

Growing up on a farm leads to lifelong protection against allergic rhinitis

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Abstract

Background: Various studies have reported a low prevalence of allergic rhinitis in farmers and farmers' children. We sought to investigate whether the protective effect of childhood farm environment is conserved throughout adulthood and how it corresponds to different degrees of urbanization.

Methods: A questionnaire on respiratory health was mailed in 2008 to 30 000 randomly selected subjects aged 16–75 in West Sweden, 29 218 could be traced and 18 087 (62%) responded. The questionnaire included questions on allergic rhinitis, asthma, respiratory symptoms and possible determinants.

Results: When stratified into age groups of 15 years, subjects that lived on a farm during their first 5 years of life had a lower prevalence of allergic rhinitis in all groups, even among the oldest (61–75 years). The negative correlation between childhood farm living and prevalence of allergic rhinitis was similar in 46–75 years of age (OR 0.82; 95% CI 0.70–0.95) as in 16–45 years of age (OR 0.78; 0.64–0.95). There was a significant trend of increasing prevalence of allergic rhinitis with increasing degree of urbanization independent of the effect of childhood farm living. **Conclusions:** We found a lifelong protective effect of childhood farm living on the prevalence of allergic rhinitis. In addition, we found an increasing prevalence of allergic rhinitis with increasing degree of urbanization both in those raised on a farm and those not, thus emphasizing the influence of both childhood and adult exposure for the development of allergic disease.

Allergic rhinitis is the most common immunologic disorder and it renders a considerable burden on both the affected individuals and the society (1). Rhinitis is further an important risk factor for asthma (2). Over the second half of the past century, the prevalence of allergic rhinitis has increased markedly in many countries including Sweden (1, 3). In a recent study, we found the prevalence of allergic rhinitis among adults in West Sweden to be high, 26.9%, and apparently on the increase (4).

Several environmental factors have been hypothesized to contribute to this increase, including allergen exposure, indoor and ambient air pollution, reduced early childhood infections and changes in dietary habits (5). However, none of these factors has convincingly explained the observed

increase. In the past decade, various studies reported a lower prevalence of allergic rhinitis among children living on a farm (6–10). Furthermore, some studies indicated that the protective effect of childhood farm exposure continues into adulthood (9–12). However, it remains unclear whether this effect is present in the adult population including also middle aged and elderly.

Moreover, a number of studies have reported a greater prevalence of allergic rhinitis in urban compared to rural residents (13, 14). How the effect of urbanization relates to childhood farm environment and to age is yet to be elucidated.

The aim of this study was to assess the effect of childhood farm living and the degree of urbanization on the prevalence

of allergic rhinitis in a life-long perspective and their importance as independent risk factors for allergic rhinitis in a multivariate setting.

Material and method

Study population

In 2008, a self-administered postal questionnaire was mailed to 30 000 inhabitants, aged 16–75, in the Swedish region of West Gothia. By complete computerized randomization, a sample of 15 000 subjects was selected from the metropolitan area of Gothenburg. Likewise, 15 000 subjects of same ages were randomly selected from the rest of the region. The Swedish Population Register provided the names and addresses. The invited individuals were given the possibility to respond either by mail or over the internet. The selection of the study population is extensively described elsewhere (4). The ethical committee of the University of Gothenburg approved the studies.

Questionnaire

In this study, we used the Swedish OLIN study questionnaire (15) that has been used in several studies in northern Europe (16–19) and contains questions about obstructive respiratory diseases, rhinitis, respiratory symptoms and possible determinants of disease, such as smoking, occupation and family history of allergic disease. Further, additional questions about smoking habits and occupational and environmental exposures were included as well as the Swedish version of the GA²LEN questionnaire (20).

Degree of urbanization

Localities of residence were classed into four categories based on their number of inhabitants. Metropolitan *Gothenburg*, with approximately 700 000 inhabitants, was used as a separate entity, while other localities with more than 10 000 inhabitants were considered *mid-sized towns* (all with <100 000 inhabitants). Localities with 2000–10 000 inhabitants were considered *small towns* and those with <2000 inhabitants *rural areas*. The classification was performed by matching the subjects' address information with official population data from Statistics Sweden (21).

