

**PRE-
VALENCE
OF
ATOPIC
DISEASE**

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During the last 20 to 30 years the prevalence of atopic disease has increased considerably, particularly in Western industrialized countries (1). Disparities similar to the impressive change over time can be found when the prevalence of allergic diseases in Western societies are compared to rates in countries with lower living standards, such as eastern Europe or the developing world.

Genetic factors alone can neither explain the increasing prevalence over time nor the large differences in prevalence between regions of similar ethnic backgrounds. It is thus evident that the development and expression of atopic diseases depend on an interaction between genetic and different environmental factors, and that the environmental factors play a major role in this process.

Although several studies have shown an increase in prevalence of atopic diseases, it has been argued that increased awareness and improved ability to diagnose atopic diseases might account for this increase, at least in part. However, population-based studies in defined geographical regions at intervals of 10 to 15 years using identical methods have shown a significant increase in the prevalence of atopic diseases in children.

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POPULATION SURVEYS IN THE SAME GEOGRAPHIC AREA AT DIFFERENT TIMES

In a review article by Beasley et al. the prevalence and etiology of asthma is discussed (2). Prevalences from studies, using the same methodology in the same community at different times, are presented in Table 1. The results clearly show an increased prevalence of asthma among populations in countries of widely differing lifestyles and ethnic groups.

TABLE 1

Changes in prevalence of asthma or asthma symptoms in children and young adults

Country	Period	Prevalence		Reference
		1st Study (%)	2nd Study (%)	
Australia	1982-1992	5.6	10.5	Peat et al (1994)
Canada	1980-1983	3.8	6.5	Infante-Rivard et al (1987)
England	1956-1975	1.8	6.3	Morrison Smith (1976)
	1966-1990	3.9	6.1	Whincup et al (1993)
Finland	1961-1986	0.1	1.8	Haahtela et al (1990)
France	1968-1982	3.3	5.4	Perdrizet et al (1987)
Hong Kong	1989-1994	4.6	7.6	Lai et al (1997)
Israel	1986-1990	7.9	9.6	Auerbach et al (1993)
Japan	1982-1992	3.3	4.6	Nishima (1993)
New Zealand	1969-1982	7.1	13.5	Mitchell (1983)
	1975-1989	7.9	13.3	Shaw et al (1990)
Norway	1981-1994	1.6	5.5	Nystad et al (1997)
Papua				
New Guinea	1973-1984	0.0	0.6	Dowse et al (1985)
Scotland	1964-1989	10.4	19.8	Ninan and Russell (1992)
Singapore	1967-1994	4.0	20.0	Lee et al (1997)
Sweden	1971-1981	1.9	2.8	Alberg (1989)
Tahiti	1979-1984	11.5	14.3	Liard et al (1988)
Taiwan	1974-1985	1.3	5.1	Hsieh and Shen (1988)
United States	1971-1976	4.8	7.6	Gergen et al (1988)
	1981-1988	3.1	4.3	Weitzman et al (1992)
Vietnam	1961-1991	2.1	7.6	Nguyen (1995)
Wales	1973-1988	4.2	9.1	Burr et al (1989)

Asthma or asthma symptom prevalence data for a country are only included if the same method was used on two occasions. Many different methods were used to define asthma or asthma symptoms in studies from the different countries; as a result, comparison of the asthma prevalence rates between countries should be avoided.

Adapted from: Beasley R et al. Prevalence and etiology of asthma. J Allergy Clin Immunol 2000;105:S466-72

A survey was conducted in South Wales among 12-year old children in 1973 and repeated in 1988 (3). The prevalence of history of asthma increased from 6% to 12%, eczema from 5% to 16% and hay fever from 9% to 15% (Table 2). The authors conclude that this increase cannot be wholly explained by a greater readiness to diagnose atopic disease.

The prevalence of atopic disease was assessed on two occasions, 1979 and 1991, in two different regions of Sweden with great climate differences, Gothenburg on the southwest coast and Kiruna in the northern inland mountains (4). School children 7, 10 and 14 years participated in a questionnaire study. The prevalence of all atopic diseases roughly doubled over the 12-year period (Table 3). On both occasions the prevalence was higher in the northern area, which suggests possible major risk factors may exist in a closed indoor climate.

