

Influence of early life exposures on incidence and remission of asthma throughout life

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Background: Knowledge of the effects of early environmental and congenital factors on the natural history of asthma may provide important clues to the pathogenesis of asthma.

Objective: We assessed associations between potential, early determinants and the incidence and remission of asthma throughout life, and tested whether the strength and direction of these associations varied in childhood, adolescence, and adulthood.

Methods: The data pertaining to the individual asthma history of 18,156 subjects, age 0 to 44 years, who attended the clinical stage of the European Community Respiratory Health Survey were analyzed retrospectively by life-event methods. Onset of asthma was defined as age at the first attack, and asthmatic patients were considered to be in remission if they had not been under treatment or had an attack of asthma in the past 24 months. Onset and remission were evaluated in 3 time windows: <10, 10 to 20, and ≥ 20 years of age. The associations of asthma with early determinants were estimated by hazard ratios (HRs).

Results: A family history of asthma or allergy was associated with a higher risk of developing asthma (HR, 1.89; 95% CI, 1.67-2.13) and a lower chance of remission (HR, 0.79; 95% CI, 0.64-0.99) throughout life. No matter what one's genetic predisposition was, early, acute respiratory infections were associated with an increased lifelong risk of asthma onset (pooled HR, 3.19; 95% CI, 2.75-3.69), whereas early contact with older children, which is a marker of prolonged, intermittent exposure to infectious agents, conferred permanent protection against asthma (HR, 0.84; 95% CI, 0.74-0.96) and increased the chance of remission in childhood asthma (HR, 1.50; 95% CI, 1.10-2.04). Pet ownership had a protective effect only in childhood (HR, 0.78; 95% CI, 0.74-0.96), whereas maternal smoking did not show a significant association with asthma. Female sex was negatively associated with the onset of asthma in childhood (HR, 0.62; 95% CI, 0.52-0.75) and positively in adulthood (HR, 2.01; 95% CI, 1.61-2.51). The pattern of associations was similar in sensitized (positive assay to specific IgE) and nonsensitized asthmatic patients.

Conclusion: Genetic predisposition and exposure to infectious

agents are major early determinants that influence a subsequent history of asthma. The length and type of exposure to infectious agents seem able either to promote or to suppress an anti-inflammatory process, unrelated to IgE, which can partially interfere with an acquired predisposition for asthma. (J Allergy Clin Immunol 2004;113:845-52.)

Key words: Asthma, incidence, remission, hygiene hypothesis, natural history, early infections, congenital factors, ECRHS

The decline in infectious diseases during childhood has been suggested as a possible explanation for the increase in allergic diseases in industrialized Western countries (hygiene hypothesis).¹ Early life exposure to infectious agents may direct the maturation of the immune system from a type T_H2 bias at birth toward a predominantly type T_H1 response, with a lesser risk for asthma and allergy. Accordingly, the reduction in the overall microbial burden and the consequent weak T_H1 imprinting over the past century may have contributed to the global increase in these conditions.^{2,3}

Epidemiologic findings supporting this hypothesis are the suggested protective effects on atopy of early life day care attendance and the presence of older siblings at home.⁴⁻⁶

However, the hygiene hypothesis is contradicted by the observation that the prevalence of T_H1 immune diseases is also increasing⁷ and that T_H2 skewed parasitic infections are negatively associated with the prevalence of asthma.⁸ Recent observations that long-term helminth infections increase anti-inflammatory cytokines such as IL-10 suggest that the promotion or suppression of an anti-inflammatory network as a result of different types of infectious agents may be a better unifying explanation for the somewhat contrasting epidemiologic findings on the association of infections and asthma and allergy than the simple T_H1/T_H2 imbalance theory.⁹

