

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	Wheeze	Outcome		
			Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Basic characteristics					
	Age				
	Cohort				
	Case-control				
Sex (male)					
	Cohort				
	Case-control				
	Cross-sectional				
Socioeconomic factors					
	High socioeconomic status				
	Cohort				
	Case-control				
High social class					
	Cohort				
	Case-control				
	Cross-sectional				
Poverty					
	Cohort				
	Case-control				
	Cross-sectional				
High education					
	Cohort				
	Case-control				
	Cross-sectional				
Parental high education					
	Cohort				
	Case-control				
	Cross-sectional				

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			
Inability to see a doctor due to cost	Cross-sectional		↑ : 23	N: 5
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	↑ : 25 (girls)	↓ : 64
		N: 15	↓ : 17, 64	N: 64
			N: 20, 25 (boys), 65	
Farm	Cohort		↓ : 68	N: 66
	Cross-sectional	↑ : 13	N: 65, 69	↓ : 68, 69
		N: 67	↑ : 48	
Urban	Case-control		↑ : 71	↑ : 71
	Cross-sectional	↑ : 70	N: 70	
			↑ : 72	
Urbanization	Cohort			
Dump area	Cohort			
Siblings				
Number of siblings	Cohort	↑ : 31	↓ : 57	↓ : 73, 75, 76
			N: 38, 73, 74	
	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: 82
	Case-control	N: 77	↓ : 84	
			N: 77 (wheeze + asthma)	
	Cross-sectional	N: 16	↓ : 51 (adult onset), 78 (asthma with allergic rhinitis)	↓ : 16
			N: 51 (childhood and adolescence on sel)	
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	Asthma	Atopic dermatitis Allergic rhinitis (Hay fever)
Anthropometric measurement	Case-control			
	Cross-sectional	N: 86	↓ : 85 ↓ : 20 N: 86	N : 58
	Cohort	↓ : 30 N: 80 (asthma or wheezing), 81, 87	↑ : 35, 88 N: 38, 87	↑ : 89 N: 73, 91
	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 N: 80, 89, 91
Birth length	Cross-sectional	N: 92	N: 93	N: 93
Ponderal index (g/cm ³) at birth	Cohort	N: 87	N: 57, 87 ↑ : 88	N: 73
Head circumference at birth	Cohort	N: 87	N: 73, 94	N: 89, 91
Head circumference/birth weight ratio	Cohort	N: 87	N: 87, 89 N: 87, 89	↓ : 89 N: 89
Head circumference/weight at 1 month ratio	Cohort		N: 89	N: 89
Height	Cross-sectional			N: 99 N: 89, 98
Overweight, obesity	Cohort	N: 96	↑ : 4, 40, 59, 97, 98, 99, 100, 94, 101 N: 57, 89 ↑ : 7, 8, 102 N: 84, 103	N: 43, 89
Body fat	Case-control			
	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
	Cross-sectional			↑ : 110
	Cohort		↑ : 98 N: 59, 101 N: 8, 102 ↑ : 20, 22 (men) N: 17, 22 (women), 23, 104, 105	↑ : 98
Underweight	Case-control			
	Cross-sectional	↑ : 17 ↓ : 109 N: 104, 105 N: 109		
Waist circumference	Cross-sectional		↑ : 108 (women) N: 108 (men), 109	
Maternal factors				
Maternal age	Cohort	↓ : 31 N: 31, 33	↑ : 34 N: 33, 36, 38, 73 N: 84 N: 93 N: 111 N: 38 N: 38, 57	N: 73 N: 58 N: 16, 93 N: 111
Maternal age at menarche	Case-control	N: 16		
Maternal BMI before pregnancy	Cohort			
Maternal weight gain during pregnancy	Cohort			
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		Outcome		
		Wheeze	Asthma	Atopic dermatitis
Maternal complication during delivery	Cohort	N: 80 (asthma or wheezing)		Allergic rhinitis (Hay fever)
Maternal depression	Cross-sectional		↑ : 52	N: 80
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 ↑ : 84	↓ : 73, 89
Season of birth	Case-control		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	Cohort		N: 112	N: 112
Breech delivery	Cohort	↑ : 113 N: 34, 114	↑ : 38, 57, 73 (ever), 112, 115, 116 N: 34, 73 (current), 114	↑ : 115 N: 73, 76, 112, 113, 116
Caesarean section	Cohort		N: 112	N: 112
Forceps/vacuum extraction	Cohort		↑ : 38	
Forceps, manual auxiliary, and extraction breech	Cohort		N: 38	
Vacuum extraction	Cohort			
Special procedures at delivery	Cohort		N: 38	
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			
Induced labor	Cohort	N: 80 (asthma or wheezing)		N: 76
Smoking	Cohort			
Active smoking	Cohort	↑ : 117 N: 81	↑ : 117, 118, 119 N: 4 ↑ : 8 N: 6	
	Case-control		↑ : 11, 18, 19, 20, 21, 23 (women), 120, 121 ↓ : 22 (men) N: 10, 13, 22 (women), 23 (men), 120, 122, 123	↓ : 123 N: 21, 121, 122
	Cross-sectional	↑ : 10, 11, 13, 15, 18, 120		
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	Asthma	Atopic dermatitis Allergic rhinitis (Hay fever)
Maternal smoking during pregnancy	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	↑ : 9 (current), 121, 133 (hay fever/asthma) N: 9 (ever, DD), 16, 24, 121, 123, 134, 130
	Cohort	↑ : 31 N: 31, 56, 80 (asthma or wheezing), 81	↑ : 135 (ever) N: 38	N: 125 (hay fever and/or asthma)
	Case-control		↑ : 45, 127 N: 84	N: 43, 80
Serum cotinine level	Cross-sectional	N: 86	↑ : 26, 136 N: 86, 93	N: 26, 93
	Cohort		N: 59	
Occupation				
Farmer	Cohort		↓ : 74, 38 (paternal) N: 9	N: 9
Farmer (vs civil servant)	Cross-sectional	N: 9		
Works at home	Case-control		N: 20	N: 58
Works outside home	Cross-sectional		↓ : 20	
Cleaning work	Cross-sectional		↑ : 137	↑ : 137
Duration of daily work	Cohort			
Shift work	Cohort			
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	↑ : 139		
Insecticide use	Cross-sectional	N: 139		
	Case-control		↑ : 11	↑ : 58
Pesticide	Cross-sectional	↑ : 11		
Repair pesticide equipment	Cross-sectional	↑ : 140		
Disinfectants	Cross-sectional	↑ : 139		
Fertilizer	Cross-sectional	↑ : 11	N: 122	N: 122
Natural fertilizer	Cross-sectional	↑ : 139	N: 11	

