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REVIEW ARTICLE

Environmental Factors and Allergic Disorders

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ABSTRACT

Despite numerous studies on possible associations between environmental exposure and allergic disorders, any conclusions made remain a matter of controversy. We conducted a review of evidence in relation to environmental and nutritional determinants and wheeze, asthma, atopic dermatitis, and allergic rhinitis. Identified were 263 articles for analysis after consideration of 1093 papers that were published since 2000 and selected by electronic search of the PubMed database using keywords relevant to epidemiological studies. Most were cross-sectional and case-control studies. Several prospective cohort studies revealed inconsistent associations between various environmental factors and the risk of any allergic disorder. Therefore, the evidence was inadequate to infer the presence or absence of a causal relationship between various environmental exposures and allergic diseases. However, evidence is suggestive of positive associations of allergies with heredity. Because almost all the studies were performed in Western countries, the application of these findings to people in other countries, including Japan, may not be appropriate. Further epidemiological information gained from population-based prospective cohort studies, in particular among Japanese together with other Asians, is needed to assess causal relationships between various environmental factors and allergic diseases.

KEY WORDS

allergic rhinitis, asthma, atopic dermatitis, environmental factors, review, wheeze

INTRODUCTION

Recently, the prevalence of allergic diseases has increased significantly. In 1989 Strachan observed that birth order and family size were inversely associated with the risk of allergic rhinitis and postulated the hygiene hypothesis, which suggests that infections within households in early childhood have a role in preventing allergic diseases.[1] This hygiene hypothesis has been given an immunological framework in which the balance between Th1 (associated with bacterial and viral infections) and Th2 (associated with allergic diseases) immune responses is pivotal.[2] Although the Th1/Th2 paradigm has not been confirmed in humans, the hygiene hypothesis has triggered numerous epidemiological studies on the relation between environmental factors and allergic disorders. However, so far no data conclusively explain the rising prevalence of allergic diseases. A number of epidemiological studies have focused on the relationship between dietary intake and allergic disorders. Especially, it remains unclear whether n-3 polyunsaturated fatty acid intake is preventive against allergic disorders and whether n-6 polyunsaturated fatty acid intake increases the risk of allergic disorders.[3]

Genetic factors may influence immunologic development. However the current rapid rise in allergic diseases cannot be fully explained only by genetic factors. The complex interplay between immune responses of the host, the level and variety of the environmental exposure, and the interactions between the genetic background and the range of exposures are likely to affect the development of allergic diseases. To assess the involvement of the gene-environment interaction in the onset of allergic disorders, we felt that it would be useful to list candidate environmental factors associated with allergic disorders. We have reviewed the scientific literature to identify, appraise and synthesize evidence regarding the possible association of various environmental and nutritional factors with wheeze, asthma, atopic eczema, and allergic rhinitis.

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METHODS

A literature search of the PubMed database was performed to identify epidemiologic studies in the English language from January 2000 to August 2006 using the following keyword terms: (asthma OR wheeze OR "atopic dermatitis" OR "atopic eczema" OR "allergic rhinitis") AND (risk OR prevalence OR preventive OR protective) AND (association OR relationship) AND human AND (cross-sectional OR case-control OR prospective OR cohort OR intervention) NOT polymorphism. A total of 1093 studies (original articles, correspondence, and reviews) were identified. We scanned the titles and abstracts of these studies manually to identify those that met the following *a priori* criteria: (1) original article; (2) comparative epidemiologic study design; (3) wheeze, asthma, atopic dermatitis, or allergic rhinitis (hay fever) listed as an outcome. A final set of 263 articles meeting these criteria was identified.[4-266]

From the 263 papers, we retrieved examined factors such as environmental and occupational exposure, demographic variables (e.g. sex, age, socioeconomic status), body build, past medications, medical history, and dietary factors and the results associated with each outcome: wheeze, asthma, atopic dermatitis, and allergic rhinitis. We synthesized the information regarding the examined factors and the results into 3 tables in which the direction of the associations and the cited reference numbers are listed. The results were considered statistically significant when either of the following conditions was met: (1) p value was less than 0.05, or (2) p for trend between exposure variables and the risk or prevalence of allergic diseases was statistically significant (<0.05).

Whenever possible we retrieved the results of analysis of all participants. However, for articles that presented results for only stratified analysis or that included two or more studies, we examined each of the studies presented in the paper separately. Some studies presented results for several different definitions of an outcome. In these cases we obtained the results for all definitions available.

RESULTS

OVERVIEW OF INCLUDED STUDIES

The number of studies investigating wheeze, asthma, atopic dermatitis, and allergic rhinitis as an outcome was 113, 192, 64, and 78, respectively. Almost all studies were performed in Western countries, while only 7 studies were reported from Japan.[16,41,95,121,189,245,262]

SOCIOECONOMIC FACTORS

We identified 74 reports in which the associations between socioeconomic factors such as socio-economic status, income, and education and allergic diseases were identified (Table 1). Half of these results provided a lack of association. Several studies found a lower frequency of allergic illnesses in populations with low socioeconomic status, whereas others showed positive associations with socioeconomic status. It was not possible to draw conclusions from these observations. Socioeconomic status may merely reflect predisposition to infections, less stringent control of microbial contamination of water and food, and/or poorer housing conditions.

SMOKING EXPOSURE

A number of studies examined the association between smoking exposure and allergic disorders. Many, but not all, studies found that active smoking was positively associated with the risk and prevalence of wheeze and asthma. Sex difference in the association with active smoking was observed in 2 cross-sectional studies.[22,23] In a study of New York State adults, active smoking was inversely associated with asthma in men (adjusted odds ratio [OR] = 0.49, 95% confidence interval [CI]: 0.27–0.89).[22] Another US cross-sectional study showed a positive association between active smoking and asthma in women (adjusted OR = 1.43, 95% CI: 1.20–1.64).[23] One cross-sectional study indicated that active smoking was inversely associated with the prevalence of allergic rhinitis: adjusted OR was 0.5 (95% CI: 0.4–0.7) for smoking of at least 20 cigarettes a day, compared with never smoking.[123] No association between active smoking and allergic disorders was observed in 13 studies.

Four cohort studies,[31,36,75,124] 3 case-control studies, [45,61,126] and 9 cross-sectional studies,[9,25,120,121,129,130-133] showed a positive association between passive smoking and the risk and prevalence of wheeze, asthma, and allergic rhinitis. Most of the studies found no association between passive smoking exposure and allergic disorders.

Recently, investigations of the association between maternal smoking during pregnancy and allergic disorders have been increasing. Several studies found that *in utero* exposure to maternal smoking increased the risk and prevalence of wheeze and asthma among children born to those mothers.[26,31,45,127,135,136] In contrast, no published report suggested an inverse association between maternal smoking in pregnancy and allergic diseases in offspring. More than half of the studies that examined the association between maternal smoking during pregnancy and allergic disorders found no statistically significant relationship between them.

