

PEDIATRIC ASTHMA

Associations of Age, Gender, and BMI with Prevalence of Allergic Diseases in Children: PATCH Study

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Background. Little is known about the prevalence of allergic diseases in children of different ages. This study aimed to investigate the prevalence of allergic diseases and allergic sensitization in children over a wide age range, with emphasis on the influence of age, gender, and body mass index (BMI). **Methods.** In a cross-sectional study, we assessed 5351 Taiwanese children aged 4–18 years using an International Study of Asthma and Allergies in Childhood questionnaire, BMI, and total and specific serum immunoglobulin E. **Results.** Forty-eight percent were currently symptomatic for at least one of three allergic diseases. Prevalence of wheeze ever, current wheeze, and diagnosed asthma were 17.0%, 7.5%, and 9.8%, respectively; analogous features for rhinitis were 47.8%, 44.2%, and 39.8%. Allergic sensitization was very common (57.3%). Half of the children (50.6%) with current wheeze had not been diagnosed with asthma by physicians, whereas undiagnosed rates were 32.3% for rhinitis and 25.3% for eczema. The male-to-female prevalence ratios of current wheeze increased with age from <1 at 4–5 years, peaked at 10–11 years (2.24), then reversed to 0.57 at 16–18 years. Childhood wheezing tended to remit with age, but rhinitis and eczema were more persistent. Total immunoglobulin E levels increased with age until 14–15 years, and declined thereafter. Elevated BMI was associated with greater prevalence of wheezing and eczema, with no evidence of significant effect modification by either gender or age. Multivariate analyses revealed that younger age, boys, and obesity were significantly and independently associated with current wheezing in children (all $p < .01$). **Conclusions.** The burden and co-morbidity of childhood allergies are substantial. There are striking age-dependent gender differences in asthma prevalence, exhibiting an inverted U-shaped curve for male-to-female prevalence ratios by age. Obesity is associated with a greater prevalence of asthma in children with no evidence of a significant modulation by either gender or age.

Keywords age, allergic disease, body mass index, children, gender, obesity, prevalence

INTRODUCTION

During the past few decades there has been an increase in prevalence of allergic diseases in several countries worldwide (1,2). Allergic diseases have become a global health problem and the most common chronic diseases in children. In a recent global International Study of Asthma and Allergies in Childhood (ISAAC) survey (1), Taiwan has the highest prevalence of rhinoconjunctivitis among 6–7-year-old children in the world and the prevalence has increased by 166% during a 7-year period, attracting considerable attention to the burden of childhood allergies in this country. Although a few local ISAAC surveys have been conducted (3–6), there remain important gaps in our knowledge regarding the burden of childhood allergies in Taiwan.

Although the ISAAC surveys shed light on the global prevalence of allergic diseases (1,2), children in the

ISAAC studies are limited to certain age groups (6–7 or 13–14 years). Thus, little is known about the prevalence of allergic diseases in children of different ages. Another limitation is the lack of more objective measures, such as allergic sensitization or serum total immunoglobulin E (IgE), in most local surveys. Of note, evidence has been presented during recent years demonstrating an association of obesity and asthma in adults and children (reviewed in (7)). However, it remains unclear if the same phenomenon is true in Asian children and if the effect is modulated by gender or age. More research is needed to clarify the issue of the associations of age, gender, and body mass index (BMI) with allergic diseases in children, particularly from an Asian population. The objective of this study was to provide a broader picture for the prevalence of allergic diseases and allergic sensitization in children over a wide age range, with emphasis on the influence of age, gender, and BMI.

METHODS

Study Population and Study Design

The Prediction of Allergies in Taiwanese Children (PATCH) study is a joint study initiated in 2007 to investigate the epidemiology and predictive factors of asthma and allergies in Taiwanese children, including

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subjects from a birth cohort and several cohorts of school and preschool children (8). The current study was a cross-sectional analysis of a large cohort in the PATCH study. We performed a random stratified cluster sampling of children aged 4–18 years in Keelung City located in northern Taiwan. Five schools were randomly chosen to enter the study: one senior high school, one junior high school, two elementary schools, and one kindergarten. All schools agreed to participate in this study. The parents of all children in these schools were invited to participate and answer a questionnaire regarding demographic data as well as possible clinical symptoms and physician's diagnosis of allergic diseases. The questionnaire was derived from the well-validated ISAAC questionnaire (9).

