

DR CHING-CHUN HUANG (Orcid ID : 0000-0003-1898-5330)

Article type : Original

Title: Risk Factors for Asthma Occurrence in Children With Early-Onset Atopic Dermatitis:
An 8-Year Follow-Up Study

Authors: Ching-chun Huang,^{1,4} Tung-liang Chiang,³ Pau-chung Chen,^{1,4} Shio-jean Lin,⁵
Hui-ju Wen,² Yue-liang Guo^{1,2,4}

1. Environmental and Occupational Medicine, National Taiwan University and National Taiwan University Hospital, Taipei, Taiwan
2. National Institute of Environmental Health Sciences, National Health Research Institutes, Miaoli, Taiwan
3. Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan
4. Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University, Taipei, Taiwan
5. Department of Pediatrics, Chi Mei Hospital, Tainan, Taiwan

Running title: Infantile Atopic Dermatitis and Asthma

Corresponding author: Yue-liang Guo, Rm. 341, 3F., No.17, Xuzhou Rd., Zhongzheng Dist., Taipei City 10005, Taiwan. Telephone: +886-2-33668216. Fax: +886-2-23278515.
E-mail: leonguo@ntu.edu.tw.

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.12835

This article is protected by copyright. All rights reserved.

Financial support: This paper was supported by the Ministry of Science and Technology, Taiwan under the Grant no. MOST 105-2621-M-002-008.

Conflicts of interest: None declared

Huang CC, Chiang TL, Chen PC, Lin SJ, Wen HJ, Guo YL

Risk Factors for Asthma Occurrence in Children With Early-Onset Atopic Dermatitis: An 8-Year Follow-Up Study

Pediatr Allergy Immunol

Abstract

Background

Children with early-onset atopic dermatitis (AD) are at substantial risk of developing asthma later in life, and identifying the critical window of detrimental exposure is advantageous for implementing preventive actions. The aim of this study was to evaluate the role of exposure to environmental modifiers during pregnancy and early childhood in asthma occurrence in an infantile AD cohort.

Methods

Eligible study participants were selected from the Taiwan Birth Cohort Study, which enrolled 24200 newborns in 2005. We enrolled those cases who had been diagnosed as having AD before 3 years of age and followed them up till age 8. We excluded those ever diagnosed with

This article is protected by copyright. All rights reserved.

asthma before AD onset. The dependent variable was defined in terms of whether the participant was diagnosed as having asthma before 8 years of age. We applied logistic regression models to evaluate the risks of exposure to different determinants in asthma occurrence.

Results

A total of 1549 children with AD had completed the 8-year follow-up, and 334 (21.6%) of them had asthma. The results revealed that male sex, lower birth order, maternal asthma history, maternal obesity before pregnancy, and environmental tobacco smoke exposure before 3 years of age were significant risk factors for further development of asthma. Furthermore, food allergy during early life, lower respiratory tract infection, and longer durations of symptomatic AD influenced asthma development later in life.

Conclusions

The findings confirmed the critical determinants for asthma occurrence in infantile AD, which may enable a more personalized approach to the prevention of asthma.

Keywords: Environmental tobacco smoke, Food allergy, Pregnancy, Obesity, Taiwan Birth Cohort Study

Correspondence: Yue-liang Guo, Rm. 341, 3F., No.17, Xuzhou Rd., Zhongzheng Dist., Taipei City 10005, Taiwan. E-mail: leonguo@ntu.edu.tw.

Introduction

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease among children, and the peak incidence is within the first 2 years of life. (1) Previous nationwide surveys have demonstrated that AD appeared in 6.7% of 6-month-old infants and 7.9% of 18-month-old children in Taiwan. (2, 3) A complex interplay of genetic and environmental factors was linked to AD development; (4) however, whether AD is atopic by itself remains debated. Although a previous study illustrated that approximately two thirds of the affected cases are not IgE sensitized, AD, particularly that with specific IgE antibodies, can act as a risk factor for asthma occurrence in childhood. (5, 6)

AD is considered a starting point for other atopic disorders, and longitudinal studies in the recent decade have documented that approximately 25%–80% of the affected patients with AD develop asthma later in life. (7) This typical progression from AD to asthma and eventually allergic rhinitis is described as atopic march. Commonly recognized risk factors for this atopic march are early onset and severity of AD, (8) whereas other factors such as family atopy history, early adverse reactions to foods, and respiratory tract infections have also been postulated. (6) This progressive characteristic of atopic diseases is crucial because it may allow risk stratification and implementation of plausible preventive actions.