Knowing whether the effects of early exposures persist throughout life, are transient, or affect only the onset of disease or its persistence could contribute to understanding the mechanisms through which early exposures play their role. Until now, there has been no single study investigating the associations of early exposures with incidence and remission of asthma or allergy during the life span, mainly because of the logistic difficulty in setting up a long-term follow-up of a cohort, which would make it possible to assess the role

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*Abbreviations used*ECRHS: European Community Respiratory Health Survey
HR: Hazard ratio

of potential determinants according to the age at onset of the disease.³

The aim of this article was to assess the associations among congenital factors, childhood exposures, and asthma incidence and remission in childhood, adolescence, and adulthood, and to test whether these associations varied according to the age at onset of asthma. For this purpose, we performed a retrospective analysis of the data collected during the clinical stage of the European Community Respiratory Health Survey (ECRHS) in subjects in which information on early life exposure and a personal history of asthma were available.

METHODS

Study design

The data presented in this study were collected within the framework of the ECRHS between 1991 and 1993. ECRHS is an international, cross-sectional, 2-stage study on the prevalence, determinants, and management of asthma and has been fully described previously.¹⁰ The study involved several centers in different countries; centers were defined by pre-existing administrative boundaries and had a population of at least 150,000 inhabitants. In each center, a random sample of at least 1500 men and 1500 women aged 20 to 44 years was selected.

In the first stage of the survey, a screening questionnaire was mailed to the selected subjects. In the second stage (clinical stage), a smaller (20%), random sample of subjects who had completed the screening questionnaire was invited to the clinics. There the subjects underwent a standardized clinical interview by trained interviewers, lung function tests, methacholine challenge test, and allergologic tests. Total and specific IgE was also measured.

The current analysis includes 18,156 subjects who attended the second stage of ECRHS in 36 centers representing 16 countries in Europe, North America, and Oceania.

Data management and statistical analysis

The presence of lifelong asthma was identified on the basis of a positive answer to the question, "Have you ever had asthma?" The age at onset of asthma was determined according to the answer to the question, "How old were you when you had your first attack of asthma?" The long-term reliability of these 2 questions was assessed on 633 Italian subjects who answered the same questions 10 years apart (1991, 2001) in the frame of ECRHS-II. The Cohen κ coefficients were 0.80 (95% CI, 0.71-0.87) and 0.90 (95% CI, 0.67-1.00), respectively, pointing out that asthmatic patients are highly reliable when they recall the history of their disease.¹¹

Asthmatic patients were considered to be in remission if they gave a negative answer to the questions, "Have you used any inhaled medicines to help your breathing at any time in the last 12 months?" and, "Have you used any pills, capsules, tablets or medicines, other than inhaled medicines, to help your breathing at any time in the last 12 months?" and if they reported not having had their last attack of asthma in the 2 years before the interview. Other asthmatic patients were considered to be not in remission. For asthmatic patients in remission, the age at which remission occurred was considered to be

the age of the last asthma attack ("How old were you when you had your most recent attack of asthma?").

The potential determinants of asthma considered in the current analysis were the following:

Congenital variables. Sex and parental asthma or allergies. Parental asthma or allergies were considered present in the case of a positive answer to the questions, "Did your mother ever have asthma?" "Did your mother ever have eczema, skin or nasal allergy or hay fever?" "Did your father ever have asthma?" and, "Did your father ever have eczema, skin or nasal allergy or hay fever?" Answers were coded by a 2-level variable: no parental history of asthma and allergy, or at least 1 parent with asthma and/or allergy.

Childhood exposures. Contact with older children early in life, having pets in childhood, maternal smoking, and respiratory infections in childhood. Contact with older children was determined if a subject answered affirmatively to the following questions: "Did you regularly share your bedroom with any older children before the age of five years?" and/or, "Did you go to a school, play-school or nursery with older children before the age of five years?" Pet ownership in childhood was based on the positive answer to the question, "When you were a child did anyone in your household keep any of the following pets?" (cats, dogs, horses, and so forth). Maternal smoking and respiratory infections were identified respectively from the answers to the questions, "Did your mother ever smoke regularly during your childhood, or before you were born?" and "Did you have a serious respiratory infection before the age of five years?"