Definitions

Allergic rhinitis: 'Have you ever had allergic eye or nose problems (hay fever)'; *Family history of allergy*: 'Has any of your parents or siblings ever had allergic eye or nose problems (hay fever)'; *Physician-diagnosed asthma*: 'Have you been diagnosed as having asthma by a doctor'; *Occupational exposure*: 'Have you been substantially exposed to dust, gases or fumes at work'; *Raised on farm*: 'Did your family live on a farm during your first 5 years of life'. *Smokers* reported smoking during the year preceding the survey; *Ex-smokers*

reported having stopped smoking at least 12 months preceding the survey; *Nonsmokers* reported neither smoking nor ex-smoking.

Analyses

Ten percent of the data were computerized twice in purpose of quality control of the computerization. Errors amounted to 0.1–0.2% of the computerized data with only a few exceptions. Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL, USA) version 16.0. Comparisons of proportions were tested with Fishers' exact test. One-way analysis of variance (ANOVA) was used for testing for trends. A *P*-value of <0.05 was regarded as statistically significant. Covariates used in the analyses included age, sex, family history of allergy, physician-diagnosed asthma, smoking habits, degree of urbanization, living on a farm during the first 5 years of life and occupational exposure to dust, gases and fumes. Multiple logistic regression models were performed using these independent variables as risk factors (odds ratios, OR, with 95% confidence intervals, CI) of allergic rhinitis. In order not to lose statistical power, two age groups were created and used in the multiple regression analyses.

Results

Demographics

The real study sample comprised of 29 218 subjects, 782 of the initial 30 000 could not be traced (22). Of the real study sample, 18 087 subjects (62%) participated. Participation was significantly higher among women than in men (69% vs. 55%, *P* < 0.001) as well as outside compared to inside the metropolitan area of Gothenburg (66% vs. 61%, *P* < 0.001). Participation increased significantly by age (*P* < 0.001), from 51% in 16–25 years of age to 77% in 66–75 years of age. The study population by age, sex, degree of urbanization and childhood living is presented in Table 1.

Prevalence

The prevalence of allergic rhinitis was considerably lower among subjects who lived on a farm during their first 5 years of life than among those that did not (20.1% vs. 28.0%, *P* < 0.001) (Table 2). The effect of growing up on a farm was present both in men (18.4% vs. 27.4%, *P* < 0.001) and in women (21.7% vs. 28.5%, *P* < 0.001). Further, the effect was present and significant in all age groups, being most pronounced in 16–30 years of age (19.5% vs. 30.5%, *P* < 0.001) and least so in 61–75 years of age (16.5% vs. 19.4%, *P* = 0.045).

Moreover, the prevalence of allergic rhinitis increased with increasing degree of urbanization. The highest prevalence was found in metropolitan Gothenburg (28.3%), the second highest in mid-sized towns (27.6%), the third highest in small towns (25.7%) and the lowest in rural areas (22.9%). This trend was present (*P* < 0.001) both in men and in women.

Table 1 Study population by age, sex, degree of urbanization and childhood farm living

		Age (years)				Sex		
		16–30	31–45	46–60	61–75	Men	Women	Total
<i>By degree of urbanization</i>								
Gothenburg (700 000 inh.)	<i>n</i>	2379	2416	2228	1634	3886	4771	8657
Mid-sized towns (>10 000 inh.)	<i>n</i>	893	1145	1203	1065	1963	2343	4306
Small towns (2000–10 000 inh.)	<i>n</i>	313	514	531	451	812	997	1809
Rural areas (<2000 inh.)	<i>n</i>	556	797	1055	907	1529	1786	3315
<i>By childhood living</i>								
Not raised on a farm	<i>n</i>	3766	4380	4125	3057	6904	8424	15 328
Raised on a farm	<i>n</i>	328	454	835	940	1186	1371	2557
Total	<i>n</i>	4141	4872	5017	4057	8190	9897	18 087

Table 2 Prevalence of allergic rhinitis by degree of urbanization, childhood farm living, age and sex

