

The protective role of country living on skin prick tests, immunoglobulin E and asthma in adults from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyper-responsiveness and atopy

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Summary

Background Farming environment and traditional lifestyle seem to protect from childhood allergy.

Objective The aim is to analyse the relationships of living in the country to asthma, positive skin prick tests and IgE among adults considering various windows of exposure over the life-span.

Methods The study concerns 805 adults drawn from the Epidemiological study on the Genetics and Environment of Asthma, bronchial hyper-responsiveness and atopy (EGEA) (asthmatic cases, non-asthmatic controls, and parents of cases with and without asthma). Ever living in the country concerned 55% of the subjects. Early (beginning <1 years), childhood (beginning $\leq$ 16 years), prolonged (duration $\geq$ 10 years) and current life in the country were studied.

Results The results based on the case control and family components of the study show that IgE levels were significantly lower in those who ever lived in the country and in particular in those who lived for $\geq$ 10 years. Positive skin prick tests (SPT) were significantly less prevalent in those who ever lived in the country and in particular in those with childhood ($\leq$ 16 years) exposure. These associations remained independent of age, sex, smoking or asthma with IgE levels of 64 vs. 88 IU/mL; $P = 0.004$ for those ever living in the country vs. others and odds ratio for SPT positivity of 0.72 (95% CI [0.53–0.98]). In the more specific group with traditional mode of heating in childhood (use of wood) associations were stronger. The association with asthma, studied in parents of asthmatic probands showed that fathers, but not mothers, of asthmatics were significantly less often asthmatic themselves in relation to country living.

Conclusion Country life protects from asthma and adulthood allergy. The protective effect is not restricted to exposure in early childhood.

Keywords allergy, asthma, epidemiology, IgE, prevention, rural

Submitted 27 April 2001; revised 25 August 2001; accepted 2 October 2001

Introduction

Understanding the increase in the last decades of asthma and allergy is a still unsolved challenge [1] for which several environmental hypotheses have been put forward (changes in air pollution, indoor environment, diet.). A noxious role of urban air pollution has been proposed and higher prevalences of atopy in urban environments than in rural areas could fit with such hypothesis [2]. However, results of the comparison of former East and West Germany cast it into doubt [3]. That comparison was undertaken to assess changes in lifestyle related in particular to industrial changes, using the benefit of that pseudo-experimental situation. Unexpectedly, children in the most polluted areas at baseline exhibited fewer allergic diseases, which provides one of the arguments supporting the potential noxious role of westernization [3]. The hygiene hypothesis,

proposed 10 years ago [4] was based on the observation of decreasing hayfever prevalence according to the number of siblings. It suggests that decreased infection rates (inferring cross-contamination by older siblings) could favour allergy. The observation that the maturation of the Th2-prone newborn towards a Th1 profile is favoured by infections [5] supports that hypothesis. More recently, it has been suggested that rural environment in childhood, particularly contacts with livestock, could have a protective role against allergy [6,7]. Less allergy in children was also reported in relation to traditional lifestyle, such as encountered in Steiner schools in Sweden [8] or assessed indirectly by traditional mode of heating [9]. The precise nature of the factor(s) involved and the window of exposure remain unknown [10]. Nearly all studies with precise measures of allergy on the potential protective role of farming environment concerned children or adolescents [11]; none studied total IgE quantitatively and all included a limited number of asthmatics.

The aim of the present study is to analyse the relationships of living in the country to total IgE and positive skin prick tests among adults from the Epidemiological Study on the Genetics

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and Environment of Asthma, Bronchial Hyper-responsiveness and Atopy (EGEA). That population includes a variety of subjects regarding allergy, as asthmatics recruited in chest clinics, population-based controls and family members of the cases were examined [12,13]. The role of present and past exposure is assessed by considering various windows of exposure over the life-span.

Methods

The design of EGEA combines a case control study and a family study of asthmatic cases [13,14]. Detailed analysis regarding the ascertainment of the subjects has been presented elsewhere [14]. Briefly, for cases and controls, general inclusion criteria assessed through a self-completed questionnaire were age (7–70 years), born in France as well as his/her parents, and living in a defined area in each centre. Cases were recruited in chest clinics in five French cities and they had to answer positively to four standardized questions: Have you ever had attacks of breathlessness at rest with wheezing? Have you ever had asthma attacks? Was this diagnosis confirmed by a physician? Have you had an asthma attack in the last 12 months? [13].

