Original Paper

International Archives of Allergy and Immunology

Int Arch Allergy Immunol 2007;142:79–85
DOI: 10.1159/000096031

Received: February 2, 2006
Accepted after revision: June 1, 2006
Published online: October 3, 2006

The Prevalence of Atopy in Asthmatic Children Correlates Strictly with the Prevalence of Atopy among Nonasthmatic Children

R. Ronchetti[a] Z. Rennerova[b] M. Barreto[a] M.P. Villa[a]

[a]Department of Pediatrics, Second School of Medicine, University La Sapienza, Rome, Italy;
[b]Srobar's Institute for Respiratory Diseases and Tuberculosis for Children, Dolný Smokovec, Vysoké Tatry, Slovakia

Key Words
Asthmatic children · Atopy · Epidemiology

Abstract
Background: Because asthma preferentially burdens persons with atopy, atopy is simplistically considered a primary 'cause' of asthma. Yet at the population level, the percentage of asthma cases 'attributable' to atopy ranges from less than 10% to more than 60%. Seeking to understand the rationale for the variability of atopy-attributable cases of asthma, we systematically reviewed the results of our own previous epidemiological studies and several studies conducted by others in children. ***Methods:*** From each of the 37 random pediatric populations selected by a Medline search combining the key words 'IgE or skin tests or hypersensitivity, immediate' with 'epidemiological studies, cross-sectional, case-control, prevalence, longitudinal, epidemiology of asthma' (12 from our previous pediatric surveys and a further 25 reported from 19 studies in children), we extracted the population prevalence of asthma and atopy among asthmatic subjects and among the nonasthmatic part of the population. ***Results:*** No correlation was found between the prevalence of asthma (range 1.8–44.1%) and atopy (range 5.8–63.9%) in these 37 populations of children ($r = 0.052$, $p = 0.761$). Nevertheless, the prevalence of atopy among asthmatics strictly correlated with the prevalence of atopy in nonasthmatics ($r = 0.900$, $p < 0.001$, slope 1.364). ***Conclusion:*** The prevalence of asthma and atopy varies worldwide and at various time points and independently undergoes the influence of powerful environmental factors. The almost perfect correlation we found between atopy in asthmatics and atopy in the nonasthmatic part of the childhood population shows that the prevalence of atopy in asthma depends on environmental factors that simultaneously induce atopy in asthmatic and nonasthmatic subjects.

Introduction

Epidemiological studies regularly disclose a strong association between asthma and atopy. In both adults and children, the odds ratio (OR) for asthmatic individuals being atopic varies between 2 and 7 [1, 2]. The standard way of measuring the excess of atopy among asthmatics compared with the rest of the population is to calculate the 'population attributable risk'. Despite being a statistical parameter, the term 'population attributable risk' is frequently given its literal meaning, namely that 'atopy is a risk for asthma prevalence in the population'. The widely accepted pathogenetic theory is that in predisposed subjects, allergenic exposure causes atopic sensitization (overproduction of specific IgE), and when sensitized subjects repeatedly experience exposure, the clinical symptoms of asthma develop [1]. According to this view, a variable (high) proportion of asthma cases are considered 'atopic diseases' (caused by atopy), and atopy is considered a primary cause of asthma [3–6], even in subjects with negative allergen skin prick test (ASPT) responses

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1018–2438/07/1421–0079$23.50/0

Accessible online at:
www.karger.com/iaa

Correspondence to: Prof. Roberto Ronchetti
Clinica Pediatrica, Ospedale Sant' Andrea
Via Grottarossa 1035/1039, IT–00189 Rome (Italy)
Tel. +39 06 3377 5856, Fax +39 06 3377 5001
E-Mail roberto.ronchetti@ospedalesantandrea.it

[4, 7, 8]. These beliefs are supported by the fact that the presence or absence of atopy is associated with disease phenotypes that differ immunologically and clinically (extrinsic vs. intrinsic asthma) [9–12].

Conversely, across different population studies, the proportion of cases attributable to atopy varies widely ranging from less than 10% to more than 60% of the reported cases of asthma [1, 2]. Moreover, several studies designed to measure asthma and atopy in the same population at different times found the variations in the prevalence of asthma and atopy unrelated: significant increases in asthma were associated with unchanged atopy [13, 14] and vice versa [15]. Therefore, the links between asthma and atopy and their worldwide epidemiological variability remain unexplained.

To clarify and interpret the relationship between asthma and atopy, we designed a systematic review addressing the findings from our previous surveys, single-center studies [16–22] and results of similar epidemiological studies available in the literature.

Material and Methods

Between 1983 and 2003, our group conducted 12 cross-sectional studies addressing cohorts of about 150–200 unselected schoolchildren aged 9–10 years (all fourth-grade pupils in the elementary schools of semirural villages) from 4 countries. The parents answered questions from a standardized administered questionnaire concerning respiratory and allergic illnesses, and all the children underwent an ASPT for common environmental allergens.