	Age (years)				<i>P</i> -value	Sex		<i>P</i> -value	Total
	16–30	31–45	46–60	61–75		Men	Women		
<i>Degree of urbanization</i>									
Gothenburg (700 000 inh.), %	30.7	33.7	26.5	19.3	<0.001	27.1	29.3	0.024	28.3
Mid-sized towns (>10 000 inh.), %	30.9	32.8	27.4	19.3	<0.001	27.8	27.4	0.76	27.6
Small towns (2000–10 000 inh.), %	27.8	31.5	26.4	16.9	<0.001	24.3	26.9	0.21	25.7
Rural areas (<2000 inh.), %	23.6	28.9	22.1	18.1	<0.001	21.9	23.7	0.23	22.9
<i>P</i>	0.002	0.012	0.013	0.32		<0.001	<0.001		<0.001
<i>Childhood living</i>									
Not raised on a farm, %	30.5	33.1	26.6	19.4	<0.001	27.4	28.5	0.13	28.0
Raised on a farm, %	19.5	26.0	21.3	16.5	0.006	18.4	21.7	0.043	20.1
<i>P</i>	<0.001	0.002	0.001	0.045		<0.001	<0.001		<0.001

The effect of degree of urbanization was strongest in 16–30 years of age ($P = 0.002$), where the difference between metropolitan Gothenburg and rural areas was 7% units, and decreased in magnitude with increasing age. The prevalence of allergic rhinitis was higher among women than in men in metropolitan Gothenburg (29.3% vs. 27.1%, $P = 0.024$), while no gender difference was found in the smaller localities. Independent of the degree of urbanization, the highest prevalence was found in 31–45 years of age (28.9–33.7%) and the lowest in 61–75 years of age (16.9–19.3%).

The effect of childhood farm living was present and significant in all degrees of urbanization (Fig. 1A). The effects of both variables were more pronounced in 16–30 years of age (Fig. 1B), yet present throughout adulthood (Fig. 2). However, among subjects raised on a farm, the effect of urbanization did not reach significance after 35 years of age.

Risk factors

Table 3 shows the difference in prevalence of potential confounders among subjects that either lived on a farm during the first 5 years of life or not. After adjusting for these variables in a multiple logistic regression model, growing up on a farm was significantly negatively associated with allergic rhinitis

(OR 0.82; 95% CI 0.72–0.92) (Table 4). The risk was similar in 46–75 years of age (OR 0.82; 0.70–0.95) as in 16–45 years of age (OR 0.78; 0.64–0.95). Moreover, living in metropolitan Gothenburg (OR 1.29; 1.15–1.44) or in a mid-sized town (OR 1.28; 1.13–1.45) was associated with increased risk of allergic rhinitis. When removing family history of allergy from the multivariate model, the association between allergic rhinitis and childhood farm living did not alter significantly [OR 0.82 (95% CI 0.72–0.92) vs. OR 0.76 (95% CI 0.68–0.85)]. Likewise, when degree of urbanization was removed from the model, the OR of the other variables, including childhood farm living, changed only in the second decimal. Similarly, when removing childhood farm living from the model, the associations to other variables proved to be stable. Risk factors for allergic rhinitis are listed in Table 4.

When analyzing 16–30 years of age separately in the multiple logistic regression model, the negative association of being raised on a farm proved to be significantly stronger, OR 0.67 (95% CI 0.48–0.93).

Discussion

In this large-scale cross-sectional study, we found living on a farm during the first 5 years of life to be associated with a

