

Childhood Visits to Animal Buildings and Atopic Diseases in Adulthood: An Age-Dependent Relationship

Katja Radon, PhD,* Vera Ehrenstein, MPH, Georg Praml, PhD, and Dennis Nowak, PhD

Background Several studies reported protective effects of farming environments against atopic diseases. Therefore, we aimed to establish the relevant timing of exposure in early life.

Methods A cross-sectional study was carried out in a rural town. Overall, 4,537 inhabitants aged 18–44 years were eligible. Of these, 3,112 (69%) responded to a postal questionnaire on atopic diseases, life-time exposure to farming environments, and potential confounders.

Results Those with regular childhood exposure to animal buildings had a significantly reduced risk of nasal allergies. The greatest reduction in risk was seen for respondents starting regular visits to animal stables during the 1st year of life or between ages 3 and 5. Participants reporting start of exposure after age 5 remained at a lower risk for nasal allergies (0.70, 0.49–1.01).

Conclusions The preventive effect of animal buildings' exposure against atopic respiratory diseases continues into adulthood. The magnitude of the effect appears to be age-dependent. Am. J. Ind. Med. 46:349–356, 2004. © 2004 Wiley-Liss, Inc.

KEY WORDS: livestock farming; asthma; allergies; dermatitis; Th2; hygiene hypothesis; epidemiology; cross-sectional study; endotoxins; farmer

INTRODUCTION

Several recent studies reported protective effects of farming environments against asthma and allergies [Braun-Fahrlander et al., 1999; Ernst and Cormier, 2000; Kilpelainen et al., 2000; Von Ehrenstein et al., 2000; Leynart et al., 2001; Riedler et al., 2001; Braun-Fahrlander et al., 2002]. The

protection seems to be mainly conferred by animal farming [Riedler et al., 2001; Radon et al., 2002b]. The hypothesized mechanism for the observed effect involved either induction of Th1-type responses or development of immune tolerance [Tang, 2002]. It has been suggested that endotoxin may act as the causal agent of the observed effect because of its elevated concentrations in animal farming environments [Radon et al., 2002a] and because at low levels endotoxin exposure produces cytokines that, in turn, stimulate production of Th1 [von Mutius et al., 2000]; at the same time, Th2 cell production is decreased [Renz and Herz, 2002; Weiss, 2002].

It is not clear whether the protective effect of childhood animal farming exposure is retained in adulthood. Within the European Community Respiratory Health Survey (ECRHS), Leynart et al. [2001] reported a protective effect of childhood farm living against atopic diseases in early adult life. Animal farmers were also shown to have a lower than the general-population prevalence of atopic diseases [Radon et al., 2001]. However, no data were available on whether the participants

Institute for Occupational and Environmental Medicine, Unit for Occupational and Environmental Epidemiology & Net Teaching, Ludwig-Maximilians-University, Munich, Germany
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*Correspondence to: Katja Radon, Institute for Occupational and Environmental Medicine, Unit for Occupational and Environmental Epidemiology & Net Teaching, Ziemssenstr. 1, 80336 Munich, Germany. E-mail: katja.radon@med.uni-muenchen.de

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had regular contact to farm animals or on the age at which this exposure started. Results from a longitudinal study among school-aged children suggest that living on a farm increases the likelihood of a loss of sensitization [Horak et al., 2002]. In contrast, in the cross-sectional study of primary school children by Riedler et al. [2001], only first year of life exposure to animal confinement buildings was associated with lower prevalence of atopic diseases.

Thus, data on the relevant timing, frequency, environmental and genetic cofactors of childhood exposure to farming environments and their relative importance in the preventive mechanism are scarce [Renz and Herz, 2002; Weiss, 2002]. In this cross-sectional population-based survey, we aimed to assess in detail the relevant timing of the exposure by examining the association between age at start of regular visits to animal buildings and risk of atopic diseases among adults living in a rural area.

