Early-life risk factors and incidence of rhinitis: Results from the European Community Respiratory Health Study—an international population-based cohort study

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Background: Rhinitis is an increasingly common condition with a heavy health care burden, but relatively little is known about its risk factors.

Objective: To examine the association between early-life factors and the development of rhinitis in the European Community Respiratory Health Study (ECRHS).

Methods: In 1992-1994, community-based samples of 20-44-year-old people were recruited from 48 centers in 22 countries. On average, 8.9 years later, 28 centers reinvestigated their samples. Onset of rhinitis was reported by 8486 participants in interviewer-led questionnaires. Cox regression was used to assess independent predictors of rhinitis at ages ≤5, 6-10, 11-20, and ≥21 years.

Results: The crude lifelong incidence of rhinitis was 7.00/1000/year (men) and 7.95/1000/year (women) ($P = .002$). Women developed less rhinitis in later childhood (hazard ratios [HR], 0.63; 95% CI, 0.47-0.85) and more rhinitis in adulthood (HR, 1.36; 95% CI, 1.11-1.66) than did men. In atopic subjects, siblings were associated with lower risk of rhinitis throughout life (pooled HR, 0.94; 95% CI, 0.91-0.98 per 1 sibling). Early contact with children in the family or day care was associated with less incidence of rhinitis, predominantly before age 5 years (HR, 0.84; 95% CI, 0.72-0.99). Early childhood pets or growing up on a farm was associated with less incidence of rhinitis in adolescence (HR, 0.50; 95% CI, 0.37-0.68). Combining these factors showed evidence of a dose-response relationship (trend $P = .0001$).

Conclusions: Gender is a strong risk factor for rhinitis, with age patterns varying according to atopic status. Protective effects of early contact with children and animals were suggested for incident rhinitis, with risk patterns varying by age window and atopic status. (J Allergy Clin Immunol 2011;128:816-23.)

Key words: *Rhinitis, atopy, gender, pet exposure, siblings, farming lifestyle*

Rhinitis, which includes "hay fever" or seasonal allergic rhinitis, is an increasingly common chronic condition. The International Study of Asthma and Allergies in Childhood (ISAAC) has shown that the incidence of rhinitis is increasing around the world.[1] European Community Respiratory Health Study (ECRHS) data for adults aged between 25 and 50 years have shown considerable variation in the prevalence of rhinitis, with rates ranging from 11.8% in Spain to 46% in Australia.[2] In some countries, rhinitis poses a substantial health care burden in terms of quality of life, cost of treatment, comorbidities (such as asthma), and indirect costs.[3]

Rhinitis may predispose to the development of asthma. ECRHS data analysis demonstrated a significantly increased incidence of asthma over an 8-year follow-up period for any rhinitis, allergic or not.[4] Studies have consistently demonstrated that childhood hay fever increases the likelihood of new-onset asthma after childhood and persistent asthma from childhood into middle age.[5,6] Whether the link between nasal allergies and asthma is causal or whether the disorders share common risk factors is yet to be clarified. If the relationship is causal, then early aggressive treatment of rhinitis might prevent asthma,[7] which is a major public health issue.

Many studies have found an inverse relationship between rhinitis and increasing number of siblings.[8] From this observation, the "hygiene hypothesis" evolved, suggesting that

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Abbreviations used
ECRHS: European Community Respiratory Health Study
HR: Hazard ratios
ISAAC: International Study of Asthma and Allergies in Childhood
TAHS: Tasmanian Longitudinal Health Study

infections and unhygienic contact might confer protection against allergic disease.[9] This association also prompted research into other early-life factors and how they were related to the development of allergic disease. The hypothesis is also supported by observations that people growing up within a farming environment and from eastern European countries had lower rates of allergic diseases.[10,11]

Despite the fact that many studies have investigated early-life factors and the risk of having allergic disease, to date none has investigated these factors in relation to rhinitis incidence. The Tasmanian Longitudinal Health Study (TAHS) showed that the risk factors for early-onset rhinitis may be different from the risk factors for late-onset allergic rhinitis but did not conduct an incidence analysis.[12] Understanding how early-life factors are associated with both rhinitis incidence and persistence is important to understand mechanisms of disease development and identify preventive strategies. ECRHS is the major international study of respiratory health in young adults and has collected data on early-life factors. Given the data on age at onset of rhinitis, the ECRHS provided a unique opportunity to examine the association between early-life factors and development of rhinitis.

METHODS

Study subjects and data collection

The ECRHS is a prospective population-based cohort study of respiratory health among adults in 28 study centers in 13 countries. The study design and methods have been described previously[13,14] (www.ecrhs.org). Briefly, between 1991 and 1993, 48 study centers in 22 countries participated in ECRHS I, which comprised 2 stages. Each participating center selected a random sample of 1500 men and 1500 women aged between 20 and 44 years. These study subjects were mailed a screening questionnaire in ECRHS I stage 1. Subsequently, 38 centers invited a random sample and a symptomatic sample of postal survey participants to take part in clinical investigations (ECRHS I stage 2). On average, 8.9 years (interquartile range, 8.3-9.5 years) later, 29 centers reinvestigated the participants of ECRHS I stage 2 by using similar methods (ECRHS II). A new question was included in ECRHS II to record the age at onset of rhinitis. The present study included everyone from the random sample who participated in both the surveys, with the exception of 1 center that did not ask this question (total 28 centers in 13 countries).