In research that assessed smoking exposure by using a questionnaire and/or interview, exposure misclassification was likely to occur. Only one cohort study found no association between the serum cotinine level and asthma in adults.[59]

PET OWNERSHIP

A large number of studies examined the association

Table 1 Environmental factors and allergic diseases

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
Basic characteristics					
Age	Cohort		N: 4	N: 5	
	Case-control		↑: 6, 7 ↓: 8		
	Cross-sectional	↑: 9, 10, 11 ↓: 12 N: 9 (ever), 13, 14, 15, 16, 17, 18	↑: 9 (DD), 11, 12, 17, 19, 20 ↓: 21, 22 (men), 23 N: 9 (ever), 10, 13, 14, 18, 22 (women), 24, 25, 26	↑: 27 N: 16, 24, 26, 28	↑: 16, 26, 29 ↓: 21 N: 9, 24
Sex (male)	Cohort	↑: 30, 31 N: 31, 32, 33	↑: 30, 34, 35, 36, 37, 38 ↓: 4 N: 32, 39, 40, 41, 42	N: 5, 43	
	Case-control	N: 44	↑: 45, 46 ↓: 7 N: 6, 8, 47 (grass pollen asthma), 48		
	Cross-sectional	↑: 13, 14, 17 ↓: 9, 10 (ever), 11, 15, 49 N: 9, 10 (current), 50	↑: 12, 14, 51 (childhood onset), 52 ↓: 9 (DD), 11, 19, 49 (current), 51 (adult onset) N: 9 (ever), 9, 10, 13, 24, 27, 41, 49 (ever), 51 (adolescent onset)	↓: 16, 27, 28 N: 24, 26	↓: 9 (ever), 49 N: 9, 9 (current, DD), 16, 24, 26
Socioeconomic factors					
High socioeconomic status	Cohort	N: 53	↑: 54 (with allergic rhinitis) ↓: 54 (without allergic rhinitis) N: 53	N: 43	↑: 54
	Case-control		↓: 45 N: 6		
	Cross-sectional	↑: 55	N: 55	N: 27	
High social class	Cohort			↑: 5	
	Case-control		↓: 47		
	Cross-sectional		↓: 19 N: 21		↑: 21
Poverty	Cohort	N: 33	N: 36		
High income	Cohort	N: 56	↓: 35 N: 33, 57		
	Case-control			N: 58	
	Cross-sectional	N: 15	N: 23, 24, 26	N: 24, 26	↑: 24, 26 N: 29
High education	Cohort		↓: 59 N: 57		
	Case-control		↓: 48		
	Cross-sectional	↓: 18 N: 15, 60	↓: 19, 20, 22 (men) N: 18, 19, 22 (women), 23, 60		↑: 60 N: 9
Parental high education	Cohort	N: 33	N: 33		
	Case-control		N: 61	↑: 58 N: 61	
	Cross-sectional	↑: 9, 17, 58	↑: 9 (ever), 62 ↓: 17 N: 9 (DD), 17	↑: 28	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Maternal higher education	Cohort	N: 30	↓: 34 N: 30, 36	N: 5, 63	
Paternal higher education	Cohort			N: 5	
Inability to see a doctor due to cost	Cross-sectional		↑: 23		
Beneficiary status (active duty vs retired or family member)	Case-control		↑: 7		
Health care coverage	Cross-sectional		↑: 23		
Medical insurance	Cross-sectional		↑: 22 (men)		
Marital status	Cohort		N: 38		
Residence					
Rural	Case-control		↓: 47 (grass pollen asthma)		
	Cross-sectional	↓: 17 N: 15	↑: 25 (girls) ↓: 17, 64 N: 20, 25 (boys), 65	↓: 64	N: 64
Farm	Cohort			N: 66	
	Cross-sectional	↑: 13 N: 67	↓: 68 N: 65, 69	N: 68	↓: 68, 69
Urban	Case-control		↑: 48		
	Cross-sectional	↑: 70	↑: 71 N: 70	N: 27	↑: 71
Urbanization	Cohort			N: 5	
Dump area	Cohort		↑: 72		
Siblings					
Number of siblings	Cohort	↑: 31	↓: 57 N: 38, 73, 74	N: 66	↓: 73, 75, 76
	Case-control	N: 77	N: 77 (wheeze + asthma)	N: 58	
	Cross-sectional	N: 50	↓: 52, 78 (asthma with allergic rhinitis) N: 24, 26	N: 24, 26	N: 24, 26, 29
Older siblings	Cohort	N: 30, 79, 80 (asthma or wheezing), 81	N: 30, 82	N: 43, 63, 79, 80, 82, 83	N: 82
	Case-control	N: 77	↓: 84 N: 77 (wheeze + asthma)		
	Cross-sectional	N: 16	↓: 51 (adult onset), 78 (asthma with allergic rhinitis) N: 51 (childhood and adolescence on set)	N: 16	↓: 16
Younger siblings	Case-control	N: 77	↓: 77 (wheeze + asthma)		
	Cross-sectional		N: 78 (asthma with allergic rhinitis)		
Brothers	Cross-sectional		↓: 78 (asthma with allergic rhinitis)		
Sisters	Cross-sectional		↓: 78 (asthma with allergic rhinitis)		
Older brothers	Cross-sectional		↓: 78 (asthma with allergic rhinitis)		
Older sisters	Cross-sectional		↓: 78 (asthma with allergic rhinitis)		
Younger brothers	Cross-sectional		N: 78 (asthma with allergic rhinitis)		
Younger sisters	Cross-sectional		N: 78 (asthma with allergic rhinitis)		
Family size	Cross-sectional	N: 15			
Crowding	Cohort	N: 31	↓: 57	↓: 83 N: 5	N: 76