Accepted Article

However, the identification of the critical windows of exposure to environmental modifiers influencing further atopic progression has not been completely elucidated. This study aimed to evaluate the role of exposure to detrimental factors during pregnancy and early childhood in asthma occurrence in an infantile AD cohort.

Methods

Enrollment of the cohort. The study participants were selected from the Taiwan Birth Cohort Study (TBCS); the details of the cohort are described elsewhere. (9) In brief, a multistage stratified sampling of 24200 newborns by using a national birth registry was conducted from January through December 2005. Detailed demographic characteristics and medical history of the infant–parent pairs were retrieved through home interviews when the participants were 6 months, 18 months, 3 years, 5 years, and 8 years old, after obtaining informed consent from parents. We enrolled subjects who had been first diagnosed as having AD before 3 years of age as reported by main caregivers, and we verified the doctor-diagnosed AD by using parental reports from the 8-year survey. The exclusion criteria were multiparity, congenital cardiopulmonary or chromosomal abnormalities, and diagnosis of asthma before AD onset. The study protocol was approved by the Institutional Review Board of the Health Promotion Administration, Taiwan.

Outcome and Covariates. At the 8-year follow-up, the main caregiver was asked if the participant had ever been diagnosed as having asthma by a physician, and an answer of ‘yes’

indicated that the child had an atopic progression from AD to asthma. Potential covariates were considered on the basis of previous findings on AD or asthma, including sex, preterm delivery (gestational age < 37 weeks), low birth weight (<2500 g), birth order (1st vs. ≥ 2nd order), maternal obesity before pregnancy (body mass index ≥ 27), breastfeeding (<3 mo vs. 3–6 mo vs. ≥6 mo), vitamin supplementation (during pregnancy, and before 3 y of age), probiotics intake before 3 years of age, parental education (≤12 vs. >12 y), parental atopy history (asthma, allergic rhinitis, and AD), socioeconomic status or annual household income of the family (≤20 000 vs. 20 000–40 000 vs. >40 000 USD), urbanization of the residential area (urban vs. rural), environmental tobacco smoke exposure (ETS, during pregnancy, and before 3 y of age), fur-bearing animals at home, and moldy walls at home. Furthermore, early life food allergy history (defined as positive if an answer of ‘yes’ to the question “if the participant had ever been diagnosed with food allergy before 3 years old?”), episodes of upper (ever diagnosed or hospitalized due to tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media, or common cold) or lower (ever diagnosed or hospitalized due to pneumonia, bronchitis, or bronchiolitis) respiratory tract infection before 3 years of age, and duration of symptomatic AD (defined as total years of itchy rash that will interfere with daily activity or cause night awakening when children were 2–3, 4–5, and 7–8 y old; score range, 0–3) were also considered.

Statistical analysis. First, we used a simple logistic regression model to evaluate the crude odds ratio of each potential variable in asthma occurrence. Factors with P value $< .1$ in the unadjusted model were included for further analysis. Second, we applied multiple logistic regression models with all eligible variables mutually adjusted for evaluating the association between exposure to each determinant and asthma occurrence by 8 years of age. All analyses were performed using software R (version 3.1.3) with default embedded packages, and statistical significance was set at P value < 0.05 based on a two-sided calculation.

Results

Among 24200 sampled infant–mother pairs of the original TBCS, 21248 (87.8%) had completed the 6-month interview. Reasons for non-inclusion were incorrect addresses ($n = 358$), refusal to be interviewed ($n = 1734$), movement abroad ($n = 351$), no one present at home after multiple visits ($n = 104$), death of the infant ($n = 67$), and other miscellaneous reasons ($n = 338$). By the time the 3-year survey was completed, 19910 pairs (93.7%) remained in the cohort, among which 1727 children were reported to have been ever diagnosed as having AD by a physician. We excluded 51 AD cases with asthma diagnosis before AD onset, 49 multiparity cases, and 21 cases with congenital cardiopulmonary or chromosomal abnormalities. By the time the 8-year survey was completed, an additional 57

AD cases were lost to follow-up, leaving a total of 1549 infantile AD cases enrolled in the final analysis (Fig. 1).