The prevalence of diagnosed asthma and the prevalence of respiratory symptoms were compared in two Norwegian populations of school children aged 6 to 16 years in 1981 and 1994 (5). The association between asthma and other atopic diseases was also compared. The life prevalence of asthma increased from 3.4% in 1981 to 9.3% in 1994. The prevalence of occasional wheezing during the same inter-

TABLE 2

Prevalence of history of symptoms in two surveys

	1973 Survey All (n=818) (%)	1988 Survey All (n=965) (%)	1988-1973 Difference (%)
Asthma ever	5.5	12.0	6.5
Current asthma	4.2	9.1	5.0
Wheeze ever	17.0	22.3	5.3
Wheeze in past 12 months	9.8	15.2	5.5
Breathless wheeze ever	9.2	14.0	4.8
Wheeze without cold ever	6.6	13.8	7.2
Eczema ever	4.8	15.9	11.1
Hay fever ever	9.4	14.9	5.5

Adapted from: Burr ML et al. Changes in asthma prevalence: two surveys 15 years apart. Arch Dis Child 1989;64:1452-56

TABLE 3

Prevalence of disease present during the last year according to the questionnaires in 1979 and 1991

	Total n = 4682 (%)	Göteborg n = 4255 (%)	Kiruna n = 427 (%)
1979			
1991			
Asthma			
1979	2.48	2.33	3.98
1991	5.71	5.14	6.82
Allergic rhinitis			
1979	5.45	5.46	5.39
1991	8.08	7.80	8.61
Eczema			
1979	7.05	6.75	10.07
1991	18.28	16.33	22.13
Total (One or more)			
1979	12.75	12.36	16.63
1991	25.84	23.77	29.93

Adapted from: Åberg N et al. Increase of asthma, allergic rhinitis and eczema in Swedish schoolchildren between 1979 and 1991. *Clin Exp Allergy* 1995;25:815-19

val was 9.0% and 10.8% and attacks of wheezing 3.7% and 6.8%, respectively. Eczema increased from 9.7% to 17.1% and hay fever from 6.6% to 7.8% (Table 4). However, the association between asthma and other atopic diseases decreased during the study period. The authors conclude that the increase in diagnosed asthma and respiratory symptoms supports a true increase. The larger increase in diagnosed asthma than in wheezing suggests that the increase of asthma may partly be explained by changes in diagnostic criteria.

Asthma prevalence, respiratory symptoms and lung function were investigated in a study on young adults (20 to 35 years) in Copenhagen, Denmark 15 years apart in 1976 to 78 and 1991 to 94 (6). The prevalence of self-reported asthma increased from 1.5% in the first survey to 4.8% in the second ($p < .001$). The lung function as measured by

TABLE 4

Lifetime prevalence of asthma and prevalence of current asthma and respiratory symptoms, such as attacks of breathlessness and wheezing, eczema and hay fever in school children in 1981 and 1994, with odds ratios (ORs) comparing 1994 to 1981

	1981		1994		OR
	Sample n	Symptoms %	Sample n	Symptoms %	
Lifetime prevalence					
of asthma	1529	3.4	2179	9.3	2.9
Current asthma	1529	1.6	2179	5.5	3.3
Occasional wheezing	1611	9.0	2167	10.8	1.2
Attacks of wheezing	1636	3.7	2175	6.8	1.8
Eczema	1399	9.7	2187	17.1	1.9
Hay fever	1373	6.6	2187	7.8	1.2

Adapted from: Nystad W et al. Changing prevalence of asthma in school children: evidence for diagnostic changes in asthma in two surveys, 13 yrs apart. *Eur Respir J* 1997;10:1046-51

FEV₁ was poorer in the second survey compared to the first, a difference of 10% of predicted (related to non-asthmatics) in 1991 to 94 compared to 2.4% in 1976 to 78, which indicates an increase in the severity of asthma.

The prevalence of asthma and hay fever in Scotland was studied in two epidemiological studies, 1972 to 76 and 1996 on an adult population, 30 to 64 years of age (7). Among never smokers the prevalence of asthma and hay fever was 3.0% and 5.8% respectively in 1972 to 76 and 8.2% and 19.9% in 1996. Atopic asthma increased more than twofold in 20 years, whereas non-atopic asthma did not change.

Studies from the Asian Pacific countries also show an increasing prevalence of asthma. Two epidemiological surveys of the prevalence of asthma in school children were conducted in Taiwan in 1974 and 1985 (8). The same questionnaire was used, and children of the same age at the same school were studied in the two surveys. The prevalence of asthma increased from 1.3% in 1974 to 5.1% in 1985, which shows a tendency comparable to the increase in the Western countries.