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
	Case-control		↓: 85	N: 58	
	Cross-sectional	N: 86	↓: 20 N: 86		
Anthropometric measurement					
High birth weight	Cohort	↓: 30 N: 80 (asthma or wheezing), 81, 87	↑: 35, 88 N: 38, 87	N: 80	↑: 89
Low birth weight	Cohort	↑: 56 (repeated wheeze), 90 N: 32, 56 (any wheeze), 80 (asthma or wheezing), 87	↑: 32 (ever), 34, 36 N: 30, 32 (DD), 35, 38, 57, 73, 74, 87, 89	N: 80, 89, 91	N: 73, 91
	Cross-sectional	N: 92	N: 93	N: 93	N: 93
Birth length	Cohort	N: 87	N: 57, 87		
Ponderal index (g/cm³)at birth	Cohort		↑: 88 N: 73, 94		N: 73
Head circumference at birth	Cohort	N: 87	N: 87, 89	N: 89, 91	N: 89, 91
Head circumference/birth weight ratio	Cohort	N: 87	N: 87, 89	N: 89	↓: 89
Head circumference/weight at 1 month ratio	Cohort		N: 89	N: 896	N: 89
Height	Cross-sectional				N: 99
Overweight, obesity	Cohort	N: 96	↑: 4, 40, 59, 97, 98, 99, 100, 94, 101 N: 57, 89	N: 43, 89	N: 89, 98
	Case-control		↑: 7, 8, 102 N: 84, 103		
	Cross-sectional	↑: 10, 14 (with sleep-disordered breathing), 15, 17, 18, 104 (current), 105, 106, 107 N: 14 (without sleep-disordered breathing), 104 (ever), 109	↑: 14, 17, 19, 20, 22, 23 (women), 104, 105 (women), 106, 107, 108 (women) N: 10, 18, 23 (men), 52, 105 (men), 108 (men), 109, 110	N: 110	↑: 106, 110 N: 95, 105
Body fat	Cross-sectional		N: 110	N: 110	↑: 110
Underweight	Cohort		↑: 98 N: 59, 101		↑: 98
	Case-control		N: 8, 102		
	Cross-sectional	↑: 17 ↓: 109 N: 104, 105	↑: 20, 22 (men) N: 17, 22 (women), 23, 104, 105		
Waist circumference	Cross-sectional	N: 109	↑: 108 (women) N: 108 (men), 109		
Maternal factors					
Maternal age	Cohort	↓: 31 N: 31, 33	↑: 34 N: 33, 36, 38, 73		N: 73
	Case-control		N: 84	N: 58	
	Cross-sectional	N: 16	N: 93	N: 16, 93	N: 16, 93
Maternal age at menarche	Cohort		N: 111	N: 111	N: 111
Maternal BMI before pregnancy	Cohort		N: 38		
Maternal weight gain during pregnancy	Cohort		N: 38, 57		
Maternal complications during pregnancy	Cohort	N: 80 (asthma or wheezing)		N: 80	
Maternal hospital admission during pregnancy	Cohort	N: 80 (asthma or wheezing)		N: 80	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Maternal complication during delivery	Cohort	N: 80 (asthma or wheezing)		*N*: 80	
Maternal depression	Cross-sectional		↑: 52		
Multiple birth	Cohort		*N*: 57		
Premature/preterm birth	Cohort	↑: 31 *N*: 31, 33			
	Cross-sectional	↑: 14, 50	↑: 12, 14		
Gestational age	Cohort	*N*: 87	↑: 39 ↓: 89 *N*: 38, 40, 57, 73, 74, 87	*N*: 63, 89	↓: 73, 89
	Case-control		↑: 84		
Season of birth	Cohort		*N*: 38		
Intrauterine growth retardation	Cohort		*N*: 57		
Apgar score	Cohort		↑: 38 (at 1st min) *N*: 38 (at 5th and 10th min)		
Mode of delivery					
Breech delivery	Cohort		*N*: 112	*N*: 112	*N*: 112
Caesarean section	Cohort	↑: 113 *N*: 34, 114	↑: 38, 57, 73 (ever), 112, 115, 116 *N*: 34, 73 (current), 114	*N*: 112, 113, 115, 116	↑: 115 *N*: 73, 76, 112, 113, 116
Forceps/vacuum extraction	Cohort		*N*: 112	↑: 112	*N*: 112
Forceps, manual auxiliary, and extraction breech	Cohort		↑: 38		
Vacuum extraction	Cohort		*N*: 38		
Special procedures at delivery					
Fetal-pelvic disproportion	Cohort		*N*: 38		
Fetal asphyxia	Cohort		*N*: 38		
Prolongation of labor	Cohort		*N*: 38		
Exhaustion of mother	Cohort		*N*: 38		
Duration of second-stage labour	Cohort				*N*: 76
Induced labor	Cohort	*N*: 80 (asthma or wheezing)		*N*: 80	
Smoking					
Active smoking	Cohort	↑: 117 *N*: 81	↑: 117, 118, 119 *N*: 4		
	Case-control		↑: 8 *N*: 6		
	Cross-sectional	↑: 10, 11, 13, 15, 18, 120	↑: 11, 18, 19, 20, 21, 23 (women), 120, 121 ↓: 22 (men) *N*: 10, 13, 22 (women), 23 (men), 120, 122, 123	*N*: 27, 121	↓: 123 *N*: 21, 121, 122
Passive smoking	Cohort	↑: 31 *N*: 30, 31, 33, 117	↑: 36, 124 (at 1, 2 y) *N*: 117, 40, 30, 41, 33, 124, 124 (at 4 y)		↑: 75 *N*: 125 (hay fever and/or asthma)

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
	Case-control		↑: 45, 61, 126 *N*: 46, 127	*N*: 58, 61, 128	
	Cross-sectional	↑: 9, 120, 129 (girls), 130 *N*: 16, 17, 55, 86, 129 (boy), 130	↑: 9, 25 (boys), 120, 130, 131, 132 *N*: 17, 20, 24, 25 (girls), 25, 41, 51, 55, 65, 86, 121, 123, 129, 130, 131	*N*: 16, 24, 121, 123	↑: 9 (current), 121, 133 (hay fever/asthma) *N*: 9 (ever, DD),16, 24, 121, 123, 134, 130
Maternal smoking during pregnancy	Cohort	↑: 31 *N*: 31, 56, 80 (asthma or wheezing), 81	↑: 135 (ever) *N*: 38	*N*: 43, 80	*N*: 125 (hay fever and/or asthma)
	Case-control		↑: 45, 127 *N*: 84		
	Cross-sectional	*N*: 86	↑: 26, 136 *N*: 86, 93	*N*: 26, 93	*N*: 26, 93
Serum cotinine level	Cohort		*N*: 59		
Occupation					
Farmer	Cohort		↓: 74, 38 (paternal)		
	Cross-sectional	*N*: 9	*N*: 9		*N*: 9
Farmer (vs civil servant)	Case-control			*N*: 58	
Works at home	Cross-sectional		*N*: 20		
Works outside home	Cross-sectional		↓: 20		
Cleaning work	Cross-sectional		↑: 137		↑: 137
Duration of daily work	Cohort			↑: 5 (father) *N*: 5 (mother)	
Shift work	Cohort			*N*: 5 (parents)	
Occupational agents					
Asbestos	Cohort	*N*: 138	*N*: 138		
Replace asbestos brakes	Cross-sectional	↑: 139			
Quartz	Cohort	*N*: 138	*N*: 138		
Dust/fumes	Cohort	↑: 138	↑: 138		
	Cross-sectional	↑: 10	*N*: 10		
Grind metal	Cross-sectional	↑: 139			
Drive combines	Cross-sectional	↑: 139			
Drive trucks	Cross-sectional	↑: 139			
Diesel tractors	Cross-sectional	↑: 139			
Gasoline to clean	Cross-sectional	↑: 139			
Gas tractors	Cross-sectional	↑: 139			
Repair engines	Cross-sectional	↑: 139			
Weld	Cross-sectional	↑: 139			
Paint	Cross-sectional	↑: 139			
Hand pick (crop activities)	Cross-sectional	↑: 139			
Plant (crop activities)	Cross-sectional	*N*: 139			
Insecticide use	Case-control			↑: 58	
	Cross-sectional	↑: 11	↑: 11		
Pesticide	Cross-sectional	↑: 140			
Repair pesticide equipment	Cross-sectional	↑: 139			
Disinfectants	Cross-sectional		*N*: 122		*N*: 122
Fertilizer	Cross-sectional	↑: 11	*N*: 11		
Natural fertilizer	Cross-sectional	↑: 139			