Table 1 presents the basic demographics of the infantile AD cohort. Among the 1549 children with AD, 880 (56.8%) were boys and 848 (54.7%) had the first birth order. The proportion of parental atopic history was higher for the father (31.5%) than for the mother (29.1%). Approximately 61% of the enrolled AD children were exposed to ETS at home during pregnancy, and the proportion increased to 77.6% after birth. Nearly 43% of the participants reported to have moldy walls at home, and 17.9% had fur-bearing animals at home. By 8 years of age, 334 (21.5%) infantile AD cases had developed asthma.

The crude odds ratios for developing asthma among different variables are listed in Table 2. Determinants that significantly increased the risk of atopic progression included male sex, lower birth order, maternal atopic history of asthma and allergic rhinitis, maternal obesity before pregnancy, higher annual household income, postnatal ETS exposure before 3 years of age, early life food allergy, longer durations of symptomatic AD, and lower respiratory tract infection before 3 years of age. Moreover, paternal atopic history of asthma, more urbanization of residence, and vitamin supplementation during pregnancy had borderline significance and were included in further multiple adjusted models.

The results of the multiple logistic regression are presented in Table 3. The results revealed that demographic characteristics such as male sex (adjusted odds ratio [aOR] = 1.25, 95% confidence interval [CI] = 1.10–1.42), lower birth order (aOR = 1.15, 95% CI = 1.01–1.32), maternal atopic history of asthma (aOR = 1.52, 95% CI = 1.09–2.11), maternal obesity before pregnancy (aOR = 1.57, 95% CI = 1.20–2.04), and postnatal ETS exposure before 3 y of age (aOR = 1.26, 95% CI = 1.07–1.47) increased the risks of asthma occurrence. Furthermore, early life food allergy history (aOR = 1.22, 95% CI = 1.07–1.39), longer durations of symptomatic AD (3 y vs. none, aOR = 1.71, 95% CI = 1.37–2.17), and episodes of lower respiratory tract infection (aOR = 1.43, 95% CI = 1.19–1.72) were significantly associated with the development of asthma.

Discussion

This is the first nationwide sampling cohort study to verify the critical windows of environmental exposure from pregnancy to early childhood in infantile AD progression to asthma. In this study, the results clearly revealed that lower birth order, maternal asthma history, maternal obesity before pregnancy, postnatal ETS exposure before 3 years of age, early life food allergy, longer durations of symptomatic AD, and lower respiratory tract infection before the age of 3 increased the risk of asthma occurrence by 8 years of age in children with infantile AD.

AD is generally considered as the initial presentation of atopic march, followed by asthma and allergic rhinitis, and approximately one in every three affected children develops asthma later in life. (1) Although IgE sensitization may not be the requisite for AD development, results from birth cohort studies have markedly linked AD to subsequent asthma occurrence. (1, 10) Previous studies have demonstrated that the severity of AD, family history of AD, early onset of AD, early wheezing, viral respiratory tract infections, and early food allergy can increase the risk of atopic disease progression. (6, 11, 12) In the present study, 21.5% of the children with infantile AD developed asthma by 8 years of age, and the risk was higher in boys than in girls. In addition to previously mentioned determinants, we confirmed that maternal asthma history but not AD or allergic rhinitis, lower birth order, maternal obesity before pregnancy, ETS exposure before 3 years of age but not during pregnancy, and longer durations of symptomatic AD were risk factors for infantile AD progression to asthma.