POPULATION SURVEYS IN DIFFERENT GEOGRAPHIC AREAS

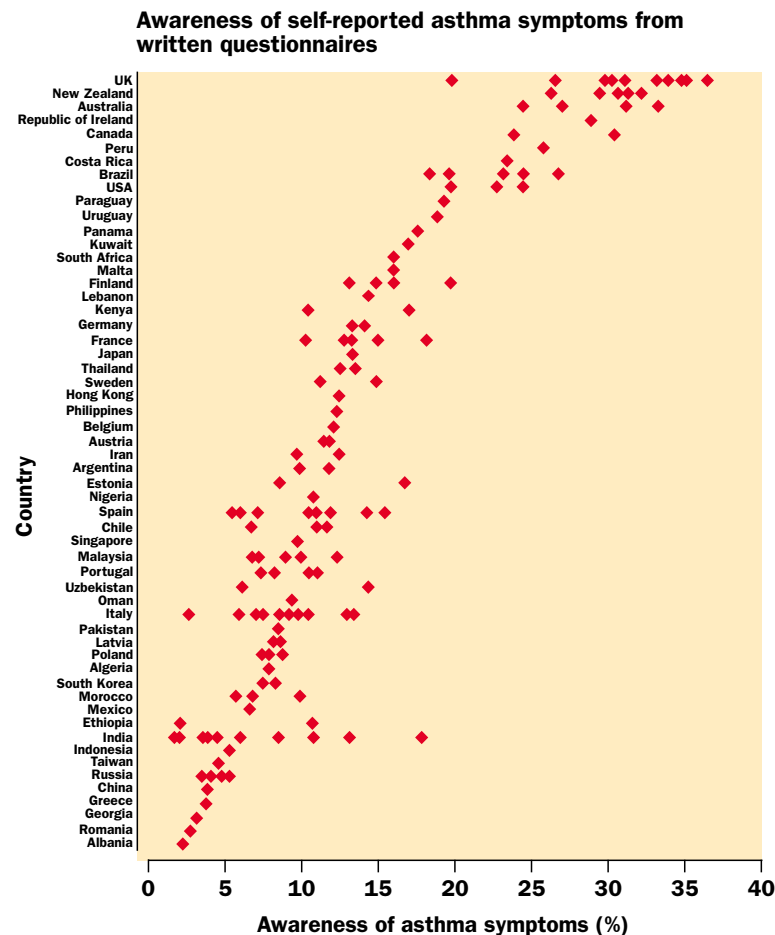
The International Study of Asthma and Allergies in Childhood (ISAAC) was designed to compare atopic disease in populations in different countries of the world. Two age groups, 6 to 7 and 13 to 14 years, were studied (9,10). The 6 to 7 year old children (257 800 subjects) were studied in 91 centers in 38 countries and the 13 to 14 year old children (463 801 subjects) in 155 collaborating centers in 56 countries. A marked variation in the prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema was observed between centers.

The awareness of asthma symptoms (13 to 14 year group) for each center by country is presented in Figure 1. The highest prevalence was about 20 times higher than in the center with the lowest prevalence, 1.6 to 36.8%. The corresponding differences for allergic rhinoconjunctivitis between centers were 1.4 to 39.7% and for atopic eczema 0.3 to 20.5%. For asthma symptoms the highest prevalence was reported from centers in UK, New Zealand, Australia and the lowest from several eastern European countries, Indonesia, Greece and China. In some countries such as India, Italy and Spain large variations were seen between centers within the same country. There are thus opportunities for investigation of possible causative factors within countries and regions.

Difficulties in the comparability of information and translation problems into 39 languages have unavoidably influenced the results. The findings may not be applicable to countries in which infectious disorders with symptoms similar to atopic symptoms may be prevalent. Furthermore, the medical service in many countries with a low prevalence of asthma is not as developed as in the Western countries and the awareness of atopic symptoms and disease is low, which may contribute to the low prevalence presented from these countries.

The hypothesis that prevalence of allergic diseases differs between western Europe and eastern Europe/Asia was investigated in some of the countries participating in the ISAAC study. A total of 79 000 children from both age groups were included (11). The calculated prevalence of wheezing among the 13 to 14 year old children was 11.2 to 19.7% in Finland and Sweden, 7.6 to 8.5% in Estonia, Latvia

FIGURE 1

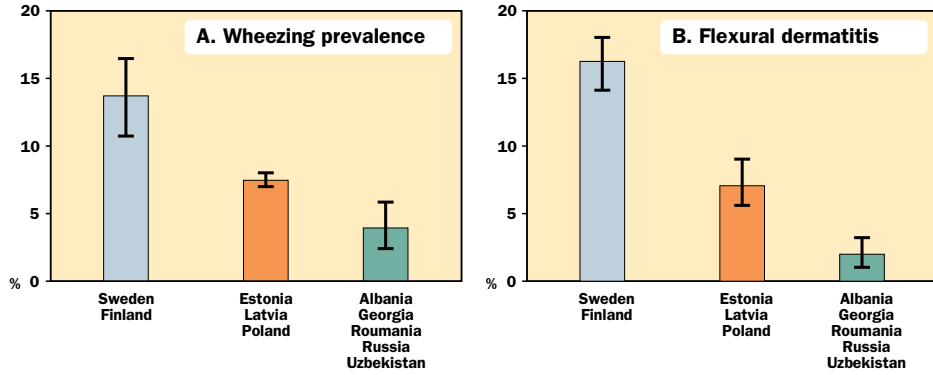


Adapted from: ISAAC Steering Committee, World wide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet* 1998; 351: 1225-32

and Poland and 2.6% to 5.9% in Albania, Romania, Russia, Georgia and Uzbekistan. The prevalence of flexural dermatitis varied in a similar manner between the three regions (Fig.2 A and B). This finding supports the hypothesis that Western lifestyle is associated with a high prevalence of childhood allergy.