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
Chemical fertilizer	Cross-sectional	*N*: 139			
Livestock	Cross-sectional		↑: 13		
Cattle kept inside house	Case-control		↓: 126		
Rats	Cross-sectional		*N*: 122		*N*: 122
Rat allergen (Rat n 1)	Cross-sectional		*N*: 122		*N*: 122
IgE to rat urinary proteins	Cross-sectional		*N*: 122		↑: 122
Air pollution					
NO	Cross-sectional		*N*: 141		
NO_2	Cohort	*N*: 141	↑: 41		
	Case-control	*N*: 143	↑: 144		
	Cross-sectional	↓: 55 (ever)	*N*: 41, 55, 141, 145	*N*: 145	*N*: 145
		N: 55 (current), 145			
NOx	Cross-sectional		*N*: 141		
SO_2	Cross-sectional	↑: 145	↑: 145	*N*: 145	*N*: 145
		N: 55	*N*: 55		
Particulate matter < 10μm	Cohort	↑: 147	*N*: 41		
	Cross-sectional	*N*: 145	*N*: 41, 141, 145	*N*: 145	*N*: 145
Particulate matter 2.5 μm	Cohort	*N*: 142			
	Cross-sectional		*N*: 141		
Particulate matter 2.5 μm absorbance	Cohort	*N*: 142			
Total suspended particle	Case-control		↑: 144		
Black carbon	Cross-sectional		*N*: 141		
O_3	Cross-sectional	*N*: 55, 145	*N*: 55, 145	*N*: 145	*N*: 145
Air quality	Cohort			*N*: 5	
Home environment					
Temperature	Case-control		↑: 6, 147		
Carpeting	Case-control		↓: 45	*N*: 148	
	Cross-sectional	↓: 129			
Vacuuming	Case-control			↓: 148 (house)	
				N: 148 (bedroom)	
Dust	Cohort	*N*: 149	*N*: 149		
	Cross-sectional	↑: 13	*N*: 13		
House dust allergens					
Der f 1	Cohort		*N*: 150		
	Case-control	*N*: 151	*N*: 151		
	Cross-sectional	*N*: 152		*N*: 152	*N*: 152
	Ecological	*N*: 153	*N*: 153		
Der p 1	Cohort	*N*: 154 (atopic wheeze)	*N*: 150	*N*: 83	
	Case-control	*N*: 151	↑: 6		
	Cross-sectional	*N*: 152		*N*: 152	*N*: 152
	Ecological	↑: 153 (13 - 14 y)			
		N: 153 (6 - 7 y)	*N*: 153		
Der f 1 + Der p 1	Cohort		*N*: 155		
	Case-control	*N*: 151	*N*: 151		
Fel d 1	Cohort	↑: 157 (with maternal asthma)			
		↓: 157 (without maternal asthma)			
		N: 154 (atopic wheeze), 157, 158	*N*: 157	*N*: 83	
	Case-control	*N*: 151	*N*: 151		

Factors	Design	Outcome: Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Can f 1	Cohort	*N*: 157, 158	*N*: 157		
Dog allergen	Cohort	*N*: 90, 156			
Bla g 1	Cohort	*N*: 158			
	Cross-sectional	↑ : 56 (repeated wheeze) *N*: 56 (any wheeze)			
Cockroach allergen	Cohort	↑ : 33, 90	↑ : 33		
Mouse allergen	Cohort	↑ : 90			
House dust endotoxin	Cohort	↑ : 56 (repeated wheeze), 90, 159 (at 13 – 24 mo: concentration), 160 *N*: 56 (any wheeze), 149, 159 (at 0 – 12 mo, 25–36 mo: concentration), 159 (at 0 – 36 mo: load)	↓ : 149	↓ : 159 (at 12 mo: concentration) *N*: 159 (at 24 mo, 36 mo: concentration), 159 (at 0 – 36 mo: load), 160	*N*: 159
	Case-control	*N*: 151	*N*: 151		
	Cross-sectional	↑ : 161 *N*: 67	*N*: 122		*N*: 122
Glucann	Cohort	*N*: 96, 149	*N*: 149		
	Cross-sectional	*N*: 67			
EPS	Cross-sectional	*N*: 67			
EPS from Penicillium and Aspergillus	Cohort	↓ : 149 (persistent) *N*: 149 (current and transient)	↓ : 149		
Pet ownership	Cohort	↑ : 156 (cat: with maternal asthma) ↓ : 156 (cat: without maternal asthma), 162 (cat: < 18 y ownership), 163 (dog: without parental asthma) *N*: 32 (cat, dog), 56 (dog), 156 (dog), 161 (cat: < 18 and 18 + y ownership, 18 + y ownership), 163 (cat), 163 (dog: with parental asthma), 164 (dog, cat)	↓ : 162 (cat: < 18 y ownership, < 18 and 18 + y ownership) *N*: 32 (cat, dog), 162 (cat: 18 + y ownership), 165 (cat, dog)	↓ : 63 (furred pets), 66, 166 (pets), 166 (dog) *N*: 43 (cat, dog), 166 (cat, hamster, rabbit or guinea pig)	
	Case-control		↑ : 45, 167 (past ownership) *N*: 167 (cat, dog, bird, rodent) ↓ : 167 (current ownership)	*N*: 148	
	Cross-sectional	↑ : 168 (at time of birth ownership) ↓ : 169 (cat) *N*: 16, 17 (dog), 129 (cat, dog, bird, rodent), 169 (cat + dog), 170 (furred pets), 171 (cat), 172 (cat, dog)	↑ : 132, 168 (ownership at time of birth) ↓ : 51 (cat and/or dog: childhood onset), 169 (cat + dog), 172 (dog: current ownership) *N*: 17 (dog), 51 (cat and/or dog: adolescent and adult onset), 65, 129 (cat, dog, bird, rodent), 169 (cat), 170 (furred pets), 171 (cat), 172 (cat: current ownership), 172 (cat, dog: ownership in first year of life)	↓ : 172 (dog: ownership at first year of life) *N*: 16, 58, 168 (ownership at time of birth), 172 (cat, dog: current ownership), 172 (cat: ownership at first year of life)	↑ : 168 (ownership at time of birth), 171 (cat: current) ↓ : 169 (cat + dog), 172 (dog) *N*: 16, 169 (cat), 171 (cat: DD), 172 (cat)

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Fuel					
Coal as fuel	Cross-sectional	*N*: 11	*N*: 11		
Cornstalks as fuel	Cross-sectional	*N*: 11	*N*: 11		
Wood as fuel	Case-control			↓: 58	
	Cross-sectional	*N*: 11	*N*: 11		
Electricity as fuel	Case-control			↑: 58	
Cooking					
Gas cooking	Case-control		*N*: 6 (heating and cooking), 45	*N*: 148	
	Cross-sectional	*N*: 86, 129	↑: 86 *N*: 129		
Wood, animal dung, or crop residues as fuel	Cross-sectional		↑: 20		
Separate kitchen	Cross-sectional		↓: 20		
Heating					
Gas as fuel	Case-control			*N*: 148	
	Cross-sectional	*N*: 129	*N*: 129		
Coal as fuel	Cross-sectional	*N*: 129	*N*: 129		
Oil as fuel	Cross-sectional	*N*: 129	*N*: 129		
Wood as fuel	Cross-sectional	*N*: 129	*N*: 129		
Wood stove	Cohort	*N*: 158			
	Cross-sectional	*N*: 173	*N*: 173	*N*: 173	*N*: 173
Gas stove	Cohort	*N*: 158			
	Cross-sectional	*N*: 174			
Unvented heater	Cohort		*N*: 41		
	Cross-sectional		*N*: 41		
Stove (kerosene, coal, wood, dung, straw)	Cross-sectional	*N*: 9	↓: 9 (DD) *N*: 9 (ever)		↓: 9 (ever) *N*: 9 (current, DD)
Biosmoke (open fire or burning smoke without a fuel *vs*. gas or kerosene stove)	Case-control		↑: 126		
Fume emitting heaters	Cross-sectional	↑: 175 (first year of life) *N*: 175 (current)	*N*: 175		
Radiator in bedroom	Case-control			*N*: 148	
Hearth or open fire place	Case-control		*N*: 45		
Central heating or electricity as fuel	Case-control		*N*: 45		
Space heating					
Gas as fuel	Cross-sectional	*N*: 129	*N*: 129		
Coal as fuel	Cross-sectional	↑: 129 (boys) *N*: 129 (girls)	↑: 129 (girls) *N*: 129 (boys)		
Oil as fuel	Cross-sectional	*N*: 129	*N*: 129		
Wood as fuel	Cross-sectional	*N*: 129	*N*: 129		
Air conditioning	Case-control		↓: 6		
	Cross-sectional		*N*: 25		
Water heating					
unvented gasgeyser	Case-control		↑: 45		
Dampness					
Dampness/humidity	Cohort	↑: 176 *N*: 32	*N*: 32, 176	*N*: 43	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
	Case-control	↑: 177		↑: 148 (current) N: 128, 148 (ever)	
	Cross-sectional	N: 178	↑: 178 N: 6 (living room)	N: 178	↑: 178 (DD) N: 178 (current)
Mold or mold odour	Cohort	↑: 158 (with maternal asthma) N: 158 (without maternal asthma)		N: 43	N: 75
	Case-control	↑: 177	↑: 45	N: 128	
	Cross-sectional	↑: 86 N: 129	↑: 86 N: 129		
Condensation	Cross-sectional	N: 178	↑: 178	N: 178	↑: 178
Water leakage	Cross-sectional	N: 178	N: 178	↑: 178	↑: 178 (current) N: 178 (DD)
Water damage	Cross-sectional	↑: 86	N: 86		
Flooding	Case-control			N: 128	
Floor moisture	Cross-sectional	↑: 178	↑: 178	↑: 178	↑: 178 (current) N: 178 (DD)
Chemical agents					
Formaldehyde	Case-control		↑: 147		
Volatile organic compounds	Case-control		↑: 6		
Butyl benzyl phthalate in house dust	Case-control		N: 179	↑: 179	↑: 179
Di (2-ethylhextl)phthalate in house dust	Case-control		↑: 179	N: 179	N: 179
Chemical household products (disinfectant, bleach etc)	Cohort	↑: 180 (persistent) N: 180 (transient, late onset)			
Repainting child's room	Case-control	↑: 177			
Biological exposure at home					
Pig ownership	Cross-sectional	N: 9	N: 9		N: 9
Poultry kept inside house	Case-control		N: 126		
Mouse	Cohort	↑: 90			
Bedding items					
Cocoon use	Cohort	↑: 181	↑: 181		
Bottom bunk bed	Cross-sectional	↑: 50			
Foam mattress	Cross-sectional	N: 50			
Old mattress	Case-control			N: 148	
Electric blanket	Cross-sectional	↑: 50			
Feather quilt	Cohort		↓: 182		N: 182
Sheepskin underbedding	Cross-sectional	↓: 50			
Synthetic pillow	Cohort	↑: 183			
	Case-control			↑: 148	
	Cross-sectional	↑: 50, 183, 184	↑: 184		
Synthetic quilt (duvet)	Case-control			N: 148	
	Cross-sectional	↑: 50, 183			
Synthetic blanket	Cross-sectional	↑: 184	↑: 184		
Number of synthetic bedding items	Cohort	↑: 185	↑: 185		

