Prevalence and risk factors for early presentation of asthma among preschool children in Taiwan

Kuo-Wei Yeh[1,2], Liang-Shiou Ou[1,2], Tsung-Chieh Yao[1,2], Li-Chen Chen[1,2], Wen-I Lee[1,2], Jing-Long Huang[1,2] and the PATCH study group*

Summary

Background: **Traditional asthma prevalence surveys were based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, which focuses on children aged 6-7 and 13-14. However, asthma-like symptoms usually commence in preschool aged children, in whom it is difficult to make a definite diagnosis of asthma. It is worth determining the prevalence rate of asthma or asthma-like symptoms and analyzing the risk factors for this phenomenon among preschool aged children.**

Methods: **Children aged 3–6 years were recruited from kindergartens in Keelung City, northern Taiwan. The questionnaire used was based on the ISAAC phase III core and environmental questionnaires and included questions on asthma, rhino-conjunctivitis, and eczema, along with questions to elicit common and early presentations of asthma, as well as other demographic and environmental data. The questionnaires were delivered and completed by parents.**

Results: **2,395 questionnaires were delivered to parents with children at 50 kindergartens, of which 2,170 questionnaires were returned (return rate 90.6%). 9.9% of these preschool children had physician-diagnosed asthma. However, 20.4% of them experienced asthma like symptoms while attending kindergarten. Both the physician-diagnosed asthma and asthma-like symptoms groups had more clinical symptoms in all seasons except summer, compared to children without asthma. It was significant that the asthma-like symptoms commenced after joining a kindergarten ($p < 0.001$), and 66.5% of the children started to experience the symptoms within one month of beginning kindergarten. Using antibiotics or antipyretics in young infancy and mothers having asthma were the risk factors for developing asthma and asthma-like symptoms ($p < 0.001$), but parental smoking was not contributory to asthma development in preschool children. More frequent use of antipyretics in a year had a higher risk for the development of asthma and asthma-like symptoms.**

Conclusions: **Asthma and asthma-like symptoms were common in preschool children. Early infection of the respiratory tract and use of antibiotics were associated with presentation of symptoms. Attending a kindergarten is also a risk factor for early presentation of asthma among preschool children. *(Asian Pac J Allergy Immunol 2011;29:120-6)***

Key words: *asthma, preschool, epidemiology*

Introduction

Asthma is a chronic inflammatory airway disease. Although its prevalence rate seems to have reached a plateau in western countries, hospitalization rates in children are still increasing in developing countries.[1,2] With regards to prevalence surveys, epidemiology data are usually based on International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires. These surveys focus on two age groups; 6-7 years old and 13-14 years old.[3]

According to a cohort study by the Tucson group, the development of atopic dermatitis symptoms usually start in young infancy, followed by symptoms of allergic rhinitis. The symptoms of asthma usually began at the age of 3 to 4 years, and whether they are outgrown depends on the atopic background.[4] One questionnaire-based survey

From the [1]Division of Allergy Asthma and Rheumatology, Department of Pediatrics, Chang Gung Memorial Hospital, Taoyuan, Taiwan
[2]Community Medicine Research Center, Chang Gung Memorial Hospital at Keelung, Keelung, Taiwan
*PATCH (Prediction of Allergies in Taiwanese Children) study group: Study Director: JL Huang. Principal Investigators: KW Yeh, LS Ou, TC Yao, LC Chen, WI Lee.
Corresponding author: Jing-Long Huang
E-mail: long@adm.cgmh.org.tw
Submitted date: 16/1/2011
Accepted date: 18/4/2011

reported that 40% of children had experienced wheezing at some point during the first 6 years of life.[5] Different phenotypes of wheeze and cough based on pattern and frequency were elicited in preschool children in another cohort survey.[6] However, the most practical issues for practitioners are how to make appropriate diagnosis, followed by when to initiate chronic maintenance therapy in preschoolers. Identifying possible risk factors of asthma can help doctors to make proper decisions.