Factors	Design	Outcome	
		Asthma	Allergic rhinitis (Hay fever)
Chemical fertilizer	Cross-sectional		
Livestock	Cross-sectional	N: 139	
Cattle kept inside house	Case-control	↑ : 13 ↓ : 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	↑ : 41	
	Case-control	↑ : 144	
	Cross-sectional	N: 41, 55, 141, 145	N: 145
		N: 55 (current), 145	
NOx	Cross-sectional	N: 141	
SO ₂	Cross-sectional	↑ : 145 N: 55	N: 145
Particulate matter < 10μm	Cohort	N: 41	
	Cross-sectional	N: 41, 141, 145	N: 145
Particulate matter 2.5 μm	Cohort	N: 141	
Particulate matter 2.5 μm absorbance	Cross-sectional	N: 141	
Total suspended particle	Case-control	↑ : 144	
Black carbon	Cross-sectional	N: 141	
O ₃	Cross-sectional	N: 55, 145	N: 145
Air quality	Cohort	N: 5	
Home environment			
Temperature	Case-control	↑ : 6, 147	
Carpeting	Case-control	↓ : 45	
	Cross-sectional	N: 148	
Vacuuming	Case-control	↓ : 148 (house) N: 148 (bedroom)	
Dust	Cohort	N: 149	
	Cross-sectional	N: 13	
House dust allergens			
Der f 1	Cohort	N: 150	
	Case-control	N: 151	
	Cross-sectional	N: 152	N: 152
	Ecological	N: 153	
Der p 1	Cohort	N: 150	N: 83
	Case-control	↑ : 6	
	Cross-sectional	N: 151	
	Ecological	↑ : 153 (13–14 y) N: 153 (6–7 y)	N: 152
Der f 1 + Der p 1	Cohort	N: 153	
	Case-control	N: 155	
Fel d 1	Cohort	N: 151	
		↑ : 157 (with maternal asthma) ↓ : 157 (without maternal asthma)	
		N: 154 (atopic wheeze), 157, 158	
	Case-control	N: 157 N: 151	N: 83

Factors	Design	Outcome		
		Wheeze	Asthma	Atopic dermatitis
Can f 1 Dog allergen Bla g 1	Cohort	N: 157, 158	N: 157	Allergic rhinitis (Hay fever)
	Cohort	N: 90, 156		
	Cohort	N: 158		
	Cross-sectional	↑ : 56 (repeated wheeze) N: 56 (any wheeze) ↑ : 33, 90 ↑ : 90	↑ : 33	
Cockroach allergen Mouse allergen	Cohort			
	Cohort			
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
	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 EPS from Penicillium and Aspergillus	Cross-sectional	N: 67		
	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)	↑ : 168 (ownership at time of birth), 171 (cat: current) ↓ : 169 (cat + dog), 172 (dog)
	Cross-sectional			N: 16, 169 (cat), 171 (cat: DD), 172 (cat)