The gene–environment interaction model is the most commonly proposed mechanism for atopic march. (8) The defective skin barrier in AD due to filaggrin gene null mutations or environmental risk factors permits allergen exposure through the epidermis, initiating systemic allergy, which predisposes to asthma and allergic rhinitis later in life. (13, 14) Previous studies have demonstrated that more than half of the children with severe AD eventually developed asthma later in life. (6, 11, 15) In the present study, a longer duration of

Accepted Article

symptomatic AD increased the risk of asthma occurrence, which is consistent with the hypothesis. Several investigations have documented the important role of both prenatal and postnatal exposure to ETS on the occurrence of AD as well as asthma. (16-18) Furthermore, cessation of ETS exposure was also reported to reduce allergic responses and plasma neurotrophins (19). However, few study has focused on the effect of ETS exposure on asthma occurrence among those already diagnosed with AD. A recent multi-cohort study has identified the co-occurrence of asthma, rhinitis, and/or AD a common phenotype among 4- and 8-year-old children, and about 6 – 7% of the high prevalent group had symptoms of both eczema and asthma. The authors suggested that the allergic cluster could be the effects of common environmental determinants but less likely the influence of IgE sensitization. (20) In the present work, ETS exposure during early life, but not during the prenatal period, was associated with atopic progression, indicating the critical window of environmental toxicant exposure on skin integrity and precipitation of subsequent allergen entrance. (21, 22)

Food allergy typically co-occurs with AD in early life; however, the role of food allergy in subsequent atopic march progression remains unclear. A study demonstrated that food sensitization and filaggrin gene mutations increased the risk of asthma in children with early onset AD; however, the combination of the two factors was not effective in identifying high-risk children. (23) Gustafsson et al. demonstrated that early adverse reaction to foods in children with AD was associated with other atopic diseases. (6) Other studies have reported

that IgE-positive cow's milk allergy diagnosed in early life predicted airway inflammation and bronchial hyperresponsiveness at school age. (24, 25) In the present study, a history of early life food allergy was a risk factor for asthma occurrence. However, whether the observed association was a co-manifestation of AD or just an influence from food allergy itself remained to be elucidated.

Previous studies have demonstrated the crucial role of maternal, but not paternal, allergy and obesity on fetal programming. (26, 27) In addition, a recent review documented that maternal atopy can influence IgE production during both the prenatal and postnatal periods, whereas paternal atopy affects IgE production during the postnatal period only. (28) Traherne et al. reported that the maternally transmitted FcεRI-β gene and the polymorphism of the high-affinity IgE receptor β chain were strongly associated with positive allergy skin-prick tests and greater allergen-specific IgE levels. (29) Other studies have proposed that maternal allergen-specific IgG detected in cord bloods may exert an influence on offspring by interfering with IFN-γ excretion from Th1 cells. (30) Furthermore, maternal obesity, linked to a chronic inflammatory status, has been postulated to influence fetal programming by interfering with early immune regulation in the uterus. (31, 32) In the present study, maternal atopic history of asthma and obesity were associated with atopic progression, implying that the maternal–fetal environment during the critical window of pregnancy may have a greater effect on the fetus even after the onset of AD. (4)

The major strength of this study was that the participants with AD were enrolled from the TBCS, which is a large and nationwide representative cohort. The two-stage sampling strategy based on total fertility and urbanization of townships ensured the TBCS's representativeness of newborns in Taiwan. Furthermore, the high retention rate (91.8%) of the TBCS by 8 years of age and the prospective cohort study design in this study ensured an unbiased investigation of the causal relationship between temporal exposure to environmental modifiers and allergic progression of diseases.

The study had some limitations. First, the diagnosis of the allergic diseases including AD, asthma, and food allergy could be retrieved only through parental reports of a doctor diagnosis. Because the major caregivers were not aware of the main hypothesis of this study, any misclassification between cases and non-cases were unlikely to be different. Furthermore, the diagnosis of AD before 3 years of age was verified using the 8-year survey to increase the accuracy of AD diagnosis. Second, we enrolled only children with AD diagnosed before 3 years of age due to the prospective cohort design of the TBCS. Although most of the AD cases manifest within 2 year of life, 10% of them were diagnosed after 5 years of age. (33) The study findings can be applied only to the AD cases diagnosed before the age of 3 years. Third, previous studies have documented that AD can be categorized into atopic and non-atopic forms, and IgE sensitization can increase the risk of AD progression to asthma. (34, 35) Although, information on IgE sensitization was unavailable for this study because

the TBCS only surveyed participants with questionnaires, recent studies suggested that specific IgE sensitization should no longer be considered the dominant mechanism for the comorbidity cluster of allergic diseases. (20) Further studies are required to clarify the influence of allergic sensitization on other risk factors.