Factors	Design	Outcome: Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Housing characteristics					
Building age (40 + yrs *vs* ≤ 10 yrs)	Cross-sectional	↑: 86	*N*: 86		
Building material (Concrete vs wood)	Cross-sectional	*N*: 86	*N*: 86		
House of steel or reinforced concrete	Cohort		*N*: 41		
	Cross-sectional		*N*: 41		
Residence near a major road	Cross-sectional	↑: 186 (among 13-14 y), 187 *N*: 86, 187 (among 6-7 y), 188, 189	*N*: 86, 186, 188	↑: 27 *N*: 189	↑: 186 (rhinitis), 189 *N*: 186 (hay fever), 188
Seaside living	Cross-sectional			↑: 27	
Living near opencast coal mining site	Cross-sectional	*N*: 190	*N*: 190	*N*: 190	*N*: 190
Living in apartment	Cohort	*N*: 56 (repeated wheeze)			
Living in mobile home (vs apartment)	Cross-sectional	*N*: 17	*N*: 17		
Living in condominium/town home (vs apartment)	Cross-sectional	*N*: 17	*N*: 17		
Living in detached house (vs apartment)	Cross-sectional	*N*: 17	*N*: 17		
Dwelling type (Single-family house vs other dwelling type)	Cross-sectional		*N*: 25		
Area of residence (> 60 m² *vs* < 25 m²)	Cross-sectional	*N*: 86	*N*: 86		
Floor (cement)	Case-control			*N*: 58	
Lifestyle related factor					
Watches TV every week	Cross-sectional		*N*: 20		
Reads newspaper/magazine every week	Cross-sectional		*N*: 20		
Sleep position	Cross-sectional	*N*: 50			
Spending first 24 h of life in mothers bed only	Cohort				↑: 76
Physical activity	Cohort		*N*: 4, 59		
	Cross-sectional		↓: 23 (men) *N*: 22, 23 (women)		
Medical history					
Allergy or atopy	Cohort		↑: 37, 40, 41		
	Case-control		↑: 6		
	Cross-sectional	↑: 12	↑: 12, 41, 122 *N*: 191		↑: 122
Asthma	Cohort			↑: 43	
	Cross-sectional			↑: 27	
Asthma or bronchitis	Cohort		*N*: 57		
Wheezing	Cohort			↑: 43	
Wheezy bronchitis (< 2 y)	Cohort				↑: 125 (hay fever and/or asthma)
Allergic rhinitis or hay fever	Cohort		↑: 4		
	Case-control		↑: 8		
	Cross-sectional	↑: 50		↑: 27	
Rhinitis	Cross-sectional		↑: 19		
Eczema	Cohort		↑: 4	↑: 43	
	Cross-sectional	↑: 50	↑: 132		

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
Hay fever and eczema	Cohort		↑: 4		
Respiratory allergy	Cross-sectional		↑: 25		
Respiratory illness	Cohort	↑: 158	*N*: 41		
	Cross-sectional		↑: 25, 41		
Pneumonia	Cohort		*N*: 57	N: 66	
Bronchial hyperresponsiveness	Cohort		↑: 42		
Cough	Cross-sectional		↑: 132		
Chronic bronchitis emphysema	Cross-sectional			↑: 27	
Chronic obstructive pulmonary disease	Case-control		*N*: 8		
Chronic lung diseases	Cohort		↑: 36		
History of tuberculosis	Cross-sectional	*N*: 9	↑: 9		↑: 9 (ever, DD) *N*: 9, 9 (current)
RSV bronchiolitis	Cohort	↑: 192	↑: 192		
Lower respiratory tract illness	Cohort	↑: 33, 56, 90	↑: 33, 82, 193	N: 82	*N*: 82
Respiratory disease in infancy	Cross-sectional	↑: 55	↑: 55		
Transient tachypnoea of newborn or respiratory distress syndrome	Cohort		↑: 194		
Adenoidectomy and/or tonsillectomy	Cohort		*N*: 195	N: 195	*N*: 195
Adenoidectomy	Cohort		↑: 196		
	Cross-sectional		↑: 196		
Otitis media	Cohort			N: 66, 197	
	Case-control		*N*: 82	N: 82	↓: 82
Parotitis	Cross-sectional			N: 93	
Fever	Case-control		↑: 198 (during pregnancy)		
	Cross-sectional	↑: 199	↑: 199		
Flu	Case-control		↑: 198 (during pregnancy)		
Cold lasting 3 + days	Cohort			N: 66	
Dyspnea	Cross-sectional		↑: 132		
Gastroesophageal reflux disease	Case-control		*N*: 8		
Acute gastroenteritis	Cross-sectional	↑: 199	↑: 199		
Stomach ulcer	Case-control		↑: 7		
Diarrhoea lasting 3 + days	Cohort			↑: 66	
Depression	Case-control		↑: 7		
Illness or health problems in first week of life	Cohort	*N*: 80 (asthma or wheezing)		N: 80	
Infantile colic	Cohort		*N*: 200		
Rash	Cohort			↑: 43	
Exanthema subitum	Cohort			N: 66	
Viral warts	Cross-sectional			N: 93	
Arthritis	Case-control		↑: 7		
Hypertension	Case-control		↑: 7		
Infection					
Infection	Cohort	*N*: 80 (asthma or wheezing: during pregnancy)		N: 80 (during pregnancy)	
Total number of infections	Cohort			↑: 66	
Respiratory infection	Cohort	↑: 32 *N*: 81	↑: 32 (ever) *N*: 32 (DD)	N: 197	