Other potential confounders taken into account in the analysis of incidence and remission in adults were body mass index (classified as ≤ 25 and > 25), total IgE (≤ 100 kU/L and > 100 kU/L), smoking habits (never vs ever smoked), passive exposure to tobacco smoking (positive answer to the question, "Have you been regularly exposed to tobacco smoke in the last 12 months?"), and occupational exposure (positive answer to the question, "Have you ever worked in a job which exposed you to vapours, gas, dust or fumes?").

For specific analyses, asthmatics were classified according to their sensitization status. Sensitization, measured as a positive assay to specific IgE (specific IgE to *Dermaphagoides pteronyssinus*, timothy grass, *Cladosporium herbarum*, cat, and *Parietaria judaica* [for Southern Europe] or birch [for Northern Europe], or ragweed [for non-European countries] was measured in serum samples in a central laboratory by the CAP system [Pharmacia Diagnostics, Uppsala, Sweden]), was considered present if values > 0.35 kU/L (the lowest detection limit of the assay) for at least 1 specific allergen were found.

Analysis of asthma incidence

Incidence rates were computed by dividing the number of occurrences (the first attack of asthma) by the total number of person-years at risk—that is, the time from birth to the age of the first attack of asthma for asthmatic subjects, or the time from birth to the age at the time of the interview for nonasthmatic subjects. Person-years at risk and occurrences were then split according to 3 time windows reflecting childhood (0-10 years), adolescence (10-20 years), and adulthood (≥ 20 years). Incidence rates were computed within each time window (Fig 1).

To study the association between risk factors and incidence of asthma according to the age at onset, the Cox regression model¹² was fitted to the data within each time window, using the time to the onset of asthma as the dependent variable, countries and age as potential confounders, and congenital characteristics and childhood exposure as potential predictors.

Variables related to adults (body mass index, total IgE, active and passive smoking, occupational exposure) were included only in the model of the third time window (≥ 20 years) as potential confounders.

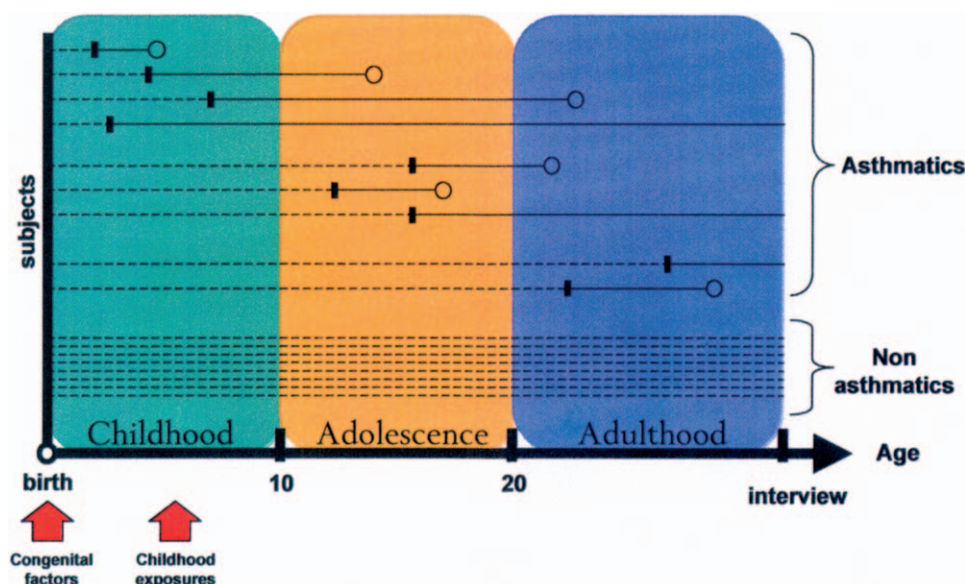


FIG 1. Natural history of asthma in the studied subjects. Dashed lines indicate the time at risk for incidence, and continuous lines indicate the time at risk for remission. Onset is indicated by ■, remission by ○.