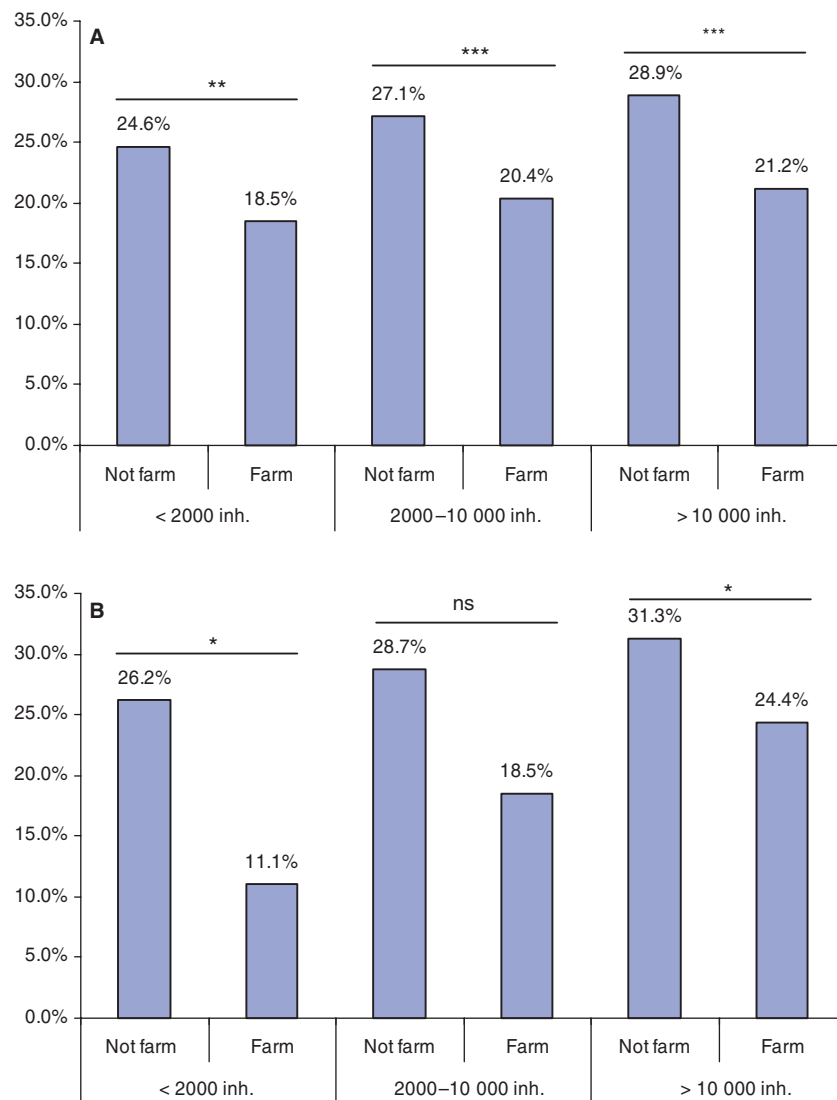


Figure 1 (A) Prevalence of allergic rhinitis by childhood farm living and degree of urbanization. (>10 000 inh includes metropolitan Gothenburg.) ***P*-value <0.01, ****P*-value <0.001. (B) Prevalence

of allergic rhinitis in 16–30 years of age by childhood farm living and degree of urbanization. (>10 000 inh includes metropolitan Gothenburg.) **P*-value <0.05.

lower prevalence of allergic rhinitis. When stratified by age, this association was present and significant in all age groups. Further, we found a trend of increasing prevalence of allergic rhinitis with increasing degree of urbanization. In risk assessment adjusting for the effect of potential confounders such as sex, family history of allergic disease, smoking, degree of urbanization and occupational exposure, growing up on a farm was associated with a lower risk of allergic rhinitis in younger adults (16–45 years of age), as well as in older adults (46–75 years of age). Thus, our results are the first to demonstrate a lifelong protective effect of childhood farm living on the prevalence of allergic rhinitis.

The protective effect of childhood farm environment has been attributed to exposures such as animal sheds, hay lofts and consumption of unpasteurized milk (23). Particular inter-

est has been given to endotoxin, a cell wall component from gram-negative bacteria. Significantly higher levels of endotoxin have been found in mattresses from farmers than from nonfarmers and high levels of endotoxin are inversely related to the occurrence of allergic rhinitis and atopy both among farmers and nonfarmers (24). Exposure to microbial components such as endotoxin is thought to promote a skewing of the Th1/Th2 balance toward nonallergic Th1 responses (23, 25). The immune deviation into either Th1 or Th2 polarization is further suggested to be established already at 5 years of age (26), thus indicating long-term effects of childhood environmental exposure on sensitization and allergic disease (27, 28). Accordingly, we found the protective effect of having lived on a farm during the first 5 years of life to be present throughout adulthood. Even so, our results suggest