MATERIALS AND METHODS

Study Population

The study region is a part of Northern Germany with intensive animal production. All adults aged 18–44 years ($n = 4,537$) living in one rural town in the study region were invited to answer a mail-in questionnaire. The local population registry provided the addresses. Up to two postal reminders have been sent. Subjects not responding within 6 weeks after the first mailing were contacted by phone. Overall, 3,112 (68.6%) persons returned the completed questionnaire.

Questionnaire

All 77 questions were taken from pre-existing validated questionnaire instruments [Galobardes et al., 1998; Sunyer et al., 2000; Riedler et al., 2001]. Additionally, reliability of the questions was tested in 150 residents of a small town in the study region. Except for the question on skin allergies, all questions used for this analysis were shown to have good or very good reliability. In order to improve the specificity of the atopic dermatitis definition, we added the question “Have you had itchy rash that was coming and going for at least 6 months?” after the results of the initial testing (2002).

Questions on exposure to farming environments were taken from the questionnaire of the Allergies and Endotoxin (ALEX)-study group [Riedler et al., 2001; Braun-Fahrlander et al., 2002]. Subjects exposed to animal buildings during childhood were asked to indicate the age at which regular contacts began. Those who could not remember whether they were exposed to animal buildings during childhood were considered unexposed ($n = 97$).

Questions on respiratory diseases, atopic skin diseases, and on potential confounding factors for these conditions

were taken from the questionnaire of the European Community Respiratory Health Survey [2002]. Four outcomes were evaluated in this study: nasal allergies; atopic asthma symptoms; non-atopic asthma symptoms; and atopic dermatitis defined as follows: nasal allergies were defined as a positive response to the question “Do you have any nasal allergies, including hay fever?” Subjects were considered to have symptoms of asthma if they reported having had either wheezing or whistling in the chest without having a cold, or wheezing or whistling in the chest combined with being awakened by a feeling of shortness of breath during the previous 12 months [Nowak et al., 1996]. Atopic asthma symptoms were defined as having nasal allergies in addition to symptoms of asthma; non-atopic asthma symptoms were defined as asthma symptoms without nasal allergies. Atopic dermatitis was defined as reporting either eczema or skin allergies and recurrent itching rash for at least 6 months.

Based on previous research, the following variables were considered potential confounders in our study: age, gender, living on a farm, working on a farm, having no siblings, having siblings with a history of allergy, parental history of allergy, childhood exposure to second-hand smoke, participants' own smoking history, having a cat or a dog, and country of birth.

The study protocol was approved by the Ethical Committees of the Ludwig-Maximilians-University Munich and the Association of Physicians of Lower Saxony.

Statistical Analysis

We used cross-tabulation to visualize bivariate distributions of categorical predictors and outcomes. We calculated mean and standard deviation for age among those with and without regular contacts to animal buildings and evaluated the prevalence of each outcome in the age deciles. After failing to detect a pattern, age in years was entered in all multivariate analyses as a continuous variable. Because the question on nasal allergies had the highest validity, we used this outcome to build the final model for all four closely related outcomes of this study proceeding in the following manner. First, we compared the crude odds ratio with the odds ratios adjusted individually for each a priori defined risk factor for allergic diseases, in order to determine whether a single variable was responsible for the bulk of confounding. Second, we evaluated the joint confounding in a multivariate logistic regression model that included all confounders and compared the fully adjusted odds ratio to the crude odds ratio. Finally, we eliminated terms, one at a time, from the model in the order of least statistical significance and assessed the resulting change in the adjusted odds ratio for the main exposure. A term was left in the model if its deletion substantially ($>10\%$) changed the adjusted odds ratio estimate or if the removal adversely affected predictive ability of the model. The latter was assessed with the Likelihood Ratio

Chi-square test [Kleinbaum et al., 1982]. Age and gender were retained in all models.