FIGURE 2

The 12-month prevalence of wheezing (A) and cumulative prevalence of flexural dermatitis (B) among 13-14 year old children participating in the International Study of Asthma and Allergy in Children (ISAAC)



Adapted from: Björkstén B. et al., Prevalence of childhood asthma, rhinitis and eczema in Scandinavia and Eastern Europe. Eur Respir J 1998; 12: 432-37

TABLE 5A

Results of skin prick tests (%) in West and East Germany

	West Germany (n=4,451)	East Germany (n=2,335)	OR
Mite	10.3 *	4.2	2.6
Cat	7.3 *	2.9	2.6
Dog	2.5	2.7	0.9
Mixed grass pollen	21.3 *	7.9	3.1
Birch pollen	12.7 *	3.3	4.3
Hazel pollen	18.3 *	8.1	2.5
Sensitization to one or more allergens	36.7 *	18.2	2.6
Sensitization to more than one allergen	19.2 *	7.3	3.0

*p<0.05 when comparing with East Germany.

Adapted from: von Mutius E et al. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994;149:358-64

TABLE 5B

Prevalence (in %) of respiratory and allergic diseases in West and East Germany

	West Germany (n=5,030)	East Germany (n=2,623)	OR
Doctor's diagnosis			
Asthma ever	9.3 *	7.2	1.3
Current asthma	5.9 **	3.9	1.5
Bronchitis	15.9 **	33.7	0.4
Hay fever	8.6 **	2.7	3.4
Reported symptoms			
Wheeze	17.0 **	26.8	0.6
Breathlessness	8.7	9.6	0.9
Nocturnal cough	3.4 **	6.1	0.5
Cough with exercise or foggy weather	11.7 *	14.2	0.8

*p<0.05 when comparing with East Germany.

**p<0.0005 when comparing with East Germany.

Adapted from: von Mutius E et al. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994;149:358-64

The impact of environmental factors on the development of allergic disorders in ethnically similar populations was studied after the German unification in children living in former East and West Germany (12). The prevalence of asthma, hay fever, atopy and bronchial hyperresponsiveness in 9 to 11 year old children was investigated. Atopic sensitization was more frequent in children living in West Germany than children living in East Germany, 36.7% vs. 18.2%. Sensitization to mite, cat and pollen was significantly more frequent in West Germany (Table 5A). The prevalence of asthma and hay fever was also significantly higher in West Germany compared to East Germany, 5.9% vs. 3.9% and 8.6% vs. 2.7% (Table 5B). The authors speculate that the Western lifestyle is a risk factor for the development of atopy.

ENVIRONMENTAL RISK FACTORS AND DEVELOPMENT OF ATOPIC DISEASE

The environment of Western nations has undergone major change in recent decades (13,14). The concept of lifestyle should therefore be expanded considerably (Table 6), including dietary changes, altered microbial environment, extended travelling and stress.

The role of infections as a risk factor for the development of childhood allergic disease is complex. An infection induces an inflammatory reaction in the respiratory mucosa, which modifies the local immune response. There is an ongoing debate about the potential causative role of virus infections, mainly respiratory syncytial virus (RSV) for the development of childhood wheezing, asthma and atopy. It is also known that infections may trigger clinical symptoms in already sensitized patients, and that infections increase bronchial hyperreactivity.

Reduced number of infections during childhood has, on the other hand, been suggested as a possible explanation for the higher prevalence of atopic diseases. This is based on the findings that many infections, both viral and bacterial, induce a switch to Th1 lymphocyte activities. Atopy, on the contrary, is characterized by the dominance of Th2 lymphocytes.

TABLE 6

Examples of changes in "life style" and environment after the Second World War in industrialized countries with a market economy that may possibly have affected the incidence of sensitization to allergens

Urbanization;	Major changes in habits, exposure to air pollution.
Diet;	A wider range of foods and many that are new to the area, food additives, foods processed by industry, altered intestinal microbial flora.
Buildings;	New building materials, more efficient insulation, altered methods for construction, construction around the year even in temperate climates.
Homes;	Larger dwellings, many new chemicals at home, increased indoor humidity in temperate and cold climates.
Life style;	Most time spent indoors, extensive travelling and exposure to new environments.

Adapted from: Björkstén B. The environmental influence on childhood asthma. *Allergy* 1999;54:17-23

FAMILY SIZE, SOCIOECONOMIC STATUS, NONSPECIFIC INFECTIONS

In 1989 an explanation for the apparent increase in the prevalence of atopic disease was proposed and colloquially named the "hygiene hypothesis" (15). During the past century family size has declined and household amenities have improved. Higher standards of personal cleanliness have reduced opportunities for cross-infections in families. A decline in exposure to infections early in life may thus be partly responsible for the increased prevalence of atopic disease.

A large number of siblings and the birth order in the family (several older siblings) have been associated with less atopy.