Definitions

Rhinitis was defined as an affirmative response to the following question: "Do you have any nasal allergies, including hay fever?" Age at onset of rhinitis was defined by the following question: "How old were you when you first had hay fever or nasal allergy?"

Specific IgE level was measured in serum samples in a central laboratory by the CAP system (Pharmacia Diagnostics, Uppsala, Sweden). Atopy was defined as a positive assay (if values >0.35 kU/L, the lowest detection limit of the assay) to specific IgE at ECRHS II for at least 1 specific allergen. More detail about the measurement of IgE level is available in this article's Online Repository at www.jacionline.org.

Definitions of the exposures. The questions used to define the exposures are available in this article's Online Repository at www.jacionline.org. The number of siblings was recorded in ECRHS I and was either coded as a discrete variable (number of siblings) or divided into categories (0, 1, 2, 3, 4, or 5 or more siblings). Data on bedroom-sharing, day-care attendance, and serious respiratory infection before the age of 5, maternal and paternal smoking in childhood/pregnancy, and parental allergic disease were recorded in ECRHS I. Data on pet exposure and growing up on a farm were recorded in ECRHS II.

The combined effect of siblings, pets, and farming environment in early life was examined together as a "combined early-life variable." Individuals were given a score for the number of factors (0, 1, 2, 3 factors). The level of education was used as a proxy measure of socioeconomic status. Subjects were grouped into those who completed their full-time education earlier than age 19 years and those who completed their full-time education later than age 19 years; these data were collected at ECRHS I. Personal smoking status was recorded in ECRHS II and defined as never smoked, ex-smoker, and current smoker.

Statistical methods

Incidence rates were calculated by dividing the incidence of rhinitis by the total number of person-years at risk. Person-years at risk were calculated as the time from birth to the age at first occurrence in those with rhinitis or age at interview for those without rhinitis. Initially, lifetime risk was examined stratified by atopic status.

Person-years at risk were split into 4 time windows to reflect early childhood (0-5 years), later childhood (6-10 years), adolescence (11-20 years), and adulthood (21+ years). The association between rhinitis incidence and early-life factors was examined using multivariate Cox regression to calculate hazard ratios (HR) with 95% CIs. The final models were adjusted for sex, age, level of education, parental allergy, and testing center. The Cox model with "rhinitis onset after the age of 21 years" as the outcome was also adjusted for adult smoking status. A pooled estimate of the effect of early-life factors on rhinitis risk over the whole life span was computed by performing a meta-analysis of the estimates for each life stage from the Cox model. Cochran's Q statistic was used as a test for homogeneity of the pooled estimate. All analyses were performed using Stata/IC for windows (StataCorp, Stata Statistical Software: Release 10, College Station, Tex).

RESULTS

Out of 8486 participants in ECRHS II 2,352 (27.7%) reported rhinitis. The crude lifelong incidence of rhinitis was 7.00/1000/year in males and 7.95/1000/year in females (log-rank test for equality $P = .002$; see Fig E1 in this article's Online Repository at www.jacionline.org). The crude incidence rates of rhinitis overall and stratified by allergic sensitization are presented in Table I. Overall rhinitis increased over time in both males and females, with the peak incidence in both males and females in adolescence. However when stratified by atopy at ECRHS II, the incidence of rhinitis in atopic subjects was higher in males in childhood, but reversed to be higher in females in adolescence and adulthood (log-rank test $P = .002$; Fig 1). For rhinitis in nonatopic subjects, females had a higher incidence than males from later childhood onward (log-rank test $P = .00001$, Fig 2).

Incidence of rhinitis and early-life factors

In the Online Repository we have provided a comparison of participants and nonparticipants in ECRHS II based on the information collected during ECRHS I (see Table E1 in this article's Online Repository at www.jacionline.org). Table II describes the crude incidence rate of rhinitis by selected early-life factors. Overall, the incidence of rhinitis decreased with

TABLE I. Crude incidence of rhinitis with 95% CIs for age and sex in total group and stratified by atopy

	Males			Females			Incidence rate ratio (95% CI)	
	Person-time	Rhinitis	Rate* (95% CI)	Person-time	Rhinitis	Rate* (95% CI)	(Males/females)	*P* value
Total group								
<5 y	20,166	83	4.1 (3.3-5.1)	21,997	78	3.6 (2.8-4.4)	1.16 (0.84-1.60)	.17
6-10 y	19,540	187	9.6 (8.3-11.0)	21,481	149	6.9 (5.9-8.1)	1.38 (1.11-1.72)	.002
11-20 y	36,501	333	9.1 (8.2-10.2)	40,309	394	9.8 (8.9-10.8)	0.93 (0.80-1.08)	.18
21+ y	74,171	450	6.1 (5.5-6.7)	79,576	678	8.5 (7.9-9.2)	0.71 (0.63-0.80)	.00001
Total	150,378	1,053	7.0 (6.6-7.4)	163,363	1,299	7.9 (7.5-8.4)	0.88 (0.81-0.96)	.001
Atopic								
<5 y	5,158	50	9.7 (7.4-12.8)	4,015	41	10.2 (7.5-13.9)	0.95 (0.62-1.47)	.40
6-10 y	4,754	126	26.5 (22.3-31.6)	3,736	68	18.2 (14.4-23.1)	1.46 (1.06-1.99)	.006
11-20 y	7,832	199	25.4 (22.1-29.2)	6,155	199	32.3 (28.1-37.2)	0.79 (0.64-0.96)	.0082
21+ y	12,919	191	14.8 (12.8-17.0)	8,884	202	22.7 (19.8-26.1)	0.65 (0.53-0.80)	.00001
Total	30,663	566	18.5 (17.0-20.0)	22,790	510	22.4 (20.5-24.4)	0.82 (0.73-0.93)	.0008
Nonatopic								
<5 y	10,935	16	1.5 (0.9-2.4)	12,733	19	1.5 (1.0-2.3)	0.98 (0.47-2.01)	.48
6-10 y	10,838	20	1.9 (1.1-2.9)	12,609	44	3.5 (2.6-4.7)	0.53 (0.30-0.92)	.008
11-20 y	21,305	71	3.3 (2.6-4.2)	24,458	113	4.6 (3.8-5.5)	0.72 (0.53-0.98)	.02
21+ y	46,587	173	3.7 (3.2-4.3)	51,509	339	6.6 (5.9-7.3)	0.56 (0.47-0.68)	.00001
Total	89,665	280	3.1 (2.8-3.5)	101,309	515	5.1 (4.7-5.5)	0.61 (0.53-0.71)	.00001

