

Article Type: Original

1) Title: Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors

2) Authors: Hui-Ju Wen ^{1,2}, Tung-Liang Chiang ³, Shio-Jean Lin ⁴, Yue Leon Guo ²

3) Institutions of authors:

¹ Division of Environmental Health and Occupational Medicine, National Health Research Institutes, Miaoli, Taiwan;

² Environmental and Occupational Medicine, National Taiwan University (NTU) College of Medicine and NTU Hospital, Taipei, Taiwan;

³ Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan;

⁴ Department of Pediatrics, Chi-Mei Medical Center, Tainan, Taiwan.

4) Running title: Predicting childhood asthma

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/pai.12374

This article is protected by copyright. All rights reserved.

5) Reprint requests and correspondence author:

Yue Leon Guo, MD, MPH, PHD

Environmental and Occupational Medicine, National Taiwan University (NTU) College of Medicine
and NTU Hospital.

Rm 339, 17 Syujhou Road, Taipei 100, Taiwan.

Tel: 886-2-3366-8216; Fax: 886-2-2327-8515; .E-mail: leonguo@ntu.edu.tw

1) Authors' surnames and institutions:

Wen ¹, Chang ², Lin ³, Guo ⁴.

¹ Division of Environmental Health and Occupational Medicine, National Health Research
Institutes, Miaoli, Taiwan;

² Environmental and Occupational Medicine, National Taiwan University (NTU) College of
Medicine and NTU Hospital, Taipei, Taiwan;

³ Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan;

⁴ Department of Pediatrics, Chi-Mei Medical Center, Tainan, Taiwan.

2) Title: Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors

4) Abstract

Background: Symptoms of atopic disease start early in human life. Predicting risk for childhood asthma by early-life exposure would contribute to disease prevention. A birth cohort study was conducted to investigate early-life risk factors for childhood asthma and to develop a predictive model for the development of asthma.

Methods: National representative samples of newborn babies were obtained by multistage stratified systematic sampling from the 2005 Taiwan Birth Registry. Information on potential risk factors and children's health was collected by home interview when babies were 6 months old and 5 years old, respectively. Backward stepwise regression analysis was used to identify the risk factors for childhood asthma for predictive models that were used to calculate the probability of childhood asthma.

Results: A total of 19,192 children completed the study satisfactorily. Physician diagnosed-asthma was reported in 6.6% of 5-year-old children. Pre-pregnancy factors (parental atopy and socioeconomic status), perinatal factors (place of residence, exposure to indoor mold and painting/renovations during pregnancy), and postnatal factors (maternal postpartum depression and presence of atopic dermatitis before 6 months of age) were chosen for the predictive models, and the highest predicted probability of asthma in 5-year-old children was 68.1% in boys and 78.1% in girls; the lowest probability in boys and girls was 4.1% and 3.2%, respectively.

Conclusions: This investigation provides a technique for predicting risk of childhood asthma that can be used to developing a preventive strategy against asthma.

5) Keywords: asthma, birth cohort, prediction, childhood.

6) Reprint requests author:

Yue Leon Guo, MD, MPH, PHD

Environmental and Occupational Medicine, National Taiwan University (NTU) College of Medicine
and NTU Hospital.

Rm 339, 17 Syujhou Road, Taipei 100, Taiwan.

Tel: 886-2-3366-8216; Fax: 886-2-2327-8515; .E-mail: leonguo@ntu.edu.tw

Introduction

Asthma is one of the most important chronic respiratory inflammatory diseases of childhood, and its socioeconomic consequences and effects on quality of life in children and their families are profound (1). The prevalence of asthma worldwide and in Taiwan has increased during the past two decades (2, 3). In Taiwan, the prevalence of physician-diagnosed asthma in school-age children increased from 4.5% in 1995–96 to 6.5% in 2001, 7.5% 2007 and had reached 11.7% by 2011 (3-5).