Factors	Design	Wheeze	Outcome	
			Asthma	Atopic dermatitis
Fuel				Allergic rhinitis (Hay fever)
Coal as fuel	Cross-sectional	N: 11	N: 11	
Comstalks 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	
	Cross-sectional	N: 86, 129	↑ : 86	N: 148
			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
Gas stove	Cohort	N: 158		
Unvented heater	Cross-sectional	N: 174		
	Cohort			
	Cross-sectional		N: 41	
Stove (kerosene, coal, wood, dung, straw)	Cross-sectional	N: 9	N: 41	
			↓ : 9 (DD)	
Biosmoke (open fire or burning smoke without a fuel vs. gas or kerosene stove)	Case-control		N: 9 (ever)	↓ : 9 (ever)
Fume emitting heaters	Cross-sectional	↑ : 175 (first year of life)	↑ : 126	N: 9 (current, DD)
		N: 175 (current)		
Radiator in bedroom	Case-control		N: 175	
Hearth or open fire place	Case-control		N: 45	N: 148
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)	↑ : 129 (girls)	
		N: 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 gas/gyser	Case-control		↑ : 45	
Dampness				
Dampness/humidity	Cohort	↑ : 176	N: 32, 176	N: 43
		N: 32		

Factors	Design	Outcome		
		Wheeze	Asthma	Atopic dermatitis
	Case-control	↑ : 177		↑ : 148 (current) N: 128, 148 (ever)
	Cross-sectional	N: 178	↑ : 178 N: 6 (living room)	↑ : 178 (DD) N: 178 (current) N: 75
Mold or mold odour	Cohort	↑ : 158 (with maternal asthma) N: 158 (without maternal asthma)		
	Case-control	↑ : 177		
	Cross-sectional	↑ : 86 N: 129	↑ : 45 ↑ : 86 N: 129	N: 43
Condensation	Cross-sectional	N: 178	↑ : 178	N: 128
Water leakage	Cross-sectional	N: 178	N: 178	↑ : 178 N: 178 (DD)
Water damage	Cross-sectional	↑ : 86	N: 86	↑ : 178 (current) N: 178 (DD)
Flooding	Case-control			
Floor moisture	Cross-sectional	↑ : 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
Di (2-ethylhexyl)phthalate in house dust	Case-control		↑ : 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			
Sheepskin underbedding	Cross-sectional	↓ : 50	↓ : 182	
Synthetic pillow	Cohort	↑ : 183		N: 182
	Case-control			
	Cross-sectional	↑ : 50, 183, 184	↑ : 184	↑ : 148
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		↑ : 27	↑ : 186 (rhinitis), 189
		N: 86, 187 (among 6–7 y), 188, 189	N: 86, 186, 188	N: 189	N: 186 (hay fever), 188
Seaside living	Cross-sectional			↑ : 27	
Living near opencast coal mining site	Cross-sectional	N: 190	N: 190	↑ : 27	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				
	Case-control		↑ : 37, 40, 41		
	Cross-sectional	↑ : 12	↑ : 6		↑ : 122
			↑ : 12, 41, 122		
			N: 191		
Asthma	Cohort			↑ : 43	
	Cross-sectional			↑ : 27	
Asthma or bronchitis	Cohort		N: 57		
Wheezing	Cohort			↑ : 43	
Wheezy bronchitis (< 2 y)	Cohort				
Allergic rhinitis or hay fever	Cohort		↑ : 4		↑ : 125 (hay fever and/or asthma)
	Case-control		↑ : 8		
	Cross-sectional	↑ : 50		↑ : 27	
Rhinitis	Cross-sectional		↑ : 19		
Eczema	Cohort		↑ : 4	↑ : 43	
	Cross-sectional	↑ : 50	↑ : 132		