Six of these studies were conducted in central Italy, north of Rome (Ronciglione 1983, 1992, 1998, 2001 and 2003, and Guardea 2001), 3 in Poland (Starachowice 1998 and 2001, Legnica 2001), 2 in Libya (Samno and Al-Azyzia 2001) and 1 in Slovakia (Poprad 2003). These 12 studies included a cumulative number of 2,005 subjects. In all studies, the questionnaire definition of asthma was an affirmative answer to the question 'Has your child ever had asthma (wheezing or whistling attacks noted by others)?'. Current asthma in asthmatics was defined as an affirmative answer to the question 'Has your child had wheezing or whistling in the chest in the past 12 months?'. ASPTs were performed using Pepy's method [23] in Ronciglione 1983 and1992, or the procedure suggested in the International Study of Asthma and Allergy in Children (ISAAC, Phase 2) [24] in all the other studies; in Ronciglione 1998, the same group of children underwent both procedures. The results of these studies (except those in Poprad and Ronciglione 2003) have been reported in several publications [16–22] (table 1, No. 1–12).

To compare our data with reported data, we chose the papers selected by Pearce et al. [1], using the same criteria followed by these investigators (Medline search, English language, key words 'IgE or skin tests or hypersensitivity, immediate', combined with 'epidemiological studies, cross-sectional, case-control, prevalence, longitudinal, epidemiology of asthma'). We searched the literature for studies conducted in children (age range 5–18 years) from 1980 onwards in unselected populations and reported data on the prevalence of 'asthma ever' or 'current asthma' and atopy in the asthmatic and nonasthmatic part of the population. Apart from the 8 papers which Pearce et al. [1] reviewed in 1999 [7, 25–31], we studied a further 11 papers [9, 11, 32–40] not reviewed by Pearce et al. [1], even though 2 of them [32, 33] had already been published when these authors did their review.

Unlike our 12 studies, which always rigorously followed the same protocol, these 19 papers describe 25 populations of children (table 1, No. 13–37) that differed in many ways: the number of studied subjects (range 172–27,275), race (including Europeans, Americans, Chinese, Malaysians, Australians and Andean-Indians), method of selection (national surveys, local transversal studies and cohorts), age (range 5–18 years), definition of asthma (including current, 'ever', doctor diagnosed, and history of wheezing), technique used for ASPTs (immunoreactivity set at 2 or 3 mm, or according to a score, or based on erythema alone) and the number of tested allergens (range 4–16).

Statistical Methods

Atopy prevalence in both asthmatic and nonasthmatic persons was found to be normally distributed (Kolmogorov-Smirnoff goodness of fit test). Pearson's correlation coefficient (r) was used to determine the relationship between the prevalence of atopy and asthma, and between the prevalence of atopy in asthmatic and nonasthmatic subjects. Linear regression analysis was used to assess the slope of the prevalence of atopy in asthma versus atopy in nonasthmatic subjects: these slopes were compared by assessing their mean difference and 95% confidence intervals (CI) [41]. Data were analyzed with the statistical software package SPSS 9.0 for Windows. Two-tailed p values <0.05 were considered statistically significant.

Results

In the 37 child populations that met the criteria for our systematic review, the prevalence of asthma and atopy varied widely (range 1.8–44.1 and 5.8–63.9%; table 1). The difference in the prevalence of atopy between the asthmatic and nonasthmatic part of each population ranged from –7% (Samno, Libya) to 36.5% (Östersund, Sweden). The 37 populations studied came from 5 continents (but only 1 from South America and only 2 from Africa) and covered a time span of more than 30 years (1971–2005).

No correlation was found between the prevalence of asthma and the prevalence of atopy either in the 37 cohorts of children overall ($r = 0.052$, $p = 0.761$; fig. 1), by separately analyzing our 12 unselected children populations ($r = 0.450$, $p = 0.142$) (table 1, No. 1–12) or the 25 children populations drawn from the literature ($r = 0.080$, $p = 0.704$) (table 1, No. 13–37).