A total of 5773 children were invited to participate and 5476 agreed to enroll, representing an overall participation rate of 94.9%. A total of 125 children who did not return or answer the allergy questionnaire were excluded, leaving 5351 children (age 10.4 ± 2.9 years; 2616 boys, 48.9%) for analysis in this study. The study was approved by the Institutional Review Board of Chang Gung Medical Foundation (96-0370B) and an informed consent was obtained from the parents of each subject.

All participants had their weights and heights measured according to a standard protocol. Weight (in kg) was measured to the nearest 0.1 kg and height (in cm) was also measured to one decimal. BMI was defined as weight (kg) divided by the height squared (m^2): $BMI = kg/m^2$. Obesity and overweight were defined according to the age- and gender-specific BMI cut-off values from the International Obesity Task Force reference (10).

Peripheral venous blood was collected in a random sample of 1321 (24.7%) children for total and allergen-specific serum IgE. There were no significant differences between those who did and did not have these tests with regard to age and gender. Total serum IgE was measured by ImmunoCAP[®] (Phadia, Uppsala, Sweden). Allergen-specific serum IgE was measured by ImmunoCAPTM Phadiatop Infant[®] (Phadia), a reliable alternative to skin-prick tests for detecting allergic sensitization (11). The following allergens were included: house dust mite, cat, dog, birch, timothy, ragweed, wall pellitory, egg white, cow's milk, peanut, and shrimp. Allergic sensitization was defined as a positive Phadiatop Infant test result (≥ 0.35 PAU/I).

Statistical Analysis

For univariate analysis, categorical measures were compared using chi-squared test or Fisher's exact test, as appropriate; continuous measures between two unpaired groups were compared using independent *t*-test. The relationships between allergic diseases and BMI groups were assessed by logistic regression analysis with normal-weight subjects who did not meet the above definition of obesity and overweight as the reference group. For multivariate analysis, multivariate logistic regression was applied to simultaneously analyze the associations of age, gender, and BMI with current prevalence of allergic diseases. P-values of $< .05$ were considered statistically

significant. Data analysis used SPSS statistical package version 15.0 for Windows (SPSS, Chicago, IL, USA).

RESULTS

Prevalence of Allergic Diseases and Allergic Sensitization

Seventeen percent of children had a history of wheezing at any age (wheeze ever) and 7.5% had wheezed in the past 12 months (current wheeze) (Table 1). In total, 9.8% of the study population had been diagnosed by a physician as having asthma at some time in the past. Rhinitis problems were more common than asthma problems; the prevalences of rhinitis ever, current rhinitis, and diagnosed rhinitis were 47.8%, 44.2%, and 39.8%, respectively. Children had had a recurrent itchy rash suggestive of eczema for at least 6 months at some time (eczema ever) comprised 10.8%, while 9.1% still had it (current eczema). Eczema had been diagnosed in 21.0% of children. A high prevalence of allergic sensitization (57.3%) was found.

The prevalence of allergic disorders was significantly higher in boys than in girls, with more pronounced differences observed for asthma, rhinitis, and allergic sensitization (Table 1). Geometric mean total IgE levels were also higher in boys than in girls (335.3 vs. 250.9 IU/ml, $p = .004$; Table 1).

A significant proportion of children with current symptoms suggestive of allergic diseases had not been diagnosed by a physician. Half of the children (50.6%) with current wheeze had not been diagnosed with asthma by a physician, whereas undiagnosed rates were 32.3% for rhinitis and 25.3% for eczema.

Co-morbidity of Allergic Diseases

Current prevalence and co-morbidity of wheeze, rhinitis, and eczema in the study population are illustrated in Figure 1. Overall, 48.0% of all children currently had at least one of three allergic diseases. Among these currently symptomatic children, the majority (76.0%) had symptoms of one of the three disorders in the past 12 months, 21.3% had two, while 2.7% had all three allergic disorders concurrently.