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

Factors	Design	Outcome		
		Wheeze	Asthma	Allergic rhinitis (Hay fever)
	Case-control			
	Cross-sectional	N: 12	↑ : 19 (infection before 5 yrs), 51 (childhood and adolescent 12onset)	N: 201
Upper respiratory tract infections	Cohort			
Lower respiratory infection	Cohort	↑ : 202	N: 51 (adult onset)	N: 82
	Cross-sectional		N: 82, 193	N: 93
Ear infection	Cross-sectional	↑ : 203	↑ : 39, 202	
Gastrointestinal infection	Cohort	N: 202	↑ : 93	
	Case-control	N: 201	↑ : 203	
Viral infection	Cohort	N: 202	N: 202	N: 201
	Case-control	↑ : 44 (among < 2 y)	↓ : 202	N: 197
		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	
Measles	Cohort		N: 202	N: 205
	Case-control	N: 77, 206	↓ : 77 (≤ 3 y, wheeze + asthma) N: 77 (> 3 y, wheeze + asthma)	↑ : 207
	Cross-sectional		↑ : 207	N: 93
Rubella	Case-control	N: 77, 206	N: 77 (wheeze + asthma)	↓ : 93
	Cross-sectional			N: 208 (suspected)
Epstein-Barr virus	Cohort	N: 208	N: 77 (wheeze + asthma)	
Mumps	Case-control	N: 77, 206		
Varicella	Cohort		N: 77 (wheeze + asthma)	N: 66
Bacterial infections	Case-control	N: 77, 206	N: 77 (wheeze + asthma)	
Chlamydia pneumoniae	Cohort	N: 202	N: 202	N: 209
	Cohort		↓ : 209	↓ : 209
			N: 118	
			N: 210	
	Cross-sectional	↑ : 210 (prior infection)		
Pertussis	Case-control	N: 210 (acute infection)		
Helicobacter pylori	Case-control	N: 77	N: 77 (wheeze + asthma)	
Salmonellosis	Cohort	N: 77	N: 77 (wheeze + asthma)	
Scarlet fever	Case-control	↓ : 211	↓ : 211	↓ : 211
Geohelminth	Cross-sectional	N: 207		N: 212
		↓ : 212 (exercise-induced)	N: 129	
		N: 170, 212		
Helminth	Cross-sectional		N: 213	
Malaria	Case-control			↑ : 58
Hookworm	Case-control			N: 58
Ascariis	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	Allergic rhinitis (Hay fever)
Parasite egg in stool	Cross-sectional			
Parasite presence	Case-control			
Fungal	Cohort	N: 202		N: 29
Toxoplasma gondii	Case-control	N: 77		
	Cross-sectional			↓ : 204
Vaccine				
DTP vaccine	Cohort			
	Case-control		N: 216, 217	↓ : 58
DPPT vaccine	Cross-sectional	N: 199		
MMR vaccine	Cohort		N: 199	↑ : 218
	Cohort		↑ : 218	↑ : 205, 218
	Cohort		N: 217	
	Cohort		N: 47	
	Case-control		N: 199	
Measles or MMR vaccine	Cross-sectional	N: 199		
	Cohort		N: 216	
Measles or MMR, DTP and OPV	Cohort		↑ : 216	
Snailpox vaccine	Cohort		↓ : 219	
Oral poliovirus vaccine	Cohort		N: 216, 217	
	Case-control		N: 47	
	Cross-sectional	N: 199		↓ : 58
Hepatitis B virus vaccine	Cohort		↑ : 217	
	Cohort		N: 216	
	Case-control		N: 46	
	Cross-sectional	N: 199	↑ : 199	
	Cohort		↑ : 217	N: 219
Haemophilus influenzae type b vaccine	Cohort			
Influenza vaccine	Cohort		↑ : 216	
BCG	Cohort		N: 216	
	Cohort		N: 199, 220	
Tuberculin skin test	Cross-sectional		N: 24, 26	↓ : 24, 26, 29
Antibiotics				
	Cohort		↑ : 82, 222	
	Case-control		N: 202, 221	N: 82, 125 (hay fever and/or asthma), 221, 222
	Cross-sectional	↑ : 199, 224	↑ : 198 (during pregnancy)	N: 223
			↑ : 199, 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 (< 12 mo at first treatment)
			N: 222	N: 222
Cephalosporins	Cohort			
	Case-control			
	Cohort		↑ : 222 (broad spectrum penicillin)	
Penicillins	Cohort		N: 222	N: 222
				N: 223
Aminoglycosides	Case-control			
Macrolides	Cohort		N: 222	N: 222
	Cohort		N: 222	N: 222
Sulfonamides	Case-control			
Tetracyclines	Cohort		↑ : 222	N: 223
	Cohort		↑ : 222	N: 222
Medicine				
Analgesic or anesthetic	Cohort			
		N: 80 (asthma or wheezing: during labor)		N: 80 (during labor)