To test the homogeneity of the hazard ratios (HRs) across age at onset strata, a meta-analysis was performed by using a fixed-effect general variance-based method,¹³ which yielded a pooled HR.

Analysis of asthma remission

Only asthmatic patients were considered for the analysis of remission. The time during which an asthmatic patient was at risk of remission was calculated as the time from age at onset of asthma to age of remission (last attack), or to age at time of the interview if the subject was not in remission. Person-years at risk and events were stratified according to the age of asthma onset: <10 years, 10 to 20 years, and ≥20 years. Within each stratum, a Cox regression model was fitted to the data, using as the dependent variable the time to the remission and as predictors the same covariates used for the incidence analysis.

RESULTS

A total of 1558 of 18,156 valid responders (8.6%) reported lifelong asthma. The main characteristics and distribution of studied determinants are given in Table I.

The crude lifelong incidence of asthma was 2.61/1000/y in males and 2.72/1000/y in females ($P = .45$; Table II); incidence decreased in males as age increased, whereas it remained stable in females. The rate of remission was higher in male patients than in female patients (34% vs 27%; $P = .004$); in both sexes, the percentage of remittent cases was significantly higher ($P < .001$) in childhood (≥42%) than in adult-onset asthma (≤16%).

Table III shows the associations of congenital and early life exposures with asthma incidence in children, adolescents, and adults. Females had a significantly lower risk of developing asthma during childhood than males (HR, 0.62; 95% CI, 0.52-0.75), whereas the opposite was found for adult-onset asthma (HR, 2.01; 95% CI, 1.61-

2.51). A family history of asthma and allergy was positively associated with a higher risk of asthma at all ages (pooled HR, 1.89; 95% CI, 1.67-2.13); this association was particularly strong in adolescents and adults. A positive family history was also related to lower remission rates (Table IV).

When considered separately, both the parental history of asthma and allergy significantly increased the lifelong risk of asthma onset (Fig 2), even if the specific effect of parental asthma (pooled HR, 2.47; 95% CI, 2.14-2.85) was much stronger than that of parental allergy (pooled HR, 1.39; 95% CI, 1.22-1.58). However, because there was no statistically significant interaction between them and because the overall pattern of association did not change (data not reported), only the results related to parental history of asthma and/or allergy are reported here.

Contact with older children showed a consistent negative association with the onset of asthma (test for HR's homogeneity nonsignificant: pooled HR, 0.84; 95% CI, 0.74-0.96), which was more pronounced for adult onset of asthma (HR, 0.73; 95% CI, 0.59-0.90; Table III). Contact with older children was also associated with higher remission of childhood onset of asthma (Table IV). The presence of respiratory infections in childhood showed a consistent positive association with the incidence of asthma (pooled HR, 3.19; 95% CI, 2.75-3.69; Table III). The strength of the association decreased as age at onset increased: the HRs were 5.69, 1.77, and 1.27 in children, adolescents, and adults, respectively. Pet ownership in childhood was negatively associated with the incidence of asthma starting in childhood (HR, 0.78; 95% CI, 0.64-0.96), but not in adolescence or adulthood. Maternal smoking was not significantly associated with the incidence of asthma.

TABLE I. Number of subjects participating in the clinical stage of the ECRHS, number of asthmatic patients, person-years, incidence, and percentage of subjects in remission among asthmatic patients, by congenital variables and early exposures before age 5 years.