While both environmental and genetic factors contribute to the development of asthma, environmental factors might be more important in the increased prevalence of asthma over a short period. Early childhood is considered the most critical stage for the development of atopy and asthma, and it is important to identify the significant early-life risk factors that predispose to later atopic disease. Most previous epidemiological studies on asthma have focused on preschool- or school-age children (3-5). However, as symptoms of atopic disease appear early in life (6), important risk factors may be missed when participants are preschool-age or older. Moreover, it may be difficult to eliminate the causal relationship between early environmental exposure and disease in case-control and cross-sectional studies. A birth cohort study is therefore of value for investigating pre-pregnancy, perinatal, and early-postnatal risk factors for asthma.
This article is protected by copyright. All rights reserved.

The aims of this study were to investigate pre-pregnancy, perinatal, and postnatal risk factors for asthma among 5-year-old children enrolled in the Taiwan Birth Cohort Study (TBCS) (7) and to establish a model for predicting asthma risk in children.

Materials and methods

Recruitment and sampling

The study population was recruited from the TBCS, which is the first nationwide birth cohort study in Taiwan. The sampling method for the TBCS has been described previously (7). Briefly, nationally representative samples were obtained using a multistage stratified systematic sampling design based on national birth registration data in Taiwan in 2005. Beginning in January 2005, candidate pairs of mothers and their newborn infants from 88 study areas were randomly sampled every month, and a total of 24,200 pairs were recruited. The infants, with informed consent from their parents or main caretakers, were evaluated by home interview at the ages of 6 months, 18 months, 3 years, and 5 years. The protocols used in this study were approved by the Institutional Review Board of the Bureau of Health Promotion, Taiwan.

Data collection

Structured questionnaires were completed during each home interview to catalog physical data, parental histories of atopic disease (asthma, allergic rhinitis [AR], and atopic dermatitis [AD]), health status of children, and indoor environmental conditions.

At the 5-year interview, the main caretaker was asked if the child had ever had physician-diagnosed asthma, and an answer of 'yes' was considered to indicate that the child had asthma by 5 years of age.

This article is protected by copyright. All rights reserved.

Information about personal characteristics, breast-feeding, and vaccination was also collected by the questionnaires, as was information regarding environmental factors in the house, including pets, carpeting, cockroach sightings, incense burning, indoor mold, and painting/home renovation during pregnancy.

Statistical analysis

Since boys and girls have different lifetime prevalence of asthma, the children were stratified by gender for determination of risk factors and establishment of predictive models. Odds ratios (OR) and 95% confidence interval (CI) were used to assess statistical relationships between potential risk factors and asthma. Backward stepwise regression was used to simplify multiple regression model and select the predictive factors in predictive model. Factors with the highest p-value were eliminated one by one till all the remaining factors had p-value <0.1. Factors with p-value <0.05 in backward stepwise regression model were considered significant and included in the predictive model for childhood asthma. Prediction probability of asthma was calculated as $probability = 1 - (1 / [1 + E\{training\ logical\ model\}])$ (7). To test the predictive model, a mutually exclusive group of 20% of all participants was randomly selected. Five runs of predictive modeling were carried out for boys and girls, respectively, and for each run risks were categorized according to prevalence as low (below the prevalence), high (one- to twofold prevalence), and very high (more than twofold prevalence). The true percentage of boys and girls in each category was also calculated. All data analyses were performed using JMP version 5.0.1 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

Among 24,200 sampled candidates, 2,952 mother-infant pairs were excluded because of refusal to interview, incorrect address, move abroad, no one home after multiple visits, infant death, and

This article is protected by copyright. All rights reserved.

other reasons. A total of 21,248 mother-newborn pairs (87.8%) completed the first (age 6 months) interview during July 2005 to July 2006. Multiparity and children lost to follow up at the 5-year-old interview were also excluded, resulting in the inclusion of a total of 19,192 children (79.3%) in the final analysis (Fig. 1). The characteristics of the parents and children are shown in Table 1.

Approximately 53% of the children were boys. The overall prevalence of asthma was 6.6% at 5 years old, and asthma was more prevalent in boys (7.6%) than in girls (5.5%). The average parental age at birth was 29.3 years for mothers and 33.2 years for fathers. At least 45% of parents reported college or higher education degrees (Table 1).

