

Childhood environment and adult atopy: Results from the European Community Respiratory Health Survey

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Background: Previous literature has indicated that environmental exposures in childhood influence development of atopic sensitization.

Objective: We sought to study the association between childhood environment and adult atopy.

Methods: Thirteen thousand nine hundred thirty-two subjects aged 20 to 44 years from 36 areas in Europe, New Zealand, the United States, and Australia took part in the European Community Respiratory Health Survey, answering interviewer-led questionnaires and providing blood tests for measurement of specific IgE to grass, house dust mite, cat, and *Cladosporium* allergens.

Results: Atopy was negatively associated with family size (OR = 0.93; 95% CI = 0.90-0.96 per 1 sib), partly attributable to an independent protective effect of a greater number of brothers (OR = 0.92; 95% CI = 0.89-0.95 per 1 brother). Accounting for total number of siblings, no further influence was detected for number of older or younger siblings. Bedroom sharing was associated with a lower prevalence of atopy, particularly to cat allergen. A protective effect of family size and bedroom shar-

ing could only be detected in subjects reporting no parental allergy (family size, test for interaction $P = .012$). The presence of a dog in the home in childhood was negatively associated with adult atopy (OR = 0.85, 95% CI = 0.78-0.92), an effect that remained after adjustment for parental allergy, sibling allergy, and adult pet ownership.

Conclusion: Subjects from large families with brothers, shared bedrooms, and dogs in childhood were less often atopic as adults. Our findings are consistent with the hypothesis that infectious agents could inhibit development of atopy during childhood. However, in subjects with a strong genetic predisposition, environmental factors in childhood are possibly of less importance. (*J Allergy Clin Immunol* 1999;103:415-20.)

Key words: Atopy, childhood, family size, European Community Respiratory Health Survey

Previous literature has indicated that environmental exposures in childhood influence development of atopic sensitization and allergic disease. Children from large families are at reduced risk for the development of hay fever,¹⁻⁵ eczema,^{1-2,6} and allergic sensitization to common aeroallergens.^{5,7-10} This has been observed in children,^{1-2,6,9-10} adolescents,^{3,4} and adults.^{5,7-8} Some studies have shown less atopy with an increasing number of older, but not younger, siblings.^{2-3,7} However, such a difference has not been confirmed in other studies.^{5,8} In a study of self-reported inhalant allergy in women, a stronger protective effect was reported for brothers compared with sisters.⁸

The mechanisms by which childhood environment influences development of atopy are not clear. It has been hypothesized that childhood exposure to infectious agents may prevent sensitization through the preferential induction of T_H1 -type cytokines.^{2,11} The findings of less atopy in young adults from Guinea-Bissau with a history of measles infection,¹² less atopy in Italian military students with hepatitis A antibodies,¹³ and less atopic disorders among Japanese children with immunity to tuberculosis¹⁴ support this hypothesis. Patterns of growth have also been hypothesized to play a role in the development of the immune system.^{11,15} Godfrey et al¹⁵ found that serum total IgE was associated with head circumference at birth, and a study of Danish children showed an association between atopic dermatitis and high birth weight.⁶

Stage II of the European Community Respiratory Health Survey (ECRHS) includes information on several childhood factors, namely family size, shared bedrooms, day care attendance, airways infections, parental smoking, and pet ownership, in a large number of subjects from 36 centers representing 16 countries. This study address-

