

Risk of Atopic Diseases among Siblings of Patients with Attention-Deficit Hyperactivity Disorder: A Nationwide Population-Based Cohort Study

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Keywords

Attention-deficit disorder with hyperactivity · Asthma ·
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Abstract

Background: Increasing evidence suggests a positive association between attention-deficit hyperactivity disorder (ADHD) and atopic diseases. However, the risk of atopic diseases in unaffected siblings of patients with ADHD has not been investigated. **Objective:** To investigate the risk of developing atopic diseases among unaffected siblings of ADHD probands. **Methods:** Using data from the Taiwan National Health Insurance Research Database, 20,170 unaffected siblings of patients with ADHD born between 1980 and 2000 and 80,680 age-, birth time-, and residence-matched controls were included in this study. Diagnoses of atopic diseases, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, were ascertained from 1996 or the birth time until the end of 2011. **Results:** Breslow-Cox proportional hazard regression analyses with adjustment for demographic data showed that compared with the controls, unaf-

ected siblings of patients with ADHD had a higher risk of developing asthma (relative risk [RR], 1.19; 95% confidence interval [CI], 1.15–1.24), atopic dermatitis (RR, 1.10; 95% CI, 1.04–1.16), allergic rhinitis (RR, 1.17; 95% CI, 1.14–1.21), allergic conjunctivitis (RR, 1.13; 95% CI, 1.09–1.17), and any of these atopic diseases (RR, 1.13; 95% CI, 1.10–1.15). **Conclusion:** The unaffected siblings of ADHD probands were more likely to develop atopic diseases compared with the controls, suggesting shared risk factors for both diseases.

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Introduction

Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is characterized by persistent hyperactivity, impulsivity, or inattention to the extent that it severely affects function in social and academic activities [1]. It often starts from early childhood

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and may persist throughout adolescence or even adulthood [1]. The prevalence of ADHD is approximately 7% in children and adolescents, making it the most commonly diagnosed mental disorder in childhood [2]. Boys are 2–3 times more likely to be diagnosed with ADHD than girls [3]. The pathogenesis underlying ADHD remains unclear. Genetic influences on the dysregulation of neurotransmitters and neuroanatomic abnormalities appear to play a primary role, whereas environmental factors have been recognized to modify the risk of developing ADHD [4].

The increasing prevalence of atopic diseases, such as atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, and food allergy, among children is a worldwide trend and has raised significant public concern [5]. Clustering of these disorders is not uncommon; the atopic march tends to be initiated in affected individuals during their infancy with the manifestation of eczema, and it progresses into their childhood and adolescence with the development of allergic symptoms in the airways and eyes [6]. Similar to ADHD, atopic diseases are genetically complex with variable heritability, and their presentation is highly influenced by exogenous factors [7, 8]. The coexistence of atopic diseases and ADHD has been observed since 1980, and the relationship between these two common chronic illnesses in children has been extensively studied in the past decade [9–17]. Atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis, and food allergy are positively associated with ADHD, while pathophysiological associations between these atopic diseases and ADHD remain to be clarified.

The unaffected individuals with ADHD siblings may share some psychological and biological characteristics with their affected siblings, making them more susceptible to certain mental and physical disorders compared with those without siblings diagnosed with ADHD [18]. In agreement with the findings of some earlier investigations, our previous study demonstrated an increased risk of developing depression, anxiety, bipolar disorders, and alcohol and substance abuse among the unaffected siblings of patients with ADHD [19]. We also found an elevated risk of developing physical disorders related to health risk behavior, such as sexually transmitted diseases and traumatic brain injury, among these individuals [19]. However, the risk of developing atopic diseases has not been explored in this population. Clarifying whether having ADHD siblings is a risk factor for developing atopic diseases may facilitate the understanding of the pathophysiology linking ADHD and atopy as well as offer clinical value in terms of the prevention and management

of atopic diseases. This nationwide population-based study aims to investigate the risk of developing atopic diseases, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, among the unaffected siblings of patients with ADHD.