		ECRHS attenders*		Asthmatic patients		Person- years	Incidence × 1000 (95% CI)	Remission % (95% CI)†
		N	%	N	%			
Congenital variables								
Sex	M	8,683	48	726	8.4	277,718	2.61 (2.43-2.81)	34 (30-37)
	F	9,473	52	832	8.8	306,201	2.72 (2.54-2.91)	27 (24-30)
Parental asthma and/or allergies	No	9,929	63	570	5.7	325,783	1.75 (1.61-1.90)	33 (29-37)
	Yes	5,849	37	746	12.8	182,169	4.10 (3.81-4.40)	25 (22-29)
Childhood exposures								
Respiratory infections	No	15,336	90	1062	6.9	498,923	2.13 (2.00-2.26)	29 (26-32)
	Yes	1,698	10	313	18.4	50,826	6.16 (5.51-6.88)	36 (31-42)
Early exposures to older children	No	4,694	26	437	9.3	157,393	2.78 (2.53-3.05)	28 (24-33)
	Yes	13,019	74	1079	8.3	412,239	2.62 (2.47-2.78)	32 (29-35)
Having had cats and/or dogs	No	6,010	33	466	7.8	190,637	2.44 (2.23-2.68)	37 (33-42)
	Yes	11,994	67	1072	8.9	388,490	2.76 (2.60-2.93)	27 (25-30)
Maternal smoking	No	12,701	71	1040	8.2	412,647	2.52 (2.37-2.68)	31 (29-34)
	Yes	5,107	29	482	9.4	160,226	3.01 (2.75-3.29)	28 (24-32)
Total		18,156	100	1558	8.6	583,919	2.67 (2.54-2.80)	30 (28-33)

*Because of missing values, data could not sum to 18,156.

†For 36 subjects, it was impossible to define remission status, so they were excluded.

TABLE II. Crude incidence and percentage of remission, with 95% CI, for age at onset and sex

Sex	Age at onset (y)	Asthma cases	Person-years	Incidence $\times$ 1000 (95% CI)	Percentage of subjects in remission* (95% CI)
Male	[0-10]	380	84,424	4.50 (4.07-4.98)	44 (39-49)
	[10-20]	176	81,911	2.15 (1.86-2.49)	31 (24-38)
	[20-44]	170	111,383	1.53 (1.31-1.77)	15 (10-21)
	Totals	726	277,718	2.61 (2.43-2.81)	34 (30-37)
Female	[0-10]	272	92,955	2.93 (2.60-3.30)	42 (36-48)
	[10-20]	206	90,839	2.27 (1.98-2.60)	27 (21-33)
	[20-44]	354	122,407	2.89 (2.61-3.21)	16 (12-20)
	Totals	832	306,201	2.72 (2.54-2.91)	27 (24-30)

*For 36 subjects, it was impossible to define remission status, so they were excluded.

When the interaction between family history of asthma and/or allergies and childhood exposures was tested, no statistically significant interaction term was found, pointing out that the pattern of association was similar in subjects with and without familiar history of asthma or allergy.

Of 1175 asthmatics with available specific IgE assay, 809 (69%) had a positive result for the test (sensitized asthmatic patients) when interviewed (age ≥ 20 years). The adjusted HRs for the lifelong association between early exposures and asthma onset were estimated separately in sensitized and in nonsensitized subjects. There was no statistically significant difference between

the pooled HRs of sensitized and nonsensitized asthmatic patients for respiratory infections (HR, 3.23 vs 3.91; $P = .33$), contact with older children (HR, 0.81 vs 0.98; $P = .25$), pet ownership (HR, 0.90 vs 1.00; $P = .51$), and maternal smoking (HR, 1.01 vs 1.07; $P = .24$), suggesting that the influence of early exposure is independent of the sensitization status of asthmatic patients (except for random variations).