Table 1. Population-based studies reporting the prevalence rates of asthma and atopy in asthmatic and nonasthmatic persons

Setting			Reference	Asthma %	Atopy %	Atopy in subjects with asthma, %	Atopy in subjects without asthma, %	Number of children
1	Italy	Ronciglione (1983)	16 (1988)	13.5	15.9	39.1	12.2	172
2	Italy	Ronciglione (1987)	17 (1990)	14.7	26.3	39.1	24.1	142
3	Italy	Ronciglione (1998)	18 (1992) 19 (2003)	14.6	25.3	41.4	22.5	346
4	Poland	Starachowice (1998)	20 (2003)	21.0	16.7	31.0	12.8	138
5	Italy	Ronciglione (2001)	21–22 (2005)	19.9	27.7	48.5	22.6	166
6	Italy	Guardea (2001)	21–22 (2005)	26.7	31.7	51.9	24.3	101
7	Poland	Starachowice (2001)	21–22 (2005)	28.6	17.9	21.9	16.3	112
8	Poland	Legnica (2001)	21–22 (2005)	27.3	18.0	29.3	13.8	150
9	Libya	Al Azizia (2001)	21–22 (2005)	9.1	5.8	0	6.4	154
10	Libya	Samno (2001)	21–22 (2005)	4.4	6.7	0	7.0	180
11	Italy	Ronciglione (2003)		18.9	31.7	38.7	30.1	148
12	Slovakia	Poprad (2003)		36.8	21.9	27	18.9	196
13	USA	National study (1976)	25 (1988)	6.7	22.6	45.0	21.0	27,275
14	USA	Tucson (1971)	7 (1989)	8.2	46.8	79.0	44.0	2,657
15	New Zealand	Dunedin (1985)	26 (1989)	44.1	44.6	57.0	35.0	737
16	Sweden	Ulmea (1987)	27 (1994)	11.0	42.7	66.0	40.0	1,112
17	Hong Kong	Hong Kong (1992)	28 (1994)	12.1	57.7	80.7	54.6	1,062
18	Malaysia	Kota Kinabalu (1992)	28 (1994)	6.5	63.9	90.5	62.0	409
19	China	San Bu (1992)	28 (1994)	1.8	49.0	83.3	48.3	737
20	Germany	Munich (1989)	29 (1994)	5.4	38.7	69.0	37.0	5,030
21	Germany	Leipzig, Halle (1991)	29 (1994)	3.8	18.8	40.0	18.0	2,623
22	USA	Tucson (1980)	30 (1995)	29.7	41.3	56.0	35.0	826
23	UK	Leicester (1995)	31 (1995)	19.7	31.4	54.0	26.0	482
24	Estonia	Tallinn, Tartu (1992)	32 (1995)	7.7	11.1	28.7	9.6	1,580
25	Finland	Kuopio (1995)	33 (1996)	17.4	51.4	77.0	46.0	244
26	Sweden	Norrbotten (1996)	9 (1999)	8.0	20.6	46.6	18.1	3,431
27	Estonia	Tallinn (1996)	34 (2001)	24.0	13.3	25.9	9.3	979
28	Sweden	Linköping (1996)	34 (2001)	24.2	24.6	50.0	16.5	911
29	Sweden	Östersund (1996)	34 (2001)	33.3	33.7	58.0	21.5	1,197
30	Albania	Tirana (2001)	35 (2001)	4.8	14.9	29.5	14.2	1,057
31	UK	West Sussex (2001)	35 (2001)	16.6	17.8	40.0	13.4	1,050
32	Peru	Lima (1997)	36 (2001)	20.5	23.9	28.4	22.7	793
33	Australia	Perth (1989)	37 (2002)	18.5	41.5	55.5	38.3	2,602
34	Australia	Canberra (1999)	11 (2002)	34.3	45.6	58.0	39.0	758
35	UK	Ashford (1990)	38 (2004)	17.4	16.7	40.6	11.6	552
36	USA	Detroit (1987)	39 (2004)	7.0	33.6	66.0	31.2	428
37	Australia	Perth (1995)	40 (2005)	15.1	55.2	84.6	50.0	172

Studies 1–12 were conducted by the author's group; studies 11 and 12 are not yet published.

Conversely, a strict correlation was found between the prevalence of atopy in asthmatic subjects and the prevalence of atopy among the remaining nonasthmatic part of the population ($r = 0.900$, $p < 0.001$, slope 1.364; fig. 2). The correlation remained highly significant also when we analyzed the data for our 12 unselected children populations ($r = 0.791$, $p = 0.002$) and the 25 children populations drawn from the literature ($r = 0.926$, $p < 0.001$).

The 12 studies conducted by our group yielded data for comparing the regression lines for boys and girls and showed no difference between sexes. Similarly, when in these 12 studies the variable 'current asthma' was used to define asthmatic subjects or serum-specific IgE was >0.35 kU/l for at least one allergen to define atopy, the relationship between atopy in asthmatics and atopy in nonasthmatics remained unchanged.