Materials and Methods

Data Source

Data analyzed in this study were retrieved from the Taiwan National Health Insurance Research Database (NHIRD). The NHIRD comprises health care information of >99% Taiwanese people (approximately 23 million residents) and has been widely used in epidemiological studies in Taiwan [20, 21]. Data of beneficiaries recorded in the NHIRD include comprehensive information about the insured subjects, including demographic details (date of birth, sex, monthly premium, and residential location) and claim information (outpatient and inpatient care, medical diagnoses, prescriptions, and operations). To maintain privacy, a unique identification number is assigned to each beneficiary and is enciphered before data are released for scientific purposes. We used the unique identification number to link all the health care records of each beneficiary. Following the method of Kuo et al. [22], the recorded family kinships in the NHIRD were used for genealogy reconstruction. The diagnostic codes used were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM).

Study Cohort and Matched Controls

The study cohort was established by enrolling subjects born between 1980 and 2010 without a diagnosis of ADHD (ICD-9-CM code 314) at any time but with siblings diagnosed with ADHD by board-certified psychiatrists. The age-, sex-, birth time-, and residence-matched (1:4) controls were randomly selected after excluding the study cases, those who had been diagnosed with ADHD, and those with any ADHD siblings. To elucidate the comorbid effects of ADHD on atopic diseases in patients with ADHD and their unaffected siblings, respectively, the ADHD-affected siblings of our study subjects were identified to establish an ADHD cohort. Residence is classified into 5 levels of urbanization, with level 1 indicating the most urbanized area and level 5 the least [23]. All of the enrolled subjects were followed from 1996 or the birth time to the end of 2011. Occurrence of atopic diseases, including asthma (ICD-9-CM code 493), atopic dermatitis (ICD-9-CM code 691), allergic rhinitis (ICD-9-CM code 477), and allergic conjunctivitis (ICD-9-CM codes 372.05, 372.10, and 372.14), was identified during the follow-up period. The diagnosis of the atopic diseases was established at least 3 times by board-certified pediatricians, physicians, ophthalmologists, and dermatologists based on their comprehensive judgment. This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (VGHIRB No. 2018-07-016AC).

Statistical Analysis

Demographic characteristics were expressed as counts with percentages for categorical variables and means with standard deviations or medians with an interquartile range for continuous variables. The independent *t* test or Wilcoxon rank sum test was used

Table 1. Demographic data and incidence of atopic diseases among ADHD patients, unaffected ADHD siblings, and controls

	ADHD patients (<i>n</i> = 15,122)	Unaffected siblings (<i>n</i> = 20,170)	Controls (<i>n</i> = 80,680)	<i>p</i> ₁₂ ^a	<i>p</i> ₁₃ ^a	<i>p</i> ₂₃ ^a
<i>Demographic data</i>						
Age (mean ± SD), years	14.5 (4.7)	15.7 (6.3)	15.7 (6.4)	<0.001	<0.001	0.64
Sex, <i>n</i> (%)				<0.001	<0.001	1.00
Male	12,202 (80.7)	9,128 (45.3)	36,512 (45.3)			
Female	2,920 (19.3)	11,042 (54.7)	44,168 (54.7)			
Monthly premium, <i>n</i> (%)				<0.001	<0.001	0.002
0–500 USD	14,425 (95.4)	17,949 (89.0)	71,060 (88.1)			
501–800 USD	584 (3.9)	1,576 (7.8)	6,833 (8.5)			
≥800 USD	113 (0.7)	645 (3.2)	2,787 (3.5)			
Level of urbanization, <i>n</i> (%)				<0.001	<0.001	1.00
1 (urbanized)	2,456 (16.2)	3,655 (18.1)	14,620 (18.1)			
2	4,571 (30.2)	6,271 (31.1)	25,084 (31.1)			
3	1,306 (8.6)	1,909 (9.5)	7,636 (9.5)			
4	1,304 (8.6)	1,770 (8.8)	7,080 (8.8)			
5 (rural)	5,485 (36.3)	6,565 (32.5)	26,260 (32.5)			
<i>Outcome</i>						
Incident cases of atopic diseases, <i>n</i> (%)						
Asthma	3,331 (22.0)	3,600 (17.8)	12,066 (15.0)	<0.001	<0.001	<0.001
Atopic dermatitis	1,329 (8.8)	1,554 (7.7)	5,668 (7.0)	<0.001	<0.001	<0.001
Allergic rhinitis	6,198 (41.0)	6,141 (30.4)	20,973 (26.0)	<0.001	<0.001	<0.001
Allergic conjunctivitis	3,810 (25.2)	3,566 (17.7)	12,645 (15.7)	<0.001	<0.001	<0.001
Comorbid atopic diseases, <i>n</i> (%)				<0.001	<0.001	<0.001
0	6,538 (43.2)	10,899 (54.0)	47,794 (59.2)			
1	4,225 (27.9)	5,201 (25.8)	19,210 (23.8)			
2	2,879 (19.0)	2,754 (13.7)	9,509 (11.8)			
3	1,235 (8.2)	1,112 (5.5)	3,544 (4.4)			
4	245 (1.6)	204 (1.0)	623 (0.8)			
Median age at diagnosis of atopic diseases (IQR), years						
Asthma	4.5 (2.8–6.8)	3.9 (2.2–6.0)	3.9 (2.2–5.7)	<0.001	<0.001	0.31
Atopic dermatitis	2.6 (0.7–7.2)	1.5 (0.5–6.3)	1.2 (0.4–5.2)	<0.001	<0.001	<0.001
Allergic rhinitis	5.5 (3.3–8.6)	4.9 (2.7–8.7)	5.0 (2.9–8.7)	<0.001	<0.001	0.07
Allergic conjunctivitis	6.6 (4.6–8.7)	6.8 (4.8–9.6)	6.8 (4.7–9.5)	<0.001	<0.001	0.27