Comparability between cases and controls was controlled for centre, season, sex and 10-year age class. Furthermore, in the two biggest cities (Paris and Marseille), two control groups were recruited, one of which was the surgery department from the same hospital as the cases to take into account the area of attraction of the hospital. In Marseille, the other control group comes from a check-up centre from the social security system in which affiliates are invited independently of health characteristics (a setting already used in other epidemiological surveys). For the second control group in Paris and control groups in all other cities, subjects were recruited through electoral rolls, as has been done in the European Community Respiratory Health Survey (ECRHS). Furthermore, in order to control the influence of other local relevant characteristics, attention was given within each centre to major social characteristics (residential/industrial) around Grenoble, or specific environment, such as the presence of a petrochemical complex near Lyon (source of industrial pollution) and the proximity of a mere near Montpellier (source of moulds). Electoral rolls were therefore chosen in two areas in these centres to balance these factors between cases and controls. Overall there were ten combinations of cities and type of controls and eight combinations of cities and areas of residence for cases. Results were consistent for the various types of controls and analyses conducted with and without the surgery controls gave similar results.

No consideration of country living was taken into account in the recruitment, as this was not considered of importance when the study was designed in 1990/1991, but the information was collected. Nearly all (98%) of the controls recruited through electoral rolls from the cities of the hospital or cities in the suburbs reported not currently living in the country, which supports the validity of the report of country living. The area of residence for cases was broader than for most controls, reflecting the area of attraction of the hospital and more cases were currently living in the country than controls (14.5 vs. 6.2; $P = 0.004$). Therefore, the analysis regarding the association of country living with their personal history of asthma was conducted only

in the parents of the asthmatic probands, who should not be biased towards country living residence in their life.

The analysis regarding total IgE and skin prick test (SPT) response was conducted in cases, controls and parents of asthmatic cases. This sample includes adults with a large variation in allergy who did not share their childhood environment. These adults correspond with subjects from the same cohort, as most of the parents of asthmatics were parents of paediatric cases.

Subjects answered a questionnaire regarding respiratory symptoms and environment based on standardized questionnaires. Asthma in parents was defined by attacks of breathlessness at rest with wheezing or asthma attacks [13]. Information regarding home characteristics, based on the ECRHS [15] questionnaire, included presence of pet animals, mode of heating and cooking. Subjects were also asked whether they had lived during their life for at least 1 year in the country ('Have you ever lived in the country for at least one year?'). In the case of a positive answer they were interviewed about the age at which they started living in the country and when they left the country. As the window of exposure (early/late onset, duration of exposure) was a question of interest, besides ever living in the country, four variables were constructed: beginning < 1 years, beginning ≤ 16 years, duration ≥ 10 years and current exposure (yes/no).

Most of the analysis was conducted on IgE score corrected for age, sex and smoking [16], by linear regression of log₁₀ (IgE) on age, sex and smoking (never smokers, ex-smokers, current smokers) in the whole EGEA control group. Analyses conducted on crude log IgE with models including age, sex and smoking gave similar conclusions. SPT positivity was defined by wheal diameter greater by ≥ 3 mm than the negative control for at least one allergen (cat, *Dermatophagoides pteronyssinus*, *Blattella germanica*, timothy grass, olive, birch, *Parietaria judaica*, ragweed, *Aspergillus*, *Cladosporium herbarum*, *Alternaria tenuis*). Polysensitization was defined by a positive response to at least three allergens. Complete data were available for 805 adults, representing 93% of those ≥ 18 years. Slightly more subjects had missing IgE or SPT in those who never lived in the country than in others (8.8% vs. 5.8%; $P = 0.09$) but they were similar otherwise.

The dependence of subjects from the same family was taken into account by mixed linear models for quantitative variables and generalized estimating equations for qualitative variables, with an exchangeable correlation matrix in the models [17,18]. Such analyses took into account what the members of these families have in common, such as genetic factors and the effect of shared environment.

Results

The study sample (mean age 43 years, 49.8% men) included 186 asthmatic cases and 242 non-asthmatic controls and 377 parents of asthmatics. Ever living in the country was reported overall by 55% of the study sample, 29% with an age at beginning of less than 1 year, 45% with an age at beginning ≤ 16 years and 33% with a duration of 10 years or more (Table 1). Currently living in the country was reported by 11%. Traditional modes of heating decreased from childhood to adulthood. Coal was used for heating by 42% in childhood and less than 1% in adulthood, whereas for wood figures were, respectively, 17% and 8%.

Country life and skin prick test response and IgE

In all the study sample, SPT positivity was observed for 45.1% and polysensitization for 15.3%. The allergens with the greatest percentages of positive skin tests were Der p (25%), timothy grass (17%), *Blattella germanica* (13%) and cat (12%). Geometric mean of IgE in the study sample was 58 IU/mL [95% CI 2–1637]. As expected (and already reported), both SPT+ and IgE were highly related to asthma, with parents of asthmatics with intermediate values between asthmatic cases and non-asthmatic controls. The prevalence of positive skin prick tests and IgE level were significantly lower in those who ever lived in the country than in the remaining subjects. For

Table 1. Beginning and duration of living in the country

Duration	Beginning of country living			
	< 1 years	1–16 years	> 16 years	Never
< 10 years	31 (0)	85 (0)	45 (17)	365
≥ 10 years	199 (41)	42 (12)	22 (18)	–

Figures are numbers of subjects in each category with numbers of those currently living in the country in parentheses. For 16 subjects the ages of beginning to live in and leaving the country were unknown.