We plotted prevalence of each outcome against the year of age of the start of regular animal building visits. Based on this visualization, the following ages were combined for inclusion in the multiple logistic regression models: regular contact to animal buildings starting in the first year of life, in the second to third year of life, during kindergarten (fourth to sixth year of life), or at school age (after sixth year of life). Because no atopic asthma event was observed in the 1st year of life or among those with missing status with respect to farm living, these categories ($n = 71$) were dropped from the multivariate analysis of the atopic asthma symptoms.

In order to assess the possible extent of reporting bias, we restricted the above multivariate analyses to those not living or working on a farm. This did not affect the results.

Statistical analyses were carried out using SAS statistical package [SAS/STAT Software, 2000].

RESULTS

The mean age (SD) of the 3,112 participants was 33.0 (7.8) years as compared with 32.3 (7.7) years in the eligible population. The proportion of women among the participants was slightly higher than in the source population (51.2% vs. 48.2%, respectively).

Table I shows demographic characteristics and prevalence of respiratory symptoms for subjects with and without regular visits to animal buildings. Those with regular visits were less educated, and more likely to be born in Western Germany, to have siblings, and to keep a cat or a dog. They had a significantly lower prevalence of nasal allergies than those without regular visits to animal buildings. Additionally, the prevalence of atopic asthma symptoms and atopic dermatitis was lower (n.s.).

The prevalence and 95% CI of each outcome by age at start of regular visits to animal buildings are plotted in Figure 1. These plots suggest a trend for increasing prevalence of adulthood nasal allergies and atopic asthma symptoms by year of age of start of regular contact to animal buildings. By contrast, no clear trend can be seen for non-atopic symptoms of asthma or for atopic dermatitis.

Tables II and III display the results of adjusted analyses. Those who never had regular contact to animal buildings were taken as reference category. After adjustment for current exposure to cats or dogs, having no siblings, parental and sibling history of allergy, smoking habits, age, sex, and presently living on a farm, age at start of regular visits to animal confinement buildings was a significant predictor of nasal allergies and atopic asthma. The greatest reduction in risk was seen for participants who started regular visits to animal buildings during the 1st year of life or during kindergarten age (4th–6th year of life). Subjects who started regular visits to animal stables during the 7th year of life or

later also had a lower risk for these outcomes than those in the reference group. In contrast, no such trend was seen for the association of age of start of regular visits to animal buildings with non-atopic symptoms of asthma or with atopic dermatitis.

DISCUSSION

Our results indicate an age-dependent association between exposure to farm animals and atopic disorders. The protective effect of exposure to farm animals was most pronounced during the first year of life and at ages 3–5. However, even for those who started visiting animal buildings at school age, a lower prevalence of nasal allergies and atopic asthma was seen. These results help better understand the optimal timing of exposure to microbial compounds during the life cycle for the prevention of atopic diseases.

We used a valid and reliable questionnaire instrument that has been extensively tested within the European Community Respiratory Health Survey [Galobardes et al., 1998; Sunyer et al., 2000]. Additionally, our own study has shown good reliability for the questionnaire items included in this analysis. However, as we used no objective measurements to assess symptoms, we cannot rule out misclassification bias.