*Incidence per 1000 person years at risk.

increasing number of siblings (overall HR per increase in number of siblings, 0.93; 95% CI, 0.91-0.95; $P = .0001$) and with sharing a bedroom with older children. Exposure to pets (both cats and dogs) before 5 years and growing up on a farm were associated with lower incidence of rhinitis. A parental history of allergic disease and maternal smoking during pregnancy and childhood were associated with a higher incidence of rhinitis.

Stratifying by atopy at ECRHS II (Table III), the associations between contact with other children and lower rhinitis incidence appeared stronger among atopics. Differences according to atopy were significant for having any siblings and having younger rather than older siblings (for interaction between siblings and atopy, $P = .02$). Dog and cat ownership in the first 5 years of life and growing up on a farm were associated with a reduced incidence of rhinitis among those with atopy at ECRHS II only; the interaction between atopy and dog ownership was statistically significant ($P = .02$).

Atopy did not modify the positive association between parental allergic diseases and incidence of rhinitis. Females had an increased incidence of rhinitis in both atopic and nonatopic subjects, but the gender difference was greater for the nonatopic subjects (Table III).

Multivariate models were constructed for the atopic and nonatopic groups separately and those factors significant in the univariate analysis were included in the model (Table III). For the atopic group, exposure to any siblings and a dog before 5 years was associated with a reduced incidence of rhinitis. In the nonatopic group, only a family history of allergies and female gender were associated with an increased incidence of rhinitis.

Rhinitis incidence in childhood, adolescence, and adult life

The associations between early-life factors and rhinitis in subjects atopic at ECRHS II are presented in Table IV. Having any siblings, especially younger siblings, was associated with a consistently reduced incidence of rhinitis. Dog or cat ownership in the first 5 years of life was associated with a reduced incidence of rhinitis in adolescence, but not in adulthood. Growing up on a farm was also associated with a reduced incidence in adolescence; however, there was no evidence of heterogeneity across the age windows (test for homogeneity, $P = .174$). The combined variable of any early-life animal exposure and growing up on a farm was also associated with a reduced incidence in adolescence, but the effect size was similar to that of dog exposure alone.

Females had a lower risk of developing rhinitis in later childhood than did males; however, they had an increased risk of developing rhinitis as adults. Maternal smoking in pregnancy and early childhood was associated with a consistently increased risk of rhinitis across all life stages. A similar result was found for having a family history of allergies.

For nonatopic subjects (see Table E2 in this article's Online Repository at www.jacionline.org), females and a family history of allergies were associated with a consistently increased risk of rhinitis throughout life.

Exposure to children and animals

The combined effect of siblings, pets, and farming environment in early life was examined by creating a combined early-life variable. For each additional factor, the incidence of rhinitis was successively lower in a dose-dependent manner (trend P value = .0001). This was most pronounced among subjects atopic at ECRHS II; there was a significant interaction between the combined early-life variable and atopy (interaction $P = .011$; HR for 1 factor, 0.77, 95% CI, 0.62-0.95; HR for 2 factors, 0.74, 95% CI, 0.58-0.94; HR for 3 factors, 0.68, 95% CI, 0.51-0.91; HR for 4 factors, 0.30, 95% CI, 0.16-0.57). The cumulative probability of rhinitis by the multiple factors in atopic individuals is displayed in Fig E2 (see this article's Online Repository at www.jacionline.org). The log-rank test for equality of the functions was $P = .0004$.

DISCUSSION

This is the first study to examine the influence of early-life exposures on lifetime incidence of rhinitis in a large international

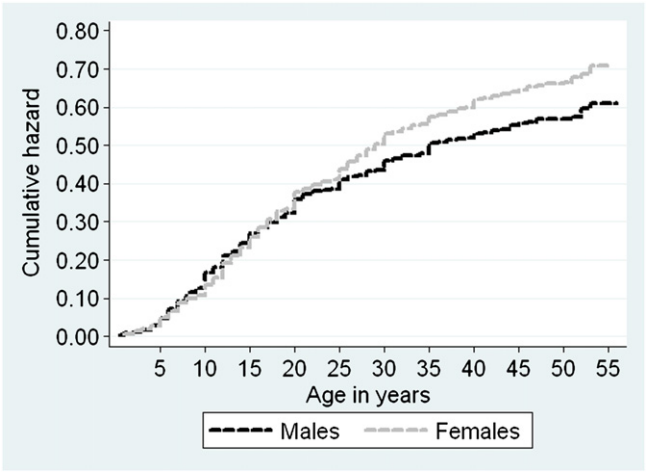

FIG 1. Cumulative probability of rhinitis by gender in subjects who are atopic at ECRHS II.