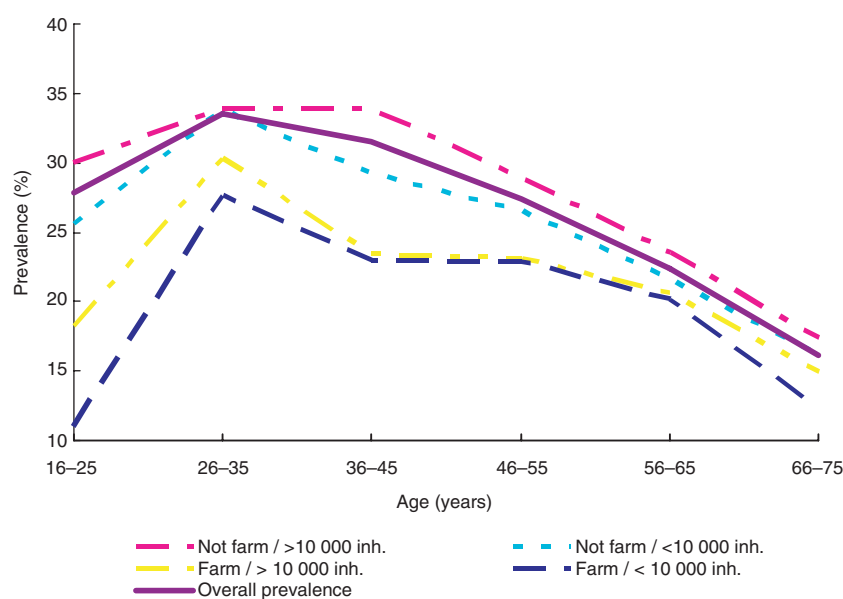


Figure 2 Prevalence of allergic rhinitis by age and childhood living on a farm and degree of urbanization. (>10 000 inh includes metropolitan Gothenburg.)

Table 3 Difference in distribution of background variables between subjects raised on a farm and those not raised on a farm

	Raised on a farm, %	Not raised on a farm, %	P-value
<i>Family history of allergy</i>			
Yes	20.2	30.2	<0.001
<i>Smoking</i>			
Current smoker	16.0	16.9	0.074
Ex-smoker	24.4	22.4	0.027
Never smoker	59.6	60.8	0.27
<i>Sex</i>			
Men	46.4	45.0	0.21
<i>Exposed to dust, gases and fumes at work</i>			
Yes	28.4	21.2	<0.001
<i>Age</i>			
16–30 years	12.8	24.6	<0.001
21–45 years	17.8	28.6	<0.001
46–60 years	32.7	26.9	<0.001
61–75 years	36.8	19.9	<0.001
<i>Degree of urbanization</i>			
Gothenburg	31.5	50.6	<0.001
Mid-sized towns	22.2	24.1	0.040
Small towns	11.3	9.8	0.016
Rural areas	35.0	15.5	<0.001

that the magnitude of the protection decreases with increasing age. It is, however, plausible that other protective factors were present in the nonfarming environment during the childhood of the older subjects, such as more childhood infections and

different dietary habits, diminishing the sole effect of childhood farm living.

Furthermore, in agreement with a number of studies worldwide (13, 14), we found a trend of increasing prevalence of allergic rhinitis with increasing degree of urbanization. The trend was significant until 60 years of age, while no difference due the degree of urbanization was found in 61–75 years of age. It is likely that at the time critical for development of allergy in the older subjects, urban and rural environmental exposure diverged less than later on. Adjusting for potential confounders in a multivariate regression analysis, living both in a mid-sized town and in metropolitan Gothenburg was associated with an increased risk of allergic rhinitis. However, the odds ratio for allergic rhinitis for subjects living in Gothenburg was similar to that of subjects living in a mid-sized town. Thus, it is likely that the protective effect on the prevalence of allergic rhinitis is most pronounced in areas of low degree of urbanization. By means of multiple logistic regression analysis, we could confirm that the effect of urbanization could not be explained by a lower proportion of subjects growing up on a farm in the more populated localities. Hence, the trend of higher risk of allergic rhinitis associated with higher degree of urbanization is likely to be due to the environmental factors other than childhood farm environment. Traffic-related air pollution has been suggested to contribute to the increasing prevalence of allergic disease in urban cities (29), and toxicological studies have shown diesel exhaust particles to increase airway inflammation and induce a rise in production of total and specific IgE (30). Further, diesel exhaust particles may act as carriers of antigens and increase their allergenic potential in the airways (30). However, epidemiological studies that explicitly analyze the associations between traffic exposure and allergic rhinitis are few and their results are inconsistent (29). Another factor that has been hypothesized to contribute to