ADHD, attention-deficit hyperactivity disorder; IQR, interquartile range; SD, standard deviation. ^a*p*₁₂, ADHD patients vs. unaffected siblings; *p*₁₃, ADHD patients vs. controls; *p*₂₃, unaffected siblings vs. controls. Bold type denotes significance (*p* < 0.05).

to compare the continuous variables between groups, as appropriate, while Pearson's χ^2 test was used for categorical variables. The relative risk (RR) of atopic diseases was calculated in individuals with ADHD-affected siblings compared with the matched controls. Given an equal follow-up time for all subjects in each matched set, the Cox proportional hazard model was used to evaluate the overall RR of atopic diseases between the study and controlled cohorts by means of Breslow's method, adjusting for age, sex, residential location, and monthly premium [24, 25]. Monthly premium was regarded as an estimate of monthly income, which was not recorded in the NHIRD. A second regression model was performed by including atopic comorbidities in the adjusted covariates. The regression analyses were further stratified by sex to investigate the role of sex in the risk of subsequent atopic diseases. The increased risk of type I error due to multiple comparisons was corrected by the Bonferroni method. A two-sided *p* value less than the critical level (0.05

divided by the number of variates) was considered statistically significant. Data analyses were performed using the Statistics Analysis System (SAS), version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

There were 15,122 ADHD patients, 20,170 unaffected individuals with ADHD siblings, and 80,680 matched controls included in our study (Table 1). χ^2 tests revealed that ADHD patients had a higher frequency of asthma (22.0 vs. 17.8%, *p* < 0.001; 22.0 vs. 15.0%, *p* < 0.001), atopic dermatitis (8.8 vs. 7.7%, *p* < 0.001; 8.8 vs. 7.0%, *p* < 0.001), allergic rhinitis (41.0 vs. 30.4%, *p* < 0.001; 41.0 vs.

Table 2. Relative risk of developing atopic diseases among individuals with ADHD siblings and controls

	With ADHD siblings, <i>n</i> (%)	Controls, <i>n</i> (%)	RR ^a (95% CI)	<i>p</i> value ^b	RR ^c (95% CI)	<i>p</i> value ^d
Asthma	3,600 (17.9)	12,066 (15.0)	1.19 (1.15–1.24)	<0.001	1.11 (1.07–1.16)	<0.001
Atopic dermatitis	1,554 (7.7)	5,668 (7.0)	1.10 (1.04–1.16)	0.001	1.04 (0.98–1.10)	0.22
Allergic rhinitis	6,141 (30.4)	20,973 (26.0)	1.17 (1.14–1.21)	<0.001	1.11 (1.08–1.14)	<0.001
Allergic conjunctivitis	3,566 (17.7)	12,645 (15.7)	1.13 (1.09–1.17)	<0.001	1.08 (1.04–1.12)	<0.001
Any atopic disease ^e	9,271 (46.0)	32,886 (40.8)	1.13 (1.10–1.15)	<0.001	–	–

ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; RR, relative risk.