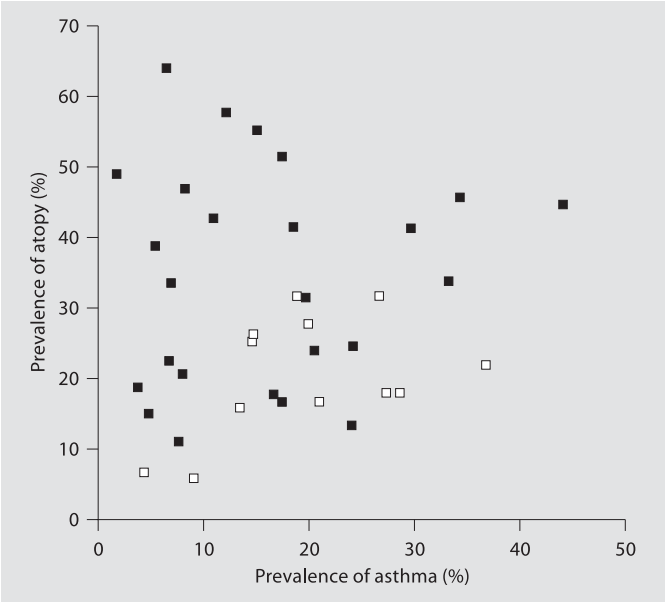

Fig. 1. Absence of correlation between the population prevalence of asthma (affirmative answer to the question: Have you ever had asthma?) and atopy (at least 1 positive ASPT response) in the 37 studies reviewed ($p = 0.761$, $r = 0.052$). □ = Populations studied by the author's group; ■ = populations studied by others.

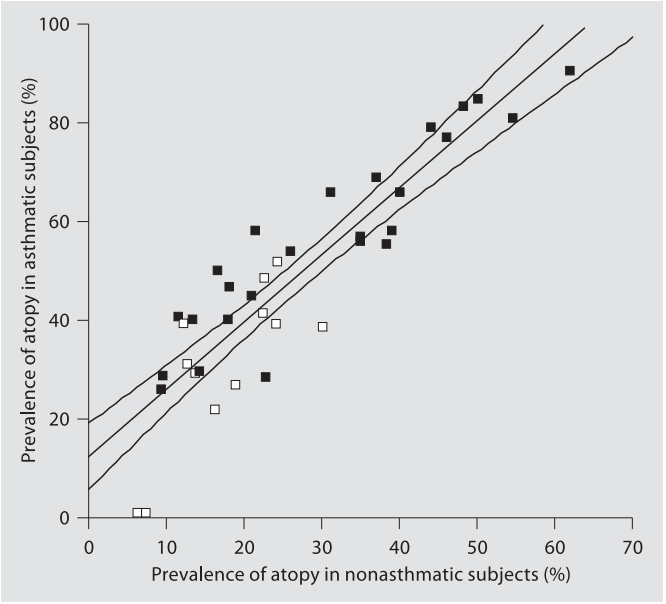

Fig. 2. Linear correlation between the prevalence of atopic asthma (asthmatic subjects with positive prick tests) and the prevalence of atopy in the rest of the nonasthmatic population in the 37 studies reviewed ($y = 1.364x + 12.145$; $p < 0.001$, $r = 0.900$). □ = Populations studied by the author's group; ■ = populations studied by others.

Discussion

In this international analysis encompassing 37 populations of children, the prevalence rates for asthma and atopy varied 10–20 fold. In these widely differing study samples, two findings emerged as statistically proven: (1) the lack of a correlation between the prevalence of asthma and the prevalence of atopy (high asthma prevalence rates often coincide with low sensitization rates and vice versa), and (2) a strict, robust correlation between the prevalence of atopy in asthmatic subjects and the prevalence of atopy among the nonasthmatic part of the population ($r = 0.900$, $p < 0.001$; fig. 2). In the 12 populations studied by our group, this relationship was unaffected by sex or how asthma (history of asthma or current asthma) or atopy (positive ASPT responses or serum-specific IgE levels) was defined.

The lack of a relationship between the prevalence of asthma and atopy at a population level implies that certain environmental factors may separately influence (increase) the prevalence of asthma or atopy. An independent environmental origin of asthma and atopy receives strong support from epidemiological data showing that even though specific allergen exposure causes specific IgE production (sensitization) [3, 4, 42], trials of extensive allergen avoidance generally fail to reduce the incidence of asthma [43]. Hence, at the epidemiological level, the causes of asthma and atopy apparently differ.

Yet at the individual level, everyday clinical practice regularly shows that asthma is associated with atopy. Probably because asthma and atopy have some common genetic features [44], many asthmatic individuals are predisposed to the development of atopy. Also at the population level, excluding the singular findings in African rural populations [45, 46] (as well as our two populations from Libya), within each single population, the prevalence of atopy in asthmatics compared with nonasthmatic subjects invariably yields high ORs (in most studies, between 2 and 7) [1, 2].

A plausible reason why the literature fails to keep these two statements conceptually and practically distinct is that many environmental conditions influence the prevalence rates of both asthma and atopic sensitization in the same direction. For example, exposure during the first year of life to tobacco smoke or high concentrations of house dust increases asthma and atopy [42, 47]; vice ver-

sa, 'farming' (i.e. regular contact with livestock during pregnancy or the first year of life) [48, 49] or early attendance at day-care centers [50, 51] significantly protects from both asthma and atopy.