In conclusion, the study results confirmed the critical exposure windows for asthma occurrence in children with infantile AD, and potentially modifiable risks included maternal obesity before pregnancy and early life ETS exposure. The findings may enable a more personalized approach to prevention of asthma.

Acknowledgments

This study is based on the data from the Taiwan Birth Cohort Study database, provided by the Health Promotion Administration, Ministry of Health and Welfare, Taiwan, R.O.C. The views expressed herein are the authors' own. We also thank all the pairs of mothers and babies who participated in this study, the interviewers who supported data collection, and the study groups in the TBCS.

References

- 1 van der Hulst AE, Klip H, Brand PL. Risk of developing asthma in young children with atopic eczema: a systematic review. *J Allergy Clin Immunol.* 2007; **120**: 565-9.
- 2 Huang CC, Wen HJ, Chen PC, Chiang TL, Lin SJ, Guo YL. Prenatal air pollutant exposure and occurrence of atopic dermatitis. *Br J Dermatol.* 2015; **173**: 981-8.
- 3 Wang IJ, Guo YL, Hwang KC, *et al.* Genetic and environmental predictors for pediatric atopic dermatitis. *Acta paediatrica Taiwanica = Taiwan er ke yi xue hui za zhi.* 2006; **47**: 238-42.
- 4 Jones CA, Holloway JA, Warner JO. Does atopic disease start in foetal life? *Allergy.* 2000; **55**: 2-10.
- 5 Flohr C, Johansson SG, Wahlgren CF, Williams H. How atopic is atopic dermatitis? *J Allergy Clin Immunol.* 2004; **114**: 150-8.
- 6 Gustafsson D, Sjoberg O, Foucard T. Development of allergies and asthma in infants and young children with atopic dermatitis--a prospective follow-up to 7 years of age. *Allergy.* 2000; **55**: 240-5.
- 7 Ker J, Hartert TV. The atopic march: what's the evidence? *Ann Allergy Asthma Immunol.* 2009; **103**: 282-9.
- 8 Bantz SK, Zhu Z, Zheng T. The Atopic March: Progression from Atopic Dermatitis to Allergic Rhinitis and Asthma. *Journal of clinical & cellular immunology.* 2014; **5**.

- Accepted Article
- 9 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.
 - 10 Saunes M, Oien T, Dotterud CK, *et al*. Early eczema and the risk of childhood asthma: a prospective, population-based study. *BMC Pediatr*. 2012; **12**: 168.
 - 11 Ciprandi G, Cirillo I, Vizzaccaro A, Milanese M, Tosca MA. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. *Clin Exp Allergy*. 2004; **34**: 891-6.
 - 12 Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. *Lancet*. 2008; **372**: 1058-64.
 - 13 Ohshima Y, Yamada A, Hiraoka M, *et al*. Early sensitization to house dust mite is a major risk factor for subsequent development of bronchial asthma in Japanese infants with atopic dermatitis: results of a 4-year followup study. *Ann Allergy Asthma Immunol*. 2002; **89**: 265-70.
 - 14 Spergel JM. Atopic march: link to upper airways. *Current opinion in allergy and clinical immunology*. 2005; **5**: 17-21.
 - 15 Peroni DG, Piacentini GL, Alfonsi L, *et al*. Rhinitis in pre-school children: prevalence, association with allergic diseases and risk factors. *Clin Exp Allergy*. 2003; **33**: 1349-54.
 - 16 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.