^a Adjusted for age, sex, residence, and monthly premium. ^b Bold type denotes significance ($p < 0.01$). ^c Adjusted for age, sex, residence, monthly premium, and comorbid atopic diseases. ^d Bold type denotes significance ($p < 0.008$). ^e Any atopic disease refers to asthma, atopic dermatitis, allergic rhinitis, or allergic conjunctivitis.

26.0%, $p < 0.001$), and allergic conjunctivitis (25.2 vs. 17.7%, $p < 0.001$; 25.2 vs. 15.7%, $p < 0.001$) during the follow-up period compared with their unaffected siblings and controls, respectively. Regarding the comparison between individuals with ADHD siblings and controls, age, sex, and residence were well matched without between-group differences. Individuals with ADHD siblings had a higher frequency of asthma (17.8 vs. 15.0%, $p < 0.001$), atopic dermatitis (7.7 vs. 7.0%, $p < 0.001$), allergic rhinitis (30.4 vs. 26.0%, $p < 0.001$), and allergic conjunctivitis (17.7 vs. 15.7%, $p < 0.001$) than the controls during the follow-up period, indicated by χ^2 tests. Additionally, individuals with ADHD siblings were more likely to have multiple atopic diseases than the controls. Evaluated by the Wilcoxon rank sum test, the median age of developing atopic diseases was similar in both groups, except that those with ADHD siblings developed atopic dermatitis at a slightly older age (1.5 vs. 1.2 years, $p < 0.001$).

Breslow-Cox proportional hazard regression with adjustment for age, sex, residence, and monthly premium revealed that individuals with ADHD siblings had a higher risk of developing asthma (RR, 1.19; 95% confidence interval [CI], 1.15–1.24), atopic dermatitis (RR, 1.10; 95% CI, 1.04–1.16), allergic rhinitis (RR, 1.17; 95% CI, 1.14–1.21), allergic conjunctivitis (RR, 1.13; 95% CI, 1.09–1.17), and any of the these atopic diseases (RR, 1.13; 95% CI, 1.10–1.15) compared with those of the controls (Table 2). Stratified by sex, the risk of developing atopic diseases remained elevated, except for atopic dermatitis in the brothers of ADHD patients (Table 3). After controlling for comorbid atopic diseases, having ADHD siblings was still a risk factor for asthma, allergic rhinitis, and allergic conjunctivitis, but not for atopic dermatitis, in both males and females (Tables 2, 3).

Discussion

In accordance with previous studies, we found a strong comorbidity of ADHD and atopic diseases in this nationwide population-based cohort study. We further detected a dose-response relationship between individuals' association with ADHD (individuals with ADHD, with ADHD-affected siblings, or without ADHD-affected siblings) and the cumulative incidence of asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis. Even if they were not affected by ADHD, individuals with ADHD-affected siblings had a modestly increased risk of developing these atopic diseases. The elevated risks were similar in both sexes and independent of the comorbid atopic conditions, except for those of atopic dermatitis.

The association between ADHD and atopic diseases has long been suspected. Pelsser et al. [26] hypothesized that ADHD was a hypersensitivity disorder similar to allergy. Since then, there has been an increasing number of observational studies demonstrating positive associations between ADHD and atopic diseases [9–13, 16]. The systematic review with meta-analyses published by Miyazaki et al. [14] revealed an increased odds ratio (OR) of developing asthma (OR, 1.80; 95% CI, 1.57–2.07), atopic dermatitis (OR, 1.43; 95% CI, 1.09–1.88), allergic rhinitis (OR, 1.59; 95% CI, 1.13–2.23), and allergic conjunctivitis (OR, 1.69; 95% CI, 1.04–2.76), but not food allergy (OR, 1.13; 95% CI, 0.88–1.47), in patients with ADHD compared with that of the controlled individuals. Another systematic review with meta-analyses performed by Schans et al. [15] showed an elevated OR of developing ADHD in patients with asthma (OR, 1.34; 95% CI, 1.24–1.44), atopic dermatitis (OR, 1.32; 95% CI, 1.20–1.45), and allergic rhinitis (OR, 1.52; 95% CI, 1.43–1.63) relative