Several groups have studied the association between family size and development of atopy. Stage II of the European Community Respiratory Health Survey (ECRHS) includes information on several

TABLE 7

Effect of total number of siblings on atopy and specific IgE and mutually adjusted effects of childhood exposures on atopy according to parental allergy

	No parental allergy (n=8991)		Parental allergy (n=4929)	
	OR	P value	OR	P value
Effect of family size (per 1 sib) on the following outcomes:				
Atopy*	0.91	<.001	0.99	.7
IgE grass	0.90	<.001	0.98	.5
IgE house dust mite	0.94	.006	1.02	.5
IgE cat	0.91	.006	0.91	<.001
Mutually adjusted effects on atopy of the following exposures:				
Family size (per 1 sib)	0.93	<.001	0.99	.7
Bedroom sharing	0.88	.01	1.10	.2
Cat in childhood	1.00	1.0	0.86	.03
Dog in childhood	0.85	.002	0.82	.003
Other pet in childhood	0.96	.5	0.95	.5

*specific IgE to 1 or more allergens.

OR = odds ratio

Adapted from: Svanes C et al. Childhood environment and adult atopy: Results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999;103:415-20

childhood factors such as family size (16). Thirteen thousand nine hundred thirty-two subjects (13 932) aged 20 to 44 years, from 36 areas in Europe, New Zealand, USA and Australia participated. Measurements of specific IgE to house dust mite, cat, grass pollen and mold were performed. Atopy was found negatively associated with family size, and bedroom sharing was associated with a lower prevalence of atopy. However, a protective effect of family size and bedroom sharing could only be detected in subjects reporting no parental allergy (Table 7).

If infections in early childhood help prevent allergies in later life, early attendance at nurseries and day-care centers would protect against atopy by frequent cross infections. This was investigated in a large cross-sectional study in Germany (17). Sensitization to common allergens was assessed by SPT and RAST tests. The results showed that among children from small families, all allergy related diseases showed an upward trend with older age at entry to day nursery. For children from large families, on the other hand, age at entry to day nursery had no effect (Table 8). These findings accord with the hypothesis that early infection may protect against allergies in later life.

The association of number of siblings and day-care attendance in children aged 1 to 3 years with atopic disease was analyzed in a cross-sectional survey of 8 387 school-children aged 13 to 14 years in Finland (18). Having no siblings, compared to three or more, was associated with significantly higher lifetime history of asthma, hay fever and atopic eczema. Attending a day-care center at the age of 1 to 3 years did not decrease the risk for any of the atopic diseases studied (Table 9), which suggests that factors other than early infections explain the association between number of siblings and future risk of atopic diseases.

Aeroallergen skin-test reactivity in relation to socioeconomic status, number of siblings and respiratory infections in early life was evaluated in 2 226 school children in Italy (19). The prevalence of prick-test positivity was higher among children whose fathers were in the highest educational level, and there was a lower prevalence of

TABLE 8

Allergy-related symptoms, diagnoses, and sensitizations by age of entry to day nursery in children aged 5-14 years

	Age (months) of entry to day nursery		
	6 - 11	12 - 23	≥24
Whole group (n=2430)			
Asthma ever	446 (0.5)	1464 (1.2)	504 (2.4)
Wheezing ever	392 (25.0)	1294 (30.1)	456 (24.3)
Hayfever ever	447 (4.3)	1469 (4.0)	507 (5.1)
Positive skin-prick test	399 (19.1)	1310 (20.2)	447 (23.0)
Positive RAST test	387 (43.9)	1276 (37.7)	440 (43.9)
Small families (n=669)			
Asthma ever	147 (0.0)	383 (1.0)	134 (3.0)
Wheezing ever	124 (22.6)	338 (27.2)	117 (25.6)
Hayfever ever	148 (2.7)	386 (4.4)	134 (8.2)
Positive skin-prick test	134 (15.7)	331 (21.8)	111 (27.0)
Positive RAST test	126 (35.7)	327 (33.9)	112 (45.5)
Large families (n=1761)			
Asthma ever	229 (0.7)	1081 (1.3)	370 (2.2)
Wheezing ever	268 (26.1)	956 (31.2)	339 (23.9)
Hayfever ever	299 (5.0)	1083 (3.8)	373 (4.0)
Positive skin-prick test	263 (20.2)	971 (19.2)	332 (21.4)
Positive RAST test	261 (47.9)	949 (39.0)	328 (43.3)

Data are number (%)

Adapted from: Krämer U et al. Age of entry to day nursery and allergy in later childhood. Lancet 1998;352:450-54

atopy among children with a larger number of siblings. A history of bronchitis or bronchiolitis before the age of 2 years was weakly associated with an increased risk of atopy, whereas a history of pertussis or pneumonia was not (Table 10). This study indicates that atopic sensitization to common aeroallergens is associated with socioeconomic levels and negatively and independently with the number of siblings.