Table 4 Risk factors for allergic rhinitis by multiple logistic regression analysis

Independent variables		Dependent variable = Allergic rhinitis		
		16–45 years	46–75 years	16–75 years
Variables	Categories	OR (95% CI)	OR (95% CI)	OR (95% CI)
Sex	Women (reference: men)	0.81 (0.73–0.90)	0.98 (0.87–1.11)	0.89 (0.82–0.96)
Family history of allergy	Yes (reference: no)	5.12 (4.61–5.68)	6.16 (5.41–7.00)	5.60 (5.16–6.07)
Physician diagnosed asthma	Yes (reference: no)	5.80 (4.87–6.92)	5.24 (4.30–6.39)	5.62 (4.93–6.41)
Smoking	Non-smoker	1	1	1
	Ex-smoker	1.16 (0.99–1.35)	0.97 (0.85–1.10)	1.02 (0.92–1.12)
	Current smoker	0.92 (0.80–1.07)	0.70 (0.59–0.83)	0.81 (0.73–0.91)
Age	16–30 years			1
	31–45 years			1.48 (1.33–1.64)
	46–60 years			1.31 (1.17–1.47)
	61–75 years			1.03 (0.91–1.17)
Degree of urbanization	Rural areas	1	1	1
	Small towns	1.07 (0.86–1.35)	1.26 (1.01–1.58)	1.16 (0.99–1.36)
	Mid-sized towns	1.16 (0.97–1.38)	1.39 (1.17–1.65)	1.28 (1.13–1.45)
	Metropolitan Gothenburg	1.22 (1.04–1.43)	1.29 (1.10–1.51)	1.29 (1.15–1.44)
Occupational exposure to dust, gases and fumes	Yes (reference: no)	1.10 (0.97–1.25)	1.18 (1.03–1.36)	1.13 (1.03–1.24)
Raised on a farm	Yes (reference: no)	0.78 (0.64–0.95)	0.82 (0.70–0.95)	0.82 (0.72–0.92)

*All associations in each age group derive from a single multiple logistic regression analysis. Significant odd ratios are given in bold.

the urbanization effect is the decreased exposure to pollen in the urban environment, possibly leading to lower tolerance to pollens (31).

Our results suggest that living in a rural locality exerts an additive effect to that of growing up on a farm on the prevalence of allergic rhinitis, in particular among young adults (16–30 years). This finding is in line with studies demonstrating a greater risk reduction of allergic rhinitis among subjects living on a farm during both childhood and adulthood compared to those living on a farm during childhood only (9, 32).

When assessing the risk reduction for allergic rhinitis associated with childhood farm living, the influence of confounding factors needs to be carefully considered. We noted that subjects raised on a farm reported family history of allergy to a significantly lower extent than those not raised on a farm, suggesting a 'healthy farmer effect', i.e. selection out of farming because of the allergic disease. However, a Finnish study demonstrated that quitting or avoiding farming because of allergy was as common in parents and grandparents of nonfarmers' children as in those of farmers' children (33). Moreover, when adjusting for family history of allergy, the association between allergic rhinitis and childhood farm living remained statistically significant. In addition, removing family history of allergy from the multivariate model did not alter the association between allergic rhinitis and childhood farm living.

This study benefits from its population-based design and large scale. Further, it covers a large geographic area with a variety of types of locality, including rural areas and metropolitan Gothenburg, as well as a number of mid-sized and small towns, thus, representing well the population composition of Sweden. In addition, individuals from the full age

span of adulthood were enrolled in the study rendering possible analyses with lifelong perspectives.

The response rate of the study is comparable to other recent European surveys. In addition, a study of nonresponse on the current study population showed no difference in the prevalence of allergic rhinitis between responders and nonresponders (22).