Factors			Outcome		
	Design	Wheeze	Asthma	Atopic dermatitis	Allergic rhinitis (Hay fever)
Isosuprine	Case-control		↑ : 198 (during pregnancy) N: 225		
Aspirin	Case-control		↑ : 226 N: 18		↑ : 226
Hormone replacement therapy	Cross-sectional	↑ : 18, 226			
Oral contraceptive	Cohort	↑ : 80 (asthma or wheezing), 227 (without asthma) ↓ : 227 (with asthma) N: 18		N: 80	
Paracetamol	Cross-sectional		N: 18, 228	↑ : 228	N: 228
Salicylate	Case-control		↑ : 225		
Trimethoprim/co-trimox.	Case-control		N: 198 (during pregnancy)		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) ↓ : 95 (DD + reported)
Heart rate	Cross-sectional				
Catch-up growing	Cohort		N: 97		
Child care/day care	Cohort		N: 40 (in first 3 mo) ↑ : 229	↑ : 66 (before 6 mo)	
Child psychological risk	Cohort		N: 57		
Neonatal hospital admission	Cross-sectional	↑ : 92	N: 22		
Expulsion of intestinal worms	Cohort		↑ : 61		
Physical examination	Cross-sectional		N: 230	↑ : 61	N: 61
Life events	Case-control		N: 230		
Life satisfaction	Cohort		N: 230		
Stress	Cross-sectional		N: 230		
Neuroticism	Cohort	↑ : 15	N: 230		
Extroversion	Cross-sectional		N: 230		
Nitric oxide levels in exhaled air	Cross-sectional		↑ : 230 (women) N: 230 (men)		
Early age at menarche	Cohort	N: 231	↑ : 231		
Number of pregnancies	Cohort	N: 60	↑ : 227		
Number of live births	Cross-sectional	N: 60	N: 60		N: 60
Mechanical ventilation	Cohort		N: 97		↓ : 60 (allergic conjunctivitis)
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			Outcome		
	Design	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			
Sensitization (skin prick test)			N: 234 (current)		
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
Molds	Case-control		↑ : 47 (grass pollen asthma)		
Peanut	Case-control		N: 47 (grass pollen asthma)		
Soya	Cohort		N: 235	↑ : 235	N: 235
Wheat	Cohort		N: 235	N: 235	N: 235
Dermatophagoides pteronyssius	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			
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)			
HDL cholesterol	Cross-sectional		N: 239	N: 239	N: 239
Estradiol	Case-control		N: 240 (serum)	↑ : 240 (serum)	↑ : 240 (serum)
Haemoglobin	Cohort		N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)	N: 241 (serum at early pregnancy)
Ratio of progesterone/estradiol	Case-control		N: 241 (serum at early pregnancy)	N: 43 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	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 ≥ 4 infections *vs* ≤ 1 infection) and asthma (adjusted OR = 4.46 [95% CI: 2.07–9.64] for ≥ 4 infections *vs* ≤ 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 ≥ 8 viral infections *vs* ≤ 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	
Green, leafy vegetables	Cross-sectional		N: 20	N: 58
Fruit	Case-control			↑ : 58
	Cross-sectional		N: 20	
Fruit and vegetable	Cross-sectional	N: 246	↑ : 23 (women) N: 23 (men)	
Citrus/kiwi fruit	Cohort	↓ : 247 ↑ : 247		
	Cross-sectional			N: 247
Fish	Case-control		N: 248	↓ : 247
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	
	Case-control		N: 248	
	Cross-sectional		N: 20	
Semi-skimmed milk	Cross-sectional		N: 20	
Unpasteurized milk	Cohort	N: 30	N: 30	
Whole milk	Cross-sectional		N: 68	↓ : 68
Milk products	Cohort	N: 30	↓ : 30	
Cheese	Cohort	N: 30	N: 30	
Butter	Case-control		N: 248	
	Cohort	↓ : 30 (current) ↑ : 30 (ever)		
	Cohort		N: 248	
Margarine	Case-control			N: 249
	Cross-sectional		N: 30	
	Cohort	N: 30	↑ : 248	
	Case-control			
	Cross-sectional			N: 249
Margarine only (vs exclusive butter)	Cross-sectional		N: 250	↑ : 249 (men) N: 249 (women)
Margarine and butter (vs exclusive butter)	Cross-sectional		N: 250	↑ : 250 (allergic rhinitis) N: 250 (hay fever) N: 250

Factors	Design	Outcome		
		Wheeze	Asthma	Atopic dermatitis Allergic rhinitis (Hay fever)
Vegetable oils	Case-control Cross-sectional		N: 248	
Alcohol	Cohort		N: 251 N: 8	↑ : 249 (women) N: 249 (men) N: 249
Carbonated beverages	Case-control	N: 15		
Deep-fried foods	Cross-sectional	N: 252	N: 252	N: 252
Hamburger	Cross-sectional	↑ : 71	↑ : 71	N: 252
Takeaways	Cross-sectional	↑ : 252	N: 252	N: 252
Early introduction of cereal into children's diets (before age of 3 mo)	Case-control	N: 252	↑ : 47	
Intake of nutrients				
Carbohydrates	Case-control		N: 244	
Fiber	Case-control		N: 48	
Total protein	Case-control		N: 244	N: 245
Soy protein	Cross-sectional			
Total fat	Case-control		N: 248	↑ : 249
Calcium	Cross-sectional		N: 48, 244	
Magnesium	Case-control		↑ : 48	
Iron	Case-control		N: 244	
Sodium	Case-control		N: 244	
Zinc	Case-control		↑ : 48	
Yttrium	Case-control		N: 244	
Selenium	Case-control		N: 244	
Vitamin A	Case-control		↑ : 244	
Vitamin D	Case-control		N: 244, 253 (supplementation)	
Vitamin E	Cohort	N: 254 (during pregnancy)		N: 254 (during pregnancy)
Vitamin K	Case-control		↑ : 48, 244	
Vitamin C	Case-control		N: 244	↑ : 254 (during pregnancy)
	Cohort	↑ : 254 (during pregnancy)		
	Case-control		↑ : 244	
Thiamine	Cross-sectional	N: 11	N: 48	
Riboflavin	Case-control		N: 10	
Niacin	Case-control		N: 244	
Vitamin B6	Case-control		N: 244	
Vitamin B12	Case-control		N: 244	
Folic acid	Case-control		N: 244	
Antioxidant	Case-control		N: 84	
Catechins	Case-control		N: 255	
Flavones	Case-control		N: 255	
Flavonols	Case-control		N: 255	
Daidzein	Cross-sectional			↑ : 245