Backward stepwise regression analysis was applied to select significant risk factors of asthma. The result stratified by gender after adjusted for covariates was presented in Table 2. Among boys, factors associated with asthma risk included higher family income, atopic disease (particularly asthma) in parents, residence in an urban area, physician-diagnosed AD, and maternal postpartum depression. Among girls, those whose parents had ever had asthma and those with AD onset before the age of 6 months had higher risk of developing asthma. Maternal education level, indoor mold or painting/renovations during pregnancy, and maternal postpartum depression were also associated with childhood asthma.

These factors were incorporated in the predictive models, and the proposed β values of the pre-pregnancy, perinatal, and postnatal factors are shown in Table 3. Among pre-pregnancy factors, parental atopy and socioeconomic status were associated with the highest risk for asthma (51.0% in boys, 51.8% in girls). After adding the perinatal factors of place of residence for boys and indoor mold and painting/renovations for girls, the highest probability of asthma increased to 52.3% and 65.9%, respectively. After adding postnatal factors, maternal postpartum depression and onset of

AD by 6 months, the highest probability of ever having asthma at 5 years reached 68.1% for boys and 78.1% for girls.

To test predictive model 3 (Table 3), Table 4 shows the risk categorization based on the estimated probability of asthma, and the true proportion of physician-diagnosed asthma in each category in five mutually exclusive subpopulations of boys and girls (Table 4). The results showed that the actual rates of physician-diagnosed asthma were consistent with predicted rates for both boys and girls.

Discussion

The TBCS, the first nationally representative birth cohort study in Taiwan, was used in this study to establish a predictive model for the probability of early childhood asthma. Parental socioeconomic status (SES), parental history of atopic disease, place of residence (i.e. urban vs. rural area), indoor mold or painting/renovations during pregnancy, maternal postpartum depression, and onset of physician-diagnosed AD before the age of 6 months were important predictors of asthma risk in 5-year-old children.

The association of residence in an urban area and of higher socioeconomic status (SES), including higher parental education levels and higher family income, with higher risk of asthma are consistent with the hygiene hypothesis, which holds that a poorer living environment is preventive against allergic disease (8), and with Wennergren's finding of a lifelong protective effect of childhood farm living in terms of the prevalence of physician-diagnosed asthma and the likelihood of using asthma medications (9). Exposure to animal sheds, hay lofts, and consumption of unpasteurized milk have all been credited with contributing to this protective effect (10). Braun-Fahrlander has reported that significantly higher levels of endotoxin, which is negatively associated with development of childhood asthma, are found in farming households (11). Endotoxin is thought to promote skewing of the T-helper 1 (Th₁)/T-helper 2 (Th₂) balance toward Th₁ responses and to reduce the allergic response. This article is protected by copyright. All rights reserved.

immune response (10, 11). Many SES-related lifestyle and household environmental characteristics can affect environmental allergy risk (12). Higher SES may include relatively cleaner living environments that reduce the risk of infection, but limited microbial exposure may increase the risk of developing atopic conditions (13). Finally, parents with higher education levels may be more avid healthcare consumers, and their children could therefore be more likely have physician-confirmed asthma. Further analysis is needed to determine whether the association between SES and childhood asthma is in line with the hygiene hypothesis or whether it is due to study bias.

Indoor mold and painting/renovations were also identified as risk factors for asthma in the present study. Furniture, paints, and surface materials contain and release surfactants, biocides, binders, pigments, monomers, amines, and solvents, and many of these compounds have been associated with allergic diseases (14). Hulin reported that exposure to high levels of acetaldehyde and toluene was associated with increased risk of childhood asthma (15), and Rumchev found that every 10 $\mu\text{g}/\text{m}^3$ increase in toluene and benzene concentration was associated with a two- to threefold increase in asthma risk in children between the ages of 6 months and 3 years (16). Allergen-specific responses in asthma are attributed to a skew towards a Th₂ phenotype with elevated levels of serum interleukin (IL)-4 and IgE, and animal experiments have shown that volatile organic compounds (VOCs) cross the placenta and affect neonatal immune status by increasing IL-4 production and reducing interferon- γ production (17). Bonisch showed that VOCs may favor allergic responses by inducing oxidative stress and interfering with dendritic cell function in mice (18). Our finding that indoor painting during pregnancy could contribute to childhood asthma is also consistent with another birth cohort study that found higher levels of IL-4 and IL-5 in the cord blood of neonates who were exposed to home renovations during pregnancy (19). However, the exact causal agents and the exposure mechanisms will still warrant further study.