To better understand the relationship between atopic sensitization and asthma, we think it useful to cite, as an example, the results of the German Multicenter Allergy Study [42, 52] which followed more than 1,100 children from birth to 7 years and found that early and persistent allergic sensitization was strongly associated with asthma (OR = 15) only in that portion of the children with a family history of asthma or atopy. Hence, sensitization alone does not cause asthma. Rather, the underlying genetic factors related to the positive family history appear responsible for the development of asthma in the presence of atopy [53]. If this genetic predisposition is absent, evidence linking allergen exposure to an increased incidence of asthma is weak, and allergen sensitization per se is probably not a primary cause of asthma [4, 54].

The principal finding from our papers – the strict correlation of the prevalence of atopy in asthmatics and the prevalence of atopy in the nonasthmatic part of the population (fig. 2) – should be viewed in the context of an allergic epidemic taking place all over the world at different speeds and starting from different levels in the various geographical settings. Hence, the atopic phenotype has steadily become more common over time [19, 55–57]. In the surroundings of Rome, we ourselves previously documented this increase (and the parallel increase in immediate skin reactivity to histamine) in 2 of the 12 cohorts of unselected children reported here (+65% over 16 years) [19]. The mainstream explanatory theories affirm that human immune function, including the ability to produce measurable amounts of specific IgE, is programmed early in life by external factors and link increasing atopy to altered hygienic conditions and the lacking pressure of microbial stimulation [58]. This theory, based on the Th1/Th2 imbalance paradigm, might have oversimplified the far more complex and largely unknown interaction between environmental factors that in past decades caused a substantial increase in the prevalence of atopy [59].

Simultaneous to this worldwide increase in atopy prevalence, the literature documented a parallel increase in the prevalence of asthma taking place in the past decades in several geographical settings around the world [60]. We ourselves documented a significant increase in the prevalence of asthma in children in the city of Rome (approximately +150% over about 20 years) [61].

The question arises whether these two epidemics concerning atopy and asthma are in some way causally linked, for example whether the increase in atopy is the most important causative factor for the progressively more common asthmatic condition. The two main findings in the present review suggest that it is not.

First, at the population level, no correlation exists between the prevalence of asthma and the prevalence of atopy (fig. 1), with some populations having a high prevalence of atopy and a low prevalence of asthma and vice versa. If the two conditions were causally linked, one would expect that if environmental factors cause a certain increase in the prevalence of atopy, the prevalence of asthma should also increase.

Second, the strong correlation we found between atopy in asthmatics and atopy in the nonasthmatic part of the population implies that when environmental factors cause an increase in the general prevalence of atopy, the new cases of atopic sensitization do not preferentially occur among asthmatics but they tend to distribute evenly among the population independent of the presence of asthma. Nevertheless, the conclusion that asthmatic persons share the effects of environmental causes inducing atopic sensitization with the rest of the population is probably too simple. Indeed, the positive slope of the linear regression line shown in figure 2 (1.364) shows that asthmatics are more sensitive to these environmental factors and are therefore generally more atopic than the rest of the population. In most of the populations addressed by the epidemiological studies reported in this paper, this excess of atopy in asthmatics seems relatively stable, i.e. about 20% compared with the rest of the population.

Yet one cannot assume tout court that this excess of atopy among asthmatic persons is causative of asthma. Because the data from the 37 studies reviewed indicate a higher prevalence of atopy in subjects who were already asthmatic, asthma could have been initially caused by atopy (primary causation), simply aggravated by coexisting atopy (secondary causation) or be independent from atopy, according to the genetic predisposition, timing and intensity of specific exposures.

An interesting finding was that in our two semirural populations of Libyan children who had a low level of atopic sensitization, in contrast to all other reported cohorts, atopy, far from being a risk factor, was actually 'protective' for asthma. This observation confirms similar findings in African countries, one with a low level of atopy (in a rural but not in an urban population in Ethiopia) [45], and the other with a high level of atopy [46]. Therefore, it is suggested that when the prevalence of asthma and/or atopy is very low, the relationship between these two conditions undergoes the influence of other

factors (for example parasite infections) [62], which are, on the other hand, obscured by more powerful factors in countries with more intense allergen exposure.

We consider it unlikely that our findings in this paper are flawed by artifacts. In this systematic review, together with the results of our previous studies, we used the papers selected for the well-known review by Pearce et al. [1] and a further 11 papers selected with the same criteria, all published in first-rank journals. There was no selection bias because these 11 papers represent the complete list of papers found using the reported search criteria.