TABLE 9

Associations of lifetime history of atopic diseases with number of siblings, birth order and mode of day care at the age 1-3 years among Finnish school children aged 13-14 years

	Diagnosed asthma		Hay fever		Atopic eczema	
	%	OR	%	OR	%	OR
Number of siblings						
None	5.3	1.26	30.7	1.53 **	26.2	1.28 *
1	5.8	1.37	27.6	1.32 **	25.2	1.18 *
2	4.5	1.04	24.7	1.13	25.8	1.22 *
3 or more	4.4	1	21.9	1	22.4	1
<i>p-value for trend test</i>	0.04		<0.001		0.06	
Birth order						
First	5.6	1.35	28.7	1.29 **	25.7	1.12
Second	5.2	1.28	25.1	1.07	25.1	1.06
Third	4.0	1	22.9	1	23.3	1
<i>p-value for trend test</i>	0.08		<0.001		0.12	
Day care						
Home	5.1	1	25.7	1	25.0	1
Family care	5.5	1.08	26.6	1.06	25.4	1.04
Day care center	4.8	0.88	29.2	1.17 *	24.7	0.97
<i>p-value for trend test</i>	0.8		0.04		0.9	

*p<0.05

**p<0.01

Odds ratios adjusted for sex, age, area and family history of atopy

Adapted from: Pekkanen J et al. Infections in early childhood and risk of atopic disease. Acta Paediatr 1999;88:710-14

TABLE 10

Prevalence of positive skin tests, prevalence ratios (PR) for various family factors and early respiratory infections

Variable	%	PR
Father's education (years)		
<6*	17.8	1.00
6-8	21.1	1.18
9-13	22.5	1.26
>13	28.1	1.58
Number of siblings		
0*	19.6	1.00
1	22.5	1.15
2	21.1	1.08
3	15.8	0.81
≥4	7.4	0.38
Day care attendance		
No*	17.3	1.00
Yes	21.3	1.23
Household crowding (inhabitants/room)		
Low (<1)*	22.9	1.00
Medium (1-2)	21.8	0.95
High (>2)	22.7	0.99
Respiratory infections in first 2 years of life		
<i>Pneumonia</i>		
No*	21.2	1.00
Yes	17.2	0.82
<i>Bronchitis</i>		
No*	21.0	1.00
1 episode	18.3	0.87
2 episodes	25.5	1.21
≥3 episodes	26.7	1.27
<i>Bronchiolitis</i>		
No*	20.9	1.00
1 episode	19.5	0.93
≥2 episodes	34.6	1.66
<i>Pertussis</i>		
No*	21.6	1.00
Yes	19.5	0.90

*Referent category

Adapted from: Forastiere F et al. Socioeconomic status, number of siblings, and respiratory infections in early life as determinants of atopy in children. Epidemiology 1997;8:566-70

TABLE 11

Skin sensitization to common airborne allergens, specific IgE concentrations, and respiratory allergy in Italian military students according to presence of antibodies to hepatitis A virus

	Seronegative (n=1216) (%)	Seropositive (n=443) (%)	Odds ratio
Skin sensitization			
<i>No of sensitizations:</i>			
1	14.1	13.3	1.07
2	9.6	5.9	1.71 *
≥3	6.4	2.7	2.46 **
at least 1	30.2	21.9	1.54 **
<i>Prevalence of sensitization to allergens:</i>			
Dermatophagoides			
pteronissinus	18.8	12.9	1.57 **
Cat epithelium	7.7	4.1	1.98 **
Mixed grass pollens	14.3	9.0	1.68 **
Parietaria judaica	8.5	6.1	1.43
Olea europaea	2.6	1.6	1.68
Artemisia vulgaris	1.7	0.7	2.58
Alternaria alternata	1.8	0.9	2.02
Specific serum IgE to common inhalants			
Low positivity	17.5	18.7	0.92
High positivity	18.4	9.7	2.10 ***
Respiratory allergic disease			
Allergic rhinitis and/or asthma	16.7	8.4	2.20 ***

*P<0.05

**P<0.01

***P<0.001

Adapted from: Matricardi PM et al. Cross sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. BMJ 1997;314:999-1003

SPECIFIC INFECTIONS AND VACCINATION

The possibility that measles infection might be protective against atopic disease arose from a study of children in Guinea-Bissau (20). A substantially reduced prevalence of atopy was observed in subjects who had had measles infection (12.8%) compared to those who had been vaccinated or not had measles earlier (25.6%).

Consistent evidence of an inverse relationship between infection and atopic sensitization has come from studies on hepatitis A infection, known to vary with family size and socioeconomic status, opposite to the trends seen for allergy (21).

In a retrospective study, 26.7% of 1 659 Italian military students were seropositive for hepatitis A. Only 21.9% of the seropositive subjects had a positive reaction to at least one of seven aeroallergens tested, compared with 30.2% of the subjects who were seronegative. The prevalence of allergic rhinitis or asthma, or both, was significantly higher in the seronegative than in the seropositive group, 16.7% vs. 8.4% (Table 11). This effect was independent of age, number of siblings, birth order and other potential risk factors.