According to the Ministry of Education in Taiwan, 44% of children in this age group are registered at kindergartens. Children attending kindergartens or day care centers usually stay there for more than eight hours a day. Because of the commencement and various presentations of early symptoms in this age group, it is not easy to make a definite diagnosis of asthma. However, this leads to parents taking their children to visit doctors frequently and furthermore to take additional unnecessary medication. More attention to the initial presentations of symptoms needs to be paid for children in this age group. Although various risk factors have been discussed with asthma prevalence in school age children, there are currently no useful strategies to prevent asthma development. The primary aim of this study was to understand current conditions and prevalence of allergic diseases among preschool children and to identify putative causative factors for these allergic symptoms which could help health care providers to prevent them as early as possible when children are growing up.

Methods

Study population

This is a cross-sectional survey which was conducted from December 2007 to February 2008. There were a total of 3,862 preschool children in 66 kindergartens in Keelung City and 50 of them with 2,395 preschool children, aged from 3 to 6, agreed to participate in this survey. Questionnaires were delivered to these kindergartens, and distributed to parents by teachers. The questionnaires were collected within one week and sent back to the Department of Education which governs these institutes.

Questionnaire

The questionnaire was based on the ISAAC phase III core and environmental questionnaires and included questions on asthma, rhino-conjunctivitis and eczema, along with questions to elicit other demographic and risk factors.

Demographic data obtained included age, sex, race, birth weight, type of delivery, number of younger and older siblings, maternal age, and maternal education level. Environmental data included breastfeeding, exposure to livestock during pregnancy and during the first year of the child's life, antipyretics or antibiotic consumption during the first year of the child's life, father's and mother's tobacco consumption (currently and during pregnancy), pets at home during the first year of the child's life as well as during the previous 12 months, type of fuel used in heating and cooking systems, frequency of vigorous physical activity of sufficient duration to make the child breathe hard and hours spent watching television per day.

The questionnaires were distributed to all kindergartens by the Department of Education, Keelung City Government. They were completed by caregivers and collected by teachers at the kindergartens within two weeks.

Definition of asthma and asthma-like symptoms

Physician-diagnosed asthma was defined as a diagnosis made by doctors in teaching hospitals. We defined asthma-like symptoms as cough without wheeze for more than three weeks, or wheeze after playing at least two different episodes. No skin tests or blood samples were taken from these children and the diagnosis of atopy was based on clinical presentations.

Relative frequencies were compared with the chi-square test and McNemar test, and a P-value below 0.05 was considered significant. No multivariable analysis was carried out.

Results

Prevalence rate

A total of 2,395 questionnaires were distributed to 50 kindergartens in Keelung City; 2,170 questionnaires were returned (return rate 90.6%), and 2,037 questionnaires were suitable for analysis. Overall, 9.9% of the children were reported to have physician-diagnosed asthma. However, 20.4% of them had experienced asthma-like symptoms. The average age of the children was 5.5 ± 2.8 years. Gender distribution was also similar, with boys accounting for 50.3% of asthma cases.

Presentation patterns by season

Both the physician-diagnosed asthma and non-asthma groups showed similar seasonal variations. The symptoms usually developed in spring and autumn into winter and were most common in