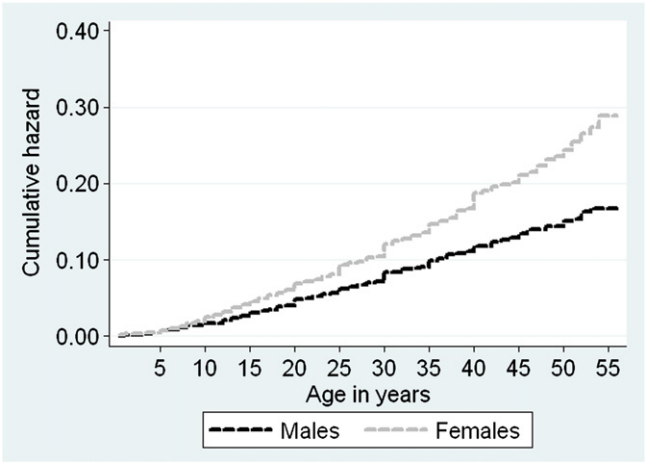

FIG 2. Cumulative probability of rhinitis by gender in subjects who are nonatopic at ECRHS II.

population-based sample. Until now there have been only a few studies of the natural history of rhinitis and these have been limited to reports of incidence by age and gender[15] or medical databases with limited information on early-life exposures.[16] Furthermore, we have shown for the first time an important protective effect of siblings and pet exposure on the incidence of rhinitis. Rhinitis incidence was consistently lower throughout life among those growing up with siblings, and pet keeping in early childhood was related to lower incidence of rhinitis 10 years later—in adolescence. The lowest incidence of rhinitis was present in those exposed to both children and animals early in childhood. Despite the heterogeneity in the prevalence of these exposures across countries, they show a consistent protective effect on rhinitis incidence across sociocultural and geographical borders.

Our results show for the first time a gender reversal for rhinitis incidence in subjects who were atopic at follow-up, but not in subjects who were not. In subjects who were atopic in adult life, the incidence of rhinitis was higher in boys, but this higher incidence reversed in adult life when women have a higher risk than do men. In subjects without atopy in adult life, females have a consistently increased risk of rhinitis compared with males throughout life. Studies of pediatric cohorts have observed an increased incidence of allergic rhinitis[17,18] and aero-allergen sensitization[19] in boys than in girls. One previous study of Finnish adolescents reported the incidence of rhinitis between follow-up surveys conducted at 16, 22, and 32 years of age. In males, it found a higher cumulative incidence of rhinitis at 16 years and new incidence between 17 and 22 years than in females. But this trend reversed between 23 and 32 years when females had a slightly higher incidence than did males.[15] This gender reversal has previously been demonstrated for other atopic diseases such as asthma.[5,20,21] Hormonal factors are a possible explanation for the gender differences in incidence.[19] Gender-related differences in other exposures/risk factors that predispose to allergic diseases were not likely given that we did not observe any interaction between other risk factors and gender. Some studies have found gender differences in rhinitis perception, reporting, and diagnosis.[22] However, gender-specific reporting differences are not likely to vary by atopic sensitization, as found in our study, and are unlikely to explain the findings.

Siblings were found to be associated with a reduced incidence of rhinitis in atopic subjects in this study consistently across the different age windows into adult life. This result is consistent with the results of numerous previous studies including a large cross-sectional meta-analysis[8] and a previous cross-sectional analysis of the ECHRS stage 1 data,[23] both of which found a reduced risk of having rhinitis with increasing number of siblings. Most of the previous studies of the association between rhinitis and siblings have been cross-sectional. One previous study of a British birth cohort has examined the association between siblings and rhinitis incidence, but only until the age of 6 years.[16] This study also found a reduced incidence of rhinitis with an increasing number of siblings. This study also demonstrated an increased incidence of rhinitis in boys than in girls. Previous analysis of the ECRHS cohort has also found that rhinitis was less common in those with many siblings and also in those without siblings but exposed to other children in day care.[23] Previous work has shown that the protective effect of siblings may be strongest on rhinitis that develops in early life and that the protective effect is related to early exposure to infection from other siblings that is dose (number of siblings) and time (age at exposure to other siblings) dependent.[12] Our data support the idea that there is a protective effect of siblings on rhinitis incidence, at least in individuals atopic in adulthood.