The three allergic disorders frequently occurred concurrently with each other. Current wheeze was associated with increased risk of current rhinitis (OR = 6.61; 95% CI = 5.08–8.60) and current eczema (OR = 2.87; 95% CI = 2.24–3.68). Current rhinitis was associated with increased risk of current wheeze (OR = 6.61; 95% CI = 5.08–8.60) and current eczema (OR = 3.40; 95% CI = 2.83–4.08); current eczema was associated with increased risk of current wheeze and current rhinitis (ORs are shown as above).

Prevalence of Allergic Diseases and Allergic Sensitization by Age

The proportion of children reported as having ever wheezed decreased with increasing age, from 22.2%

TABLE 1.—Prevalence of asthma, rhinitis, eczema, and allergic sensitization in children aged 4–18 years.

	Total	Boys	Girls	<i>p</i> ^a
Number of questionnaires	5351	2616	2735	
Asthma				
Wheeze ever	17.0%	20.4%	13.6%	<.001
Current wheeze	7.5%	9.3%	5.8%	<.001
Diagnosed asthma	9.8%	11.7%	8.1%	<.001
Rhinitis				
Rhinitis ever	47.8%	54.1%	41.7%	<.001
Current rhinitis	44.2%	49.3%	39.4%	<.001
Diagnosed rhinitis	39.8%	45.1%	34.7%	<.001
Eczema				
Eczema ever	10.8%	11.7%	10.0%	.045
Current eczema	9.1%	9.6%	8.5%	.162
Diagnosed eczema	21.0%	22.5%	19.5%	.008
Number of laboratory tests	1321	644	677	
Allergic sensitization	57.3%	63.7%	51.3%	<.001
Total IgE (mean ± SD [IU/ml])	292.1 ± 528.4	335.3 ± 557.3	250.9 ± 496.3	.004

Note: ^aBoys versus girls. P-values <.05 are listed in bold.

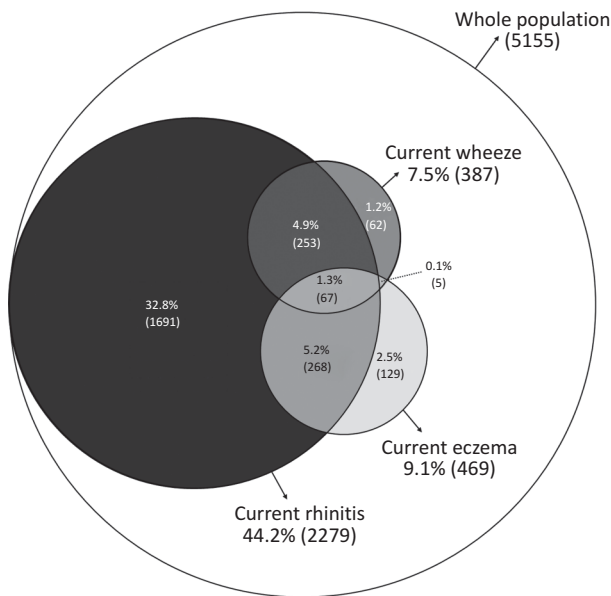


FIGURE 1.—The current prevalence and co-morbidity of wheeze, rhinitis, and eczema in the study population. Only subjects with no missing answers on current symptoms of allergic diseases (5155 children) are included in this figure.

among 4–5-year-old children to 11.8% among 16–18-year-old adolescents (Figure 2A). A similar, nearly parallel downward trend was observed for the prevalence of current wheeze with increasing age; the proportion of children with current wheeze among children who had ever wheezed was significantly higher in younger children than in older children (66.7% at 4–5 years vs. 24.6% at 16–18 years, $p = .016$). The proportion of children who had been diagnosed with asthma slightly increased with increasing age from 4 to 13 years, but declined thereafter.