Taiwan has a tropical/subtropical climate with an average year-round temperature of 15–30°C and 70–80% relative humidity, and this is conducive to mold. Our finding that indoor mold is a risk factor for childhood asthma agrees with previous studies that have associated indoor mold with early childhood asthma, including a meta-analysis of eight European birth cohorts in which exposure to residential mold during the first two years of life showed significant association with childhood asthma, particularly among children of allergic parents (20). Children with greater exposure to fungal spores in the first 3 months of life have also shown increased risk of early wheezing (21). *Penicillium*, *Aspergillus* and basidiospores are among the fungal species that are associated with asthma and atopy in children (4), and further investigation of the role of indoor mold in childhood asthma in Taiwan will be useful.

Onset of allergic dermatitis (AD) before 6 months of age was another important risk factor in the present study. AD is a common skin disorder in children and it is often the first step in the atopic march, which is defined by the progression from AD to allergic rhinitis (AR) and asthma (22). Approximately 66% of children with physician-confirmed AD have been found to have asthma, AR, or both, particularly in association with poor AD control (23). Early-onset AD is also associated with an increased risk of sensitization to inhalant allergens (24). The impairment of the skin barrier function in patients with AD causes increased allergen absorption, which is associated with the cutaneous hyperreactivity of AD (24) as well as with the progression of the atopic march (22). Animal studies have indicated that epidermal barrier dysfunction caused by repeated sensitization to skin allergens induces AD and systemic sensitization and increases the risk of lung inflammation and airway hyperresponsiveness (25). As the atopic march generally occurs during the first several years of life, a greater understanding of early-onset AD could promote the development of more effective treatment or prevention algorithms to halt it.

This article is protected by copyright. All rights reserved.

Accepted Article

Regarding the association between maternal postpartum depression and childhood asthma, it is already reported that maternal stress in early life provokes an enhanced allergy-specific proliferative response in infants (26). It is postulated that postpartum depression might be a sequel to high emotional stress during pregnancy (27), which has also been associated with pregnancy complications and increased risk of childhood illness (28, 29). Kozyrskyj reported a highly significant association between maternal distress and subsequent asthma in children (30). This seems to be a dose-response effect; i.e., in a population of 7-year-old children, long-term maternal distress was significantly associated with increased risk of asthma, while short-term episodes of maternal distress or maternal distress only during the postpartum period were not (30). In the present study, maternal postpartum depression after 6 months from childbirth was associated with asthma at the age of 5 years. Since only short-term maternal depression was addressed, the extent to which prolonged depression is associated with childhood asthma remains to be elucidated.

The strengths of this study included the birth cohort design and the enrollment of a general population with large sample size. The two-stage systemic sampling including rural, suburban, and urban populations and considering fertility in different administrative regions enhances the survey's representativeness of newborns in Taiwan. Moreover, the prospective birth cohort study design allows for unbiased investigation of the temporal sequence between early childhood predictors and health outcomes.

There are also limitations of this study. Firstly, 4,819 children from the cohort were excluded, among them 1,734 whose families declined participation and 1,306 who were lost to follow-up. Therefore, selection bias might have occurred due to differential participation. However, the main caretakers and interviewers were unaware of the main hypothesis, the predictors, and the outcome variables, making this less likely. Secondly, we had only main caretaker, and not physician,

This article is protected by copyright. All rights reserved.

confirmation of caretaker-reported physician-diagnosed atopic disease and maternal postpartum depression. Since respondents were unaware of the main hypothesis, and any misclassification was likely non-differential in different exposure groups, we believe that this was not likely to bias the study results. Finally, as risk factors were assessed by questionnaire only, but without biological markers, the representation of real exposure and health condition might not be appropriate. In our previous study on prediction of AD in 2-year-olds (29), a better predictive capacity of models based on biological markers, such as genetic susceptibility and cytokine levels, was found. Further study is required to assess which biological markers are associated with childhood asthma and whether they are useful for asthma prediction.

In conclusion, we have established gender-specific predictive models for early childhood asthma according to pre-pregnancy, perinatal, and postnatal factors. This approach allows for identification of high-risk children and for implementation of preventive measures from the prenatal to the early postnatal period, particularly for children with early AD and parental atopy.