This might especially be true for atopic dermatitis because it has been shown that the validity of this question was not as good as the validity of the items on respiratory symptoms [Kramer et al., 1998]. This might explain our finding that the association between start of exposure to animal confinement buildings and atopic dermatitis was not as clear-cut as it might have been expected. This result did not depend on the presence of nasal allergies. Of 3,112 subjects, 108 (3.5%) reported atopic dermatitis/nasal allergies co-morbidity. We examined the relation between having both conditions and age at which visits to animal buildings began. Compared with having no regular visits, adjusted odds ratios [95% CI] were 1.44 [0.42, 4.92] for the first year of life; 0.96 [0.54, 1.70] for year 2–3; 0.53 [0.24, 1.18] for year 4–6; and 0.73 [0.37, 1.46] for year 7 or older. Thus, the pattern seen for the combined atopic dermatitis/nasal allergy outcome is similar to that reported for the atopic dermatitis outcome (Table III) and although, with the exception of the first year of life, odds ratios for the combined outcome were indeed lower, the associated standard error was larger, amounting to loss of precision. Three hundred fifty-six (11%) of 3,112 subjects reported having atopic dermatitis and no nasal allergies. Adjusted odds ratios for this outcome were 1.03 [0.42–2.51] for the first year of life; 1.15 [0.82; 1.60] for year 2–3; 0.87 [0.58; 1.29] for year 4–6; and 0.90 [0.61; 1.31] for year 7 or older.

Another issue might be the definition of atopy in our study. At the time of the study, no specific IgE measurements were available for the study population, therefore, we had to rely on symptoms of hay fever.

TABLE I. Comparison of Subjects With and Without Regular Visits to Animal Buildings*

Characteristic	Without regular visits (N = 1,807)	With regular visits (N = 1,268)
Age, mean (95% CI)	32.3 (31.9, 32.6)	33.9 (33.5, 34.3)
	N, percent [95% CI]	
Gender: Female	981	599
	54.3 [52.0, 56.6]	47.2 [44.5, 50.0]
Country of birth		
West Germany	1,490	1,085
	82.9 [81.0, 84.5]	86.0 [83.9, 87.8]
East Germany	67	37
	3.7 [2.9, 4.7]	2.9 [2.1, 4.0]
Other ^a	241	140
	13.4 [11.9, 15.1]	11.1 [9.4, 13.0]
≥ 12 years of schooling	426	258
	24.0 [22.0, 26.0]	20.7 [18.4, 23.0]
Smoking habits		
Ex-smoker	317	244
	17.8 [16.0, 19.6]	19.5 [17.3, 21.8]
Current smoker	594	424
	33.3 [31.1, 35.5]	33.9 [31.3, 36.6]
No siblings	78	22
	4.3 [3.4, 5.4]	1.7 [1.1, 2.6]
At least one sibling with history of allergy	543	359
	30.0 [28.0, 32.2]	28.3 [25.8, 30.9]
Parental history of allergy	476	349
	26.6 [24.5, 28.7]	27.6 [25.2, 30.2]
Parental smoking	1,078	705
	59.8 [57.5, 62.1]	55.7 [52.9, 58.4]
Currently has cat/dog	637	563
	35.2 [33.0, 37.5]	44.4 [42.6, 47.2]
Living on a farm during the first 3 years of life	265	890
	14.8 [13.1, 16.5]	70.3 [67.7, 72.8]
Living on a farm now	129	340
	7.2 [6.0, 8.5]	26.9 [24.5, 29.5]
Farmer or farm worker	24	120
	1.5 [0.9, 2.2]	10.1 [8.4, 11.9]
Health outcomes		
Nasal allergies	286	121
	16.0 [14.3, 17.8]	9.6 [8.0, 11.4]
Atopic asthma symptoms	86	43
	4.8 [3.8, 5.8]	3.4 [2.5, 4.5]
Non-atopic asthma symptoms	119	94
	6.6 [5.5, 7.9]	7.4 [6.0, 9.0]
Atopic dermatitis	291	178
	16.2 [14.6, 18.0]	14.2 [12.3, 16.2]

*Thirty-seven observations are not included due to missing data on visits in animal buildings.

^aIncludes countries of the former Eastern Bloc, and Middle East.