Because a lack of homogeneity in the experimental data can only reduce, not increase, the strength of a statistical correlation, we believe that the various environments, geographical settings and socioeconomic conditions represented among the populations included in this systematic review and the large number of populations studied practically ensure that confounders (including socioeconomic conditions, peculiar quality of geographical settings, and climate) have no significant influence on the strength of the correlation obtained. Further, the differences in the number of persons included in each studied population and in the definition of asthma used by the various authors do not seem to interfere with our robust statistical results. This conclusion is reinforced by the fact that when we restricted the analysis to the set of data from the 12 studies conducted by our group, we found that the criteria used to define atopy (positive prick test responses or increased serum-specific IgE) or asthma ('ever' or 'current') left the strength of the correlation unchanged.

In conclusion, the data from this systematic review show that the salient point in interpreting the relationship between asthma and atopy is that the prevalence of atopy in asthmatic children correlates strictly with the prevalence of atopy among nonasthmatic children. This new concept possibly implies that as well as focusing on measures to prevent atopy in individuals, we should seek and try to reduce the causes of the growing prevalence of atopy in populations.

References

1 Pearce N, Pekkanen J, Beasley R: How much asthma is really attributable to atopy? Thorax 1999;54:268–272.

2 Sunyer J, Jarvis D, Pekkanen J, Chinn S, Janson C, Leynaert B, Luczynska C, Garcia-Esteban R, Burney P, Anto JM: Geographic variations in the effect of atopy on asthma in the European Community Respiratory Health Study. J Allergy Clin Immunol 2004; 114:1033–1039.

3 Sporik R, Ingram JM, Price W, Sussman JH, Honsinger RW, Platts-Mills TA: Association of asthma with serum IgE and skin test reactivity to allergens among children living at high altitude: tickling the dragon's breath. Am J Respir Crit Care Med 1995;151:1388–1392.

4 Peat JK, Tovey E, Toelle BG, Haby MM, Gray EJ, Mahmic A, Woolcock AJ: House dust mite allergens. A major risk factor for childhood asthma in Australia. Am J Respir Crit Care Med 1996;153:141–146.

5 Platts-Mills TA, Sporik RB, Chapman MD, Heymann PW: The role of domestic allergens; in Chadwick D, Cardew G (eds): The Rising Trends in Asthma. Ciba Foundation Symposium 206. Chichester, Wiley, 1997, pp 173–189.

6 Custovic A, Smith A, Woodcock A, Chapman MD: Indoor allergens are a primary cause of asthma. Eur Respir Rev 1998;53:155–158.

7 Burrows B, Martinez FD, Halonen M, Barbee RA, Cline MG: Association of asthma with serum IgE levels and skin-test reactivity to allergens. N Engl J Med 1989;320:271–277.

8 Sunyer J, Antò JM, Castellsagué J, Soriano JB, Roca J: Total serum IgE is associated with asthma independently of specific IgE levels. Eur Respir J 1996;9:1880–1884.

9 Rönmark E, Jönsson E, Platts-Mills T, Lundbäck B: Different pattern of risk factors for atopic and nonatopic asthma among children – report from the Obstructive Lung Disease in Northern Sweden Study. Allergy 1999;54:926–935.

10 Romanet-Manent S, Charpin D, Magnan A, Lanteaume A, Vervloet D, EGEA Cooperative Group: Allergic vs nonallergic asthma: what makes the difference? Allergy 2002;57: 607–613.

11 Ponsonby AL, Gatenby P, Glasgow N, Mullins R, McDonald T, Hurwitz M: Which clinical subgroups within the spectrum of child asthma are attributable to atopy? Chest 2002; 121:135–142.

12 Wright AL: The epidemiology of the atopic child: who is at risk for what? J Allergy Clin Immunol 2004;113:(suppl 1):S2–S7.

13 Peat JK, Haby M, Spijker J, Berry G, Woolcock AJ: Prevalence of asthma in adults in Busselton, Western Australia. BMJ 1992; 305:1326–1329.

14 Peat JK, Van Den Berg RH, Green WF, Mellis CM, Leeder SR, Wolcock AJ: Changing prevalence of asthma in Australian children. BMJ 1994;308:1591–1596.

15 Von Mutius E, Weiland SK, Fritzsch C, Duhme H, Keil U: Increasing prevalence of hay fever and atopy among children in Leipzig, East Germany. Lancet 1998;351:862–866.

16 Martinez FD, Antognoni G, Macrì F, Bonci E, Midolla F, De Castro G, Ronchetti R: Parental smoking enhances bronchial responsiveness in nine year old children. Am Respir Dis 1988;138:518–523.

17 Ronchetti R, Macri F, Ciofetta G, Indinnimeo L, Cutrera R, Bonci E, Antognoni G, Martinez FD: Increased serum IgE and increased prevalence of eosinophilia in 9-year-old children of smoking parents. J Allergy Clin Immunol 1990;86:400–407.