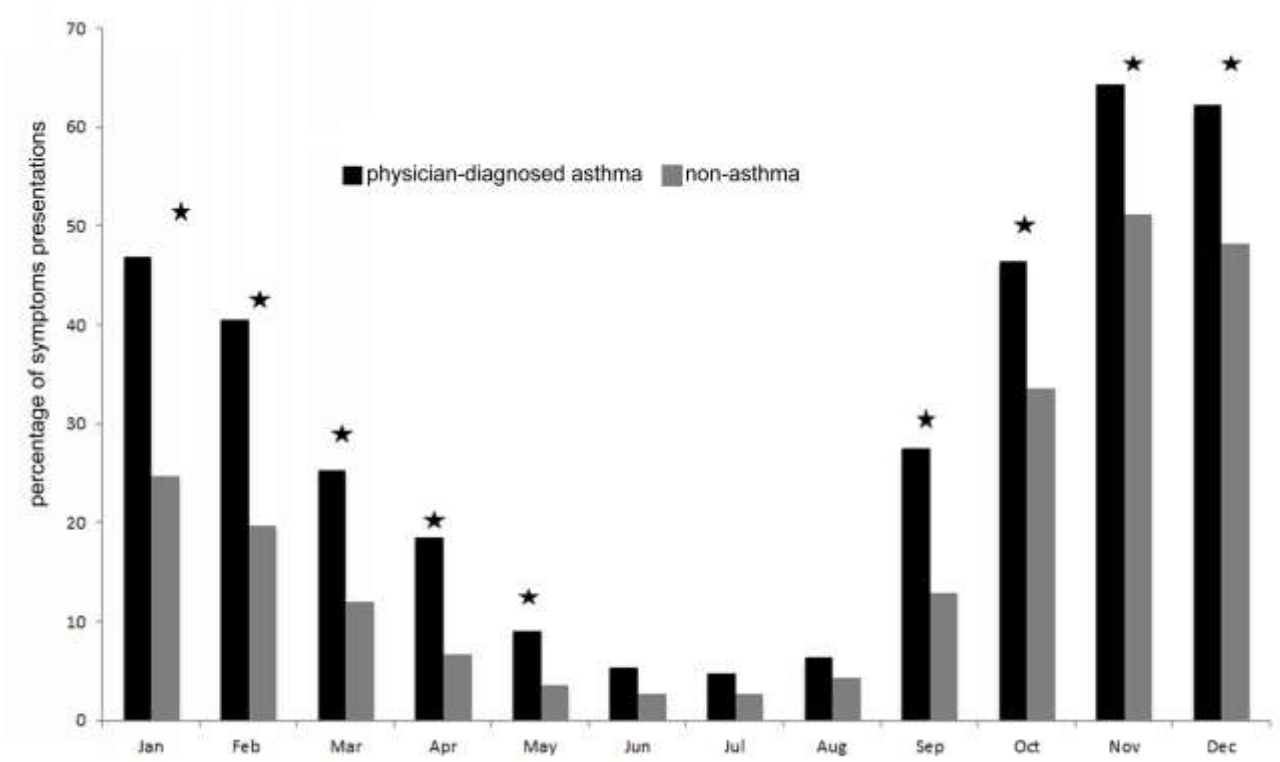

Figure 1. Both physician-diagnosed asthma and non-asthma preschoolers had similar seasonal patterns for cough symptoms, although more physician-diagnosed asthma children presented with cough symptoms in every month except in June, July and August. ★ = p <0.001

winter. However, comparing these two groups, the percentage of symptoms was significantly different during the whole year except in summer ($p < 0.001$) (Figure 1). Children who had experienced cough or wheeze also had a similar seasonal variation pattern.

The impact of asthma-like symptoms after joining a kindergarten

20.7% of all children experienced asthma-like symptoms before joining a kindergarten, and 24.3% of them had similar complaints after attending the kindergarten. This is a 1.36 fold increase (95% confidence interval 1.165-1.596) in children who experienced asthma-like symptoms after joining a kindergarten ($p < 0.001$). 66.5% of these children began to experience asthma-like symptoms within one month of joining a kindergarten.

Risk factors

Breastfeeding, even continued feeding for more than four months, did not contribute to asthma or asthma-like symptoms in this survey. For children with physician-diagnosed asthma, whether the mother smoked during pregnancy or after birth had no effect on asthma in preschool children ($p = 0.998$). A birth weight below 2500 gm was not associated with asthma presentation ($p = 0.28$). The majority (89.7%) of these children were born with a gestational age above 34 weeks, which was not different to children who were born prematurely ($p = 0.86$). There was 34.4% of children 34.4% of children who had had bronchiolitis had asthma-like symptoms after joining a kindergarten and 25.7% without previous bronchiolitis history ($p = 0.004$). The most significant factors that contributed to asthma in preschool children were early consumption of antipyretics and antibiotics in the first year of life (OR = 2.24, 95% CI 1.56-3.22, $p < 0.001$). Moreover, one of the child's parents having atopy increased the risk 2.4 fold of their child developing asthma. The impact of the factors associated with asthma presentation is shown in Table 1.