The prevalences of rhinitis ever and current rhinitis were high at >40% in most age groups, varying little by age. In contrast, the rate of diagnosed rhinitis

declined with age, particularly among the teenage groups (Figure 2B). As shown in Figure 2B, the trends for the prevalence of rhinitis ever and current rhinitis were similar in all age groups, indicating that the rate of rhinitis persistence among children who had rhinitis in the past remained very high. The trends for the prevalence of eczema ever and current eczema were also similar. The prevalence of diagnosed eczema generally decreased with increasing age (Figure 2C).

The prevalence of allergic sensitization remained fairly constant, around 50–60%, until about 15 years of age, then decreased slightly to 46.2% thereafter (Figure 2D). Geometric mean total IgE levels were lowest in preschool children, were highest at ages 14–15 years, and decreased again in late adolescence.

Male-to-Female Prevalence Ratios by Age

An inverted U-shaped relationship was found for male-to-female prevalence ratios of current wheeze by age (Figure 3A); the male-to-female prevalence ratio was slightly <1 at age of 4–5 years, increased with age and peaked at 10–11 years (2.24), then decreased during adolescence and showed a marked reversal to 0.57 at 16–18 years. Similar trends were observed for wheeze ever and diagnosed asthma (Figure 3A).

The prevalence of current rhinitis showed nearly equal distributions between the genders in preschool children, a significant male predominance between 6 and 11 years ($p < .05$), and this male predominance was generally gone by the teenage years (Figure 3B). A relatively less evident gender disparity was noted for current eczema (Figure 3C).

A higher prevalence of allergic sensitization among boys was seen in most age groups, except at ages of 4–5 years (Figure 3D). This study found that serum total IgE levels were significantly higher among boys in the age range of 6–11 years (Figure 3D).