DISCUSSION

In recent years, there has been a great epidemiologic effort devoted to the study of environmental factors early

TABLE III. Mutually adjusted HRs* for the association of congenital variables and early life exposures with asthma incidence in children, adolescents, and adults; *P* value for homogeneity test among HRs and pooled HR with 95% CIs

	Age at onset (y)			Homogeneity test: <i>P</i> value	Pooled HR‡ (95% CI)
	[0-10]	[10-20]	[20-44]†		
	HR (95% CI)	HR (95% CI)	HR (95% CI)		
Congenital variables					
Sex (female vs male)	0.62 (0.52-0.75)§	0.93 (0.74-1.17)	2.01 (1.61-2.51)§	<.001§	—
Parents with asthma and/or allergies	1.58 (1.30-1.91)§	2.16 (1.70-2.75)§	2.10 (1.71-2.58)§	.056	1.89 (1.67-2.13)§
Childhood exposures					
Respiratory infections	5.69 (4.69-6.90)§	1.77 (1.27-2.48)§	1.27 (0.94-1.71)	<.001§	3.19 (2.75-3.69)§
Early exposures to older children	0.99 (0.80-1.24)	0.83 (0.63-1.08)	0.73 (0.59-0.90)§	.137	0.84 (0.74-0.96)§
Having had cats and/or dogs	0.78 (0.64-0.96)§	1.20 (0.91-1.57)	0.95 (0.76-1.20)	.047§	—
Maternal smoking	0.96 (0.78-1.19)	0.86 (0.66-1.13)	1.22 (0.98-1.52)	.110	1.02 (0.90-1.16)

*Obtained from a semiparametric Cox model split by age at onset and adjusted for countries and age at the interview.

†Also adjusted for IgE, body mass index, smoking habits, passive smoking exposure, occupational exposures.

‡Only in the case of nonsignificant test for homogeneity or when all the HRs were in the same direction.

§*P* < .05.**TABLE IV.** Mutually adjusted HRs* for the association of congenital variables and early life exposures with asthma remission in children, adolescents, and adults; *P* value for homogeneity test among HRs and pooled HR with 95% CIs

	Age at onset (y)			Homogeneity test: <i>P</i> value	Pooled HR‡ (95% CI)
	[0-10]	[10-20]	[20-44]†		
	HR (95% CI)	HR (95% CI)	HR (95% CI)		
Congenital variables					
Sex (female vs male)	1.04 (0.81-1.33)	0.96 (0.65-1.43)	0.93 (0.55-1.56)	.906	1.00 (0.82-1.22)
Parents with asthma and/or allergies	0.74 (0.56-0.98)§	0.87 (0.56-1.35)	0.89 (0.54-1.47)	.751	0.79 (0.64-0.99)§
Childhood exposures					
Respiratory infections	0.86 (0.65-1.13)	0.61 (0.29-1.29)	1.08 (0.54-2.18)	.543	0.85 (0.67-1.09)
Early exposures to older children	1.50 (1.10-2.04)§	0.74 (0.48-1.15)	0.91 (0.55-1.51)	.023§	—
Having had cats and/or dogs	0.81 (0.62-1.05)	0.95 (0.61-1.48)	0.96 (0.58-1.58)	.740	0.86 (0.70-1.06)
Maternal smoking	1.06 (0.79-1.41)	0.68 (0.42-1.11)	1.16 (0.69-1.93)	.241	0.98 (0.79-1.23)

*Obtained from a semiparametric Cox model stratified by age at onset and adjusted for countries and age at the interview.

†Also adjusted for IgE, body mass index, smoking habits, passive smoking exposure, occupational exposures.

‡Only in the case of nonsignificant test for homogeneity or when all the HRs were in the same direction.