Factors	Design	Outcome: Wheeze	Outcome: Asthma	Outcome: Atopic dermatitis	Outcome: Allergic rhinitis (Hay fever)
	Case-control			N: 201	
	Cross-sectional	N: 12	↑: 19 (infection before 5 yrs), 51 (childhood and adolescent 12onset) N: 51 (adult onset)		
Upper respiratory tract infections	Cohort		N: 82, 193	N: 82	N: 82
Lower respiratory infection	Cohort	↑: 202	↑: 39, 202		
	Cross-sectional		↑: 93	N: 93	N: 93
Ear infection	Cross-sectional	↑: 203	↑: 203		
Gastrointestinal infection	Cohort	N: 202	N: 202		
	Case-control	N: 201		N: 201	
Viral infection	Cohort	N: 202	↓: 202	N: 197	
	Case-control	↑: 44 (among < 2 y) N: 44 (among 2 - 12 y)			
Hepatitis A virus	Case-control	N: 77	N: 77 (wheeze + asthma)		
	Cross-sectional		↓: 204		↓: 204
Hepatitis B virus	Cross-sectional		N: 204		N: 204
Hepatitis C virus	Cross-sectional		N: 204		N: 204
Herpes	Cohort	↓: 202	↓: 292		
Herpes simplex	Cross-sectional			N: 93	
Herpes simplex virus type 1	Cross-sectional		↓: 204		
Herpes simplex virus type 2	Cross-sectional		N: 204		N: 204
Measles	Cohort		N: 202	N: 205	
	Case-control	N: 77, 206	↓: 77 (≤ 3 y, wheeze + asthma) N: 77 (> 3 y, wheeze + asthma)		
	Cross-sectional		↑: 207	↑: 207 N: 93	↑: 207
Rubella	Case-control	N: 77, 206	N: 77 (wheeze + asthma)		
	Cross-sectional			↓: 93	
Epstein-Barr virus	Cohort	N: 208			N: 208 (suspected)
Mumps	Case-control	N: 77, 206	N: 77 (wheeze + asthma)		
Varicella	Cohort			N: 66	
	Case-control	N: 77, 206	N: 77 (wheeze + asthma)		
Bacterial infections	Cohort	N: 202	N: 202		
Chlamydia pneumoniae	Cohort		↓: 209 N: 118	N: 209	↓: 209
	Cross-sectional	↑: 210 (prior infection) N: 210 (acute infection)	N: 210		
Pertussis	Case-control	N: 77	N: 77 (wheeze + asthma)		
Helicobacter pylori	Case-control	N: 77	N: 77 (wheeze + asthma)		
Salmonellosis	Cohort	↓: 211	↓: 211		↓: 211
Scarlet fever	Case-control	N: 207			
Geohelminth	Cross-sectional	↓: 212 (exercise-induced) N: 170, 212	N: 129	N: 212	N: 212
Helminth	Cross-sectional		N: 213		
Malaria	Case-control			↑: 58	
Hookworm	Case-control			N: 58	
Ascaris	Cross-sectional		↑: 214		
	Case-control			N: 58	
Worm	Cross-sectional			↓: 28	
Toxocara	Case-control		N: 215		
Trichuris	Case-control			↑: 58	

Factors	Design	Outcome: Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Parasite egg in stool	Cross-sectional				N: 29
Parasite presence	Case-control			↑: 58	
Fungal	Cohort	N: 202	N: 202		
Toxoplasma gondii	Case-control	N: 77	N: 77 (wheeze+asthma)		
	Cross-sectional				↓: 204
Vaccine					
DTP vaccine	Cohort		N: 216, 217		
	Case-control			↓: 58	
	Cross-sectional	N: 199	N: 199		
DPPT vaccine	Cohort		↑: 218	↑: 218	
MMR vaccine	Cohort		↑: 218	↑: 205, 218	
			N: 217		
	Case-control		N: 47		
	Cross-sectional	N: 199	N: 199		
Measles or MMR vaccine	Cohort		N: 216		
Measles or MMR, DTP and OPV	Cohort		↑: 216		
Smallpox vaccine	Cohort		↓: 219		N: 219
Oral poliovirus vaccine	Cohort		N: 216, 217		
	Case-control		N: 47	↓: 58	
	Cross-sectional	N: 199	N: 199		
Hepatitis B virus vaccine	Cohort		↑: 217		
			N: 216		
	Case-control		N: 46		
	Cross-sectional	N: 199	↑: 199		
Haemophilus influenzae type b vaccine	Cohort		↑: 217		
Influenza vaccine	Cohort		↑: 216		
BCG	Cohort		N: 216		
	Cross-sectional	N: 199, 220	N: 199, 220		
Tuberculin skin test	Cross-sectional		N: 24, 26	↓: 24, 26	↓: 24, 26, 29
Antibiotics					
Antibiotics	Cohort	N: 202, 221	↑: 82, 222	N: 43, 82, 221	N: 82, 125 (hay fever and/or asthma), 221, 222
			N: 202, 221		
	Case-control		N: 198 (during pregnancy)	N: 58	N: 223
	Cross-sectional	↑: 199, 224	↑: 199, 224 (number of treatments, <24 mo at first treatment)	↑: 224 (number of treatments, <24 mo at first treatment)	↑: 224 (number of treatments, 12+mo at first treatment)
			N: 224 (24 + mo at first treatment)	N: 224 (24 + mo at first treatment)	N: 224 (< 12 mo at first treatment)
Cephalosporins	Cohort		N: 222		N: 222
	Case-control			N: 223	
Penicillins	Cohort		↑: 222 (broad spectrum penicillin)		
			N: 222		N: 222
	Case-control				N: 223
Aminoglycosides	Cohort		N: 222		N: 222
Macrolides	Cohort		N: 222		N: 222
	Case-control				N: 223
Sulfonamides	Cohort		↑: 222		N: 222
Tetracyclines	Cohort		↑: 222		N: 222
Medicine					
Analgesic or anesthetic	Cohort	N: 80 (asthma or wheezing: during labor)		N: 80 (during labor)	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Isoxsuprine	Case-control		↑: 198 (during pregnancy)		
Aspirin	Case-control		*N*: 225		
Hormone replacement therapy	Cross-sectional	↑: 18, 226	↑: 226 *N*: 18		↑: 226
Oral contraceptive	Cohort	↑: 80 (asthma or wheezing), 227 (without asthma) ↓: 227 (with asthma)		N: 80	
	Cross-sectional	*N*: 18	*N*: 18, 228	↑: 228	*N*: 228
Paracetamol	Case-control		↑: 225		
Salicylate	Case-control		*N*: 198 (during pregnancy)		
Trimethoprim/co-trimox.	Case-control				*N*: 223
Medical/health related factor					
Admitted to hospital for infection	Cohort			N: 66	
Visits to the GP in previous year	Case-control		↑: 8		
Referral/hospitalization in previous year	Case-control		*N*: 8		
Blood pressure	Cross-sectional				↓: 95 (diastolic) *N*: 95 (systolic)
Heart rate	Cross-sectional				↓: 95 (DD + reported)
Catch-up growing	Cohort		*N*: 97		
Child care/day care	Cohort		*N*: 40 (in first 3 mo)	↑: 66 (before 6 mo)	
Child psychological risk	Cohort		↑: 229		
Neonatal hospital admission	Cross-sectional	↑: 92			
Expulsion of intestinal worms	Cohort		*N*: 57		
Physical examination	Cross-sectional		*N*: 22		
Life events	Case-control		↑: 61	↑: 61	*N*: 61
Life satisfaction	Cohort		*N*: 230		
	Cross-sectional		*N*: 230		
Stress	Cohort		*N*: 230		
	Cross-sectional	↑: 15	*N*: 230		
Neuroticism	Cohort		*N*: 230		
	Cross-sectional		*N*: 230		
Extroversion	Cohort		↑: 230 (women) *N*: 230 (men)		
	Cross-sectional		*N*: 230		
Nitric oxide levels in exhaled air	Cohort	*N*: 231	↑: 231		
Early age at menarche	Cohort		↑: 227		
Number of pregnancies	Cross-sectional	*N*: 60	*N*: 60		*N*: 60
Number of live births	Cross-sectional	*N*: 60	*N*: 60		↓: 60 (allergic conjunctivitis)
Mechanical ventilation	Cohort		*N*: 97		
Threatened abortions	Case-control		*N*: 198		
Total IgE	Cohort	↑: 79, 232	↑: 229, 233 (at 10 y: in cord serum) *N*: 233 (at 4 y: in cord serum)	↑: 43 N: 79	
Specific IgE					
Mite, cockroach, cat, dog, egg, milk, soy, wheat, fish, or peanut	Case-control	↑: 44			
Mite, cockroach, cat, or dog	Case-control	↑: 44			
Ascaris lumbricoides	Case-control	*N*: 44			
Timothy grass	Cohort		↑: 42		