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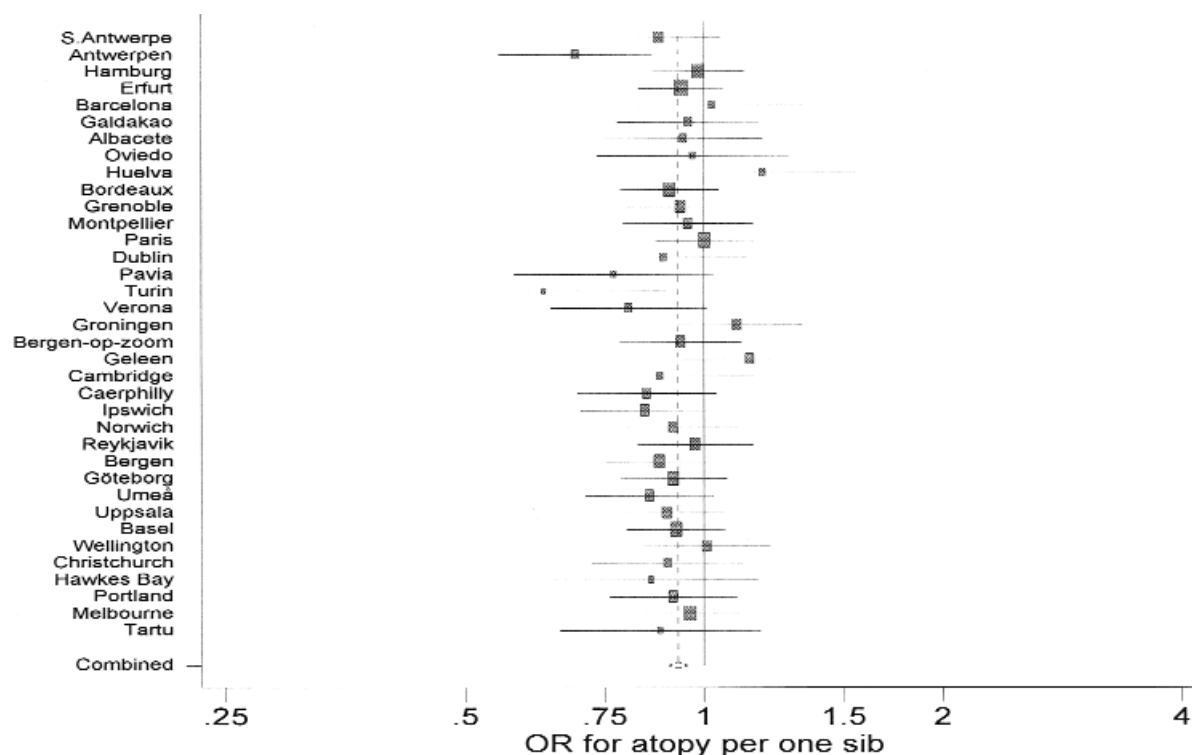


FIG 1. Adjusted odds ratios (*squares*) and 95% confidence intervals (*horizontal lines*) of atopy (specific IgE to 1 or more allergen) with an increase of 1 sibling by center (adjusted for sex, age, occupation, and smoking), with combined odds ratio (*diamond*) from model with center as random effect. Size of squares is proportional to sample size in each center.

TABLE I. Unadjusted prevalence and adjusted odds ratios for atopy (specific IgE to 1 or more allergen) and serum-specific IgE to 4 common allergens according to family size

No of siblings	Prevalence of sensitization (%)					OR (95% CI)*	P value
	0	1	2	3	4+		
Atopy (4522/13,932†)	34.0	34.5	32.9	32.0	28.6	0.93 (0.90-0.96)	<.001
IgE grass (2660/13,929†)	19.8	21.4	20.0	17.9	15.2	0.93 (0.89-0.96)	<.001
IgE house dust mite (2754/13,931†)	19.1	19.9	20.1	20.0	19.3	0.96 (0.93-1.00)	.04
IgE cat (1236/13,932†)	12.0	9.6	9.1	8.0	6.7	0.91 (0.86-0.95)	<.001
IgE mold (435/13,928†)	3.0	3.5	2.9	3.4	2.6	0.98 (0.91-1.06)	.6

*Per 1 sibling; estimated by logistic regression adjusted for age, gender, current smoking, current occupation, and study center.

†Number with outcome/number investigated.