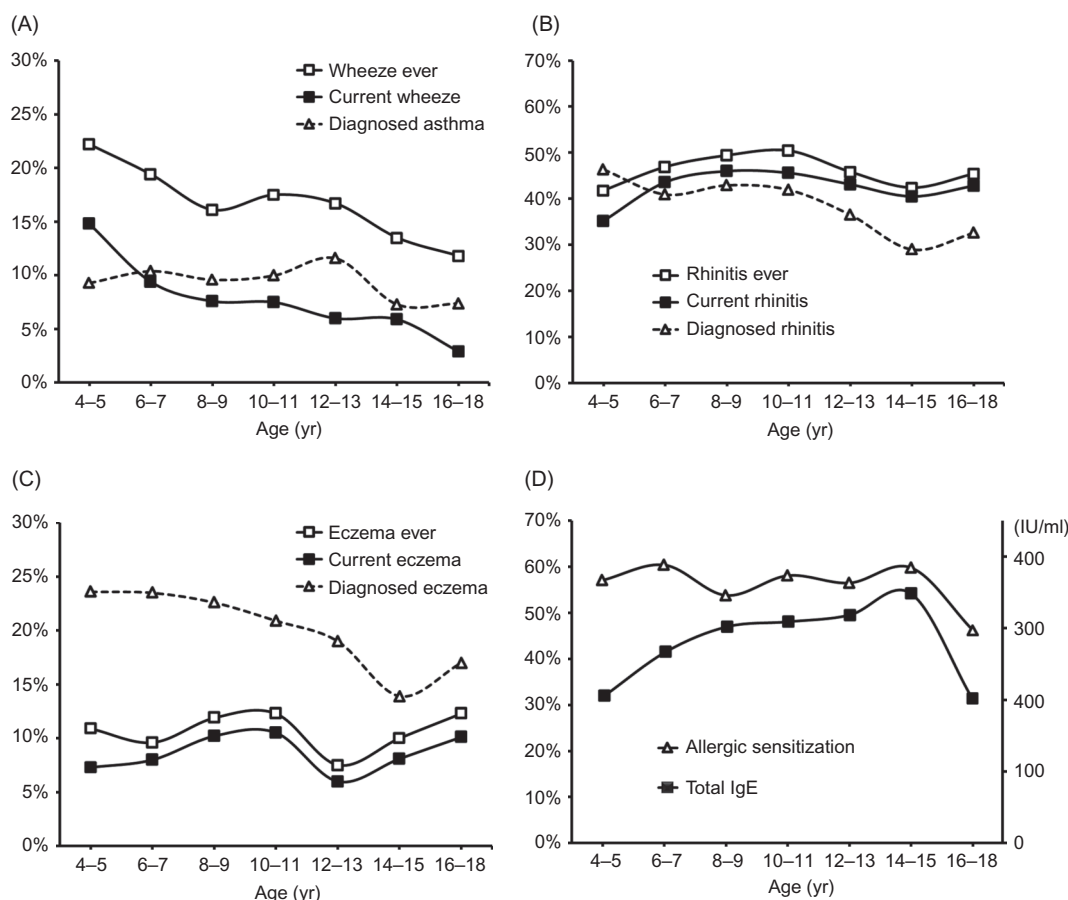


FIGURE 2.—Prevalence of asthma, rhinitis, eczema, and allergic sensitization at different ages. (A) Asthma, (B) rhinitis, (C) eczema, (D) allergic sensitization and serum total immunoglobulin E (IgE) levels.

Body Mass Index

The odds of wheeze ever in obese children was 1.60 times higher than that in children of normal weight ($p < .001$); the corresponding ORs of current wheeze and diagnosed asthma in obese children were 1.80 ($p < .001$) and 1.52 ($p = .006$), respectively (Table 2). There was no evidence of a statistically significant effect modification by gender for the three asthma-related categories. We found no significant temporal trend in the effect of obesity with age.

The ORs of rhinitis ever, current rhinitis, and diagnosed rhinitis in obese or overweight children tended to be slightly higher than in normal-weight children; however, most of these trends did not reach statistical significance. Obese and overweight children both had significantly higher likelihoods of eczema ever, current eczema, and diagnosed eczema compared to normal-weight children, with ORs ranging from 1.24 to 1.45 (all $p < .05$; Table 2). There was no statistical evidence of effect modification by gender for the three eczema-related categories. This study did not observe a significant association between BMI and allergic sensitization, as the ORs of allergic sensitization in obese and overweight children were not significantly different from that in normal-weight children (Table 2).

Multivariate Analyses

Multivariate analyses (Table 3) revealed that younger age, boys, and obesity were all significantly and independently associated with current wheeze in children (all $p < .01$). After controlling for other variables, boys had a significantly higher likelihood of having current rhinitis compared to girls ($p < .001$). The likelihood of current eczema marginally increased among children in both the obese and overweight groups compared to those children in the normal-weight group. As for allergic sensitization, boys retained a significant and independent association with allergic sensitization in the multivariate model ($p < .001$).

DISCUSSION

This study highlights the significant burden and comorbidity of allergic diseases in a population of Asian children and suggests a potential problem of substantial underdiagnosis of these diseases. Strikingly, almost half (48%) of the children are currently symptomatic for at least one of three allergic diseases, including asthma, rhinitis, and eczema. It could be argued that studies using questionnaires alone may overestimate the true prevalence