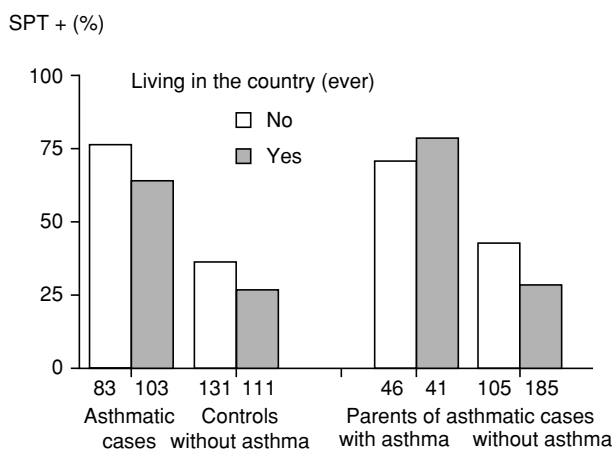


Fig. 1. Skin prick test positivity according to ever living in the country.

SPT+ the association of living in the country corresponded with an odds ratio of 0.66 [95% CI 0.50–0.87]. Geometric means of IgE were 40% less in those who ever lived in the country (49.7 IU/mL vs. 69.8 IU/mL; $P < 0.001$). The pattern was similar for SPT and IgE in the case-control component and consistent for the family component of the study, as shown in Figs 1 and 2. Considering separately these two components of the study and adjusting for asthma, odds ratios for SPT+ for ever living in the country were 0.60 (0.40–0.92) and 0.68 (0.45–1.04) for the case control and the family components of the study. After adjustment for asthma, geometric means for IgE were 61.8 IU/mL vs. 92.2 IU/mL, $P = 0.004$, and 67.3 IU/mL vs. 80.4 IU/mL, $P = 0.30$, for the case-control and the family components of the study for those who ever lived in the country vs. the others, respectively.

Living in the country was unrelated to gender in the whole study sample, but subjects who lived in the country were 5 years older ($m \pm SD = 45.1 \pm 9.8$ vs. 40.1 ± 11.7 ; $P < 0.001$). Living in the country was significantly related to mode of heating (more wood, less gas) in childhood, to a greater prevalence of pets in childhood and lower educational level (Table 2). Associations of ever living in the country with positive skin tests and IgE remained after adjustment for age, sex, smoking (for IgE) and taking into account the mode of ascertainment of the subjects, and asthma summarized by a four-class variable described the category of subjects (asthmatic cases, non-asthmatic controls, parents with and without asthma) (Table 3). Analyses were performed by logistic regressions for positive skin tests and by linear regressions for IgE. Adjustment for age, sex and smoking was done for the study of IgE, both by using scores adjusted prior to the analysis or by including the variables in the models, which gave similar results. Analyses stratified by gender gave similar patterns. For SPT and IgE the analysis of the variables built to study various windows of exposure did not show stronger relationships by considering those with beginning < 1 years. The most significant associations were observed for childhood beginning (≤ 16 years) for skin prick tests and for duration ≥ 10 years for IgE (Table 3). A significant protective role of ever country living was also observed for Der p ($OR = 0.65$ [0.46–0.93]). Considering polysensitization did not show stronger relationships. In fact, the associations were weaker and not significant. This was observed either when comparing subjects with polysensitization to all others or comparing subjects with polysensitization to no positive skin test at

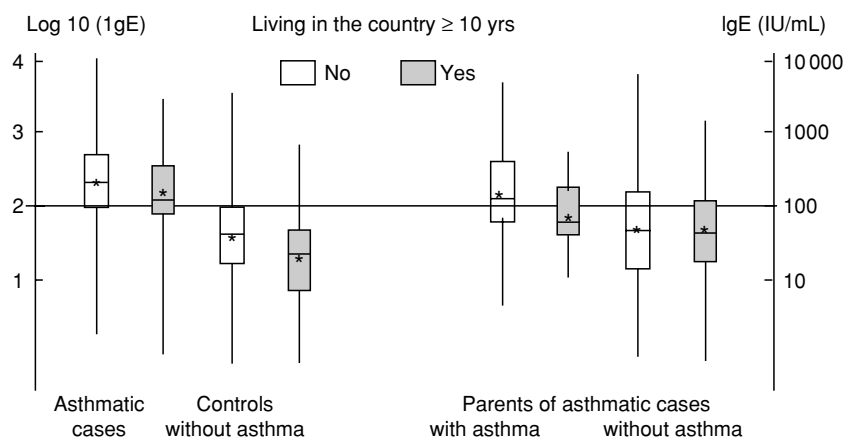


Fig. 2. Age, sex and smoking-adjusted total IgE according to living in the country for 10 years or more. Box plots are represented by horizontal lines at the 25th, 50th and 75th percentiles; * = the mean; vertical bars figure the range.

all. For example, in that case ($SPT \geq$ three allergens/no response) in models similar to those of Table 3, figures for ever living in the country were 0.80 (0.50–1.27) and for beginning of country living ≤ 16 years 1.05 (0.60–1.52), respectively.