A strong inverse association between delayed hypersensitivity to *Mycobacterium tuberculosis* and atopy was reported from a study of Japanese children (22). Mycobacteria are known as potent inducers of Th1 responses. Symptoms of atopic disease were found signifi-

TABLE 12

Prevalence of allergy in BCG-immunized and nonimmunized children

Place of birth	BCG vaccination	Prevalence of allergy			Total (%)
		Group 1 (4-5 yrs) (%)	Group 2 (8-9 yrs, rural) (%)	Group 3 (8-9 yrs, city) (%)	
Sweden	No	167/732 (22.8)	470/2059 (22.8)	687/3289 (20.9)	1324/6080 (21.8)
Sweden	Yes	7/34 (20.6)	13/38 (34.2)	29/160 (18.1)	49/232 (21.1)

Adapted from: Strannegård I-L et al. Prevalence of allergy in children in relation to prior BCG vaccination and infection with atypical mycobacteria. Allergy 1998;53:249-54

cantly less likely in positive tuberculin responders compared with negative responders. Furthermore, remission of atopic symptoms between the ages of 7 to 12 years was more likely in positive tuberculin responders. The authors speculate that exposure and response to *Mycobacterium tuberculosis* may inhibit development of atopic disease.

These results could not be confirmed by a Swedish group who investigated whether previous BCG vaccination or infection with atypical mycobacteria might protect against the development of atopic disease (23). Vaccinated children born in Sweden did not have significantly lower allergy prevalence than age-matched, unvaccinated children (Table 12). The overall frequencies of reactivity to atypical mycobacteria were rather higher than lower in allergic than in non-allergic children. These findings do not support the hypothesis that early mycobacterial infection or BCG vaccination has a suppressive effect on the development of atopic disease.

ANTIBIOTICS

The role of infections in infancy in promoting or protecting against the development of atopic disease has raised a related hypothesis concerning the role of medical response to infections, including the widespread use of antibiotics.

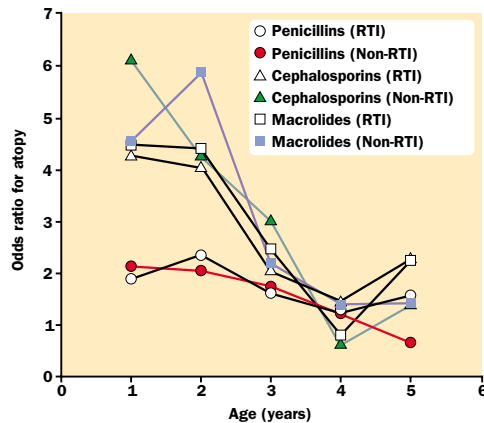
This has been evaluated in a retrospective study, including 1934 subjects from a family physician practice in southern England (24). A significant association between a range of infections and subsequent atopic diseases was observed. The receipt of an antibiotic in the first two years predicted subsequent asthma, hay fever and eczema. This association was more marked for infections treated with broad-spectrum antibiotics and principally seen for treatment in the first and second year of life (Fig.3). The authors state that interpretation of the prediction of atopic disease by treatment with antibiotics should be cautious due to possibilities for confounding effects, and further investigation of this association is warranted.

The association between antibiotic use in infancy and risk for the development of asthma by age 5 to 10 years has been investigated in children in New Zealand attending Rudolf Steiner schools, where antibiotics are more rarely used, according to the anthroposophic philosophy of the school (25). After controlling for potential confounders, antibiotic use was significantly associated with having a history of asthma. The use of antibiotics during the first year of life was also associated with an increased risk of asthma as was an increasing number of courses of antibiotics (Table 13). These results suggest that antibiotic use in infancy may be associated with an increased risk for developing asthma, but further studies are required to determine the reasons for this association.

The positive association with between antibiotic use and asthma should, however, be interpreted with great caution because a potential bias by reverse causation cannot be excluded; i.e. children with pre-existing asthma symptoms may receive more antibiotics because of their disease. Another possibility is that antibiotics could directly influence the immune system through the effect on the gastrointestinal flora, resulting in impaired Th1 immune responses.

FIGURE 3

Antibiotic treatments of respiratory tract infections (RTI) and Non-RTI in the first five years of life. (Non-RTI = skin, urinary tract infections)



Adapted from: Farooqi IS. *et al.*, Early childhood infection and atopic disorder. *Thorax* 1998; 53: 927-32

TABLE 13**Antibiotics used and number of courses used during the first year of life**

	Asthma	No asthma	Adjusted * odds ratio
Antibiotics used under 1 year			
Used first year of life	40	112	4.05
Only used after first year of life	20	142	1.64
Not used at all	6	105	1.00
Number of courses under 1 year			
None during the first year of life	26	247	1.00
1-2 courses	26	78	2.27
≥3 courses	10	29	4.02

* Adjusted for age (5-6, 7-8 or 9-10 years), gender, ethnicity, family size, family history of asthma, eczema and hay fever, and mother's and father's smoking currently and during the child's first year of life.

