Furthermore, Nasierowski and Wolynczyk (2007) proposed that schizophrenia and depression were associated with atopic dermatitis or dermatologic sequelae. As mentioned, some have proposed cytokine regulation disturbances play a substantial role in the pathogenesis of both schizophrenia and such dermatologic disorders.

However, our findings of decreased risk of allergic rhinitis and urticaria for schizophrenia patients are not consistent with the studies mentioned above. In addition to possible biological, sociocultural, and environmental influences, one reason for the inconsistency might be that schizophrenia

patients have insufficient access to medical care for such disorders. Previous studies have shown that, compared with the general population, schizophrenia patients are significantly less likely to have blood pressure or cholesterol recorded—32% and 42% respectively (Roberts et al., 2007)—and were much less likely to be prescribed heart catheterization (Lawrence et al., 2003). In sum, they were rarely treated for physical disease unless it was severe or life-threatening (Muck-Jorgensen et al., 2000). Except for asthma, atopic disorders such as allergic rhinitis, urticaria, and atopic dermatitis can be distressing but not fatal. Despite the very low out-of-pocket copayments for medical services in Taiwan's National Health Insurance program, it is possible that schizophrenic patients might tend not to seek treatment for diseases that are not life threatening on account of their poor economic circumstances (Cooper, 2005). In sum, our study suggests under-use of physical healthcare for such chronic, but milder, atopic disorders among schizophrenia patients. Finally, it is worth noting that patients were as likely to seek treatment seeking for atopic dermatitis as other ailments such as urticaria and allergic rhinitis. This may reflect greater psychological distress associated with dermatitis, as suggested by Annesi-Maesano's report of higher levels of anxiety among dermatitis patients than among patients with other atopic diseases such as allergic rhinitis (Annesi-Maesano et al., 2006).

Our study leads the way toward examining schizophrenia as one of the psychiatric disorders associated with atopic disorders. However, some limitations deserve consideration. First, the diagnoses of atopic disorders in our study were based on clinical interviews, due to assessment time constraints within a clinical setting. Patients may or may not undergo biological measures of atopy (e.g., a skin prick test or an IgE-test) to verify the diagnoses. However, previous studies have reported a good correlation between clinical diagnosis and specific IgE against inhaled allergens (Sanz et al., 1996). Second, the NHIRD database represents patients who sought treatment for both schizophrenia and atopic disorders. The likely underuse of somatic healthcare among schizophrenia patients for non-lethal atopic diseases such as allergic rhinitis, urticaria, and atopic dermatitis, might result in underestimation of their risk.

Lastly, overpowering could be a concern, because some minor differences appeared highly statistically significant in our study. However, when we cut down the sample size, results obtained were quite consistent. Specifically, in 1,000 randomly selected schizophrenia patients and 3000 patients from the comparison cohort, we found that schizophrenia patients had a lower likelihood of allergic rhinitis (OR=0.62, 95% CI=0.46–0.82, $p<0.001$) and urticaria (OR=0.61, 95% CI=0.46–0.82, $p<0.001$) and a higher likelihood of asthma (OR=1.37, 95% CI=1.02–1.84, $p=0.031$) than the comparison cohort, after controlling for other factors. Similarly, no significant difference in atopic dermatitis between these two cohorts (OR=1.02, 95% CI=0.72–1.45, $p=0.901$) was observed. Since these results were consistent, we are reporting findings based on the total sample.

Because we did not recruit a control group with other (non-schizophrenia) psychiatric disorders, it is not possible to distinguish whether the results we found are specific to schizophrenic patients or applicable to psychiatric patients in

general. Finally, because we used a claims database, we were unable to examine the effects of risk factors such as dietary habits, domestic environment, and family history of psychiatric and atopic diseases in the regression model, which could compromise our findings.

Our findings revealed an increased risk of asthma and decreased risks of allergic rhinitis and urticaria among schizophrenia patients. Replication of these results is needed to confirm the associations between schizophrenia and atopic disorders. As for clinical implications, psychiatrists should be more aware of, detect and treat physical comorbidities common among schizophrenia patients, including distressing illnesses like atopic disorders, as part of effective management of the disease. Future studies on the identification of common etiologic pathways for these two diseases could be clinically significant for developing innovative treatment targeting both illnesses concurrently. Finally, longitudinal studies that can investigate the sequence of onset and the effects of biological, psychosocial and environmental risk factors in the association between schizophrenia and atopic disorders are needed to illuminate possible shared etiopathogenesis mechanisms.

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None.

Contributors

Dr. Chen and Dr. Lin designed the study and wrote the draft. Dr. Lee managed the literature search and analyses. Dr. Lin undertook the statistical analyses. All authors contributed to and approved the final manuscript.

Conflict of interest

None.

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