Acknowledgments

We thank all children and parents who participated in this study, the interviewers who supported data collection, and all of the study groups who participated in the Taiwan Birth Cohort Study (TBCS). Drs Wen and Guo contributed to the acquisition of the data and analysis and interpretation of the results, drafted the initial manuscript, and reviewed and revised manuscript. Drs Chiang and Lin conceptualized and designed the project and supervised data collection. All authors approved the final manuscript as submitted. This investigation was conducted and supported by The Bureau of Health Promotion, Department of Health, Taiwan (DOH94-HP-1802, DOH95-HP-1802, DOH96-HP-1702, and DOH99-HP-1702).

This article is protected by copyright. All rights reserved.

References

- 1 Petsios KT, Priftis KN, Hatziaorou E, Tsanakas JN, Antonogeorgos G, Matziou VN. Determinants of quality of life in children with asthma. *Pediatr Pulmonol*. 2013; **48**: 1171-80.
- 2 Asher MI, Montefort S, Bjorksten B, *et al*. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006; **368**: 733-43.
- 3 Lee YL, Lin YC, Hwang BF, Guo YL. Changing prevalence of asthma in Taiwanese adolescents: two surveys 6 years apart. *Pediatr Allergy Immunol*. 2005; **16**: 157-64.
- 4 Chen CH, Chao HJ, Chan CC, Chen BY, Guo YL. Current asthma in schoolchildren is related to fungal spores in classrooms. *Chest*. 2014; **146**: 123-34.
- 5 Tsai CH, Huang JH, Hwang BF, Lee YL. Household environmental tobacco smoke and risks of asthma, wheeze and bronchitic symptoms among children in Taiwan. *Respir Res*. 2010; **11**: 11.
- 6 Sly PD. The early origins of asthma: who is really at risk? *Curr Opin Allergy Clin Immunol*. 2011; **11**: 24-8.
- 7 Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. *Br J Dermatol*. 2009; **161**: 1166-72.
- 8 Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science*. 2002; **296**: 490-4.
- 9 Wennergren G, Ekerljung L, Alm B, Eriksson J, Lotvall J, Lundback B. Asthma in late adolescence--farm childhood is protective and the prevalence increase has levelled off. *Pediatr Allergy Immunol*. 2010; **21**: 806-13.

- Accepted Article
- 10 Schaub B, Lauener R, von Mutius E. The many faces of the hygiene hypothesis. *J Allergy Clin Immunol*. 2006; **117**: 969-77; quiz 78.
 - 11 Braun-Fahrlander C, Riedler J, Herz U, *et al*. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med*. 2002; **347**: 869-77.
 - 12 Lannero E, Kull I, Wickman M, Pershagen G, Nordvall SL. Environmental risk factors for allergy and socioeconomic status in a birth cohort (BAMSE). *Pediatr Allergy Immunol*. 2002; **13**: 182-7.
 - 13 Schmitz R, Atzpodien K, Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. *Pediatr Allergy Immunol*. 2012; **23**: 716-23.
 - 14 Mendell MJ. Indoor residential chemical emissions as risk factors for respiratory and allergic effects in children: a review. *Indoor Air*. 2007; **17**: 259-77.
 - 15 Hulin M, Caillaud D, Annesi-Maesano I. Indoor air pollution and childhood asthma: variations between urban and rural areas. *Indoor Air*. 2010; **20**: 502-14.
 - 16 Rumchev K, Spickett J, Bulsara M, Phillips M, Stick S. Association of domestic exposure to volatile organic compounds with asthma in young children. *Thorax*. 2004; **59**: 746-51.
 - 17 Lehmann I, Thielke A, Rehwagen M, *et al*. The influence of maternal exposure to volatile organic compounds on the cytokine secretion profile of neonatal T cells. *Environ Toxicol*. 2002; **17**: 203-10.
 - 18 Bonisch U, Bohme A, Kohajda T, *et al*. Volatile organic compounds enhance allergic airway inflammation in an experimental mouse model. *PLoS One*. 2012; **7**: e39817.
 - 19 Herberth G, Herzog T, Hinz D, *et al*. Renovation activities during pregnancy induce a Th2 shift in fetal but not in maternal immune system. *Int J Hyg Environ Health*. 2012; **216**: 309-16.