Adapted from: Wickens K et al. Antibiotic use in early childhood and the development of asthma. Clin Exp Allergy 1999;29:766-76

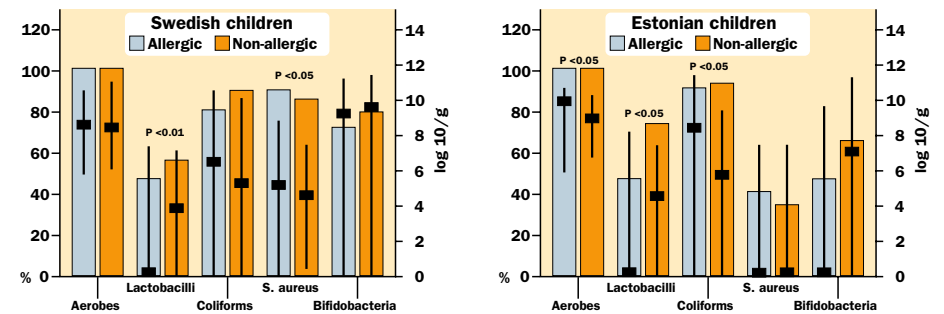
DIETARY HABITS, INTESTINAL FLORA

The gastrointestinal tract is a likely source of microbial stimulation of the immune system, and a reduced stimulation during infancy and early childhood has been associated with increasing prevalence of atopic disease in many countries. There are also considerable variations in the gut flora between industrial and developing countries (26,27).

The intestinal flora in healthy Estonian and Swedish infants was compared in a study (28). The major differences observed were high counts of lactobacilli and eubacteria in the Estonian infants and clostridia in the Swedish infants. Lactobacilli may be of particular interest in this context since they are known to be potent inducers of cytokines engaged in Th1 immunity. The microflora of the Estonian infants was in many aspects similar to the flora of western Europe in the 1960s, suggesting a change in the Western industrialized countries. It is also of interest to note that the anthroposophic lifestyle includes a diet with acidified vegetables, which contain lactobacilli, and

FIGURE 4

Intestinal microflora of allergic and non-allergic children. The results are presented as colonization rate (%), and counts (log CFU/g, range and median, lines and filled symbols)



Adapted from: Björkstén B. et al., The intestinal microflora in allergic Estonian and Swedish 2-year-old children Clin Exp Allergy 1999; 29: 342-46

that children from an anthroposophic environment have less atopic disease than other children (29).

Another prospective study was performed in the same countries among 2-year old children, both allergic and nonallergic (30). The allergic children in both Estonia and Sweden were less often colonized with lactobacilli as compared with the nonallergic children. In contrast, the allergic children had higher counts of aerobic bacteria, particularly coliforms and Staphylococcus aureus (Fig.4). The role of the intestinal flora in relation to the development of infant immunity and consequences for atopic diseases in later life thus needs further study.

NONSPECIFIC ENVIRONMENTAL FACTORS, “ADJUVANTS”

Various environmental factors may enhance sensitization and also trigger an allergic reaction in a sensitized individual. Some of these suggested factors are shown in Table 14 (31). Among the adjuvant factors proposed as responsible for the increase of atopic disease, tobacco smoke is of particular importance and most documented. Several studies have shown a significant association between parental (particularly maternal) smoking and increased wheezing and asthma in children (32,33). The severity of symptoms has also been related to the extent of exposure. Passive smoking has been associated with sensitization to both food and indoor allergens (34). Furthermore, maternal smoking during pregnancy has shown to be significantly associated with reduced respiratory function and recurrent wheezing in early infancy (35,36).

TABLE 14

Adjuvant factors believed to be involved in either sensitization, manifestation of allergic disease, or both

Air pollution and sources

Tobacco smoke

Industrial and traffic pollution: solid particles, SO₂, NO_x

Combustion byproducts: CO₂, CO, SO₂, NO₂, NO; formaldehyde; volatile vapors

Photochemical reactions; ozone; NO₂

Building materials; formaldehyde; decoration and paint; solvents; furnishings

Tight, poorly ventilated homes

Pesticides and consumer products; organic substances; aerosols

Respiratory tract infection: viral, pertussis

Vaccines: aluminum? pertussis?

Ongoing allergic reaction (facilitates sensitization to new allergens)

Adapted from: Björkstén B. Risk factors in early childhood for the development of atopic diseases. Allergy 1994;49:400-7

Results from the studies above suggest that:

- The prevalence of atopic diseases is increasing in many countries.
- The increasing prevalence of atopic disease will give rise to a greater need for diagnosis and consequently a greater need for IgE testing.
- The reasons for the increasing prevalence are unknown, but there is evidence that several environmental factors play an important role, exerting much of their influence during the first years of life.
- There is an association between the increasing prevalence of atopic disease and changing lifestyles.
- The potential relation of atopic disease with infections/vaccinations/gastrointestinal microflora is presently an area of particular interest.
- The future challenge is to tackle the complex interplay between genetic determinants and environmental factors that will contribute to better understanding and better prevention strategies for atopic disease.

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