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Chlamydia pneumoniae	Case-control		↓: 234 (self-reported)		
Cat dander	Cross-sectional		↑: 19		
Cladosporium	Cross-sectional		↑: 19		
Dermatophagoides pteronyssius	Cross-sectional		↑: 19		
Food	Case-control		↑: 47 (grass pollen asthma)		
IgG	Cohort	N: 232			
			N: 234 (current)		
Sensitization (skin prick test)					
Alternaria	Cohort		N: 235	N: 235	N: 235
Animal	Case-control		↑: 47 (grass pollen asthma)		
Cat	Cohort		N: 235	↑: 235	N: 235
Cladosporium herbarum	Cohort		N: 235	N: 235	N: 235
Cod	Cohort		N: 235	N: 235	N: 235
Cockroach	Cross-sectional	↑: 170	N: 170		
Dog	Cohort		N: 235	N: 235	N: 235
Egg	Cohort		N: 235	N: 235	↑: 235
Grass pollen	Cohort		N: 235	↑: 235	↑: 235
Milk	Cohort		N: 235	N: 235	N: 235
Mites	Cohort		↑: 235	↑: 235	N: 235
	Case-control		↑: 47 (grass pollen asthma)		
Molds	Case-control		N: 47 (grass pollen asthma)		
Peanut	Cohort		N: 235	↑: 235	N: 235
Soya	Cohort		N: 235	N: 235	N: 235
Wheat	Cohort		N: 235	N: 235	N: 235
Dermatophagoides pteroyssinus	Cross-sectional	N: 170	↑: 170		
Dermatophagoides pteroyssinus, cockroach, cat, Alternaria tenuis, mixed grasses and mixed trees	Cohort			↑: 43	
Birch, timothy, mugwort, cat, dog, horse, Dermatophagoides pteronyssinus, Dermatophagoides farinae, Cladosporium, and Alternaria	Cohort	↑: 32	↑: 32		
Silk	Cross-sectional		↑: 236		
Reported food intolerance	Cohort			↑: 83 (reported) N: 83 (DD)	
Blood test					
Lead level	Cohort		N: 237		
Dichlorodiphenyldichloroethylene	Cohort	↑: 238 (cord serum)			
	Cross-sectional		N: 239	N: 239	N: 239
HDL cholesterol	Case-control		N: 240 (serum)	↑: 240 (serum)	↑: 240 (serum)
Estradiol	Case-control		N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)
Haemoglobin	Cohort			N: 43	
Ratio of progesterone/estradiol	Case-control		N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)
Breast milk					
Progesterone	Case-control		N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)
soluble CD14	Cohort		↓: 242 (without maternal atopy) N: 242 (with maternal atopy)	N: 242	

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Others					
Oil-fire smoke (Gulf War)	Cross-sectional		↑: 243		
Parenting difficulties	Cohort		↑: 229		
Source of water	Cohort				
(Well vs piped)	Case-control			*N*: 58	
(River vs piped)	Case-control			↓: 58	
(Spring vs piped)	Case-control			↓: 58	

↑: significant positive association
↓: significant inverse association
N: not statistically significant
DD: Doctor-diagnosed
Numerals in columns indicate reference numbers.

between pet ownership and allergic diseases, but the conclusions were contradictory. Several studies reported that pet ownership was associated with a decreased risk and prevalence of allergic diseases. In an Australian cohort study, having had a cat in childhood protected against adult asthma, irrespective of the presence of a cat in adulthood.[162] Age at the first exposure to pets or the critical period (*i.e.* the time window of immune maturation) might relate to the development of allergies. Some cross-sectional studies showed inverse associations between contact with a pet or pets and the prevalence of allergic diseases.[51,169,172] These findings may reflect pet avoidance because of allergic diseases in the family. A Swedish study showed a decreased prevalence of wheeze, asthma, and rhinitis among children exposed to pets soon after birth: crude ORs for wheeze, asthma, and rhinitis were 0.86 (95% CI: 0.78–0.95), 0.82 (95% CI: 0.69–0.98), and 0.78 (95% CI: 0.69–0.88), respectively.[168] However, in that study, adjustment for pet avoidance apparently changed the results: a positive association between exposure to pets at the time of birth and the prevalence of allergic diseases was observed. Adjusted ORs for wheeze, asthma, and rhinitis were 1.13 (95% CI: 1.01–1.26), 1.51 (95% CI: 1.23–1.84), and 1.05 (95% CI: 0.91–1.21), respectively.[168] A potential selection bias should be considered when interpreting results of the association between pet ownership and allergic diseases, if avoidance behaviour has not been dealt with properly. A parental history of allergy also might affect the relation between exposure to pets and allergic disorders in offspring. A birth cohort study in Finland found an inverse association of dog ownership with wheeze among children without parental asthma, but not among those with parental asthma.[163]

DAMPNESS

Epidemiological studies of dampness and allergic diseases have employed a variety of definitions for indoor dampness such as water leakage, visible mould, and condensation on windows. Five cohort studies,[32,43,75,158,176] 4 case-control studies,[45,128,148,177] and 4 cross-sectional studies,[6,86,129,178] examined the relation between dampness and allergic diseases. One half found positive associations between indoor dampness and the risk and prevalence of allergic disorders while no significant associations were observed in the remaining half.

HOUSE DUST ALLERGENS

A number of investigators have examined whether house dust allergen exposure contributes to the development of allergic diseases. In many communities, house dust mite (designated Der f1 for one species of mite and Der p1 for another) is the principal allergen. Eight reports analyzed the association between house dust mite allergens and allergies. Among children in

Australia, Der p1 exposure was related to an increased risk of asthma (adjusted OR = 2.04, 95% CI: 1.08–3.86).[6] Most of the studies reported no associations with house dust mite. A few, however, found that exposure to cockroach allergen (Bla g1) was positively associated with the risk and prevalence of wheeze and asthma.[33,56,90] The evidence is likely to be insufficient to infer the presence or absence of a relationship between indoor allergen exposure and allergic diseases.