Other allergic diseases

In this survey, other atopic disorders were also investigated. The rate of physician diagnosed allergic rhinitis was 37.2%, and 36.1% of children experienced allergic rhinitis-like symptoms. The rates of physician-diagnosed allergic conjunctivitis

Table 1. The factors associated with asthma among preschool children

	% of asthmatic preschoolers	Odds ratio	95% confidence interval	P value*
Birth condition				
Prematurity before 34 weeks	5.0	1.04	0.49-2.20	0.93
Breastfed	66.0	1.36	1.00-1.86	0.05
Maternal smoking in first 6 months	8.1	1.00	0.58-1.71	1.00
Low birth weight <2500 gm	6.0	0.70	0.37-1.33	0.28
Cesarean section	42.6	0.95	0.71-1.28	0.75
Food style (seldom or occasional)				
Meat	13.8	1.15	0.68-1.95	0.61
Seafood	25.2	1.42	0.88-2.28	0.15
Fruit	10.0	0.91	0.51-1.63	0.75
Vegetable	8.8	0.81	0.44-1.46	0.48
Peas	67.3	1.10	0.72-1.70	0.64
Nuts	91.5	1.34	0.68-2.60	0.73
Milk	17.0	1.27	0.80-2.04	0.31
Egg	12.4	1.18	0.66-2.09	0.58
Rice	0	0.32	0.13-0.76	0.01
Wheat	14.5	1.07	0.61-1.87	0.82
Medication				
Antipyretics in 1st year of life	23.0	2.24	1.56-3.22	<0.001
Antipyretics in the past 1 year	89.2	0.69	0.43-1.11	0.12
Antibiotics in 1st year of life	27.8	2.35	1.52—3.66	<0.001
Siblings				
More than 2 siblings	14.4	1.09	0.72-1.66	0.69
Any sibling has asthma	21.2	4.05	2.50-6.55	<0.001
Any sibling has atopy	35.6	2.09	1.42-3.06	<0.001
Pets				
Cats in 1st year of life	2.1	0.82	0.29-2.29	0.70
Dogs in 1st year of life	13.2	1.02	0.66-1.58	0.93
Respiratory infections				
Bronchiolitis	44.4	3.78	2.71-5.25	<0.001
pneumonia	21.7	2.13	1.43-3.17	<0.001
Pneumonia ≥ 2/year	5.6	4.70	1.98-11.18	<0.001
Croup	11.1	3.57	2.04-6.26	<0.001

and allergic eye symptoms were 19.4% and 23.0%, respectively. The rate of current atopic dermatitis was 10.0% and 17.3% of preschool children had experienced skin rashes such as atopic dermatitis (Figure 2).

Discussion

The early symptoms of asthma are quite similar to those of respiratory tract infection in preschool children. To date, even though some guidelines have been published regarding diagnosis and management for children younger than 5 years[7,8], there is still no consensus on the definite diagnostic criteria of asthma in preschool aged children. However, in real world practice, patients at this young age do experience asthma-like symptoms and may frequently take anti-asthmatic medication.

The "hygiene hypothesis" has been proposed for decades.[9] It states that living on a farm in childhood could have protective effects for asthma through modulating the immune system by deviating it to non-allergic pathways. Prenatal exposure to a farm environment does have some influence on immune deviation in early life[10] and has a protective effect with regard to the development of asthma in school-age children.[11,12] Keelung is a modern satellite city near the capital, Taipei, in Taiwan. In our survey, only 5.5% of these children had had contact with livestock in the first year of life and this did not appear to have a protective effect with regard to asthma in the preschool period. The issue of the hygiene hypothesis could not be fully be investigated in our study because it involved a younger age group living in an urban environment . In addition, 12.9% and 2.5% of these children had raised dogs or cats, respectively, in their first year of life in our survey and this was not a protective or risk factor for asthma presentation in the preschool period.

A systemic review proposed that wheezing or asthma has an inverse association with sibling numbers.[13] In that review, asthma presentation decreased by 28% if there were more than three siblings. This was not the case in a Japanese study, where having two or more older siblings was not related to wheeze or asthma.[14] In our survey, only 3.9% of children had at least three siblings. The birth rate has significantly decreased in recent years in Taiwan and the majority of the children in our study had only one sibling. We did not find an association between sibling numbers and asthma. However, a history of atopy in siblings was a significant risk factor for early presentation of asthma.