18 Ronchetti R, Bonci E, Cutrera R, De Castro G, Indinnimeo L, Midolla F, Tacredi G, Martinez FD: Enhanced allergic sensitization related to parental smoking. Arch Dis Child 1992;67:496–500.

19 Ronchetti R, Villa MP, Pagani J, Martella S, Guglielmi F, Paggi B, Bohmerova Z, Falasca C, Barreto M: Immediate skin reactivity to histamine and to allergens in cohorts of 9-year-old schoolchildren studied 16 years apart. Clin Exp Allergy 2003;33:1232–1237.

20 Ronchetti R, Haluszka J, Martella S, Falasca C, Guglielmi F, Parmiani S, Zakrzewski J, Bednarek AL, Barreto M, Villa MP: Skin reactivity to histamine and to allergens in unselected 9-year-old children living in Poland and Italy. Pediatr Allergy Immunol 2003;14:201–206.

21 Ronchetti R, Villa MP, Bohmerova Z, Martella S, Falasco C, Barreto M, Lesiak-Bednarek A, Zakrzewski J, Bednarek AL, Barreto M, Villa MP: Skin reactivity to histamine and codeine in unselected 9-year-old children from Italy, Poland and Libya. Int Arch Allergy Immunol 2004;135:136–142.

22 Ronchetti R, Villa MP, Rennerova Z, Haluszka J, Dawi EB, Di Felice G, Al-Bousafy A, Zakrzewski J, Barletta B, Barreto M: Allergen skin weal/radioallergosorbent test relationship in childhood populations that differ in histamine skin reactivity: a multi-national survey. Clin Exp Allergy 2005;35:70–74.
23 Pepys J: Skin testing. Br J Hosp Med 1975;14:412–417.
24 ISAAC-Phase II Modules. Institute of Epidemiology and Social Medicine, University of Munster, Germany, May 1998.
25 Gergen PJ, Mullally DI, Evans R 3rd: National survey of prevalence of asthma among children in the United States, 1976 to 1980. Pediatrics 1988;81:1–7.
26 Sears MR, Herbison GP, Holdaway MD, Hewitt CJ, Flannery EM, Silva PA: The relative risks of sensitivity to grass pollen, house dust mite and cat dander in the development of childhood asthma. Clin Exp Allergy 1989;19:419–424.
27 Norrman E, Rosenhall L, Nyström L, Jönsson E, Stjernberg N: Prevalence of positive skin prick tests, allergic asthma and rhinoconjunctivitis in teenagers in northern Sweden. Allergy 1994;49:808–815.
28 Leung R, Ho P: Asthma, allergy, and atopy in three south-east Asian populations. Thorax 1994;49:1205–1210.
29 Von Mutius E, Martinez FD, Fritzsch C, Nicolai T, Roell G, Thiemann HH: Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994;149:358–364.
30 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ: Asthma and wheezing in the first six years of life. N Engl J Med 1995;332:133–138.
31 Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H: The natural history of respiratory symptoms in preschool children. Am J Respir Crit Care Med 1995;152:1872–1878.
32 Riikjärv MA, Julge K, Vasar M, Bråbäck L, Knutsson K, Björkstén B: The prevalence of atopic sensitization and respiratory symptoms among Estonian schoolchildren. Clin Exp Allergy 1995;25:1198–1204.
33 Remes ST, Korppi M: Asthma and atopy in schoolchildren in a defined population. Acta Paediatr 1996;85:965–970.
34 Annus T, Björkstén B, Mai XM, Nilsson L, Riikjarv MA, Sandin A, Braback L: Wheezing in relation to atopy and environmental factors in Estonian and Swedish schoolchildren. Clin Exp Allergy 2001;31:1846–1853.
35 Priftanji A, Strachan D, Burr M, Sinamati J, Shkurti A, Grabocka E, Kaur B, Fitzpatrick S: Asthma and allergy in Albania and the UK. Lancet 2001;358:1426–1427.
36 Penny ME, Murad S, Madrid SS, Herrera TS, Pineiro A, Caceres DE, Lanata CF: Respiratory symptoms, asthma, exercise test, spirometry and atopy in schoolchildren from a Lima shanty town. Thorax 2001;56:607–612.
37 Oddy WH, de Klerk NH, Sly PD, Holt PG: The effects of respiratory infections, atopy, and breastfeeding on childhood asthma. Eur Respir J 2002;19:899–905.
38 Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, Newman Taylor AJ: Early allergen exposure, skin prick responses, and atopic wheeze at age 5 in English children: a cohort study. Thorax 2004;59:855–861.
39 Johnson CC, Ownby DR, Havstad SL, Peterson EL: Family history, dust mite exposure in early childhood, and risk for pediatric atopy and asthma. J Allergy Clin Immunol 2004;114:105–110.