§*P* < .05.

in life and their importance to subsequent asthma and allergy. However, until now, only 1 recently published article investigated prospectively the natural history of asthma in a random sample of subjects from age 9 years to age 26 years, suggesting that outcomes in adult asthma may be determined primarily in early childhood.¹⁴

The novelty of our approach is that it considers the natural history of the disease rather than its prevalence in a very large random sample, thus providing a homogeneous assessment of the effect of early exposures on the incidence and remission of asthma from birth to age 45 years. This was made possible by (1) the availability of data collected by ECRHS, in which the same measurements were performed with highly standardized methods in a large, multinational, representative sample from the general population; and (2) the retrospective use of event history analysis, which allowed us to split the individual history of asthma according to relevant and homogeneous time windows.^{15,16}

The main findings of our analysis were as follows:

- Exposure to older children early in life was associated with a reduced risk of developing asthma at any time during a person's life and with an increased rate of remission in childhood asthma.
- Early respiratory infections were a strong risk factor for asthma starting at any time during a person's life.
- A parental history of asthma and allergy was associated with a higher risk of developing asthma throughout life and worsened the prognosis of both childhood and adult asthma.

The hygiene hypothesis was suggested by Strachan,¹ who noted that the risk of developing allergies and asthma was inversely related to the number of children in the family. This finding has led to the speculation that infectious diseases, which are more likely to be transmitted in large families, contribute to a nonallergic

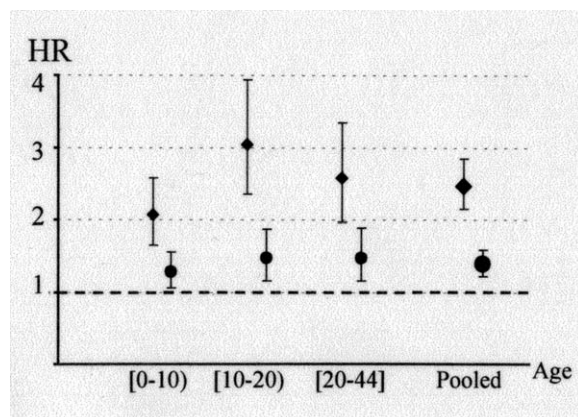


FIG 2. Association estimates (HRs) between parental asthma (◆) and parental allergy (●) and incidence of asthma in childhood, adolescence, and adulthood.

immunologic maturation, thus protecting the person against asthma and allergies throughout life.

Accordingly, we found that subjects in contact with older children in family or day care acquired permanent protection against asthma. On the other hand, our results point out that severe early respiratory infections are a strong risk factor for developing asthma in childhood and that their effect persists into adulthood, in agreement with other, previous studies.^{6,17} Together, these 2 contrasting findings strongly suggest that early exposure to infectious agents plays a bidirectional role in conferring long-lasting protection against asthma as well as increasing the lifelong risk of the onset of the disease in both genetically susceptible and nonsusceptible persons. The direction may depend on host factors, the severity of the infection, the organs involved, the type of microbe, and the length and type (acute vs intermittent or prolonged) of exposure.^{18,19}

The fact that exposure to infectious agents has the same effect on both genetically susceptible and nonsusceptible persons and on both sensitized and nonsensitized asthmatic patients suggests that this effect is probably caused by the activation of a regulatory mechanism that interfaces with the type of acquired immunologic response (T_H1/T_H2) and that is independent of sensitization or IgE-mediated mechanisms.

One of the most important causes of severe respiratory infections in infants is the respiratory syncytial virus,²⁰ which is also implicated in the pathogenesis of childhood asthma²¹ through a diminished production of anti-inflammatory cytokines, such as IFN- γ and particularly IL-10,^{21,22} which predisposes for persistent T_H2 cytokine response.²³ On the contrary, a prolonged immune challenge (such as repeated contact with other children or long-term parasite infections) seems to be associated with increased production of IL-10 by dendritic cells, which may induce a robust anti-inflammatory network, which in turn suppresses a T_H2 cytokine response.⁹ Our finding that contact with older children is a protective

factor even in predisposed subjects and that it increases the probability of remission in already asthmatic children could be explained by the activation of a similar anti-inflammatory process.