Major limitations of the study were its cross-sectional design and the self-reported measurements used. Therefore, it was not possible to obtain objective measurements of exposure during childhood and the validity of these questions

is difficult to assess. Recall bias might thus be an issue especially for animal buildings exposure under the age of 3 years. One concern was that of under-reporting of the outcome symptoms and/or exposure by farmers living in an

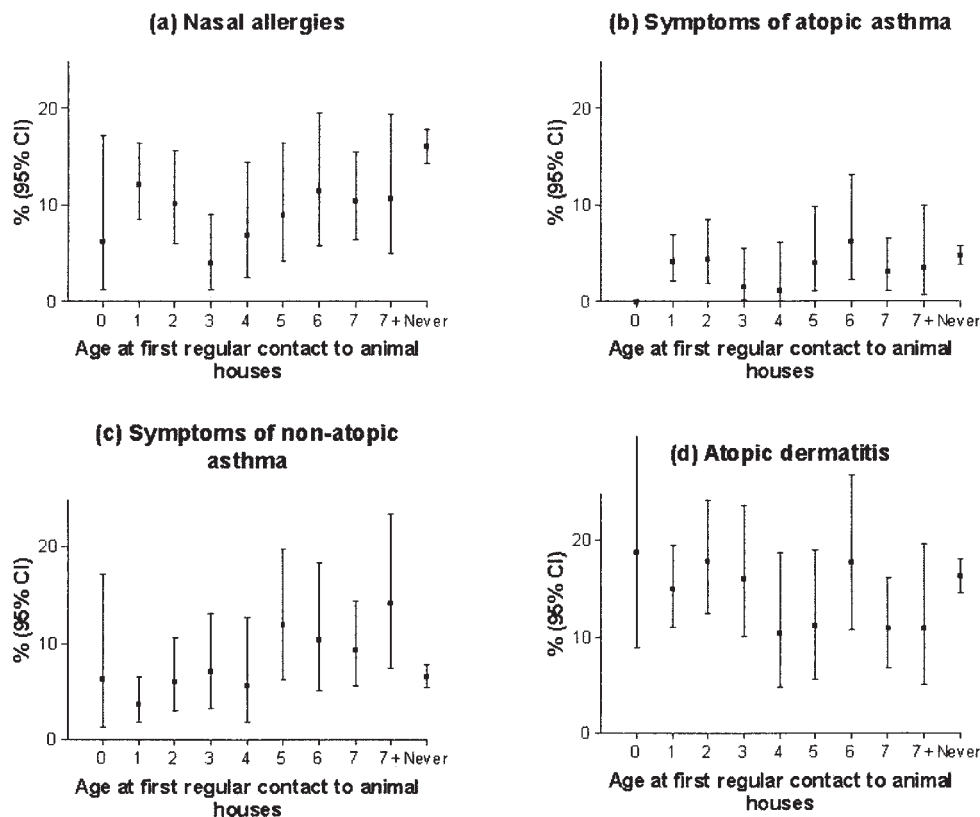


FIGURE 1. Prevalence and 95% CI of (a) nasal allergies; (b) symptoms of atopic asthma; (c) symptoms of non-atopic asthma; and (d) atopic dermatitis by age at start of regular visits to animal buildings.

area with intensive livestock farming in order to avoid an unfavorable image of farming. However, restricting our data to those not involved in farming gave no indication of systematic misclassification. Therefore, assuming that potentially mostly non-differential misclassification of exposure and outcomes took place, the estimates of effects described in this study underestimate rather than overestimate the true magnitude of the association.

Despite a reasonable response rate, selection bias cannot be completely ruled out. Attempts to contact non-respondents indicated that high proportion of them were born in Eastern Europe. The study region is an area with a large community of immigrants from the former Soviet Union who could have difficulties responding to a German-language questionnaire. Based on the fact that sensitivity analysis adjusted for the country of birth did not affect our results, we do not believe that differential representation of the immigrant community caused substantial bias. We did not consider occupations other than farming as potential confounders in the association between childhood exposure to animal stables and respiratory symptoms. Therefore, we did not adjust for other jobs.