The initial reason for recording living in the country was potential increase of allergy markers related to pollen exposure.

Table 2. Factors related to living in the country (ever)

	No ($n = 365$)	Yes ($n = 440$)
Smoking habits		
Never smokers (%)	49.5	43.1
Ex-smokers (%)	25.1	32.6†
Current smokers (%)	25.4	24.4
Maternal smoking in childhood (%)	18.8	13.2¶
Mode of heating in childhood§		
Electricity (%)	7.3	4.7
Gas (%)	27.9	15.8*
Wood (%)	5.6	27.0*
Fuel (%)	16.1	17.0
Coal (%)	40.0	43.7
Household size (n persons) $m \pm SD$	4.33 ± 1.99	$4.72 \pm 2.00‡$
Crowding index (n persons/room) $m \pm SD$	1.30 ± 0.71	1.37 ± 0.74
Pets in childhood		
Dog (%)	29.6	56.1*
Cat (%)	30.4	48.0*
Rodent (%)	6.3	13.9*
Bird (%)	4.1	15.7*
Educational level		
Primary (%)	25.6	37.7
Secondary (%)	24.7	24.7*
University (%)	49.7	37.7

* $P = 0.001$; † $P = 0.10$; ‡ $P = 0.01$; ¶ $P = 0.05$. For smoking and education level, tests refer to comparison based on three-class variables.

§Multiple sources possible.

Skin tests increased (although not significantly) in those currently exposed (Table 3), and skin test positivity to an outdoor allergen such as timothy grass was significantly increased during the pollen season (April–November) in those currently living in the country compared with those who did not ($OR = 2.12$ [1.07–4.17]). All models were therefore rerun after excluding those currently exposed, which gave in general lower OR for skin tests and greater differences for IgE (Table 3), but the association of skin tests and IgE to early exposure (< 1 years of age) remained the weakest. For polysensitization ($SPT \geq$ three allergens/no response), figures for ever living in the country and for beginning of country living ≤ 16 years were 0.74 (0.44–1.23) and 0.77 (0.46–1.31), respectively. Including pets in childhood, family size or maternal smoking in childhood in models did not change the results. Including variables such as mode of heating or educational level in models could lead to over-adjustment, as they were not hypothesized to be potential intermediate variables. However, including simultaneously age, sex, smoking, category, mode of heating (use of wood in childhood), number of pets in childhood and educational level, the association of IgE with living in the country for at least 10 years remained significant (79.0 vs. 56.9 IU/mL; $P = 0.01$). To address the influence of ascertainment, the analyses regarding the relation of living in the country for at least 10 years with age, sex and smoking adjusted IgE were performed in all possible combinations of cases (centre, area of residence) and of controls (centre, area and type of controls) (data not shown). In six out of eight combinations for cases and in ten out of ten for controls, lower IgE levels were observed in those exposed to country living, showing a consistent pattern.

Traditional lifestyle in country and contact with livestock were not directly assessed. As wood used in heating in childhood was the variable most strongly related to living in the country, with odds ratios of 6.2 for ever living and of 6.9 for beginning < 1 years, the association of living in the country with

Table 3. Relationships of living in the country to skin prick test response and IgE. Logistic and linear regression models

	n	SPT + OR [95% CI]		IgE, GM, IU/mL	
		All	Current excluded	All	Current excluded
Ever					
No	365			88.0	87.8
Yes	440	0.72 [0.53–0.98]	0.64 [0.47–0.91]	64.0, $P = 0.004$	63.6, $P = 0.006$
Beginning of country living < 1 years					
No	559			77.4	81.0
Yes	230	0.88 [0.62–1.24]	0.83 [0.57–1.23]	65.0, $P = 0.14$	61.7, $P = 0.04$
Beginning of country living ≤ 16 years					
No	432			81.4	86.0
Yes	357	0.74 [0.54–1.01]	0.70 [0.49–0.99]	65.0, $P = 0.04$	63.6, $P = 0.01$
Duration ≥ 10 years					
No	526			83.4	85.1
Yes	263	0.85 [0.61–1.18]	0.74 [0.50–1.07]	57.4, $P = 0.001$	54.4, $P = 0.0006$
Current					
No	701		–	75.3	–
Yes	88	1.26 [0.75–2.11]	–	62.3, $P = 0.28$	–

SPT was the dependent variable in the logistic models and the independent variables were age, sex, category, living in the country. For IgE, the dependent variables in the linear regression models were age, sex, smoking adjusted $\log_{10}$ IgE and the independent variables were category (asthmatic cases, non-asthmatic controls, parents with and without asthma), living in the country. In all models, familial dependence was taken into account (see Methods).