Table 3. Relative risk of developing atopic diseases among individuals with ADHD siblings and controls, stratified by sex

	Male						Female					
	with ADHD siblings, n (%)	controls, n (%)	RR ^a (95% CI)	<i>p</i> ^b	RR ^c (95% CI)	<i>p</i> ^d	with ADHD siblings, n (%)	controls, n (%)	RR ^a (95% CI)	<i>p</i> ^b	RR ^c (95% CI)	<i>p</i> ^d
Asthma	1,940 (21.3)	6,494 (17.8)	1.19 (1.13–1.26)	<0.001	1.12 (1.06–1.19)	<0.001	1,660 (15.0)	5,572 (12.6)	1.19 (1.13–1.26)	<0.001	1.09 (1.03–1.16)	0.006
Atopic dermatitis	744 (8.2)	2,751 (7.5)	1.08 (1.00–1.17)	0.06	1.04 (0.96–1.13)	0.35	810 (7.3)	2,917 (6.6)	1.11 (1.03–1.20)	0.008	1.03 (0.95–1.12)	0.43
Allergic rhinitis	3,041 (33.3)	10,760 (29.5)	1.13 (1.09–1.18)	<0.001	1.06 (1.02–1.11)	0.005	3,100 (28.1)	10,213 (23.1)	1.21 (1.17–1.26)	<0.001	1.16 (1.11–1.21)	<0.001
Allergic conjunctivitis	1,640 (18.0)	5,877 (16.1)	1.12 (1.06–1.18)	<0.001	1.08 (1.02–1.14)	0.009	1,926 (17.4)	6,768 (15.3)	1.14 (1.08–1.20)	<0.001	1.09 (1.03–1.14)	0.002
Any atopic disease ^e	4,412 (48.3)	16,062 (44.0)	1.10 (1.06–1.14)	<0.001	–	–	4,859 (44.0)	16,824 (38.1)	1.16 (1.12–1.19)	<0.001	–	–

ADHD, attention-deficit hyperactivity disorder; CI, confidence interval; RR, relative risk. ^a Adjusted for age, residence, and monthly premium. ^b Bold type denotes significance ($p < 0.013$). ^c Adjusted for age, residence, monthly premium, and comorbid atopic diseases. ^d Bold type denotes significance ($p < 0.01$). ^e Any atopic disease refers to asthma, atopic dermatitis, allergic rhinitis, or allergic conjunctivitis.

to those without atopy. The presented associations were independent of common confounding factors and other atopic diseases. A connection between ADHD and atopic diseases among individuals with affected kinship has also been reported by Schans et al. [15], who found that children were more likely to receive medical treatment for ADHD if their parents had drug-treated asthma (OR, 1.2; 95% CI, 1.1–1.3) or allergic rhinitis (OR, 1.3; 95% CI, 1.1–1.5) [16]. Our study demonstrated an increased risk of atopic diseases among the unaffected siblings of patients with ADHD, which has never been reported.

The results of our study suggest a common pathogenesis underlying the development of atopic diseases and ADHD. Genetic associations between certain atopic diseases and ADHD have been discovered recently. Certain variants in the gene of dopamine receptor D5, a member of D1-like dopamine receptor (D1LDR), have been recognized to be risk factors of ADHD [27]. In addition to the widespread expression in the central nervous system, D1LDRs were identified on the surface of peripheral lymphocytes and mast cells, playing a role in allergic inflammation [28, 29]. Animal studies have shown that D1LDR antagonists can reduce the severity of atopic dermatitis and asthma by inactivating T-helper 2- and 17-mediated inflammation, respectively [30, 31]. In addition to the dopaminergic system, the histaminergic system was also possibly involved. Gene polymorphisms in histamine degradation have been shown to affect the severity of ADHD symptoms [32]. Antihistamine use was found to be a risk modifier in the development of ADHD symptoms among children with allergic rhinitis and atopic dermatitis [12, 13]. Additionally, gene polymorphisms in signal transducer and activator of transcription 6

(STAT6), an important molecule involved in immune response regulation, have been implicated in the pathogenesis of both atopic diseases and ADHD [33–36].