Abbreviation used

ECRHS: European Community Respiratory Health Survey

es the relationship between these childhood exposures and specific IgE to common allergens in young adults.

METHODS

Data collection

The methodology for the ECRHS has been fully described elsewhere.^{16,17} Briefly, participating centers selected an area defined by preexisting administrative boundaries with a population of at least

150,000. When possible, an up-to-date sampling frame was used to select randomly at least 1500 men and 1500 women aged 20 to 44 years. In stage I, subjects were sent the ECRHS screening questionnaire, a self-completed 9-item questionnaire asking about symptoms suggestive of asthma, the use of medication for asthma, and the presence of hay fever or nasal allergies. In stage II, a smaller random sample of subjects who had completed the screening questionnaire was invited to attend for a more detailed interviewer-led questionnaire and blood tests for the measurement of specific IgE to house dust mite, cat, timothy grass, and *Cladosporium* allergens.

Serum samples were obtained by centrifugation of 10 mL whole blood at 4000g for 10 minutes. All samples were stored at -20°C and analyzed in a central laboratory by the CAP system (Pharmacia Diagnostics, Sweden), except for samples from Melbourne, which were analyzed locally by using the same analytic technique. The

TABLE II. Effects of brothers, sisters, older siblings, and younger siblings on atopy (specific IgE to 1 or more allergen) as estimated in separate models and adjusted for total number of siblings (family size)

Separate models				Adjusted for family size			
Variable	OR	(95% CI)*	P value	Variable	OR	(95% CI)*	P value
Family size	0.93	(0.90-0.96)	<.001	—	—	—	—
Older siblings	0.96	(0.93-0.99)	.004	Older siblings	1.00	(0.96-1.04)	1.0
				Family size	0.93	(0.90-0.97)	<.001
Younger siblings	0.94	(0.91-0.97)	<.001	Younger siblings	0.97	(0.93-1.01)	.1
				Family size	0.95	(0.91-0.98)	.004
Brothers	0.92	(0.89-0.95)	<.001	Brothers	0.95	(0.91-1.00)	.04
				Family size	0.96	(0.92-1.00)	.08
Sisters	0.96	(0.93-0.99)	.02	Sisters	1.03	(0.98-1.08)	.2
				Family size	0.92	(0.88-0.96)	<.001

*Per 1 sibling; estimated by logistic regression adjusted for age, gender, current smoking, current occupation, and study center.

test response for specific IgE was considered to be positive if greater than 0.35 kU/L (the lowest detection limit of the assay).

This study included data from 36 centers representing 16 countries. The distribution of serum IgE for all but one of these centers has been described previously.¹⁸ Altogether, 18,530 subjects were included, of whom 13,932 (75%) provided a blood sample. "Atopy" was defined as having specific IgE to 1 or more of the allergens tested.

Statistical analysis

Logistic regression models were used to assess the independent effects of the childhood exposure variables on serum-specific IgE to grass, house dust mite, and cat allergen and to any 1 of these allergens (denoted "atopy"). Multiple linear regression was used to assess the associations between the childhood factors and serum total IgE. Potential heterogeneity between centers in the effect of each exposure variable was studied by metaanalyses, according to the method of DerSimonian and Laird.¹⁹ Number of siblings, brothers, sisters, older siblings, and younger siblings was categorized as 0, 1, 2, 3, and 4 or more. Because a logistic regression model including all categories of siblings did not fit the data better than a model with siblings used as a continuous variable, the latter was used for most purposes. In all analyses, adjustments were made for age, gender, smoking habits, study center, and current occupation (European Economic Community Status Groups - 14).²⁰ All analyses were carried out with the statistical software program Stata.²¹

RESULTS

Family size, brothers and sisters, older and younger siblings

Specific IgE to one or more allergens decreased with increasing number of siblings (Table I). This association was strong for grass and cat sensitization and only indicated for sensitization to house dust mite. The effects were consistent between centers (tests for heterogeneity: atopy, $P = .5$; IgE grass, $P = .2$; IgE house dust mite, $P = .7$). Fig 1 shows the odds ratio for each center, as well as a combined odds ratio for the effect of number of siblings on atopy. Number of siblings was not related to total IgE ($P = .9$).