In our study, early exposure to cats and/or dogs seemed to be a protection against asthma in childhood, but not in adolescence and adulthood. Epidemiologic literature provides complex findings on this topic.²⁴ Some studies showed a protective effect on subsequent allergy,^{25,26} others no or positive associations,^{27,28} and others that the association varied according to allergic predisposition.^{6,29} The protective effect of exposure to domestic animals on asthma and allergy may be explained by allergen stimulation inducing tolerance³⁰ and/or microbial immune stimulation, possibly through endotoxins.³¹ In any case, our results suggest that the protective effect of exposure to domestic pets on incidence is confined to asthma starting in childhood. A possible alternative explanation is that parents of asthmatic or allergic children often choose not to have pets, resulting in an apparent protective effect on childhood asthma onset.

Our finding that a parental history of asthma and, to a minor extent, of allergy is a lifelong risk factor for the onset of asthma agrees with previous evidence.^{28,32,33} As far as we know, no other studies have investigated the effect of such genetic predisposition on the persistence of the disease. Our analysis showed that it decreased the probability of remission in both childhood and adulthood. Parental asthma is associated with increased and persistent peripheral blood eosinophilia, which is a characterizing feature of the presence of a T_H2 -mediated response and which may be responsible for chronic asthma and allergy.³⁴

Finally, our results confirm previous findings about the existence of a gender reversal during puberty caused by an increase in reported asthma in women and a decrease in men. It has been suggested that airway caliber, in addition to hormonal factors, could play an important role in explaining the different pattern of incidence in men and women.¹⁶

As a whole, our analysis provides strong support that events occurring early in life contribute to determine the subsequent asthmatic phenotype, possibly by the activation of a regulatory mechanism independent of the acquired T_H1/T_H2 pattern of immune response. Furthermore, if we assume that the IgE status in adults (≥ 20 years) summarizes the history of sensitization of a person, our findings seem to point out that the effects of early exposure were not mediated through production of specific IgE. It has been suggested that the first months of life^{35,36} could be the most crucial period in the natural history of asthma; however, our data, based on the report of events before age 5 years, do not allow us to verify this hypothesis.

The strength of our analysis is that it gives information on the determinants of incidence and remission of asthma in a wide age range and in a large, multicultural, population-based sample. Its weakness is the dependence on the recall of past events.

In our study, incidence and remission were defined in relation to either the occurrence or the absence of a relevant clinical event, an attack of asthma, which is a traumatic experience for a patient and is less prone to be influenced by the recall bias. Furthermore, questions on asthma have a higher reproducibility¹¹ and specificity than symptoms³⁷ and are therefore more suitable for studies on risk factors than other definitions. The recall of early exposures may be more prone to error, especially when questions that are not directly related to an emotional experience are taken into consideration. Nondifferential misclassification of the exposure is expected to bias the association estimates toward the null, and this could be a likely explanation for the failure of our analysis to find an association between maternal smoking and the onset of asthma, an association that has been reported in several studies.³⁸ The recall bias should be of less importance in the recall of childhood pets, which usually represents an important feature of childhood. Serious respiratory infections are a salient experience whose recall is usually reinforced by the reminder of the event by family members^{39,40}; however, the recall could be more complete in subjects experiencing childhood asthma. Thus, differential recall could possibly contribute to the stronger association with early-onset asthma.

In conclusion, our analysis suggests that genetic factors as well as microbial environment early in life play a major role in either promoting or preventing asthma throughout life. Parental asthma and allergy is associated with a lifelong increased risk of developing chronic, persistent asthma. Independently of a genetic background, early acute respiratory infections were associated with an increased lifelong risk of asthma onset, whereas contact with older children, reflecting prolonged, intermittent exposure to infectious agents, appeared to confer permanent protection against asthma and to increase the likelihood of remission in already asthmatic children. Deeper insight into the basic mechanisms associated with an immune response to early infections in children could help understanding of the pathogenesis of this heterogeneous disease and provide the opportunity to improve the cure for and prevention of asthma.

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