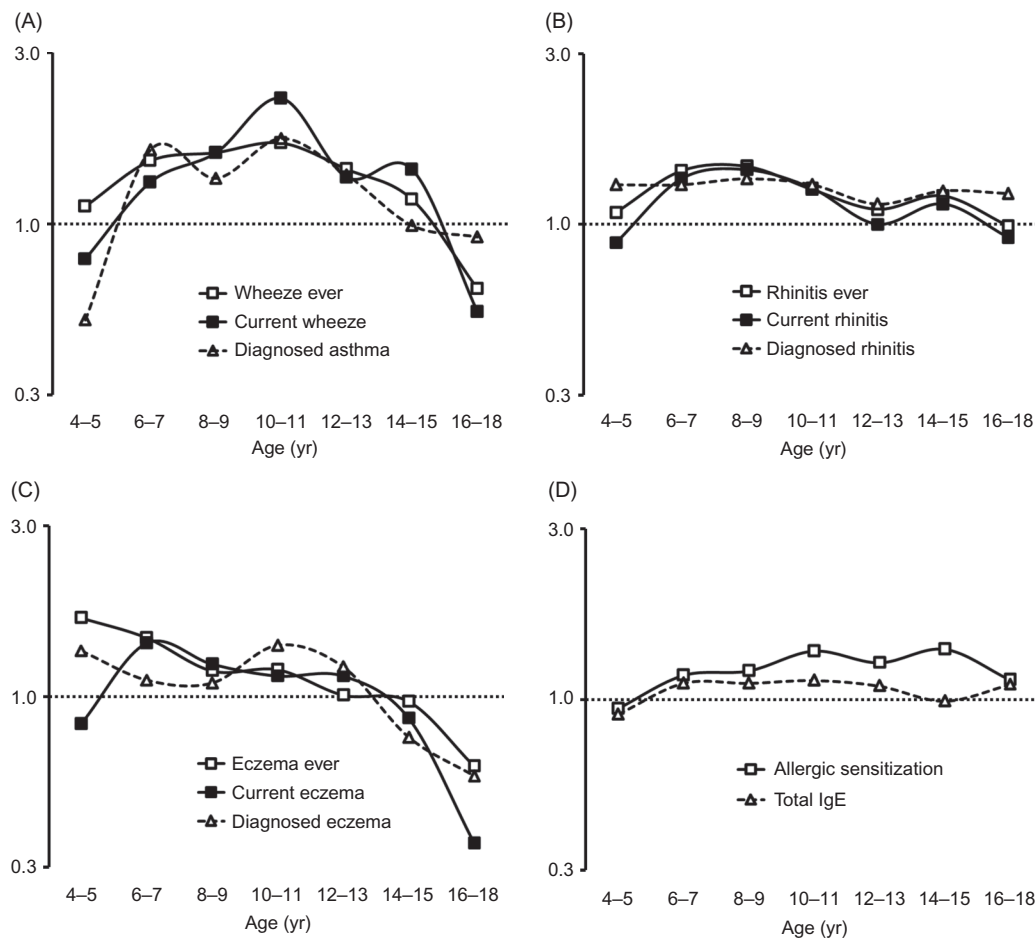


FIGURE 3.—Male-to-female prevalence ratios for asthma, rhinitis, eczema, and allergic sensitization at different ages. Values greater than 1 indicate male predominance and values less than 1 indicate female predominance. (A) Asthma, (B) rhinitis, (C) eczema, (D) allergic sensitization and serum total immunoglobulin E (IgE) levels.

TABLE 2.—Odds ratios for asthma, rhinitis, eczema, and allergic sensitization in overweight and obesity groups in comparison with the normal-weight group.

	Normal weight	Overweight	Obesity
Number of questionnaires	3746	1094	435
Asthma			
Wheeze ever	1	1.26 (1.05–1.50)	1.60 (1.25–2.04)
Current wheeze	1	1.26 (0.98–1.62)	1.80 (1.31–2.48)
Diagnosed asthma	1	1.19 (0.95–1.49)	1.52 (1.13–2.06)
Rhinitis			
Rhinitis ever	1	1.14 (0.99–1.31)	1.17 (0.96–1.43)
Current rhinitis	1	1.14 (0.99–1.31)	1.14 (0.94–1.40)
Diagnosed rhinitis	1	1.28 (1.11–1.47)	1.13 (0.92–1.39)
Eczema			
Eczema ever	1	1.24 (1.01–1.54)	1.45 (1.08–1.94)
Current eczema	1	1.26 (1.01–1.59)	1.39 (1.01–1.92)
Diagnosed eczema	1	1.34 (1.14–1.58)	1.45 (1.15–1.83)
Number of laboratory tests	935	276	95
Allergic sensitization	1	1.03 (0.78–1.35)	1.32 (0.85–2.04)

Note: Significant associations ($p < .05$) are listed in bold.

of allergic diseases. As revealed by an objective allergy test, however, it is striking that allergic sensitization is very common, up to 57.3%, in this population. To date, there have been insufficient epidemiologic data collected using objective allergy tests (12). The prevalence of

allergic sensitization ranges from 16% to 54% in the populations of the United States, Europe, Australia, and New Zealand (13–16). Thus, this study reports extremely high prevalence of allergic sensitization in Taiwanese children, perhaps among the highest in the world. We

TABLE 3.—Multivariate logistic regression models on current wheeze, rhinitis, eczema, and allergic sensitization.