To separate the effects of family size, older and younger siblings, and brothers and sisters, each variable was first analyzed in separate models and then allowed to compete with the general effect of family size (Table II).

In separate models the protective effects of younger and older siblings were fairly similar. When total number of siblings was accounted for, there was no further effect detected for the number of older or younger siblings. Following a similar procedure to separate the effects of brothers, sisters, and family size, separate models showed a stronger protective effect of brothers than of sisters. After adjustment for family size, an effect of brothers could still be identified, whereas no effect of sisters was found. This was similar for men and women (data not given). Specific IgE to grass, house dust mite, and cat allergen showed similar patterns in individual analyses. The effect of brothers on atopy, adjusted for family size, was consistent between the 36 centers (test for heterogeneity, $P = .6$).

All childhood factors

Family size, a history of bedroom sharing, and pet ownership in childhood were significantly related to atopy in separate analyses of each factor (Table III). No association with atopy was found for day care attendance, serious respiratory infections, maternal and paternal smoking, and adult height.

Mutual adjustment of family size and bedroom sharing (Table III) attenuated the effect of family size slightly, whereas the effect of bedroom sharing was no longer significant. These variables were not altered by adjustment for other childhood factors. Bedroom sharing was independently associated with sensitization to cat allergen when adjustments were made for family size (OR = 0.84, 95% CI = 0.72-0.96).

Dog ownership in childhood was associated with less atopy in adulthood (Table III). The effects of cat and other pet ownership were no longer significant when adjusted for dog ownership (Table III). The association between dog ownership in childhood and adult atopy remained after adjustment for parental allergy, sibling allergy, or cat or dog ownership at the time of study.

Reported serious respiratory infections before the age of 5 years were significantly associated with specific IgE to house dust mite and cat allergen, but when subjects

TABLE III. Childhood exposures and associations with atopy (specific IgE to 1 or more allergens) in separate analyses of each exposure and in mutually adjusted analysis

Variable	Category	Number*	Separate effects		Mutually adjusted effects	
			OR (95% CI)†	P value	OR (95% CI)†	P value
Family size	0 sibs	1355	1	—	—	—
	1 sib	4084	0.97 (0.85-1.11)	—	—	—
	2 sibs	3546	0.90 (0.79-1.04)	—	—	—
	3 sibs	2145	0.88 (0.76-1.02)	—	—	—
	4+ sibs	2802	0.75 (0.65-0.87)	—	—	—
	Per 1 sib	—	0.93 (0.90-0.96)	<.001	0.95 (0.91-0.98)	.001
Bedroom sharing	No	7523	1	—	1	—
	Yes	6230	0.90 (0.83-0.97)	.005	0.95 (0.88-1.03)	.3
Day care attendance	No	6789	1	—	—	—
	Yes	6867	1.03 (0.94-1.11)	.5	—	—
Serious respiratory infection	No	11,774	1	—	—	—
	Yes	1344	1.10 (0.97-1.25)	.1	—	—
Paternal smoking	No	4460	1	—	—	—
	Yes	9025	0.98 (0.91-1.06)	.6	—	—
Maternal smoking	No	9996	1	—	—	—
	Yes	3769	1.03 (0.95-1.12)	.5	—	—
Cat in childhood	No	7295	1	—	1	—
	Yes	6622	0.88 (0.82-0.95)	.002	0.94 (0.87-1.02)	.1
Dog in childhood	No	7154	1	—	1	—
	Yes	6768	0.82 (0.76-0.89)	<.001	0.85 (0.78-0.92)	<.001
Other pet in childhood	No	4740	1	—	1	—
	Yes	9181	0.91 (0.84-0.99)	.02	0.96 (0.89-1.05)	.4
Adult height	≤158 cm	1070	1	—	—	—
	159-164 cm	2668	0.92 (0.78-1.09)	—	—	—
	165-170 cm	2477	0.96 (0.81-1.14)	—	—	—
	171-177 cm	3890	0.93 (0.78-1.10)	—	—	—
	178-183	2004	0.87 (0.71-1.07)	—	—	—
	>183	1645	0.82 (0.67-1.02)	—	—	—
	Per 5 cm	—	0.98 (0.95-1.01)	.2	—	—