Exposure to cats and dogs in early life was found to be inversely associated with rhinitis incidence in adolescence. The relationship between pet exposure and allergic disease has been controversial. There have been limited studies of the relationship between pets and rhinitis and no studies that have looked at rhinitis incidence. Nafstad et al observed a slightly protective effect of any pet exposure, but not for either cat or dog exposure individually on rhinitis in a cohort of 4-year-old children.[24] Similarly, Fasce et al[25] found no evidence of a protective effect of early-life cat exposure in school-aged children. However, since the peak incidence of rhinitis is in adolescence, the participants in these studies were not old enough for such an effect to be optimally observed. Similar to our results, past analysis of ECRHS stage 1 data found that exposure to dogs in childhood was negatively associated with adult atopy.[26]

Selective avoidance of pets by allergic parents or after early childhood reactions to pets has been suggested to explain the

TABLE II. Incidence of rhinitis and HR by sex and early-life exposures

Outcome	Person-years at risk	Rhinitis N (%)	Incidence per 1000 person years at risk (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)*
Sex					
Males	150,378	1,053	7.00 (6.59-7.44)	1.0	1.0
Females	163,363	1,299	7.95 (7.53-8.40)	1.13 (1.05-1.23)	1.07 (0.99-1.17)
Contact with other children					
Bedroom share <5 y					
No	166,932	1,312	7.86 (7.45-8.30)	1.0	1.0
Yes	141,495	1,003	7.09 (6.66-7.54)	0.90 (0.83-0.98)	0.92 (0.84-0.99)
Day care <5 y					
No	171,323	1,268	7.40 (7.00-7.82)	1.0	1.0
Yes	135,506	1,034	7.63 (7.18-8.11)	1.03 (0.95-1.12)	0.99 (0.91-1.08)
Any early exposure to children†					
No	13,934	121	8.68 (7.27-10.4)	1.0	1.0
Yes	288,449	2,155	7.47 (7.16-7.79)	0.86 (0.72-1.03)	0.80 (0.66-0.96)
Number of siblings					
0	31,263	252	8.06 (7.12-9.12)	1.0	1.0
1	93,045	785	8.44 (7.87-9.05)	1.05 (0.91-1.21)	0.98 (0.85-1.14)
2	77,979	605	7.76 (7.16-8.40)	0.96 (0.83-1.11)	0.93 (0.80-1.08)
3	48,347	330	6.83 (6.13-7.60)	0.85 (0.72-1.00)	0.84 (0.71-0.99)
4	28,150	174	6.18 (5.33-7.17)	0.77 (0.63-0.93)	0.81 (0.67-0.98)
5+	33,673	193	5.73 (4.98-6.60)	0.71 (0.59-0.86)	0.80 (0.66-0.98)
Early-life farm & pet exposure					
Dog <5 y					
No	221,119	1,738	7.86 (7.50-8.24)	1.0	1.0
Yes	70,951	462	6.51 (5.94-7.13)	0.83 (0.75-0.92)	0.86 (0.78-0.96)
Cat <5 y					
No	208,576	1,674	8.03 (7.65-8.42)	1.0	1.0
Yes	83,667	526	6.29 (5.77-6.85)	0.78 (0.71-0.86)	0.84 (0.76-0.93)
Farm growing up					
No	260,597	2,038	7.82 (7.49-8.17)	1.0	1.0
Yes	31,218	152	4.87 (4.15-5.71)	0.62 (0.53-0.73)	0.68 (0.58-0.81)
Animals and farm lifestyle					
No	209,057	1,673	8.00 (7.63-8.40)	1.0	1.0
Yes	82,313	516	6.27 (5.75-6.83)	0.78 (0.71-0.86)	0.82 (0.74-0.91)
Other					
Mother smoking					
No	241,829	1,739	7.19 (6.86-7.54)	1.0	1.0
Childhood only	36,956	287	7.77 (6.92-8.72)	1.08 (0.95-1.23)	1.04 (0.91-1.17)
Childhood and pregnancy	27,278	253	9.27 (8.20-10.5)	1.29 (1.13-1.48)	1.17 (1.02-1.34)
Father smoking					
No	111,235	875	7.87 (7.36-8.41)	1.0	1.00
Yes	201,593	1,464	7.26 (6.90-7.64)	0.92 (0.85-1.00)	0.99 (0.91-1.07)
Childhood infections					
No	282,351	2,111	7.48 (7.16-7.80)	1.0	1.0
Yes	29,436	219	7.44 (6.52-8.49)	0.99 (0.87-1.14)	0.96 (0.83-1.10)
Parental allergies					
No	209,514	1,282	6.12 (5.79-6.46)	1.0	1.00
Yes	100,214	1,042	10.4 (9.79-11.1)	1.71 (1.57-1.85)	1.64 (1.51-1.78)

*Adjusted for sex, age, center, education, and parental allergy.
†Any early child exposure includes exposure to siblings, day care, or bedroom sharing.

"protective" effects of pets on allergic disease. However, previous analysis of ECRHS data found no evidence of selective avoidance for dog ownership and no effect of parental allergy on pet avoidance in childhood.[27] It seems particularly unlikely that selective avoidance could explain less incidence of rhinitis in adolescence in those with pets before age 5 years, but not less incidence of rhinitis in childhood, and that a similar avoidance pattern in adolescence should occur for cats, dogs, and growing up on a farm. The possible mechanisms involved in protective effects of early-life pet and farm exposure are unclear. Dogs have been suggested to proxy exposure to endotoxin; however, several studies have demonstrated that the effect of dog keeping in early life was independent of endotoxin exposure.[28-30] Alternatively, pet exposure may be associated with high-allergen exposure, which induces tolerance, thereby reducing the risk of developing atopic disease.