- Accepted Article
- 20 Tischer CG, Hohmann C, Thiering E, *et al.* Meta-analysis of mould and dampness exposure on asthma and allergy in eight European birth cohorts: an ENRIECO initiative. *Allergy*. 2011; **66**: 1570-9.
 - 21 Harley KG, Macher JM, Lipsett M, *et al.* Fungi and pollen exposure in the first months of life and risk of early childhood wheezing. *Thorax*. 2009; **64**: 353-8.
 - 22 Zheng T, Yu J, Oh MH, Zhu Z. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *Allergy Asthma Immunol Res*. 2011; **3**: 67-73.
 - 23 Kapoor R, Menon C, Hoffstad O, Bilker W, Leclerc P, Margolis DJ. The prevalence of atopic triad in children with physician-confirmed atopic dermatitis. *J Am Acad Dermatol*. 2008; **58**: 68-73.
 - 24 Sator PG, Schmidt JB, Honigsmann H. Comparison of epidermal hydration and skin surface lipids in healthy individuals and in patients with atopic dermatitis. *J Am Acad Dermatol*. 2003; **48**: 352-8.
 - 25 He R, Kim HY, Yoon J, *et al.* Exaggerated IL-17 response to epicutaneous sensitization mediates airway inflammation in the absence of IL-4 and IL-13. *J Allergy Clin Immunol*. 2009; **124**: 761-70 e1.
 - 26 Wright RJ, Finn P, Contreras JP, *et al.* Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J Allergy Clin Immunol*. 2004; **113**: 1051-7.
 - 27 Ngai FW, Chan SW. Learned resourcefulness, social support, and perinatal depression in chinese mothers. *Nurs Res*. 2012; **61**: 78-85.
 - 28 Knackstedt MK, Hamelmann E, Arck PC. Mothers in stress: consequences for the offspring. *Am J Reprod Immunol*. 2005; **54**: 63-9.

- 29 Wen HJ, Wang YJ, Lin YC, *et al.* Prediction of atopic dermatitis in 2-yr-old children by cord blood IgE, genetic polymorphisms in cytokine genes, and maternal mentality during pregnancy. *Pediatr Allergy Immunol.* 2011; **22**: 695-703.
- 30 Kozyrskyj AL, Mai XM, McGrath P, Hayglass KT, Becker AB, Macneil B. Continued exposure to maternal distress in early life is associated with an increased risk of childhood asthma. *Am J Respir Crit Care Med.* 2008; **177**: 142-7.

Figure legends

Figure 1 Flow chart of recruitment of participants and data collection.

Table 1 Characteristics of parents and children (n = 19,192)

Factors	n (%)
Sex	
Boys	10,074 (52.5)
Girls	9,118 (47.5)
Gestation length (weeks)*	38.5 ± 1.5
Birth weight (g)*	3126.7 ± 426.3
Maternal age at baby birth (year)*	29.3 ± 4.8
Paternal age at baby birth(year)*	33.2 ± 5.6

Maternal education

≤ 9 years	2,785 (14.5)
10-12 years	7,710 (40.2)
> 12 years	8,665 (45.1)

Paternal education

≤ 9 years	2,619 (13.6)
10-12 years	7,643 (39.8)
> 12 years	8,788 (45.8)

Family income (*10³ USD)[¶]

< \$20	8,028 (41.8)
\$20-\$40	9,015 (47.0)
≥ \$40	2,088 (10.9)

Parental nationality

Taiwan	14,130 (73.6)
One of parents have foreign nationality	4,479 (23.3)
Both of parents have foreign nationality	487 (2.5)

Residential area

Area	5,56 (26.9)
City	5,794 (30.2)
Township	2,835 (14.8)
County	6,407 (28.2)

Some numbers do not add up to total n because of missing values.

* mean $\pm$ SD.

[†]USD: US dollars.