Our results corroborate the previous finding that exposure to farming environments during the first year of

life protects one from atopic respiratory diseases [Riedler et al., 2001]. In addition, our results suggest that such exposure originating later in childhood continues to be protective against nasal allergies and atopic asthma symptoms with the protective effect carrying through into adulthood. The 'U-shaped' pattern observed for nasal allergies, whereby the start of exposure in the 2nd and the 3rd years of life is less protective than that in either the first or after the 3rd year, is paradoxical. A similar tendency was observed for the atopic asthma outcome, though the first-year exposure effect could not be assessed. Differential recall rates for different childhood periods seem to be an unlikely explanation of the observed effect. We did not assess the duration of exposure to animal buildings, however, it seems unlikely that the duration of exposure was different for those who started exposure in the 2nd and the 3rd years of life apart from the difference conferred by the age at the start of the visits. While it is well accepted today that compartmentalization of the immune system occurs mainly before the age of 5 [Yabuhara et al., 1997], the knowledge of the kinetics of the changes in immune function until the age of 5 is limited [Prescott et al., 1999; Holt and Jones, 2000]. Recently, a study by Rowe et al. [2000] suggested peaks in Th2 cytokines in late infancy might offer a clue to the explanation of our results. More

TABLE II. Adjusted Odds Ratios* [95% CI] for the Risk of Nasal Allergies and Atopic Asthma

Outcome	N ^a	Nasal allergies	Atopic asthma symptoms
Age at which regular visits to animal stables started			
Never	1,807	1	1
Year 1	48	0.35 [0.10, 1.15]	—
Year 2–3	473	0.79 [0.56, 1.10]	1.00 [0.59, 1.70]
Year 4–6	316	0.36 [0.22, 0.59]	0.43 [0.20, 0.95]
Year 7+	375	0.70 [0.49, 1.01]	0.87 [0.49, 1.56]
Presently living on a farm			
No	2,618	1	1
Yes	471	0.57 [0.38, 0.86]	0.74 [0.39, 1.40]
Missing	23	0.37 [0.05, 2.87]	—
Having cat/dog	1,211	0.82 [0.65, 1.04]	0.80 [0.54, 1.20]
No siblings	101	1.62 [0.94, 2.80]	0.53 [0.13, 2.23]
At least one sibling with history of allergy	910	1.93 [1.54, 2.42]	2.07 [1.43, 3.02]
Number of parents with history of asthma/allergies			
Zero	2,260	1	1
One	696	1.85 [1.45, 2.37]	2.23 [1.50, 3.33]
Both	133	3.29 [2.16, 5.02]	4.28 [2.37, 7.72]
Missing	23	1.54 [0.50, 4.73]	1.56 [0.20, 12.03]
Smoking history			
Never	1,471	1	1
Former	567	1.10 [0.82, 1.46]	0.96 [0.57, 1.62]
Current	1,032	0.57 [0.44, 0.74]	1.10 [0.73, 1.66]
Missing	42	0.37 [0.09, 1.58]	0.79 [0.10, 6.10]

*Adjusted for all variables presented in the table and for age and sex.

^aNumbers do not add up to N = 3,112 due to missing data.

detailed information on the development of the immune system from infants and young children is necessary to completely understand this finding.

In contrast to our study, Riedler et al. [2001] did not see protective effect of animal farm contact if the contacts started after the first year of life. However, the study's insufficient sample size precluded appropriate stratification by age at start of exposure.