In addition to the genetic associations, shared environmental risk factors might also play a role in the observed associations in our study. Maternal stress and maternal smoking have been demonstrated to increase the risk of both ADHD and atopic diseases in the offspring [4, 7, 37]. Pollen and certain foods have been recognized to be triggers of ADHD, suggesting an immunoallergic background of ADHD [17, 26, 38]. A strict elimination diet could improve the symptoms of ADHD in a subset of patients [17]. Low socioeconomic status has also been identified as a risk factor for both disorders [37, 39]. Furthermore, the adverse emotional effects caused by the ADHD patients to their unaffected siblings might exacerbate the latter's allergic symptoms [40]. These environmental factors, however, are more likely to serve as disease triggers or modifiers in patients with genetic susceptibility, reflecting a multifactorial pathophysiological mechanism linking both disorders [14–16].

Unlike other atopic diseases, the elevated risk of atopic dermatitis among individuals with ADHD siblings was not independent of atopic comorbidities and remained significant only in females after stratification by sex. This finding implied a weaker association between atopic dermatitis and ADHD through the effect of common risk factors compared with other atopic diseases and a potential influence of sex or gender on this association. Given the fact that there has been compelling evidence indicating a comorbidity of atopic dermatitis and ADHD in the same individual, we postulated that the atopic dermatitis-ADHD relationship was primarily rooted in direct cau-

sality rather than shared risk factors [10, 11, 14, 15]. For instance, an enhanced release of inflammatory cytokines after allergen exposure in children with atopic dermatitis may lead to disruption on the growing brain and subsequent development of ADHD, or the elevated everyday stress may serve as a trigger for atopic dermatitis among patients with ADHD, depending on which occurs first [41]. Regarding the difference in the risk of atopic dermatitis between brothers and sisters with ADHD patients, the etiology remained elusive. Sex hormones have been well recognized to play a role in allergic inflammation, where estrogen is an immune booster while androgen is a suppressor [42, 43]. However, the higher cumulative incidence of atopic dermatitis in males compared with females and the identification of most cases with atopic dermatitis during their infancy indicated that there were reasons other than sex hormones leading to the elevated risk of atopic dermatitis among female individuals with ADHD siblings [44].

There were several limitations in our study. First, the NHIRD lacked information on environmental factors, such as maternal smoking, prenatal stress, and allergy toward food or inhalant allergens, which were thus not presented and controlled in our study. Adjusting these environmental factors in the regression model may further elucidate the etiology of the observed associations in our study. Second, the subthreshold ADHD symptoms among the unaffected siblings of patients with ADHD were not available in the NHIRD. Previous studies have demonstrated higher levels of ADHD symptoms among the unaffected siblings of patients with ADHD [45]. Therefore, the uncontrolled levels of ADHD symptoms in the study subjects could potentially confound our results. Third, another potential confounder – family history of atopic diseases – could not be identified in the NHIRD and hence could not be controlled for in our study. Therefore, there was the possibility that the increased prevalence of atopic diseases among patients with ADHD might contribute to the observed increased risk of

atopic diseases among their unaffected siblings, independent of the effect of ADHD. Finally, the external validity of our findings may be a concern because almost all of our subjects were Taiwanese.

In conclusion, the unaffected siblings of patients with ADHD have a higher risk for asthma, allergic rhinitis, and allergic conjunctivitis compared with that of the controlled individuals. These results suggest shared genetic and environmental risk factors in the pathogenesis of ADHD and atopic diseases. Our findings may remind clinicians to early identify these high-risk individuals to reduce the burden of atopic diseases.

Statement of Ethics

This study was approved by the Institutional Review Board of the Taipei Veterans General Hospital (VGHIRB No. 2018-07-016AC).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Tsung-Hsien Chang, Ying-Xiu Dai, Yun-Ting Chang, and Mu-Hong Chen had substantial contributions to the conception and design of the study. Data used in this study were acquired by Mu-Hong Chen while analyzed and interpreted by Ying-Hsuan Tai and Tzeng-Ji Chen. The manuscript was mainly drafted by Tsung-Hsien Chang and critically revised by all the other authors. All the authors approved the final version of the manuscript and agreed to be responsible for all aspects of the work in ensuring its accuracy and integrity.

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