Table 4. Relation of living in the country to asthma in parents of asthmatics

	All		Fathers		Mothers	
	<i>n</i>	Asthma (%)	<i>n</i>	Asthma (%)	<i>n</i>	Asthma (%)
Ever						
No	163	30.1	84	34.5	79	25.3
Yes	238	18.1	116	15.5	122	20.5
OR [95% CI]		0.51 [0.32–0.82]		0.35 [0.18–0.68]		0.76 [0.39–1.49]
				Breslow & Day, <i>P</i> = 0.11		
Beginning < 1 years of age						
No	263	26.2	130	30.0	133	22.6
Yes	134	17.2	67	11.9	67	22.4
OR [95% CI]		0.58 [0.35–0.98]		0.32 [0.14–0.71]		0.99 [0.49–2.01]
				Breslow & Day, <i>P</i> = 0.04		
Beginning ≤ 16 years of age						
No	193	29.0	97	34.0	96	24.0
Yes	204	17.7	100	14.0	104	21.2
OR [95% CI]		0.52 [0.33–0.84]		0.32 [0.16–0.63]		0.85 [0.44–1.66]
				Breslow & Day, <i>P</i> = 0.04		
Duration ≥ 10 years						
No	251	25.9	129	27.9	122	23.8
Yes	146	18.5	68	16.2	78	20.5
OR [95% CI]		0.65 [0.39–1.07]		0.50 [0.24–1.05]		0.83 [0.42–1.65]
				Breslow & Day, <i>P</i> = 0.33		
Current						
No	350	24.0	177	24.3	173	23.7
Yes	47	17.0	20	20.0	27	14.8
OR [95% CI]		0.65 [0.29–1.44]		0.78 [0.25–2.46]		0.56 [0.19–1.70]
				Breslow & Day, <i>P</i> = 0.69		

wood used in heating could be a marker of traditional lifestyle in the country. In those not currently living in the country with documented mode of heating in childhood (*n* = 684), 13% reported both living in the country in the past and use of wood for heating. The association of both skin prick tests and IgE were stronger considering this more specific marker. For those ever living in the country with wood heating in childhood vs. others, the odds ratio for SPT+ was 0.61 (0.36–1.03) and adjusted IgE were 50.0 vs. 80.5 IU/mL; *P* = 0.005.

Country life and asthma

Overall, in parents of asthmatics, 23% were asthmatics. Ever living in the country was significantly related to a lower occurrence of asthma in parents of asthmatics, with an odds ratio of 0.51 (0.32–0.82). Odds ratios were all < 1 whatever the country life variable considered, but the associations did not reach significance for duration of ≥ 10 years and current exposure (Table 4). A significant modifier effect of the gender of the parent was evidenced with an association restricted to fathers (Table 4). The interaction remained when considering the age of the subjects, or asthma age of onset. As explained in the methods section, a detailed comparison of cases and controls regarding country living was not possible due to the recruitment of cases leading to more country dwelling cases than controls (OR = 2.7 [1.43–4.98]). However, despite this difference in inclusion regarding current residence, a similar proportion reported country living before 1 year of age (OR = 0.98

[0.64–1.51]), and slightly less when current country dwellers were excluded (OR = 0.88 [0.55–1.41]).

Discussion

By the study of adults and information on life in the country over the life-span, these results extend previous knowledge on the protective effect of country lifestyle on allergic characteristics already observed in children. Results based on both the case control and family components of the study show that IgE levels were significantly lower in those who ever lived in the country and in particular in those who lived for ≥ 10 years. Positive skin prick tests (SPT) were significantly less prevalent in those who ever lived in the country and in particular in those with childhood (≤ 16 years) exposure. These associations remained independent of age, sex, smoking or asthma. In this sample of adults, the relationships of allergy markers were not stronger for infant exposure. In the more specific group with traditional mode of heating in childhood (use of wood) associations were stronger. The study on asthma conducted in parents of asthmatic probands showed that country life has protected from asthma fathers, but not mothers, of asthmatics.

The design of the EGEA study had advantages and limitations. It is not a representative sample of the general population and limited information was gathered regarding country life. Important advantages were the large proportion of asthmatics,

who were particularly well characterized, population-based controls and a group with greater sensitivity to allergy who were relatives of asthmatics. Objective measures of allergy were gathered for all subjects by a standardized protocol. The study group is heterogeneous by design. The consistency of pattern in the relation of country living with markers of allergy in asthmatic cases, non-asthmatic controls and subjects recruited because of having an asthmatic child support the hypothesis of a protective role of country living on adult allergy.