Factors	Design	Outcome		
		Wheeze	Asthma	Atopic dermatitis
Genistein	Cross-sectional			
Saturated fatty acids	Cross-sectional			
Palmitic acid	Case-control		↑ : 256 N: 248	N: 249
Stearic acid	Case-control		N: 248	
Monounsaturated fatty acids	Cross-sectional		↓ : 256	↑ : 249 N: 249
Palmitoleic acid	Case-control		N: 248	
Oleic acid	Case-control	N: 257	↑ : 257 N: 248	↑ : 249
Alpha-Linolenic acid	Cross-sectional			
	Case-control	N: 257	↑ : 257 N: 248	↑ : 249
	Cross-sectional			↓ : 258 N: 249
Eicosapentaenoic acid	Case-control	N: 257	N: 248, 257	N: 258
Docosahexaenoic acid	Cross-sectional			
Linoleic acid	Case-control		N: 248	
	Case-control		N: 248	N: 249, 258
Arachidonic acid	Cross-sectional		N: 248	N: 249, 258
Trans fatty acid	Cross-sectional			N: 249
Polysaturated/ saturated ratio	Cohort			
n-6/n-3	Cross-sectional	N: 257	↑ : 84 N: 248, 257	N: 249
Linoleic acid/Alpha-Linolenic acid	Cross-sectional			
	Case-control	↓ : 257	↓ : 257	↑ : 249 N: 249
Arachidonic acid/Linoleic acid	Cross-sectional			
Lipids	Case-control	↑ : 257	↑ : 257 N: 244	N: 249
Breastfeeding				
Breastfeeding	Cohort	↓ : 30, 31, 37 (wheeze; 3–13 y) N: 37 (wheeze; < 3 y)	↑ : 37, 57 (breastfeeding at 3, 6, and 9 mo; partial breastfeeding at 9 and 12 mo), 193 ↓ : 30, 40, 242 (without maternal atopy), 259	↑ : 43, 261 (without parental allergies) N: 63, 83, 242, 261 (with parental allergies)
			N: 57 (breastfeeding at 12 mo; partial breastfeeding at 3 and 6 mo), 242 (maternal atopy), 260	N: 76, 125 (hay fever and/or asthma)
Formula feeding	Case-control		↑ : 84	
	Cross-sectional	↓ : 50 N: 262, 263	↓ : 239 N: 26, 93, 263	↓ : 26 N: 93, 239, 262
Measurements	Cohort			N: 125 (hay fever and/or asthma)
In breast milk				
n-3	Cohort		N: 264	
Alpha-Linolenic acid	Cohort		N: 264	
Eicosapentaenoic acid	Cohort		N: 264	
Docosahexaenoic acid	Cohort		↓ : 264	

Factors	Design	Wheeze	Outcome	
			Asthma	Allergic rhinitis (Hay fever)
n-6	Cohort		N: 264	N: 264
Linoleic acid	Cohort		N: 264	N: 264
Arachidonic acid	Cohort		N: 264	N: 264
Trans fatty acid	Cohort		↓ : 264	↓ : 264
n-6/n-3	Cohort		↑ : 264	↑ : 264
Linoleic acid/Alpha-Linolenic acid	Cohort		N: 264	N: 264
Eicosapentaenoic acid/Arachidonic acid	Cohort		N: 264	N: 264
In blood				
Selenium	Cross-sectional		N: 265 (serum)	
β-Carotene	Cross-sectional	N: 246 (plasma)	N: 265 (serum)	
Vitamin A	Cross-sectional	↑ : 246 (plasma)		
Vitamin E	Cross-sectional	N: 246 (plasma)	N: 265 (serum)	
Vitamin C	Cross-sectional	N: 246 (plasma)	↓ : 265 (serum)	
Saturated fatty acids	Cross-sectional		↓ : 266 (plasma)	
Monounsaturated fatty acids	Cross-sectional		N: 266 (plasma)	
Oleic acid	Cross-sectional			N: 258 (red blood cell membranes)
Polysaturated fatty acids (PUFA)	Cross-sectional		N: 266 (plasma)	
n-3	Cross-sectional		N: 266 (plasma)	
Docosahexaenoic acid	Cross-sectional		N: 266 (plasma)	
α-Linolenic acid	Cross-sectional		↑ : 266 (plasma: asthma)	
Eicosapentaenoic acid	Cross-sectional		N: 266 (plasma)	↓ : 258 (red blood cell membranes)
n-6	Cross-sectional		N: 266 (plasma)	
Gamma-Linolenic acid	Cross-sectional		N: 266 (plasma)	
Eicosadienoic acid	Cross-sectional		↑ : 266 (plasma: asthma, DD)	
Eicosatrienoic acid	Cross-sectional		↑ : 266 (plasma)	
Docosapentaenoic acid	Cross-sectional		N: 266 (plasma)	
Linoleic acid	Case-control	↓ : 257 (serum)	↓ : 257 (serum)	
Arachidonic acid	Cross-sectional		N: 266 (plasma)	N: 258 (red blood cell membranes)
	Cohort			
	Case-control	↑ : 257 (serum)	↑ : 257 (serum)	N: 258 (red blood cell membranes)
PUFA: 22:4 n-6	Cross-sectional		N: 266 (plasma)	
Trans fatty acid	Cross-sectional		N: 266 (plasma)	
n-6/n-3	Cross-sectional		N: 266 (plasma)	N: 258 (red blood cell membranes)
Arachidonic acid/eicosapentaenoic acid	Cross-sectional			↑ : 258 (red blood cell membranes)