In addition to a farm environment, family size, birth order and daycare attendance have also been discussed with regards to the association with asthma. Early entry to daycare before the age of six months had a protective effect for the development of asthma in a Tucson cohort study.[15] It has been proposed that daycare attendance is a risk factor for preschool wheeze, but a protective factor for primary-school wheezing.[16] Children usually spend

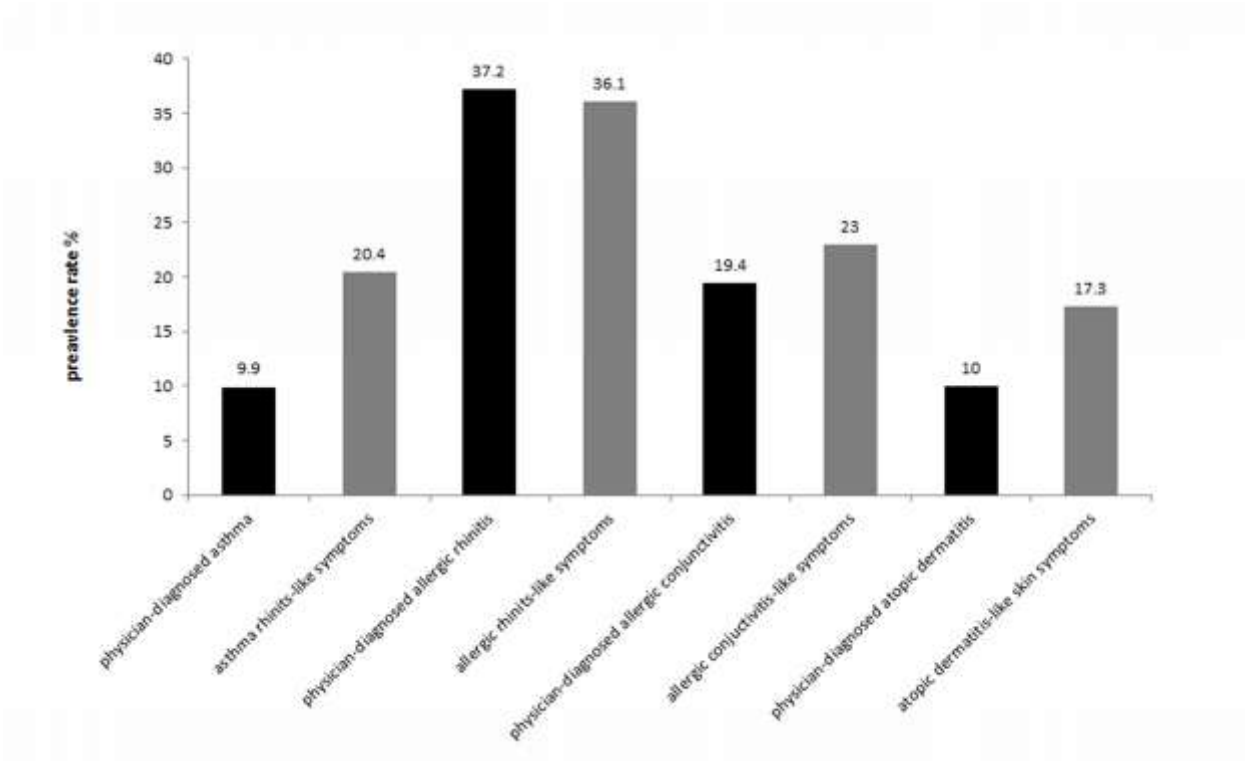

Figure 2. The prevalence rates for asthma and other allergic diseases among preschool children.

lots of time at home before joining a kindergarten and the chance of infection increases when they begin participating in a classroom situation. We also found that the proportion of children with asthma-like symptoms started to increase after attending a kindergarten. A previous survey on a comparison of indoor allergens and endotoxin levels between kindergartens and domestic dwellings showed no differences.[17] The allergen levels in different settings cannot explain the differences in presentation of respiratory symptoms before and after joining a kindergarten. Respiratory infection is one of multiple triggers for asthma exacerbation and initiation of asthma development.

Children with atopic characteristics and viral infections have a higher possibility of asthma exacerbation than those with only one of these factors.[18] It has been reported that at the beginning of a semester, children experience asthma exacerbation because of encountering viral infections.[19] It is not obligatory to study at a kindergarten. Children can join a kindergarten at any time; however, it is most common to begin in August or September. In our survey, most responders stated that their children began to experience asthma-like symptoms after joining a kindergarten. Although we did not perform general and extended viral isolation for the children, they usually began to experience intermittent and repeated cough for a long period regardless of the month or season they joined the kindergarten.