	Coefficient (95% CI)	<i>p</i>
Current wheeze		
Age	0.92 (0.88–0.95)	<.001
Boys versus girls	1.54 (1.24–1.90)	<.001
BMI		
Obesity versus normal weight	1.57 (1.14–2.18)	.006
Overweight versus normal weight	1.23 (0.95–1.58)	.112
Current rhinitis		
Age	1.00 (0.98–1.02)	.959
Boys versus girls	1.50 (1.34–1.68)	<.001
BMI		
Obesity versus normal weight	1.04 (0.85–1.27)	.706
Overweight versus normal weight	1.10 (0.96–1.26)	.180
Current eczema		
Age	1.00 (0.97–1.04)	.941
Boys versus girls	1.14 (0.94–1.38)	.194
BMI		
Obesity versus normal weight	1.36 (0.98–1.88)	.068
Overweight versus normal weight	1.25 (0.99–1.57)	.058
Allergic sensitization		
Age	1.00 (0.96–1.04)	.959
Boys versus girls	1.64 (1.31–2.05)	<.001
BMI		
Obesity versus normal weight	1.20 (0.77–1.86)	.422
Overweight versus normal weight	1.00 (0.76–1.31)	.980

Notes: Age is treated as a continuous variable. The reference groups are girls for gender and subjects of normal weight for BMI, respectively. Significant associations ($p < .05$) are listed in bold.

speculate that the high burden of allergic diseases in Taiwan could be attributed to high humidity, widely distributed urban environments, high rates of indoor exposure to tobacco smoke, and extensive vaccination policies covered by the government.

The current survey shows that allergic diseases are more common in boys, particularly for asthma, rhinitis, and allergic sensitization. It has been reported that boys are more affected by asthma than girls at younger ages, whereas the burden is shared almost equally by the mid-teens, and then becomes more frequent in females (17–19). However, preschool children are rarely included in such surveys. This is the first time an inverted U-shaped curve of male-to-female asthma prevalence ratios as a function of age is demonstrated in a single study; a small female predominance is seen in preschool children, which switches to a male predominance during the ages of 6–15 years, and then reverses again to a female predominance after the age of 15 years. Another epidemiologic study reveals that the incidence of shortness of breath with wheezing is slightly higher in very young girls than in very young boys (20), supporting the findings in preschool children in the current study. The reasons for the striking age-dependent gender difference in asthma prevalence remain largely unknown. Further study is needed.

Another major finding here is that obesity is significantly and independently associated with a greater prevalence of current wheeze in children. While numerous studies in adults are fairly consistent in finding

that excess weight is associated with asthma, limited studies in children show rather inconsistent results (7). In addition, whether the relationship between excess weight and asthma differs by gender has engendered a great deal of discussion. When gender is taken into consideration, some reports in adults have noted an association only in women, or a stronger association in women, while other studies do not find such gender differences (7). However, it is confusing that studies in children provide contradictory results (21–23). In a study in the United States (21), BMI is positively associated with the risk of asthma development among girls. Similarly, Huang et al. (22) find a relationship between BMI and wheeze even in teenage girls, but not in teenage boys. However, among 3792 participants aged 7–18 years in the Children's Health Study, the risk of asthma development increases among obese and overweight boys, but not among girls (23). Our findings indicate an increased risk of asthma among obese children, as obesity is independently associated with a 1.57-fold increased risk of current wheeze. In addition, there is no evidence of statistically significant effect modification by gender. This study also finds no modification of the effect of obesity with increasing age. An insight yielded from this study is that the effect of obesity on asthma represents a universal phenomenon in both boys and girls throughout childhood and adolescent years, rather than a gender-specific effect or one confined to particular age groups. The findings here thus provide a scientific rationale for clinicians to follow the American Academy of Pediatrics Guidelines (24), which encourages asthmatic children to develop dietary and activity patterns that decrease the risk of obesity, in hopes of consequently decreasing wheeze.