Growing up on a farm was associated with a reduced incidence of rhinitis in atopic subjects. This effect was further enhanced when combined with any childhood pet exposure. Being raised on a farm has shown a consistent inverse association with the development of rhinitis in many studies.[11] Previous ECRHS analysis found that living on a farm in childhood was associated

TABLE III. Association between early-life factors and incident rhinitis stratified by atopy at ECRHS II

Early-life factor	Nonatopic		Atopic		*P* value†
	HR (95% CI)*	Mutually adjusted model	HR (95% CI)*	Mutually adjusted model	
Contact with other children					
Bedroom sharing <5 y	0.94 (0.81-1.08)	–	0.91 (0.81-1.03)	–	.60
Day care <5 y	1.00 (0.86-1.17)	–	0.92 (0.81-1.05)	–	.80
Any early exposure to children‡	0.94 (0.67-1.32)	–	0.82 (0.63-1.05)	–	.63
Any siblings	0.99 (0.95-1.03)	–	0.94 (0.90-0.97)	0.96 (0.92-0.996)	.02
Older siblings	0.98 (0.93-1.03)	–	0.96 (0.91-1.00)	NA	.34
Younger siblings	1.00 (0.95-1.06)	–	0.93 (0.89-0.98)	NA	.03
Early-life farm and pet exposure					
Dog <5 y	1.00 (0.85-1.18)	–	0.78 (0.66-0.93)	0.83 (0.69-0.99)	.02
Cat <5 y	0.92 (0.79-1.08)	–	0.83 (0.71-0.98)	0.92 (0.77-1.08)	.17
Farm growing up	0.87 (0.69-1.09)	–	0.71 (0.53-0.96)	0.81 (0.59-1.10)	.20
Animals and farm lifestyle	0.94 (0.80-1.10)	–	0.79 (0.67-0.93)	NA	.08
Other					
Mother smoking					
In childhood only	0.99 (0.80-1.25)	–	0.96(0.81-1.15)	0.94 (0.78-1.13)	.83
In pregnancy and childhood	1.06 (0.83-1.34)	–	1.28 (1.04-1.55)	1.06 (0.76-1.47)	.84
Father smoking	0.96 (0.83-1.12)	–	0.91 (0.81-1.04)	–	.23
Childhood infections	0.93 (0.74-1.18)	–	0.97 (0.79-1.19)	–	.91
Parental allergies§	1.60 (1.38-1.84)	1.57 (1.35-1.81)	1.50 (1.32-1.69)	1.48 (1.30-1.68)	.49
Sex, female§	1.57 (1.35-1.82)	1.60 (1.38-1.84)	1.12 (0.99-1.26)	1.08 (0.95-1.23)	.001

*Adjusted for sex, age, center, education, and parental allergy.
†*P* value for the interaction between the early-life factor and atopy.
‡Any early child exposure includes exposure to siblings, day care, or bedroom sharing.
§Adjusted for age, center, education, and parental allergy. *NA,* Not included in the mutually adjusted model because of collinearity of the variables.

TABLE IV. Association between siblings, sharing bedrooms, and incident rhinitis (adjusted for sex, age) in subjects atopic at ECRHS II

Characteristics	Age at onset (y)				Test for homogeneity	Pooled HR (95% CI)
	<5 y HR (95% CI)*	6-10 y HR (95% CI)*	11-20 y HR (95% CI)*	21+ y HR (95% CI)†		
Sex, female‡	0.91 (0.60-1.39)	0.63 (0.47-0.85)	1.21 (0.99-1.49)	1.36 (1.11-1.66)	(*P* = .0001)	–
Contact with other children						
Bedroom sharing <5 y	–§	0.94 (0.71-1.25)	0.81 (0.66-0.99)	1.09 (0.89-1.33)	(*P* = .20)	0.93 (0.82-1.05)
Day care <5 y	–§	0.98 (0.72-1.33)	0.98 (0.78-1.21)	0.93 (0.74-1.17)	(*P* = .96)	0.95 (0.83-1.09)
Any early exposure to children‖	–§	0.80 (0.43-1.48)	0.92 (0.58-1.44)	1.13 (0.71-1.80)	(*P* = .07)	0.84 (0.72-0.99)
Any siblings	0.85 (0.72-0.99)	0.93 (0.84-1.03)	0.92 (0.86-0.98)	0.98 (0.92-1.04)	(*P* = .29)	0.94 (0.91-0.98)
Older siblings	0.94 (0.78-1.12)	0.97 (0.86-1.08)	0.93 (0.85-1.01)	1.00 (0.93-1.08)	(*P* = .58)	0.96 (0.92-1.01)
Younger siblings	0.81 (0.66-1.01)	0.91 (0.79-1.04)	0.94 (0.86-1.02)	0.97 (0.89-1.05)	(*P* = .52)	0.94 (0.89-0.98)
Early-life farm and pet exposure						
Dog <5 y	–§	0.92 (0.63-1.36)	0.50 (0.36-0.69)	1.02 (0.79-1.31)	(*P* = .004)	–
Cat <5 y	–§	1.08 (0.75-1.54)	0.59 (0.44-0.79)	1.01 (0.80-1.28)	(*P* = .02)	–
Farm growing up	–§	0.58 (0.26-1.31)	0.47 (0.26-0.85)	0.91 (0.59-1.38)	(*P* = .17)	0.76 (0.56-1.02)
Animals and farm lifestyle	–§	0.92 (0.63-1.33)	0.50 (0.37-0.68)	1.03 (0.81-1.31)	(*P* = .003)	–
Other						
Mother smoking						
In childhood only	1.59 (0.93-2.71)	0.78 (0.50-1.21)	0.95 (0.71-1.28)	0.91 (0.67-1.23)	(*P* = .22)	0.96 (0.80-1.15)
In pregnancy and childhood	1.95 (1.07-3.56)	1.26 (0.80-1.98)	1.08 (0.76-1.52)	1.20 (0.84-1.69)	(*P* = .41)	1.23 (1.01-1.51)
Father smoking	0.95 (0.62-1.46)	1.01 (0.75-1.35)	0.81 (0.66-0.99)	1.04 (0.84-1.28)	(*P* = .37)	0.93 (0.82-1.06)
Childhood infections	1.52 (0.84-2.75)	0.82 (0.49-1.40)	0.71 (0.48-1.03)	1.21 (0.89-1.65)	(*P* = .07)	1.00 (0.82-1.23)
Parental allergies¶	1.85 (1.21-2.83)	1.69 (1.27-2.25)	1.42 (1.16-1.74)	1.37 (1.11-1.69)	(*P* = .46)	1.48 (1.68-6.22)