- 17 Lee SL, Lam TH, Leung TH, *et al.* Foetal exposure to maternal passive smoking is associated with childhood asthma, allergic rhinitis, and eczema. *ScientificWorldJournal.* 2012; **2012**: 542983.
- 18 Pyun BY. Natural history and risk factors of atopic dermatitis in children. *Allergy, asthma & immunology research.* 2015; **7**: 101-5.
- 19 Kimata H. Cessation of passive smoking reduces allergic responses and plasma neurotrophin. *Eur J Clin Invest.* 2004; **34**: 165-6.
- 20 Garcia-Aymerich J, Benet M, Saeys Y, *et al.* Phenotyping asthma, rhinitis and eczema in MeDALL population-based birth cohorts: an allergic comorbidity cluster. *Allergy.* 2015; **70**: 973-84.
- 21 Kim K. Influences of Environmental Chemicals on Atopic Dermatitis. *Toxicological research.* 2015; **31**: 89-96.
- 22 Kramer U, Lemmen CH, Behrendt H, *et al.* The effect of environmental tobacco smoke on eczema and allergic sensitization in children. *Br J Dermatol.* 2004; **150**: 111-8.
- 23 Filipiak-Pittroff B, Schnopp C, Berdel D, *et al.* Predictive value of food sensitization and filaggrin mutations in children with eczema. *J Allergy Clin Immunol.* 2011; **128**: 1235-41 e5.

- 24 Malmberg LP, Saarinen KM, Pelkonen AS, Savilahti E, Makela MJ. Cow's milk allergy as a predictor of bronchial hyperresponsiveness and airway inflammation at school age. *Clin Exp Allergy*. 2010; **40**: 1491-7.
- 25 Saarinen KM, Pelkonen AS, Makela MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005; **116**: 869-75.
- 26 Campbell DE, Boyle RJ, Thornton CA, Prescott SL. Mechanisms of allergic disease - environmental and genetic determinants for the development of allergy. *Clin Exp Allergy*. 2015; **45**: 844-58.
- 27 Litonjua AA, Carey VJ, Burge HA, Weiss ST, Gold DR. Parental history and the risk for childhood asthma. Does mother confer more risk than father? *Am J Respir Crit Care Med*. 1998; **158**: 176-81.
- 28 Wu CC, Chen RF, Kuo HC. Different implications of paternal and maternal atopy for perinatal IgE production and asthma development. *Clinical & developmental immunology*. 2012; **2012**: 132142.
- 29 Traherne JA, Hill MR, Hysi P, *et al*. LD mapping of maternally and non-maternally derived alleles and atopy in FcepsilonRI-beta. *Hum Mol Genet*. 2003; **12**: 2577-85.
- 30 Prescott SL, Holt PG, Jenmalm M, Bjorksten B. Effects of maternal allergen-specific IgG in cord blood on early postnatal development of allergen-specific T-cell immunity.

Allergy. 2000; **55**: 470-5.

- 31 Haberg SE, Stigum H, London SJ, Nystad W, Nafstad P. Maternal obesity in pregnancy and respiratory health in early childhood. *Paediatr Perinat Epidemiol*. 2009; **23**: 352-62.
- 32 Reichman NE, Nepomnyaschy L. Maternal pre-pregnancy obesity and diagnosis of asthma in offspring at age 3 years. *Maternal and child health journal*. 2008; **12**: 725-33.
- 33 Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician*. 2012; **86**: 35-42.
- 34 Kusel MM, Holt PG, de Klerk N, Sly PD. Support for 2 variants of eczema. *J Allergy Clin Immunol*. 2005; **116**: 1067-72.
- 35 Williams HC, Johansson SG. Two types of eczema--or are there? *J Allergy Clin Immunol*. 2005; **116**: 1064-6.