In risk factor assessment by multiple regression analysis, there is always a risk for type I-errors (e.g. significant association by chance). However, as the associations in our model did not alter when the analysis was performed in many different ways, such errors are less likely to have occurred. A limitation of the study is that childhood exposures others than living on a farm, such as number of siblings, parental smoking habits and childhood infections, were not asked for. However, a number of studies assessing the confounding effect of these variables found that they did not alter the association between allergic rhinitis and childhood farm environment (6–8, 11). Another limitation is that the question on allergic rhinitis is based on self-report. However, in an ongoing clinical follow-up study including skin prick testing, data so far show that a large majority, 82%, of subjects reporting allergic rhinitis was sensitized to common airborne antigens, thus confirming the validity of the question. The skin prick tests are performed following the EAACI guidelines (34). Moreover, among subjects reporting allergic rhinitis, 99% also reported symptoms of rhinitis including a large proportion reporting chronic nasal symptoms. Thus, the question on allergic rhinitis seems to represent subjects with both seasonal and chronic disease.

In conclusion, we found a protective effect of childhood farm living on the prevalence of allergic rhinitis and, as the first to date, we could show this effect to be conserved

throughout adulthood. Further, we demonstrated an increasing prevalence of allergic rhinitis with increasing degree of urbanization, present both in subjects raised on a farm and

in those not, thus emphasizing the influence of both childhood and adult exposure for the development of allergic disease.