The results are consistent with the literature, mostly on children and adolescents, and extends it. Greater prevalence of atopy in children living in urban than in rural areas has already been observed in children [19] and in young adults in Austria [2] and in the representative sample of subjects aged 6–74 studied in the United States of America [20]. In that study, census data were used to classify current residence in rural and urban areas (usually towns with 2500 and more population size). Skin test reactivity was higher among urban than among rural dwellers, and the difference reached statistical significance in whites only. Greater prevalences in atopy in urban than in rural areas may both reflect a deleterious role of factors associated with urban environment and/or a protective role of factors associated with rural environment. Although data on air pollution levels in areas reported as country or city were not available in the study, there is little doubt that air pollution levels related to industrial sources or traffic were lower on average in the country than elsewhere and in that context, a protective role associated with country living may in fact be a deleterious role of that type of air pollution. The association of a long duration related to IgE could in particular be discussed in that respect, although to our knowledge there is no paper showing an association of IgE with air pollution. Published studies in the literature including comparisons of urban areas with different air pollution levels [3,21] did not support the hypothesis of factors associated with air pollution, whereas comparison of children in rural areas according to farming activity [6] supports the hypothesis of protective factors potentially associated with lifestyle in a farming environment. These results have been obtained in children and limited information is available for adults. The lifestyle factor(s) associated with country living are likely to have a strong effect as the index of rural environment used in our study was crude.

Study design hampered a detailed analysis of the relation of asthma to country life, as the design of the case-control component of the study indeed included more country dwellers in cases. However, whereas they were significantly more current country dwellers in cases than in controls, reflecting the design of the study, a similar proportion reported country living before 1 year of age, and slightly less when current country dwellers were excluded. A protective effect of country living on asthma was evidenced in parents of asthmatics, but the relation was restricted to fathers with an odds ratio around 0.5 and no effect in mothers. Different types of reasons may explain such gender difference [22]. Contact with livestock in the country may be more important for boys or men than for girls or women, i.e. a gender difference for a potentially relevant exposure. Other factors potentially associated with country living, such as nutrition habits, are unlikely to exhibit strong gender differences. The most tempting hypothesis would be that it reflects a difference in the aetiology of asthma according to men and women, for whom it is well known that there are numerous differences, such as asthma age of onset [23]. It cannot be excluded that the

association could reflect selective departure from the country of those with asthmatic symptoms, but it is unlikely that it occurs more often in men than in women as social pressures for staying in the country are greater in men than in women. It is also possible that the interaction observed related to the ascertainment of the subjects studied through an asthmatic child. The stronger relationship of asthma in mothers than in fathers and their children could play a role in this context. Further studies are needed to understand the complex interplay of gender with asthma in the various generations of a given family. The specificity of the organ potentially concerned by allergic inflammation is also a topic of interest and the issue of whether both the lung and the nose react in parallel currently debated. Further work should concern the association of country life with both asthma and allergic rhinitis.

No study has addressed the question of the window of exposure during the life-span. Our results suggest that the clear effect observed is not restricted to exposure in early childhood. Differences between the effects of >1 years, <16 years and ≥ 10 years exposure times may be difficult to distinguish. However, as the predominant hypothesis regarding the role of country life was early childhood and the power in the analyses conducted with various variables was similar, results suggest that further studies should include comprehensive assessments of country life exposures over the life-span. The rationale of adding the question on country life was initially to assess pollen exposure. The higher positivity to timothy grass during pollen season in those currently living in the country fits with the initial rationale of the question. Results therefore suggest that various aspects of living in the country may affect maturation of the immune system and expression of atopy. Report by subjects of periods of living in the country is unlikely to be differently biased towards more reports in those with allergy as the formulation of the hypothesis in the scientific literature was posterior to the collection of data. There are arguments to support the hypothesis that lifestyle in childhood could modify the maturation of the immune system occurring in early life [5,8]. However, the pattern may be more complicated and windows of exposure to country life could represent windows of 'opportunity' [10] for exposure to allergens, depending on the age of the subjects, their personal history of exposure to allergens and to cohort effects. Although the consistent pattern observed for asthmatic subjects and controls supports the hypothesis that the protective effect is a true phenomenon and not the reflection of a selective move in relation to allergic reactions, longitudinal data are needed to totally refute such a bias.