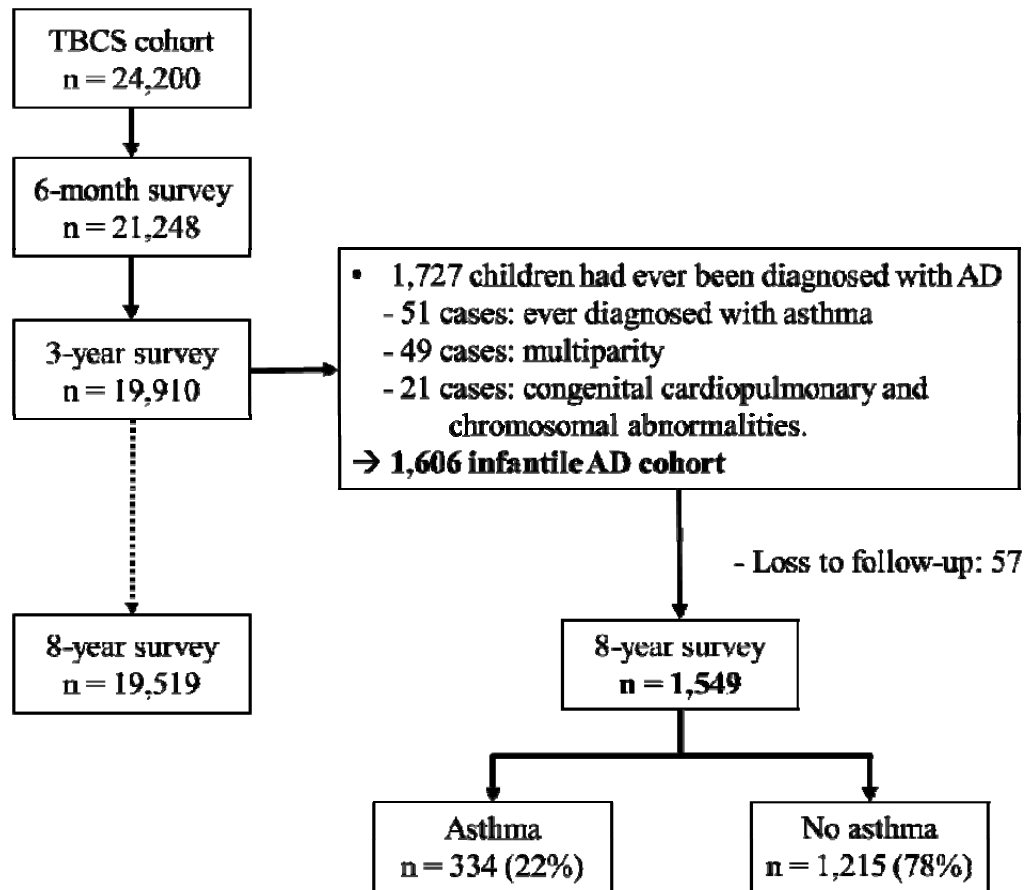


Figure 1. Flowchart of enrollment of the infantile atopic dermatitis cohort. AD, atopic dermatitis; TBCS, Taiwan Birth Cohort Study.

Table 1. Demographic characteristics of the enrolled infantile atopic dermatitis cohort ($N = 1549$).

Variables	Mean $\pm$ SD, n (%)
Fetal factors	
sex (male vs. female)	880 (56.8)
gestational age (weeks)	38.5 $\pm$ 1.5
birth weight (gram)	3155 $\pm$ 419
birth order (1 st vs. $\geq 2^{\text{nd}}$ order)	848 (54.7)
Parental factors	
maternal atopic history	450 (29.1)
paternal atopic history	488 (31.5)
maternal education (> 12 vs. ≤ 12 years)	961 (62.1)
paternal education (> 12 vs. ≤ 12 years)	985 (63.9)
annual household income (USD)	
$\leq 20,000$	441 (28.5)
20,000~40,000	850 (55.0)
> 40,000	254 (16.5)
Environmental factors	
residential area (urban vs. rural)	1051 (67.9)
moldy walls at home	660 (42.6)
fur-bearing animal at home	278 (17.9)
environmental tobacco smoke exposure	
mother, during pregnancy	951 (61.4)
child, before 3 years old	1197 (77.6)
Occurrence of asthma by 8 years old	334 (21.5)

Table 2. Simple logistic regression model for developing asthma by 8 years of age in the infantile AD cohort.