The asthma symptoms had a seasonal variation, being less frequent in the summer and peaking in the winter and early spring. This trend is similar to that for hospitalization of asthma in children report by Yeh et al.[2] However it was noted that children without asthma also had a similar seasonal variation pattern, though the proportion was significantly less among this group of children in our study. The seasonal variations in cough symptoms in both physician-diagnosed asthma and non-asthma group could be partly explained by the seasonality of virus epidemiology.[20] The seasonal change of cough presentation can't be used to help in the diagnosis of asthma or asthma-like symptoms in preschool children.

From epidemiology studies on asthma worldwide, the prevalence is still increasing in developing countries, but is stabilizing in western countries.[21,22] The association of consumption of paracetamol during the prenatal period by mothers or young infants and the increasing risk of asthma

presentation in children 6 to 7 years of age has been discussed.[23,24] In our survey, we also found that early use of antipyretics, mostly paracetamol, in infancy contributed to asthma presentation in the preschool period. This can be explained by depletion of glutathione and glutathione-dependent enzymes after introduction of antipyretics, thereby reducing the protective mechanisms against oxidative stress. The generation of reactive oxygen species after allergic or viral exposure leads to enhanced inflammation, which can lead to the development or worsening of pre-existing asthma. More evidence is required to establish the direct cause and effect relationship of antipyretics and asthma. Moreover, early use of antibiotics was also a risk factor for the development of asthma in preschool children. This cannot solely be attributed to the effect of antipyretics use.

In a British cohort study, it was observed that breastfeeding, whatever the duration, was protective for wheeze in the first three years of life, but not wheeze or bronchial hyper-responsiveness at 7 to 8 years.[25] Breastfeeding at least for 4 months also decreased asthma risk in preschool children in an Australian survey.[26] This is not in accordance with our study, where two-thirds of the children with asthma were breastfed in their infancy, almost making it a risk effect of asthma development, though the difference did not reach significant statistically. The majority of these children (75.4%) were breastfed less than 3 months. It still suggested prolonging breastfeeding duration especially for children with high atopic background.

From previous ISAAC surveys, Taiwan was in the first rank among whole countries in the prevalence of allergic rhino-conjuctivitis in school aged children.[27] In this study, physician-diagnosed allergic rhinitis and conjunctivitis were more common than asthma in preschoolers. For all allergic diseases, rhino-conjuctivits was the most common among 6-7 year-old children in Taiwan compared to other Asian countries.[28] In addition, the symptoms of allergic rhinitis usually developed earlier than those of asthma. This could explain the high prevalence rate of physician-diagnosed allergic rhinitis in preschool children.

The limitations of this study are that it is a broad cross-sectional survey conducted by questionnaire and neither immunological function nor viral isolation was done to discover immunological changes in early childhood. In addition, it was a retrospective survey based on the caregivers' memories, which may have inevitable recall bias.

In conclusion, early use of antipyretics and infection were risk factors for physician-diagnosed asthma in preschool children. For children of preschool age who attend a kindergarten and start to experience chronic cough for more than three weeks, it is important to take a detailed family history of atopy and personal medication history in the first year of life to evaluate the possibility of asthma and provide early intervention for preschool children.

Acknowledgements

1. The study was funded by grants CMRPG 260301 and CMRPG 260311 from the Chang Gung Memorial Hospital, Taiwan.
2. We would like to thank Mr. S-C Hsieh in the Department of Education, Keelung City government, for his help with the questionnaire distribution and collection.

Declaration of interest:

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

References

1. Yan DC, Ou LS, Tsai TL, Wu WF, Huang JL. Prevalence and severity of symptoms of asthma, rhinitis, and eczema in 13- to 14-year-old children in Taipei, Taiwan. Ann Allergy Asthma Immunology. 2005;95:579-85.
2. Yeh KW, Fang W, Huang JL. Increasing the hospitalization of asthma in children not in adults - from a national survey in Taiwan 1996-2002. Pediatr Allergy Immunol. 2008;19:13-9.
3. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, 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.
4. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. J Allergy Clin Immunol. 2003;111:661-75.
5. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and Wheezing in the First Six Years of Life. New Engl J Med. 1995;332:133-138.
6. Spycher BD, Silverman M, Brooke AM, Minder CE, Kuehni CE. Distinguishing phenotypes of childhood wheeze and cough using latent class analysis. Eur Respir J. 2008;31:974-81.
7. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. Allergy. 2008;63:5-34.

8. Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger. [Global Initiative for Asthma (GINA) 2009. Available from: http://www.ginasthma.org.]2009.
9. Strachan DP. Hay fever, Hygiene, and household size. BMJ 1989;299:1259-60.
10. Schaub B, Liu J, Höppler S, Schleich I, Huehn J, Olek S, et al. Maternal farm exposure modulates neonatal immune mechanisms through regulatory T cells. J Allergy Clin Immunol. 2009;123:774-82.
11. Ege MJ, Bieli C, Frei R, van Strien RT, Riedler J, Ublagger E, et al. Prenatal farm exposure is related to the expression of receptors of the innate immunity and to atopic sensitization in school-age children. J Allergy Clin Immunol. 2006;117:817-823.
12. Braun-Fahrländer C, Riedler J, Herz U, Eder W, Waser M, Grize L, et al. Environmental Exposure to Endotoxin and Its Relation to Asthma in School-Age Children. New Engl J Med. 2002;347:869-77.
13. Karmaus W, Botezan C. Does a higher number of siblings protect against the development of allergy and asthma? A review. J Epidemiol Community Health. 2002;56:209-17.
14. Ohfuji S, Miyake Y, Arakawa M, Tanaka K, Sasaki S. Sibship size and prevalence of allergic disorders in Japan: The Ryukyus Child Health Study. Pediatr Allergy Immunol. 2009;20:377-84.
15. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, Day-Care Attendance, and the Risk of Asthma and Wheezing during Childhood. New Engl JMed. 2000;343:538-43.
16. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Predictors for wheezing phenotypes in the first decade of life. Respirology. 2008;13:537-45.
17. Oldfield K, Siebers R, Crane J. Endotoxin and indoor allergen levels in kindergartens and daycare centres in Wellington, New Zealand. N Z Med J. 2007;120:U2400.
18. Murray CS, Poletti G, Kebadze T, Morris J, Woodcock A, Johnston SL, et al. Study of modifiable risk factors for asthma exacerbations: virus infection and allergen exposure increase the risk of asthma hospital admissions in children. Thorax. 2006;61:376-82.
19. Johnston NW, Johnston SL, Duncan JM, Greene JM, Kebadze T, Keith PK, et al. The September epidemic of asthma exacerbations in children: A search for etiology. J Allergy Clinical Immunol. 2005;115:132-8.
20. Lee JT, Chang LY, Wang LC, Kao CL, Shao PL, Lu CY, et al. Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001-2005 -seasonality, clinical characteristics, and disease burden. J Microbiol Immunol Infect. 2007;40:293-301.
21. Zöllner IK, Weiland SK, Piechotowski I, Gabrio T, von Mutius E, Link B, et al. No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992-2001. Thorax. 2005;60:545-8.
22. García-Marcos L, Quirós AB, Hernández GG, Guillén-Grima F, Díaz CG, Ureña IC, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain. Allergy. 2004;59:1301-7.
23. Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P, Valverde-Molina J. Is the Effect of Prenatal Paracetamol Exposure on Wheezing in Preschool Children Modified by Asthma in the Mother? Int Arch AllergyImmunol. 2009;149:33-7.
24. Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. Lancet. 2008;372:1039-48.
25. Elliott L, Henderson J, Northstone K, Chiu GY, Dunson D, London SJ. Prospective study of breast-feeding in relation to wheeze, atopy, and bronchial hyperresponsiveness in the Avon Longitudinal Study of Parents and Children (ALSPAC). J Allergy Clin Immunol 2008;122:49-54.
26. Morass B, Kiechl-Kohlendorfer U, Horak E. The impact of early lifestyle factors on wheezing and asthma in Austrian preschool children. Acta Paediatr. 2008;97:337-41.
27. Aït-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy. 2009;64:123-48.
28. Fok AO, Wong GW. What have we learnt from ISAAC phase III in the Asia-Pacific rim? Curr Opin Allergy Clin Immunol. 2009;9:116-22