*For each question some subjects answered "don't know," and thus all totals do not equal 13,932.

†Estimated by logistic regression adjusted for age, gender, smoking habits, current occupation, and study center.

with wheeze with shortness of breath were excluded, no association between atopy and childhood infections was found (data not given). Adult height tended to be negatively associated with atopy, reaching significance only for house dust mite sensitization (OR = 0.96, 95% CI = 0.93-1.00).

Metaanalyses of the associations between each exposure variable and atopy were performed to assess possible heterogeneity between centers. There was no significant heterogeneity in any of the exposure variables, and thus the protective effects of family size, brothers, shared bedrooms, and dog ownership were all consistent between centers.

Total IgE was not related to any of the childhood environmental factors.

Effect modification by parental allergy

A protective effect of siblings on adult atopy could only be found in subjects reporting no parental allergy (test for interaction, $P = .012$). This was true for sensitization to grass and house dust mite allergen, but not for sensitization to cat allergen (Table IV). Also, the effect of bedroom sharing seemed to be more pronounced in persons without parental allergy (Table IV). In subjects

reporting parental allergy, both cat and dog ownership were associated with less atopy, whereas in subjects reporting no parental allergy, a protective effect was only found for dog ownership (Table IV).

DISCUSSION

Subjects from large families with brothers, shared bedrooms, and dogs in childhood had a lower risk of atopic sensitization in adulthood. This was found in a large study of men and women from 36 centers from different parts of the Western world, strongly supporting the concept that environmental factors in childhood influence development of the immune system in an allergic or nonallergic direction. Some environmental influences, however, seem to be of less importance in subjects with a family history of allergic disease.

The negative association between atopy and number of siblings agrees with earlier reports.¹⁻¹⁰ However, when it comes to the various aspects of family size (older and younger siblings, brothers and sisters) the literature gives inconsistent conclusions. Several papers show a stronger effect of older siblings compared with younger siblings,^{2,3,7,13} whereas in one study Strachan et al⁸ could find

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

	No parental allergy (n = 8991)		Parental allergy (n = 4929)	
	OR (95% CI)*	P value	OR (95% CI)*	P value
Effect of family size (per 1 sib) on the following outcomes:				
Atopy†	0.91 (0.87-0.94)	<.001	0.99 (0.94-1.04)	.7
IgE grass	0.90 (0.85-0.94)	<.001	0.98 (0.93-1.04)	.5
IgE house dust mite	0.94 (0.90-0.98)	.006	1.02 (0.96-1.08)	.5
IgE cat	0.91 (0.85-0.97)	.006	0.91 (0.84-0.98)	<.001
Mutually adjusted effects on atopy of the following exposures:				
Family size (per 1 sib)	0.93 (0.89-0.96)	<.001	0.99 (0.94-1.05)	.7
Bedroom sharing	0.88 (0.79-0.97)	.01	1.10 (0.96-1.26)	.2
Cat in childhood	1.00 (0.90-1.10)	1.0	0.86 (0.76-0.98)	.03
Dog in childhood	0.85 (0.77-0.94)	.002	0.82 (0.72-0.93)	.003
Other pet in childhood	0.96 (0.87-1.07)	.5	0.95 (0.83-1.09)	.5

*Estimated by logistic regression adjusted for age, gender, current smoking, current occupation, and study center.