↑ : significant positive association

↓ : significant inverse association

N: not statistically significant

DD: Doctor-diagnosed

Numerals in columns indicate reference numbers.

spect to traditional Japanese food, a cross-sectional study observed that consumption of soy and isoflavones was significantly associated with a decreased prevalence of allergic rhinitis among Japanese pregnant women.²⁴⁵

Overall, epidemiological evidence on the association of food and nutrient intake and allergic disease was not sufficient to draw any conclusions.

BREASTFEEDING

Twenty-two studies were identified with investigation on whether breastfeeding practice was associated with allergic diseases. While several investigations showed a protective effect of breastfeeding on wheeze and asthma, others failed to show such a beneficial relationship. In several studies, positive associations between breastfeeding and asthma and atopic dermatitis were observed. One cohort study found that the duration of breastfeeding was inversely associated with the risk of asthma in children without a maternal history of atopic diseases: adjusted OR was 0.35 (95% CI: 0.18–0.66) in children exclusively breastfed 9 or more months in comparison with children who had never been breastfed.²⁴² On the other hand, another cohort study found an increased risk of atopic dermatitis associated with breastfeeding in children without a parental history of allergic diseases (adjusted OR for exclusive breastfeeding for at least 4 months compared with less than 4 months = 1.29, 95% CI: 1.06–1.55).²⁶¹ These results should be interpreted with caution. The main factor that may have induced bias is inherent in the breastfeeding practice itself, that is, it is the personal choice of mothers whether or not to breastfeed. This choice is subject to several influences, including previous knowledge of allergic diseases or allergic diseases in the family and perceived benefits of breastfeeding or not breastfeeding.

The beneficial influence of breastfeeding on allergic diseases may be attributed to several possible mechanisms. Breast milk stimulates intestinal colonization with specific bacterial flora. Gut colonization induces the production of Th1 cytokines, which counterbalances Th2 activity. On the other hand, a possible detriment is protection against infections that can be important stimuli for the development of allergic diseases. Breastfeeding might reduce the effect of bacteria on the immune system, so that the infant does not fully develop mature immune response mechanisms.²⁶⁷

The evidence is insufficient to infer a causal relationship between breastfeeding and allergic diseases. Further research is needed to achieve a greater understanding.

FAMILY HISTORY

A summary of the results of investigation of the association between a family history of allergy and aller-

gic diseases in offspring is shown in Table 3. Most of the studies showed that allergic diseases were likely to have a strong genetic component. The increased risk seemed to be present no matter which type of allergic diseases were in family members. No study showed an inverse relation with the presence of a family history of allergic diseases. Atopic heredity may influence susceptibility to allergic diseases. This indicates a positive association of family history of allergies and allergic disorders with such conditions in offspring.

DISCUSSION

In the present paper, we reviewed 263 studies on the associations of various environmental factors with wheeze, asthma, atopic dermatitis, and allergic rhinitis. Because to our knowledge there has not been such an extensive review on a wide range of environmental factors in relation to allergic disorders, including dietary intake and family history, this report may be useful for future research on this area.

Although a number of reports addressed the effect of environmental factors on allergic diseases, evidence is conflicting. The wide variation in results among the many epidemiological studies may be attributed, at least in part, to the limitation of environmental measurements using indirect approaches or surrogates. In addition, interpretations of findings were limited because most were case-control studies or of a cross-sectional nature which could not infer a causal relationship. However, such investigations are quite useful and much less costly, take much less time, and are more suitable for hypothesis generation than other methodologies.