*Adjusted for sex, age, center, education, and parental allergy.
†Additionally adjusted for personal smoking.
‡Adjusted for age, center, education, and parental allergy.
§Not analyzed because of temporal association between exposure and outcome.
‖Any early child exposure includes exposure to siblings, day care, or bedroom sharing.
¶Adjusted for sex, age, center, and education.

with a reduced risk of ever having nasal symptoms in the presence of pollen in adulthood.[10] This analysis shows for the first time that a farm environment in childhood is associated with a reduced incidence only in adolescence. Unfortunately, farm contact after the age of 5 years was not recorded, and so we are unable to comment on whether it is early childhood or sustained farm exposure that is important in reducing rhinitis risk.

Maternal smoking during pregnancy and early childhood was associated with a consistently increased risk of rhinitis throughout life in atopic subjects; however, smoking only in childhood was

not. This finding may suggest that priming of the immune system or epigenetic mechanisms *in utero* are important in increasing the propensity to development of allergic disease.[31] The associations between parental allergies and increased risk of rhinitis in both atopic and nonatopic individuals across the life span suggest that genetics play a role in the etiology of both phenotypes of rhinitis.

Strengths and limitations

Major strengths of this study are that it is a large international sample allowing socioeconomic, genetic, and culture variations between Western countries to be taken into account when examining these associations. This study was uniformly conducted in multiple international sites to a standardized validated protocol. Atopic status was defined by serum measurements of specific IgE to common aero-allergens. Another strength of this analysis was the availability of age of onset of rhinitis in the ECRHS II follow-up. This allows for a different examination of the association between early-life factors and rhinitis than has been done previously.

Some limitations of the study include the retrospective recall of early-life exposures and the lack of objective measures of childhood exposures (ie, childhood endotoxin levels). While the retrospective recall of some factors may lead to recall bias, it is unlikely to be systematic with regard to rhinitis incidence. For other factors such as number of siblings, early-life pet exposure, bedroom sharing, and day care, recall bias is unlikely to be an issue as these events represent important features of childhood and are likely to be recalled accurately. Furthermore, recent studies have shown that recall of pets is reasonably accurate in childhood[32] and adulthood.[33] Our definition of rhinitis may not have captured all cases of rhinitis because of the way the question was worded. The effect of this would be to underestimate the true incidence of rhinitis. We also did not test for all possible allergens and therefore some "nonallergic" individuals may actually be allergic to other allergens.

Rhinitis is important due to its link with other allergic disorders such as asthma; however, in itself it poses a significant economic and quality-of-life burden. Our study is novel in that it provides evidence that the gender reversal is related to rhinitis among atopic individuals and highlights the need for further studies to understand the biological mechanisms underlying the gender differences in rhinitis and in allergy. Our study is also novel in investigating early-life risk factors and incident rhinitis. We have demonstrated that certain childhood exposures influence the development of rhinitis in different life stages from childhood to adulthood. These findings may shed light into the biological pathways for the development of rhinitis and allergic disease and identify targets for primary preventive strategies to reduce the incidence of rhinitis.

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Clinical implications: This article provides further important evidence for clinical guidelines and recommendations to patients that pet keeping in early life could protect against the development of subsequent allergies.

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METHODS

Specific IgE

Specific IgE to *Dermatophagoides pteronyssinus*, timothy grass, *Cladosporium*, 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). Atopy was defined as a positive assay (if values were >0.35 kU/L, the lowest detection limit of the assay) to specific IgE at ECRHS II for at least 1 specific allergen.

Definitions of the exposures

Bedroom sharing was defined as a positive response to the question "Did you regularly share your bedroom with any older children before the age of five years?" *Day care attendance* was defined as a positive response to the question "Did you go to a school, play-school or nursery with other children before the age of five years?" *Any early exposure to children* was defined as having any siblings, bedroom sharing, and/or day care attendance. *A serious respiratory infection before age of 5 was* defined as a positive response to the question "Did you have a serious respiratory infection before the age of five years?"

Exposure in early life to dogs and cats before 5 years of age was defined by a positive response to either question (a) "Was there a [dog/cat] in your home during your first year of life?" or (b) "Was there a [dog/cat] in your home when you were aged 1 to 4 years?" Growing up on a farm was defined by a response of "Farm" to the question "What term best describes the place you lived most of the time when you were under the age of five years?"