Table 2 Associations between potential risk factors and asthma at 5 year-old children by backward stepwise analysis (n = 19,192)

Factors (n)	Boys (n = 10,074)				Girls (n = 9,118)			
	N	Ever having asthma			N	Ever having asthma		
		n (%)	OR (95%CI) ^a	AOR (95%CI) ^{b,c}		n (%)	OR (95%CI) ^a	AOR (95%CI) ^{b,c}
Pre-pregnancy factors								
Maternal education								
> 12years	4,587	396 (8.63)	1.31 (1.13-1.52)***	—	4,078	283 (6.94)	1.63 (1.36-1.95)***	1.53 (1.27-1.84)***
≤ 12 years	5,478	368 (6.72)	Reference		5,016	220 (4.39)	Reference	Reference
Family income (*10 ³ USD) ^d								
≥ \$40	1,105	119 (10.77)	1.77 (1.41-2.22)***	1.40 (1.11-1.77)**	982	65 (6.62)	1.45 (1.07-1.93)*	
\$20-\$40	4,786	379 (7.92)	1.26 (1.07-1.48)**	1.11 (0.94-1.31)	4,229	256 (6.05)	1.32 (1.08-1.60)**	—
< \$20	4,151	265 (6.38)	Reference	Reference	3,877	181 (4.67)	Reference	
Maternal atopy								

Asthma	144	32 (22.22)	3.93 (2.59-5.80)***	3.61 (2.36-5.37)***	141	25 (17.73)	4.08 (2.56-6.26)***	3.75 (2.33-5.79)***
AD or AR ^e	1,740	178 (10.23)	1.57 (1.31-1.87)***	1.36 (1.13-1.63)**	1,495	104 (6.96)	1.42 (1.13-1.77)**	1.25 (0.99-1.57)
None	8,190	555 (6.78)	Reference	Reference	7,481	375 (5.01)	Reference	Reference
Paternal atopy								
Asthma	128	22 (17.19)	2.81 (1.72-4.40)***	2.56 (1.56-4.04)***	99	20 (20.20)	4.79 (2.83-7.76)***	4.36 (2.55-7.12)***
AD or AR ^e	1,764	181 (10.26)	1.55 (1.30-1.84)***	1.35 (1.12-1.61)**	1,643	114 (6.94)	1.41 (1.13-1.75)**	1.25 (1.00-1.56)*
None	8,182	562 (6.87)	Reference	Reference	7,375	370 (5.02)	Reference	Reference
Perinatal factors								
Resident area								
Urban	5,750	524 (9.11)	1.70 (1.45-1.99)***	1.55 (1.32-1.83)***	5,199	318 (6.12)	1.31 (1.09-1.58)**	—
Rural	4,324	241 (5.57)	Reference	Reference	3,918	186 (4.75)	Reference	
Painting wall during pregnancy								
Yes	512	45 (8.79)	1.18 (0.85-1.60)	—	474	42 (8.86)	1.72 (1.22-2.37)**	1.63 (1.15-2.25)**
No	9,547	720 (7.54)	Reference		8,632	461 (5.34)	Reference	Reference

Fungus on wall at home

Yes	3,579	274 (7.7)	1.01 (0.87-1.18)	—	3,326	211 (6.3)	1.27 (1.06-1.52)*	1.21 (1.01-1.46)*
No	6,490	491 (7.6)	Reference		5,789	293 (5.1)	Reference	Reference

Postnatal maternal and children health

Postpartum depression

Yes	1,685	158 (9.38)	1.33 (1.10-1.59)**	1.24 (1.02-1.48)*	1,622	116 (7.15)	1.41 (1.13-1.74)**	1.28 (1.02-1.59)*
No	8,389	607 (7.24)	Reference	Reference	7,495	388 (5.18)	Reference	Reference

Children with AD ≤ 6 months

Yes	812	123 (15.15)	2.40 (1.94-2.94)***	2.01 (1.61-2.48)***	526	53 (10.08)	2.02 (1.48-2.70)***	1.68 (1.22-2.26)***
No	9,262	642 (6.93)	Reference	Reference	8,591	451 (5.25)	Reference	Reference

^a OR (95%CI) = odds ratio (95% confident interval).

^b AOR (95%CI) = adjusted OR (95%CI). AOR was adjusted by factors selected from backward stepwise analysis.

“—”, not included in adjusted regression model.

^d USD: US dollars.

^e AD: atopic dermatitis; AR: allergic rhinitis.