A hidden problem deserving our attention is the potentially substantial underdiagnosis of allergic disorders, particularly asthma. Notably, half of children with current wheeze have not been diagnosed by physicians as having asthma and this is a common phenomenon across different age groups. Although the reported current wheeze might be explained by causes other than asthma, the vast majority of wheezing in children older than 4 years is caused by asthma. Thus, a very possible explanation for the discordance between rates of current wheeze and diagnosed asthma is either the underdiagnosis of asthma or a failure to apply the diagnostic label of asthma. It appears that the problem of underdiagnosis of childhood asthma is not unique to Taiwan, as this problem has also been reported in the United States (25), Switzerland (17), Denmark (26), and New Zealand (27). In contrast, the underdiagnosis of allergic rhinitis appears to be particularly common among adolescents. This is presumably caused by a view commonly held by parents that allergic rhinitis is simply a nuisance condition rather than a severe disease (28) and the traditional pressure among adolescents in Chinese societies to pursue academic success, which may preclude them from taking time to seek medical assistance.

Age-specific prevalence of allergic diseases in the current study provides a crude view of the natural

course of these diseases. Although we have to take into account that, given its cross-sectional study design, these figures reflect a combination of the age of disease onset, disease persistence, and disease mortality. Around one-sixth (17.0%) of all participating children report having wheezed at some time in their lives, while 7.5% are still experiencing wheezing during the past year. As is well known, most asthmatic children report disease onset prior to 5 years of age and mortality among asthmatic children is extremely rare. This study estimates remission rates of allergic diseases by determining the proportion of children who report no current symptoms in the past 12 months among those who have had symptoms at some time in their lives. This leads to a crude estimate that ~55% of children who wheeze tends to remit during childhood. The epidemiologic evidence in Asian children here reinforces earlier observations that only a small portion of earlier wheezers may go on to develop persistent asthma (29). Furthermore, these data suggest that remission appears to be a continuing process with age beginning with the preschool years. In contrast, the results here underscore the chronic nature of rhinitis and eczema, as remission of these two diseases is relatively infrequent, as reflected by the similarity between the trends for cumulative and current prevalence rates in all age groups.

The strength of this study includes a high participation rate, a wide age range, and the inclusion of objective markers of atopy. One limitation of this study is that the cross-sectional design is subject to potential recall bias, cohort effects, and may suffer difficulties in assigning causality to the associations. Another concern is that the method of school-based sampling may have been a potential source of ascertainment bias. However, the proportion of children who do not attend school is very small due to obligatory education in Taiwan. Although only five schools were randomly chosen, it is reassuring that the demographics and prevalence estimates at corresponding age groups (6–7 and 13–14 years) obtained in this study are similar to those obtained in a simultaneous standard ISAAC study that enrolls 26 schools in the same city (unpublished data). Thus, we believe the study population is reasonably representative of children in the communities. Peculiarly, the decreasing trend in the prevalence of wheeze ever with age contradicts the intuitive expectation that lifetime prevalence should increase with age. Although recall bias may account for part of this puzzling pattern, another possible explanation is the increase in asthma prevalence in the population over the past one to two decades. The increasing trend in asthma prevalence in Taiwan between ISAAC phase one and three repeat surveys (1,3) supports this latter possibility. Another puzzling observation is that the prevalence of diagnosed eczema is higher than current eczema and eczema ever, which is similar to that observed in previous ISAAC studies (30). One plausible explanation is the discordance between the diagnostic labeling of eczema by clinicians and the more strict definition of eczema in the ISAAC questionnaire, in

which eczema is defined as an itchy rash affecting typical flexural locations that is coming and going for at least 6 months.

CONCLUSIONS

Attention should be paid to the substantial burden and co-morbidity of allergic diseases in children, as well as the potential problem of substantial underdiagnosis of these diseases. There are striking age-dependent gender differences in the prevalence of asthma, exhibiting an inverted U-shaped curve for male-to-female prevalence ratios by age. Obesity is associated with a greater prevalence of asthma in children with no evidence of a significant modulation by either gender or age.

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DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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