Von Mutius already reported that the traditional mode of heating (wood or coal) was associated with less allergy in children and previous studies on the effect of mode of heating should consider whether a specific mode of heating could be a surrogate for rural residence. Clearly this aspect is country and period dependent. As shown here, coal has roughly disappeared as a mode of heating in France, whereas use of wood (as main or accessory source) for heating was strongly related to rural residence. Perhaps that aspect could explain contradictory findings between countries regarding heating or cooking indoor sources of irritant exposure [24]. In France, gas was less available in the country than in urban areas. Use of wood in childhood may correspond to traditional lifestyle in the country but also reflect other factors, such as the availability or use of wood, related to climatic, geographical or social factors.

Other environmental factors modify the level of IgE and of atopy. Smoking was taken into account in the analysis of IgE. Results with living in the country in the present study could fit with the hypothesis of a protective role of pet animals [25], as pet ownership was significantly related to country life. However, adjustment on pet ownership did not modify the results. Adjustment for family size or maternal smoking did not change the findings at all. Dietary factors are likely to be different in subjects with current or past experience of country living, but no relevant information was available in the study. Emphasis was made until now of the noxious role of indoor sources of irritants. Although it is an important question, as such exposure may have a noxious role by itself or through interaction with other environmental factors, it is one of the elements of lifestyle that should be studied more comprehensively. More studies are needed to understand the environmental factors related to IgE and atopy in adults [26]. Interesting observations come from studies conducted in a parasited environment in which there is a dissociation of total serum IgE (high) and skin test reactivity to aeroallergens (low). From an evolutionary point of view, the absence of parasites may be associated with increased aeroallergen sensitivity [27]. In the present study, the negative association of country life was stronger for IgE than for SPT and there was no pattern suggesting an effect on polysensitization. Studying the effect of exposure to LPS and allergens in both parasited and non-parasited countries will help in understanding the relationships of asthma to IgE and SPT+.

Genetic influences also modulate Th1/Th2 balances and IgE synthesis. Farming environment is associated with endotoxin exposure and the interaction of antigen presenting cells with LPS is mediated by CD14 [28]. The described association of CD14 polymorphism with IgE [29] suggests that it may be one of the candidate genes in the understanding of the protective role of farming environment on IgE.

Consideration of potential protective factors changes the perspective in epidemiology in which risk factors studied are generally deleterious ones. It may influence strategies regarding the analysis of data and of prevention. Various lines of research could be developed to address the challenge of the protective role of the rural environment.

The available data on country living in the present study were very limited. No information regarding contact with livestock, for example, was available. Studies are needed to characterize factors associated with reported country living. Perception and report of what is living in the country may be cohort dependent or related to unmeasured social factors. All societies did not confer the same meaning to rural and urban areas. It varies according to the history of societies and of dwelling habits, and varies within Europe and probably within France [30,31]. Life in the country moved in the last 50 years from life in an area defined by farming activity to something including decreasing farming activity, some periurban dwelling and more recently search of the countryside with interest in natural resources. The search for protective factors related to report of living in the country should be pursued taking this complexity into account.

A multidisciplinary approach seems necessary to understand what is behind the rural and/or traditional mode of living in developed and developing countries [32] that may protect from allergy. Standard analytical approaches focused on the study of interactions of environmental factors and potential relevant

candidate genes could be combined with a more global approach using resources of sociology or geography.

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Acknowledgements

The authors thank L. Guilloux for IgE determinations.

Supported in part by convention INSERM-MSD, INSERM networks of clinical research (489012) and public health-research (493009), Ministry of Environment and Ministry of Health. Kits for IgE determinations were kindly provided by Pharmacia.

References

- 1 Becklake MR, Ernst P. Environmental factors. In 'The Challenge of Asthma'. Lancet 1997; 350 (Suppl. II): 10-13.
- 2 Popp W, Zwick H, Steyer K, Rauscher H, Wanke T. Sensitization to aeroallergens depends on environmental factors. Allergy 1989; 44:572-5.
- 3 Von Mutius E, Martinez FD, Fritzsche C, Nicolai T, Roell G, Thiemann HH. Prevalence of asthma and atopy in two areas of West and East Germany. Am J Respir Crit Care Med 1994; 149:358-64.
- 4 Strachan DP. Hay fever, hygiene and household size. Br Med J 1989; 299:1259-60.
- 5 Prescott SL, MacAubas C, Smallacombe T, Holt BJ, Sly PD, Holt P. Development of allergen-specific T-cell memory in atopic and normal children. Lancet 1999; 353:196-200.
- 6 Braun-Fahrlander Ch, Gassner M, Grize L et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. Clin Exp Allergy 1999; 29:28-34.
- 7 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.
- 8 Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. Lancet 1999; 353:1485-8.