Maternal smoking in childhood/pregnancy was defined as a positive response to the question "Did your mother ever smoke regularly during your childhood, or before you were born?" *Maternal smoking during pregnancy* was defined by a positive response to the question "When your mother was pregnant, in particular with you, did she smoke as usual during pregnancy?" *Paternal smoking in childhood* was defined as a positive response to the question "Did your father ever smoke regularly during your childhood?'' *Parental allergic disease* was recorded as present if the participant recorded a positive response 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?"

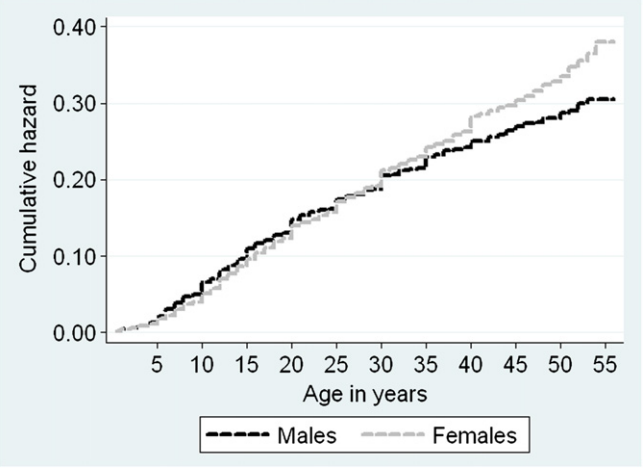

FIG E1. Cumulative probability of rhinitis by gender.

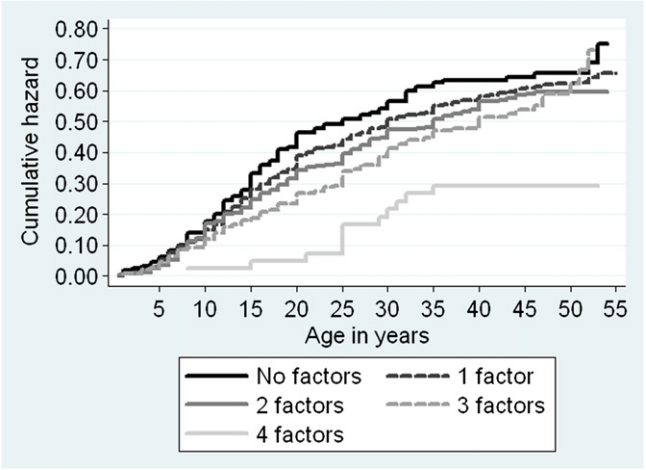

FIG E2. Cumulative probability of rhinitis by combined lifestyle factors in subjects atopic at ECRHS II.

TABLE E1. Comparison of participants and nonparticipants in ECRHS II for selected early-life characteristics

Outcome	n/N (%)		*P* value*
	Nonparticipants	Participants	
Rhinitis	2,469/9,145 (27.00)	2,358/9,037 (26.09)	.17
Sex, male	4,500/9,392 (47.91)	4,322/9,076 (47.62)	.69
Atopy	2,232/6,373 (35.02)	2,300/7,556 (30.44)	.0001
Age†	32.6 (SD, 7.15)	33.5 (SD, 7.09)	.00001
Bedroom share <5 y	3,950/9,068 (43.56)	4,061/9,042 (44.91)	.08
Day care <5 y	4,817/9,065 (53.14)	4,138/9,034 (45.80)	.0001
Median number of siblings (interquartile range)‡	2 (1-3) range 0-20	2 (1-3) range 0-18	.00001
Cat	2,281/9,047 (25.21)	1,752/9,045 (19.37)	.0001
Dog	1,858/9,045 (20.54)	1,498/9,048 (16.56)	.0001
Mother smoking			
Childhood	1,667/8,826 (18.89)	1,167/8,826 (13.22)	
Pregnancy	1,011/8,826 (11.45)	889/8,826 (10.07)	.0001
Father smoking	5,909/9,077 (65.10)	5,742/9,050 (63.45)	.000
Child infections	870/9,046 (9.62)	876/9,019 (9.71)	.28
Parental allergies	3,129/9,064 (34.52)	3,223/9,040 (35.65)	.11

*χ^2 Comparison of responders and nonresponders.
†*t* Test.
‡Mann-Whitney Rank sum test.

TABLE E2. Association between parental allergies and gender, and incident rhinitis in nonatopic participants

	HR (95% CI)* for age at onset (y)					
Characteristics	**<5 y**	**6-10 y**	**11-20 y**	**21+ y**	**Test for heterogeneity**	**Pooled HR (95% CI)**
Sex, female‡	0.96 (0.49-1.87)	1.79 (1.04-3.08)	1.33 (0.98-1.80)	1.70 (1.41-2.05)†	(P = .24)	1.57 (1.35-1.82)
Parental allergies§	1.74 (0.89-3.40)	2.36 (1.43-3.89)	1.53 (1.14-2.07)	1.52 (1.27-1.82)†	(P = .44)	1.59 (1.38-1.83)

*Adjusted for sex, age, center, education, and parental allergy.
†Additionally adjusted for personal smoking.
‡Adjusted for age, center, education, and parental allergy.
§Adjusted for sex, age, center, and education.