Variables	n	Crude OR	95% CI	<i>P</i>
Sex (male vs. female)	880	1.21	(1.07–1.37)	0.003
Preterm delivery (<37 vs. ≥ 37 weeks)	99	1.19	(0.94–1.49)	0.13
Low birth weight (<2500 vs. ≥ 2500 gram)	79	1.21	(0.94–1.55)	0.14
Birth order (1 st vs. $\geq 2^{\text{nd}}$ order)	848	1.14	(1.01–1.29)	0.03
Breast feeding duration				
< 3 months	884	Reference		
3–6 months	316	1.05	(0.88–1.25)	0.56
≥ 6 months	349	0.94	(0.80–1.11)	0.49
Maternal atopic history				
atopic dermatitis	123	1.15	(0.92–1.41)	0.21
asthma	45	1.55	(1.14–2.10)	0.007
allergic rhinitis	355	1.19	(1.04–1.36)	0.01
Paternal atopic history				
atopic dermatitis	113	1.19	(0.96–1.47)	0.11
asthma	26	1.49	(0.98–2.21)	0.06
allergic rhinitis	387	0.97	(0.84–1.11)	0.68
Maternal obesity before pregnancy (BMI ≥ 27 vs. <27)	73	1.37	(1.06–1.75)	0.02
Maternal weight gain during pregnancy (per kg increase)		1.01	(0.99–1.04)	0.37
Vitamin supplement				
mother, during pregnancy	1090	1.14	(0.99–1.31)	0.06
child, before 3 y/o	229	1.12	(0.95–1.32)	0.16

Probiotic intake before 3 y/o	313	1.08	(0.93–1.24)	0.32
Maternal education (> 12 vs. ≤ 12 years)	961	1.07	(0.95–1.21)	0.28
Paternal education (> 12 vs. ≤ 12 years)	985	1.06	(0.94–1.20)	0.36
Annual household income (USD)				
≤ 20,000	441	Reference		
20,000~40,000	850	1.21	(1.02–1.42)	0.03
> 40,000	254	1.01	(0.80–1.25)	0.96
ETS exposure				
mother, during pregnancy	951	1.07	(0.95–1.22)	0.27
child, before 3 y/o	1197	1.26	(1.08–1.47)	0.004
Moldy walls at home	660	1.01	(0.90–1.14)	0.86
Fur-bearing animal at home	278	1.04	(0.89–1.21)	0.61
Urbanization of residence (urban vs. rural)	1051	1.14	(1.00–1.30)	0.053
Early life food allergy	471	1.30	(1.15–1.47)	<0.001
Duration of symptomatic AD		1.59	(1.40–1.81)	<0.001
None	592	Reference		
1 year	447	1.04	(0.84–1.28)	0.75
2 years	150	0.78	(0.55–1.07)	0.13
3 years	341	1.85	(1.50–2.29)	<0.001
Upper respiratory tract infection before 3 y/o	1199	1.06	(0.90–1.26)	0.46
Lower respiratory tract infection before 3 y/o	156	1.46	(1.22–1.73)	<0.001

Abbreviations: AD, atopic dermatitis; BMI, body mass index; CI, confidence interval; ETS, environmental tobacco smoke; OR, odds ratio; y/o, years old.

Table 3. Risk factors and their adjusted odds ratios (aORs) for developing asthma before 8 years of age obtained using multiple logistic regression in the infantile AD cohort.

Variables	aOR ^a	95% CI
Sex (male vs. female)	1.25***	(1.10–1.42)
Birth order (1 st vs. $\geq 2^{\text{nd}}$ order)	1.15*	(1.01–1.32)
Maternal atopic history		
asthma	1.52*	(1.09–2.11)
allergic rhinitis	1.14	(0.99–1.32)
Paternal atopic history		
asthma	1.22	(0.78–1.85)
Maternal obesity before pregnancy (BMI ≥ 27 vs. <27)	1.57***	(1.20–2.04)
Vitamin supplement		
mother, during pregnancy	1.06	(0.92–1.23)
Annual household income (USD)		
$\leq 20,000$		
20,000~40,000	1.18	(0.99–1.41)
$> 40,000$	1.01	(0.80–1.28)
ETS exposure		
child, before 3 y/o	1.26**	(1.07–1.49)
Urbanization of residence (urban vs. rural)	1.09	(0.94–1.25)
Early life food allergy	1.22**	(1.07–1.39)
Duration of symptomatic AD		
none	Reference	
1 year	1.05	(0.84–1.30)
2 years	0.8	(0.57–1.11)
3 years	1.71***	(1.37–2.14)
Lower respiratory tract infection before 3 y/o	1.43***	(1.19–1.72)

Abbreviations: AD, atopic dermatitis; aOR, adjusted odds ratio; CI, confidence interval; ETS, environmental tobacco smoke; y/o, years old.

^aLogistic regression models with all variables mutually adjusted.

* $P < .5$, ** $P < .01$, *** $P < .001$