- 9 Von Mutius E, Illi S, Nicolai T, Martinez FD. Relation of indoor heating with asthma, allergic sensitisation, and bronchial responsiveness: survey of children in South Bavaria. *Br Med J* 1996; 312:1448–50.
- 10 Strachan DP. Lifestyle and atopy. *Lancet* 1999; 353:1457–8.
- 11 Ernst P, Cormier Y. Relative scarcity of asthma and atopy among rural adolescents raised on a farm. *Am J Respir Crit Care Med* 2000; 161:1563–6.
- 12 Kauffmann F, Dizier MH, Annesi-Maesano I et al. EGEA (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy) – descriptive characteristics. *Clin Exp Allergy* 1999; 29 (Suppl. 4):17–21.
- 13 Kauffmann F, Dizier MH, Pin I et al. Epidemiological study on the genetics and environment of asthma, bronchial hyperresponsiveness and atopy (EGEA) – phenotype issues. *Am J Respir Crit Care Med* 1997; 156:S123–S129.
- 14 Kauffmann F, Dizier MH, Annesi-Maesano I et al. Etude épidémiologique des facteurs génétiques et environnementaux de l'asthme, l'hyperréactivité bronchique et l'atopie (EGEA) – protocole et biais de sélection potentiels. *Rev Epidemiol Santé* 2001; 46:343–56.
- 15 Anonymous. Protocol for the European Community Respiratory Health Survey. London: United Medical and Dental Schools of Guy's and St Thomas's Hospitals, Department of Public Health Medicine, 1993.
- 16 Oryszczyn MP, Annesi-Maesano I, Charpin D, Paty E, Maccario J, Kauffmann F. Relationships of active and passive smoking to total IgE in adults of EGEA – (Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness and atopy). *Am J Respir Crit Care Med* 2000; 161:1241–6.
- 17 Littell RC, Milliken GA, Stroup WW, Wolfinger RD. SAS[®] System for Mixed Models. Cary, NC: SAS Institute Inc., 1996.
- 18 Zeger SL, Liang KY, Albert PS. Models for longitudinal data: a generalized estimating equation approach. (Published erratum appears in *Biometrics* 1989; 45: 347.) *Biometrics* 1988; 44: 1049–60.
- 19 Brabäck L, Breborowicz A, Dreborg S, Knutsson A, Pieklik H, Björkstén B. Atopic sensitization and respiratory symptoms among Polish and Swedish school children. *Clin Exp Allergy* 1994; 24:826–35.
- 20 Gergen PJ, Turkeltaub PC, Kovar MG. The prevalence of allergic skin test reactivity to eight common aeroallergens in the U.S. population: results from the second National Health and Nutrition Examination Survey. *J Allergy Clin Immunol* 1987; 80:669–79.
- 21 Charpin D, Pascal L, Birnbaum J et al. Gaseous air pollution and atopy. *Clin Exp Allergy* 1999; 29:1474–80.
- 22 Kauffmann F, Becklake MR. Sex and gender. In: Annesi-Maesano I, Viegi G, Gulsvik A, eds. *Respiratory Epidemiology in Europe*. *Eur Respir Mon* 2000; 5: 288–304.
- 23 Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human lifespan. *Thorax* 1999; 54:1119–38.
- 24 Jarvis D, Chinn S, Sterne J, Luczynska C, Burney P. The association of respiratory symptoms and lung function with the use of gas for cooking. European Community Respiratory Health Survey. *Eur Respir J* 1998; 11:651–8.
- 25 Svanes C, Jarvis D, Chinn S, Burney P for the European Community Respiratory Health Survey. Childhood environment and adult atopy: results from the European Community Respiratory Health Survey. *J Allergy Clin Immunol* 1999; 103:415–20.
- 26 Baldacci S, Omenaas E, Oryszczyn MP. Allergy markers in respiratory epidemiology. *Europ Respir J* 2001; 17:773–90.
- 27 Weiss ST. Parasites and asthma/allergy: what is the relationship. *J Allergy Clin Immunol* 2000; 105:205–10.
- 28 Martinez FD. Maturation of immune responses at the beginning of asthma. *J Allergy Clin Immunol* 1999; 103:355–61.
- 29 Baldini M, Lohman IC, Halonen M, Erickson RP, Holt PG, Martinez FD. A polymorphism in the 5' flanking region of the CD14 gene is associated with circulating soluble CD14 levels and with total serum immunoglobulin E. *Am J Respir Cell Mol Biol* 1999; 20:976–83.
- 30 Mathieu N. La notion de rural et les rapports ville-campagne en France. Des années cinquante aux années quatre-vingts. *Economie Rurale* 1990; 197:35–41.
- 31 Mathieu N. La notion de rural et les rapports ville/campagne en France: les années quatre-vingt-dix. *Economie Rurale* 1998; 247:11–20.
- 32 Yemaneberhan H, Bekele Z, Venne A, Lewis S, Parry E, Britton J. Prevalence of wheeze and asthma and relation to atopy in urban and rural Ethiopia. *Lancet* 1997; 350:85–90.