INFECTION

It has been argued that bacterial and viral infections during early life direct the maturing immune system toward Th1, which counterbalances the proallergic responses of Th2 cells. Epidemiological studies that have tested the association between infection and allergic disorders fall into 2 groups: those relating to specific infections, and those assessing more generally the burden of infectious illness.

A positive association between the number of infectious diseases and atopic dermatitis was found in a Danish birth cohort study (adjusted OR = 1.33 [95% CI: 1.16–1.53] for 3 or more infectious diseases *vs* no infection).[66] A German birth cohort showed a strong positive dose-response association of the number of lower respiratory tract infection with the risk of wheeze (adjusted OR = 3.97 [95% CI: 2.06–7.64] for $\geq$ 4 infections *vs* $\leq$1 infection) and asthma (adjusted OR = 4.46 [95% CI: 2.07–9.64] for $\geq$4 infections *vs* $\leq$1 infection) whereas there was an inverse relationship between the number of viral infectious diseases and the risk of asthma (adjusted OR = 0.16 [95% CI: 0.05–0.54] for $\geq$8 viral infections *vs* $\leq$1 viral infection).[202] In several case-control and cross-sectional studies, there were not only no material associations between infectious illness and allergic diseases but also positive relationships with infectious diseases such as respiratory infection and ear infection. Inverse relationships between infection with hepatitis A, herpes, measles, and rubella virus and the risk and prevalence of allergic disease were observed in several investigations, whereas a cross-sectional study in Finland found a strong positive association between measles and asthma (adjusted OR = 1.67, 95% CI: 1.54–1.79), atopic dermatitis (adjusted OR = 1.32, 95% CI: 1.27–1.36), and allergic rhinitis (adjusted OR = 1.41, 95% CI: 1.33–1.49).[207]

Current evidence regarding associations with common specific and non-specific infectious illness neither refute nor support the hygiene hypothesis.

VACCINATION

During the past few decades, mass immunizations have increased, leading to the hypothesis that certain vaccines may increase the risk of allergic disorders. There are theoretical reasons to suspect a possible association of vaccination with allergies. One possible mechanism is a direct impact on the immune system that leads to raised immunoglobulin E levels.[217,218] Another possibility is that vaccination reduces the burden of childhood illness. One case-control study reported a significant reduction in the risk of atopic dermatitis associated with DTP (adjusted OR = 0.66, 95% CI: 0.49–0.89) and oral poliovirus vaccine (adjusted OR = 0.62, 95% CI: 0.45–0.85).[58] One cohort study reported that smallpox vaccination was associated with a decreased risk of asthma, but not allergic rhinitis.[219] Several cohort studies demonstrated a positive association between vaccination, such as DPPT, MMR, and hepatitis B virus vaccine, and asthma and atopic dermatitis.[199,216-218] We have insufficient evidence regarding the association between vaccination and allergic diseases.

DIETARY FACTORS

Studies regarding the relation between dietary intake and allergic diseases were limited compared with investigations with respect to various environmental factors and allergy (Table 2). Among Italian children, intake of citrus fruit and kiwi fruit were protective factors for wheeze (adjusted OR = 0.66, 95% CI: 0.55–0.78 for those eating fruit 5–7 times per week compared with less than once per week) and rhinitis (adjusted OR = 0.72, 95% CI: 0.63–0.83).[247] One cohort study reported that daily consumption of butter was associated with a lower risk of wheeze and asthma, whereas no associations were observed with the consumption of fruit, vegetables, margarine, or fish.[30] For margarine intake, two cross-sectional studies found a positive association with allergic rhinitis.[249,250]

There were 13 studies on the relation between nutrient intake and allergic diseases. One case-control study showed that alpha-linolenic acid intake was positively associated with asthma (adjusted OR for comparison of the fourth with the first quartile = 3.35, 95% CI: 1.29–8.66), but not wheeze.[257] Another case-control study found no association between intake of alpha-linolenic acid and asthma.[248] In contrast, 2 cross-sectional studies observed that alpha-linolenic acid was associated with a decreased prevalence of atopic dermatitis and allergic rhinitis.[249,258] The ratio of n-6 to n-3 polyunsaturated fatty acid as well as that of linoleic acid to alpha-linolenic acid intake were not consistently related to allergic diseases. Although several studies investigated the relationship of mineral intake to allergies, most found no associations. Two case-control studies indicated an inverse association between intake of vitamins C and E and asthma.[48,244] On the other hand, maternal vitamin C intake during pregnancy was positively associated with the development of wheeze and atopic dermatitis during early childhood: adjusted OR the for fifth quintile was 3.00 (95% CI: 1.47–6.12) for wheeze, and 1.56 (95% CI: 0.99–2.45) for atopic dermatitis.[254] With re-

Table 2 Dietary factors and allergic diseases

Factors	Design	Outcome			
		Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Dietary intake					
Total energy/calories	Case-control		*N*: 84		
	Case-control		*N*: 244		
Brown bread	Cohort	*N*: 30	↓: 30		
Miso	Cross-sectional				*N*: 245
Miso soup	Cross-sectional				*N*: 245
Soy product	Cross-sectional				↓: 245
Boiled soybeans	Cross-sectional				*N*: 245
Tofu	Cross-sectional				*N*: 245
Tofu products	Cross-sectional				*N*: 245
Fermented soybeans	Cross-sectional				*N*: 245
Vegetable	Case-control		↓: 48	*N*: 58	
Green, leafy vegetables	Cross-sectional		*N*: 20		
Fruit	Case-control			↑: 58	
	Cross-sectional	*N*: 246	*N*: 20		
Fruit and vegetable	Cross-sectional		↑: 23 (women) *N*: 23 (men)		
Citrus/kiwi fruit	Cohort	↓: 247			*N*: 247
	Cross-sectional	↓: 247			↓: 247
Fish	Case-control		*N*: 248		
Meat	Case-control		*N*: 248		
Meat products	Case-control		*N*: 248		
Butcher's meats	Cross-sectional		*N*: 71		
Chicken, meat, or fish	Cross-sectional		*N*: 20		
Liver	Cross-sectional		↑: 71		↑: 71
Eggs	Case-control		*N*: 248		
	Cross-sectional		*N*: 20		
Milk	Case-control		↓: 48 *N*: 248		
	Cross-sectional		*N*: 20		
Semi-skimmed milk	Cohort	*N*: 30	*N*: 30		
Unpasteurized milk	Cross-sectional		*N*: 68	↓: 68	*N*: 68
Whole milk	Cohort	*N*: 30	↓: 30		
Milk products	Cohort	↓: 30	*N*: 30		
Cheese	Case-control		*N*: 248		
Butter	Cohort	↓: 30	↓: 30 (current) *N*: 30 (ever)		
	Case-control		*N*: 248		
	Cross-sectional			*N*: 249	*N*: 249
Margarine	Cohort	*N*: 30	*N*: 30		
	Case-control		↑: 248		
	Cross-sectional			*N*: 249	↑: 249 (men) *N*: 249 (women)
Margarine only (*vs* exclusive butter)	Cross-sectional		*N*: 250		↑: 250 (allergic rhinitis) *N*: 250 (hay fever)
Margarine and butter (*vs* exclusive butter)	Cross-sectional		*N*: 250		*N*: 250