*p < 0.05, ** p < 0.01, *** p < 0.001

Some numbers do not add up to total n because of missing values.

Table 3 The proposed β values and predictive probability for three predictive models for asthma in boys and girls (n = 19,192)

Factors (n)	Boys ^a			Girls ^a		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
Intercept	-2.86	-3.09	-3.15	-3.01	-3.35	-3.40
Pre-pregnancy factors						
Maternal education						
>12 years	—	—	—	0.23	0.45	0.43
≤12 years				0	0	0
Family income (*10 ³)						

≥ \$40	0.51	0.38	0.34	—	—	—
\$20-\$40	0.19	0.13	0.11			
< \$20	0	0	0			
Maternal atopy						
Asthma	1.36	1.35	1.28	1.36	1.36	1.32
AD or AR ^b	0.38	0.36	0.31	0.26	0.25	0.23
None	0	0	0	0	0	0
Paternal atopy						
Asthma	1.03	0.99	0.94	1.49	1.48	1.47
AD or AR ^b	0.36	0.36	0.30	0.26	0.26	0.22
None	0	0	0	0	0	0
Perinatal factors						
Resident area						
Urban		0.46	0.44		—	—

Rural	0	0		
Painting wall during pregnancy				
Yes	—	—	0.51	0.49
No			0	0
Fungus on wall at home				
Yes			0.21	0.19
No			0	0
Postnatal maternal and children health				
Postpartum depression				
Yes		0.21		0.25
No		0		0
Children with AD $\leq$ 6 months ^b				
Yes		0.70		0.52
No		0		0

Highest predictive probability [¶]	51.0%	52.3%	68.1%	51.8%	65.9%	78.1%
Lowest predictive probability [¶]	5.4%	4.4%	4.1%	4.7%	3.4%	3.2%

^a “—”, not included in adjusted regression model.

^b AD: atopic dermatitis; AR: allergic rhinitis.

[¶] Probability (P) was calculated by the equation, $P = 1 - (1 / [1 + E\{training\ logical\ model\}])^{\S}$.

[§] Training logical models (using model 1 as example)

Boys: The value = -2.86+0.51 (if family income $\geq$ \$40000)+0.19 (if family income \$20000-\$40000)+0.00 (if family income $<$ \$20000)+1.36 (if mother with asthma)+0.38 (if mother with AD or AR)+0.00 (if mother without atopy)+1.03 (if father with asthma)+0.36 (if father with AD or AR)+0.00 (if father without atopy)

Girls: The value = -3.01+0.43 (if maternal education $>$ 12 years)+0.00 (if maternal education $\leq$ 12 years)+1.36 (if mother with asthma)+0.26 (if mother with AD or AR)+0.00 (if mother without atopy)+1.49 (if father with asthma)+0.26 (if father with AD or AR)+0.00 (if father without atopy)

The calculation was the same in model 2 and model 3.

Table 4 Categories of asthma risk by each test run of the predictive model 3, and the true proportion of asthma in each category in boys and girls[¶]

Category of asthma risk	Boys						Girls					
	eP*	Run 1	Run 2	Run 3	Run 4	Run 5	eP*	Run 1	Run 2	Run 3	Run 4	Run 5
Low	<7.6%	65/1,272	68/1,258	72/1,347	74/1,271	72/1,245	<5.5%	34/1,108	54/1,120	54/1,124	49/1,120	32/1,142
		5.1%	5.4%	5.4%	5.8%	5.8%		3.1%	4.8%	4.8%	4.4%	2.8%
High	7.6%-15.2%	65/624	52/646	62/557	66/632	68/658	5.5%-11%	34/625	50/608	36/601	50/607	43/592
		10.4%	8.1%	11.1%	10.4%	10.3%		5.4%	8.2%	6.0%	8.2%	7.3%
Very High	≥15.2%	22/110	23/107	14/107	19/107	21/101	≥11%	12/83	12/90	20/91	9/93	13/80
		20.0%	21.5%	13.1%	17.8%	20.8%		14.5%	13.3%	22.0%	9.7%	16.3%

[¶] Probability (P) was calculated by the equation, $P = 1 - (1 / [1 + E\{training\ logical\ model\}])$.

* eP = Expected probability.