References

- Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;**63**(Suppl 86):8–160.
- Toren K, Olin AC, Hellgren J, Hermansson BA. Rhinitis increase the risk for adult-onset asthma—a Swedish population-based case-control study (MAP-study). *Respir Med* 2002;**96**:635–641.
- Braback L, Hjern A, Rasmussen F. Trends in asthma, allergic rhinitis and eczema among Swedish conscripts from farming and non-farming environments. A nationwide study over three decades. *Clin Exp Allergy* 2004;**34**:38–43.
- Lotvall J, Ekerljung L, Ronmark EP, Wennergren G, Linden A, Ronmark E et al. West Sweden Asthma Study: prevalence trends over the last 18 years argue no recent increase in asthma. *Respir Res* 2009;**10**:94, E-pub.
- von Mutius E. The environmental predictors of allergic disease. *J Allergy Clin Immunol* 2000;**105**(1 Pt 1):9–19.
- Braun-Fahrlander C, Gassner M, Grize L, Neu U, Sennhauser FH, Varonier HS et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. SCAR-POL team. Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution. *Clin Exp Allergy* 1999;**29**:28–34.
- Von Ehrenstein OS, Von Mutius E, Illi S, Baumann L, Bohm O, von Kries R. Reduced risk of hay fever and asthma among children of farmers. *Clin Exp Allergy* 2000;**30**:187–193.
- Riedler J, Eder W, Oberfeld G, Schreuer M. Austrian children living on a farm have less hay fever, asthma and allergic sensitization. *Clin Exp Allergy* 2000;**30**:194–200.
- Radon K, Schulze A, Nowak D. Inverse association between farm animal contact and respiratory allergies in adulthood: protection, underreporting or selection? *Allergy* 2006;**61**:443–446.
- Douwes J, Travier N, Huang K, Cheng S, McKenzie J, Le Gros G et al. Lifelong farm exposure may strongly reduce the risk of asthma in adults. *Allergy* 2007;**62**:1158–1165.
- Leynaert B, Neukirch C, Jarvis D, Chinn S, Burney P, Neukirch F. Does living on a farm during childhood protect against asthma, allergic rhinitis, and atopy in adulthood? *Am J Respir Crit Care Med* 2001;**164**(10 Pt 1):1829–1834.
- Portengen L, Preller L, Tielen M, Doekes G, Heederik D. Endotoxin exposure and atopic sensitization in adult pig farmers. *J Allergy Clin Immunol* 2005;**115**:797–802.
- Filipiak B, Heinrich J, Schafer T, Ring J, Wichmann HE. Farming, rural lifestyle and atopy in adults from southern Germany—results from the MONICA/KORA study Augsburg. *Clin Exp Allergy* 2001;**31**:1829–1838.
- Nicolaou N, Siddique N, Custovic A. Allergic disease in urban and rural populations: increasing prevalence with increasing urbanization. *Allergy* 2005;**60**:1357–1360.
- Lundback B, Nystrom L, Rosenhall L, Stjernberg N. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;**4**:257–266.
- Ekerljung L, Ronmark E, Larsson K, Sundblad BM, Bjerg A, Ahlstedt S et al. No further increase of incidence of asthma: incidence, remission and relapse of adult asthma in Sweden. *Respir Med* 2008;**102**:1730–1736.
- Lundback B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;**28**(Suppl 2):3–10.
- Pallasaho P, Lundback B, Meren M, Kiviloog J, Loit HM, Larsson K et al. Prevalence and risk factors for asthma and chronic bronchitis in the capitals Helsinki, Stockholm, and Tallinn. *Respir Med* 2002;**96**:759–769.
- Ronmark E, Lundback B, Jonsson E, Jonsson AC, Lindstrom M, Sandstrom T. Incidence of asthma in adults—report from the Obstructive Lung Disease in Northern Sweden Study. *Allergy* 1997;**52**:1071–1078.
- Bousquet J, Fokkens W, Burney P, Durham SR, Bachert C, Akdis CA et al. Important research questions in allergy and related diseases: nonallergic rhinitis: a GA2LEN paper. *Allergy* 2008;**63**:842–853.
- Population in Swedish localities 2005; Available from: <http://www.scb.se/statistik/MI/MI0810/2005A01/mi0810tab 5.xls> [cited 02/06/09].
- Rönmark EP, Ekerljung L, Lötval J, Torén K, Rönmark E, Lundback B. Large scale questionnaire survey on respiratory health in West Sweden: effects of late- and non-response. *Respir Med* 2009;**103**:1807–1815, Epub 2009 August 19.
- Schaub B, Lauener R, von Mutius E. The many faces of the hygiene hypothesis. *J Allergy Clin Immunol* 2006;**117**:969–977; quiz 978.
- Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;**347**:869–877.
- Stern DA, Riedler J, Nowak D, Braun-Fahrlander C, Swoboda I, Balic N et al. Exposure to a farming environment has allergen-specific protective effects on TH2-dependent isotype switching in response to common inhalants. *J Allergy Clin Immunol* 2007;**119**:351–358.
- Yabuhara A, Macaubas C, Prescott SL, Venaille TJ, Holt BJ, Habre W et al. TH2-polarized immunological memory to inhalant allergens in atopics is established during infancy and early childhood. *Clin Exp Allergy* 1997;**27**:1261–1269.
- Strachan DP, Harkins LS, Johnston ID, Anderson HR. Childhood antecedents of allergic sensitization in young British adults. *J Allergy Clin Immunol* 1997;**99**(1 Pt 1):6–12.
- Goksor E, Amark M, Alm B, Gustafsson PM, Wennergren G. The impact of pre- and post-natal smoke exposure on future asthma and bronchial hyper-responsiveness. *Acta Paediatr* 2007;**96**:1030–1035.
- Heinrich J, Wichmann HE. Traffic related pollutants in Europe and their effect on allergic disease. *Curr Opin Allergy Clin Immunol* 2004;**4**:341–348.
- Bartra J, Mullol J, del Cuervo A, Davila I, Ferrer M, Jauregui I et al. Air pollution and allergens. *J Investig Allergol Clin Immunol* 2007;**17**(Suppl 2):3–8.
- Linneberg A. Hypothesis: urbanization and the allergy epidemic – a reverse case of immunotherapy? *Allergy* 2005;**60**:538–539.
- Koskela HO, Happonen KK, Remes ST, Pekkanen J. Effect of farming environment on sensitisation to allergens continues after childhood. *Occup Environ Med* 2005;**62**:607–611.
- Remes ST, Iivanainen K, Koskela H, Pekkanen J. Which factors explain the lower prevalence of atopy amongst farmers' children? *Clin Exp Allergy* 2003;**33**:427–434.
- Dreborg S, Frew AJ. Allergen Standardization and Skin Tests. *Allergy* 1993;**48**(Suppl 14):49–54.