†Specific IgE to 1 or more allergen.

no such difference. Jarvis et al⁵ found a stronger effect of family size than of birth order in a subset of the ECRHS. In this study we could not identify marked differences between older and younger siblings. This could possibly indicate that the age of exposure to siblings in childhood is not of critical importance, which is consistent with the finding that infective load, rather than age of acquisition, may be of importance for T_H-cell differentiation.²²

Number of brothers was more strongly related to atopic sensitization than number of sisters and appeared to constitute a major part of the family size effect. A stronger protective effect of brothers has previously been found in women.⁸ It was suggested that this might be explained by the possibility of more severe cross-infections by opposite sex siblings.²³ In the present study a stronger effect of brothers was found in both men and women, indicating a particular effect of having male siblings. A possible explanation could be that boys, having more serious respiratory infections than girls,²⁴ could provide a stronger exposure to infectious agents. Alternatively, the number of brothers could possibly influence patterns of growth (eg, by gender differences in food sharing).

Bedroom sharing added to the protective effect of family size on atopy in subjects without parental allergy. This indicates that by whatever mechanism a large number of siblings contribute to prevent an atopic development, this mechanism is enhanced by physical proximity. Transmission of infectious agents is most likely enhanced by bedroom sharing. Day care attendance, which also promotes early infections,²⁵ was not related to adult atopy in this study, and this was in agreement with a previous report.⁷ This could be interpreted as an argument against the infection hypothesis but might also reflect that the time window studied (under 5 years) is too broad or too narrow.

We found a strong and convincing protective effect of dog ownership in childhood on adult atopy, an association that was robust after adjustment for all available confounders and consistent between study centers. An appar-

ent protective effect of pets could possibly be explained by the fact that families with allergy would less often keep pets. As the effect of dog ownership was similar in subjects with and without parental allergy (or sibling allergy, data not given), this explanation seems unlikely. A protective effect of cat ownership, however, was only seen in subjects with parental allergy and could possibly be explained by selection of pet ownership to nonatopic families. Dog ownership in childhood could possibly provide exposure to a broad spectrum of infectious agents that could favor a nonallergic development of the immune system. Although the presence of a dog could also be a proxy variable for outdoor physical activity or socioeconomic factors, this seems less likely given the consistency of the association between centers.

Large families, brothers, shared bedrooms, and dog ownership all represent an environment with exposure to infectious agents. Our findings thus support the hypothesis that contact with microorganisms may contribute to a nonatopic development of the immune system. Some studies have pointed to an increased rate of atopy in subjects with early infections; for example, Wjst et al²⁶ found that pertussis infection was related to increased allergic sensitization. It is possible that early infections could contribute both to the prevention and promotion of atopic sensitization, depending on the type of infection, infectious load, or host conditions. In this study, however, an association of atopy with recalled serious respiratory infections before age 5 years was explained by confounding with asthma.

The protective influence of environmental factors in childhood, such as shared bedrooms and large family size, seemed to be of less importance in subjects reporting parental allergic disease. Differential recall bias (ie, that recall of parental allergy should be related to family size in nonatopic but not in atopic subjects) seems unlikely. Thus the observation of a significant interaction between parental allergy and family size in this study of 36 different areas may reflect a true difference. We

hypothesize that environmental factors related to infections in childhood have a smaller potential to influence development of the immune system in an allergic or non-allergic direction in subjects who already have a high genetic predisposition for allergic disease. Further search for determinants of atopy should take into account possible differences according to genetic predisposition.

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APPENDIX.

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Norway: A. Gulsvik, E. Omenaas (Bergen).

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United Kingdom: M. Burr, J. Layzell (Caerphilly); R. Hall (Ipswich); B. Harrison (Norwich); J. Stark (Cambridge).

USA: S. Buist, W. Vollmer, M. Osborne (Portland).