It is important to note that findings should be interpreted and applied with great caution. First, the exclusion of literature in languages other than English could have introduced publication bias. Second, cited studies used various defined diagnostic criteria (e.g. doctor-diagnosed asthma, self-reported asthma, and according to questionnaires filled out by parents). Variations in outcome based on a variety of such diagnostic criteria would result in discrepant results. Third, we summarized the results without differentiating the age of subjects. The impact of risk factors among children may be different from that among adults due to age-specific differences in immune maturation or other potentially antiallergic effects. Lastly, many epidemiological investigations in terms of allergic disorders were not included in this review because our review consisted of a search of one database (PubMed) using only one set of search terms, and we did not perform additional searches from reference lists of the articles that fulfilled our inclusion criteria. Moreover, a number of reports regarding relationships with outcomes such as atopy, results of skin prick test, serum IgE levels, and bronchial hyperresponsiveness were not taken into consideration

Table 3 Family history and allergic diseases

Factors	Design	Outcome		
		Wheeze	Asthma	Allergic rhinitis (Hay fever)
Family history Asthma	Cohort	↑ : 32 N: 81	↑ : 32, 135	
	Case-control		↑ : 6	
	Cross-sectional	↑ : 18, 50, 55, 92	↑ : 18, 19, 55, 136 N: 25	
Atopy or allergy	Cohort	N: 81		
	Case-control	↑ : 44 (among < 2 y)		
	Cross-sectional	N: 44 (among 2–12 y) ↑ : 9	↑ : 9 (ever), 136 N: 9 (DD) ↑ : 48	N: 9
Asthma/allergy Atopic dermatitis Allergic rhinitis Chronic bronchitis emphysema	Case-control			
	Cross-sectional			↑ : 27 N: 27
	Cross-sectional			N: 27
	Cross-sectional			↑ : 9 (current, ever) N: 9, 9 (DD)
Household tuberculosis	Cross-sectional	N: 9	↑ : 9 N: 9	↑ : 125 (hay fever and/or asthma)
Parental history Allergy or atopy	Cohort		↑ : 74, 118 N: 41	↑ : 43
	Case-control			↑ : 61 ↑ : 24
	Cross-sectional		↑ : 24, 41, 136	↑ : 24 N: 29 ↑ : 61 N: 16
Asthma	Case-control		↑ : 61	
	Cross-sectional	↑ : 16	↑ : 93, 136	N: 16
	Case-control		↑ : 167	↑ : 76 ↑ : 16
Asthma and/or allergies	Cross-sectional		↑ : 51	
	Cross-sectional	N: 16		↑ : 16, 28, 93
	Cohort			↑ : 16 N: 93
Rhinitis or hayfever	Cross-sectional	N: 16	↑ : 93	
Maternal history Allergy or atopy	Cohort	N: 30	↑ : 30, 38	↑ : 26
	Cross-sectional		N: 26	
	Cohort	↑ : 31, 186 (persistent and late onset wheezing)	↑ : 39, 40, 259	
Asthma	Case-control	N: 33, 56, 164 (transient wheezing)		
	Cross-sectional	↑ : 9, 14, 17	↑ : 46, 84, 167 ↑ : 9, 52, 132 N: 9, 14	↑ : 9, 16
Atopic dermatitis	Cohort			↑ : 43
	Case-control		↑ : 46	↑ : 16, 93
	Cross-sectional	↑ : 16		

Factors	Design	Outcome		
		Wheeze	Asthma	Allergic rhinitis (Hay fever)
Rhinitis or hayfever	Cohort	N: 164		
	Case-control		N: 46	
	Cross-sectional	↑ : 92 N: 16		↑ : 16 N: 16
Paternal history Allergy or atopy	Cohort	↑ : 30	↑ : 30 (ever) N: 30 (current) N: 167	↑ : 43
Asthma	Case-control		↑ : 37	↑ : 43
	Cohort	N: 164	↑ : 46, 167	
	Case-control		↑ : 132	
Atopic dermatitis	Cohort		N: 46	↑ : 43
	Case-control			↑ : 93
Rhinitis or hayfever	Cohort	N: 164		↑ : 43
	Case-control		↑ : 46	
	Cross-sectional	↑ : 92		↑ : 93
in siblings				
Asthma	Cross-sectional		↑ : 93	
Atopic dermatitis	Cross-sectional			↑ : 93 N: 93
Rhinitis or hayfever	Cross-sectional		↑ : 93	↑ : 93

↑ : significant positive association

↓ : significant inverse association

N: not statistically significant

DD: Doctor-diagnosed

Numerals in columns indicate reference numbers.

in the present review.

On the basis of this review, it is clear that the data are insufficient to conclude an association between many environmental factors and allergic disorders. As most studies were conducted in Western countries, the application of these findings to people in other countries, including Japan, may not be appropriate. Further studies on the incidence of allergic diseases are required to conclude the relationship of environmental factors and allergic disease, taking into account the timing of the environmental exposure and genetic factors.

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