That start of exposure to animal buildings after the first year of life, and into school age remains associated with a lower risk of nasal allergies and atopic asthma supports the hypothesis that not only exposure to farming environments prevent sensitization, but it may also increase the rate of a loss of sensitization [Prior et al., 2001; Horak et al., 2002]. At the same time, animal studies using lipopolysaccharides (LPS) as surrogate exposure for contact to animal buildings do not support these findings. While exposure to LPS before allergic sensitization reduced the risk of allergic sensitization in rats, exposure to LPS after sensitization exacerbated the allergic immune response [Slater et al., 1998; Tulic et al., 2000]. Therefore, it remains unclear whether endotoxin—cell wall LPS of the gram-negative bacteria—represents the principal causal agent responsible for animal farming protective effect

with respect to atopic disorders. Besides inhalation [von Mutius, 2000], exposure to endotoxin or similar agents via the gastrointestinal tract may also be important in the farming environment [Alm et al., 1999; Björkstén et al., 1999; Matricardi et al., 2000; von Mutius, 2000; Riedler et al., 2001]. The recent finding that very high concentrations of cat (Fel d 1) allergens might produce an IgG and IgG4 antibody response without sensitization [Platts-Mills et al., 2001] might also apply to the other animal allergens found in the farming environment [Parvaneh et al., 1999; Radon et al., 2000].

Whereas many studies found only a weak association between farming exposure and asthma or wheezing in children or young adults [Braun-Fahrlander et al., 1999; Ernst and Cormier, 2000; Kilpelainen et al., 2000; Riedler et al., 2000; Von Ehrenstein et al., 2000; Leynart et al., 2001; Portengen et al., 2002], our results show a protective effect of contact to animal buildings for symptoms of asthma after stratifying these symptoms by atopy. As has been suggested previously [Pearce et al., 1999; Strachan, 2000], a large proportion of asthma symptoms was not attributable to atopy, which may explain lack of observed association in earlier studies. Incidentally, in our data, non-atopic asthma symptoms were

TABLE III. Adjusted Odds Ratios [95% CI] for the Risk of Non-Atopic Asthma, and Atopic Dermatitis (Footnotes as in Table II)

Outcome	N	Non-atopic asthma symptoms	Atopic dermatitis
Age at which regular visits to animal buildings started			
Never	1,807	1	1
Year 1	48	1.34 [0.40, 4.56]	1.13 [0.53, 2.45]
Year 2–3	473	0.73 [0.45, 1.20]	1.11 [0.82, 1.50]
Year 4–6	316	1.20 [0.76, 1.89]	0.75 [0.52, 1.08]
Year 7+	375	1.54 [1.03, 2.30]	0.83 [0.58, 1.17]
Presently living on a farm			
No	2,618	1	1
Yes	471	0.90 [0.57, 1.44]	0.61 [0.43, 0.87]
Missing	23	0.38 [0.05, 3.03]	1.31 [0.41, 4.21]
Having cat/dog	1,211	0.90 [0.66, 1.23]	1.18 [0.95, 1.46]
No siblings	101	1.30 [0.60, 2.82]	1.07 [0.59, 1.93]
At least 1 sibling with history of allergy	910	1.72 [1.26, 2.34]	2.00 [1.61, 2.47]
Number of parents with history of asthma/allergies			
Zero	2,260	1	1
One	696	1.48 [1.06, 2.06]	2.02 [1.61, 2.53]
Both	133	1.72 [0.93, 3.20]	2.27 [1.50, 3.44]
Missing	23	2.63 [0.72, 9.62]	1.56 [0.51, 4.74]
Smoking history			
Never	1,471	1	1
Former	567	1.57 [0.96, 2.56]	1.32 [1.00, 1.74]
Current	1,032	4.77 [3.33, 6.81]	1.16 [0.91, 1.46]
Missing	42	4.81 [1.77, 13.06]	0.40 [0.09, 1.71]

clearly associated with smoking patterns (Table III). Therefore, the symptoms of non-atopic asthma in our study population may represent precursors of chronic obstructive pulmonary disease in these adults.

Our findings indicate that the relation between early life exposure to animal farming and atopic diseases in adulthood might be age-dependent, and that this dependence may not be linear. Our findings underscore the complex nature of the atopic diseases etiology as a function of environmental and genetic cofactors, their dose and duration and continuation of their effects into adult life. These observations may advance the initiation of new prevention or treatment strategies for atopic diseases.

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