40 Heaton T, Rowe J, Turner S, Aalberse RC, de Clerk N, Suriyaarachchi D, Serralha M, Holt BJ, Hollams E, Yerkovich S, Holt K, Sly PD, Goldblatt J, Le Souef P, Holt PG: An immunoepidemiological approach to asthma: identification of in vitro T-cell response patterns associated with different wheezing phenotypes in children. Lancet 2005;365:142–149.
41 Gardner MJ, Altman DG: Statistics with Confidence: Confidence Intervals and Statistical Guidelines, ed 1. London, British Medical Journal, 1989.
42 Illi S, von Mutius E, Lau S, Nickel R, Niggemann B, Sommerfeld C, Wahn U; Multicenter Allergy Study Group: The pattern of atopic sensitization is associated with the development of asthma in childhood. J Allergy Clin Immunol 2001;108:709–714.
43 von Mutius E: Towards prevention. Lancet 1997;350(suppl II):14–17.
44 Haagerup A, Bjerke T, Schiøtz PO, Binderup HG, Dahl R, Kruse TA: Asthma and atopy – a total genome scan for susceptibility genes. Allergy 2002:57:680–686.
45 Yemaneberhan H, Bekele Z, Venn A, Lewis S, Parry E, Britton J: Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. Lancet 1997;350:85–90.
46 Sunyer J, Torregrosa J, Anto JM, Menendez C, Acosta C, Schellenberg D, Alonso PL, Kahigwa E: The association between atopy and asthma in a semirural area of Tanzania (East Africa). Allergy 2000;55:762–766.
47 Cook DG, Strachan DP: Summary of effects of parental smoking on the respiratory health of children and implication for research. Thorax 1999;54:357–366.
48 von Ehrenstein OS, von Mutius E, Illi S, Baumann L, Böhm O, von Kries R: Reduced risk of hay fever and asthma among children of farmers. Clin Exp Allergy 2000;30:187–193.
49 Riedler J, Braun-Fahrländer C, Eder W, Schrerer M, Waser M, Maisch S, Carr D, Schierl R, Nowak D, Von Mutius E; ALEX Study Team: Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. Lancet 2001;358:1129–1133.
50 Krämer U, Heinrich J, Wjst M, Wichmann HE: Age of entry to day nursery and allergy in later childhood. Lancet 1998;353:450–454.
51 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. N Engl J Med 2000;343:538–543.
52 Wahn U, Lau S, Bergmann R, Kulig M, Forster J, Bergmann K, Bauer CP, Guggenmoos-Holzmann I: Indoor allergen exposure is a risk factor for sensitization during the first three years of life. J Allergy Clin Immunol 1997;99:763–769.
53 von Mutius E: Environmental factors influencing the development and progression of pediatric asthma. J Allergy Clin Immunol 2002;109:S525–S532.
54 Pearce N, Douwes J, Beasley R: Is allergen exposure the major primary cause of asthma? Thorax 2000;55:424–431.
55 Barbee RA, Kaltenborn W, Lebowitz MD, Burrows B: Longitudinal changes in allergen skin test reactivity in a community population sample. J Allergy Clin Immunol 1987;79:16–24.
56 Broadfielled E, McKeever TM, Scrivener S, Venn A, Lewis SA, Britton J: Increase in the prevalence of allergen skin sensitization in successive birth cohorts. J Allergy Clin Immunol 2002;109:969–974.
57 Isolauri E, Huurre A, Salminen S, Impivaara O: The allergy epidemic extends beyond the past few decades. Clin Exp Allergy 2004;34:1007–1010.
58 Yazdanbakhsh M, Kremsner PG, van Ree R: Allergy, parasites, and the hygiene hypothesis. Science 2002;351:1225–1232.
59 Sheikd A, Smeeth L, Hubbard R: There is no evidence of an adverse relationship between T_H2-mediated atopy and T_H1-mediated auroimmune disorders: lack of support for the hygiene hypothesis. J Allergy Clin Immunol 2003;111:131–135.
60 Warner JO: Worldwide variations in the prevalence of atopic symptoms: what does it all mean? Lancet 1998;351:1225–1232.
61 Ronchetti R, Villa MP, Barreto M, Rota R, Pagani J, Martella S, Falasco C, Paggi B, Guglielmi F, Ciofetta G: Is the increase in childhood asthma coming to an end? Findings from three surveys of schoolchildren in Rome, Italy. Eur Respir J 2001;17:881–886.
62 Scrivener S, Yemaneberhan H, Zebenigus M, Tilahun D, Girma S, Ali S, McElroy P, Custovic A, Woodcock A, Pritchard D, Venn A, Britton J: Independent effects of intestinal parasite infection and domestic allergen exposure on risk of wheeze in Ethiopia: a nested case-control study. Lancet 2001;358:1493–1499.