

Climate and Allergic Sensitization to Airborne Allergens in the General Population: Data from the French Six Cities Study

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Abstract

Background: The results of international epidemiological surveys show large geographical variations in skin test reactivity but do not provide a rationale for such variations.

Objective: To assess the relationship between climate and allergic sensitization in schoolchildren. **Methods:** In the present study, we analyzed data from a multicenter, epidemiological survey that included 6,461 schoolchildren, aged 9–11 years, living in 6 French cities scattered around France. The protocol also included a battery of skin prick tests to common airborne allergens. The crude prevalence of sensitization to each allergen was estimated for each city and then adjusted for potential confounding factors. This analysis was repeated for monosensitization and for allergens grouped into 2 categories: indoor allergens, i.e., house dust mite (HDM), cat, and cockroach allergens, and outdoor allergens, i.e., birch pollen, grass pollen, and *Alternaria*. We also grouped cities according to their location on the coast, i.e., Marseille and Bordeaux, or inland, i.e., Créteil, Clermont-Ferrand, Reims, and Strasbourg. **Results:** A difference in prevalence of sensitization to each airborne allergen or al-

lergens grouped into indoor and outdoor categories was found between cities, even after adjusting for potential confounding factors. Also, a higher prevalence of sensitization to HDM, cat dander, and, broadly speaking, indoor allergens, was found in children living on the coast than in those living inland, whereas they showed a lower prevalence of sensitization to birch pollen. Between-city differences in the prevalence of monosensitization were also statistically significant. Children living in coastal cities had a higher rate of monosensitization to indoor allergens and a lower prevalence of sensitization to birch pollen. The higher prevalence of allergic sensitization in children from coastal cities is most likely due to climatic conditions, such as proximity from sea and humidity. Differences in sensitization to birch allergens could be due to differential exposure to these pollen. **Conclusion:** These results indicate a role of environmental exposure in sensitization to perennial as well as seasonal allergens.

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Introduction

In the last 2 decades, 4 large collaborative international studies have compared sensitization rates across countries: ISAAC [1], ECRHS [2], US NHANES [3], and the GA²LEN collaborative project [4]. ISAAC [1] compared



Fig. 1. Location of participating centers.

allergic symptoms to skin reactivity but did not analyze geographic variations in relation to climate. ECRHS [2] compared skin tests to the levels of specific IgE but did not assess the effect of climate either. NHANES [3] provided skin test results according to personal characteristics. Finally, GA²LEN [4] analyzed in detail the correlation between climate and allergic sensitization in outpatients from allergologic centers but not in samples from the general population. Other epidemiological surveys compared 2 geographic areas with contrasting climatic conditions, arid versus humid areas or altitude versus plain [5, 6]. The objective of the study was to evaluate the relationships between climate and allergic sensitization in large samples of the general population living in a country with a temperate climate.

Materials and Methods

Subjects

The data set analyzed here was part of the French Six Cities Study in primary schoolchildren living in Bordeaux, Clermont-Ferrand, Créteil, Marseille, Reims, and Strasbourg (Fig. 1). These

cities were chosen to reflect a high diversity in climatic conditions: Bordeaux: oceanic climate with mild winters, Créteil: degraded oceanic climate, Clermont-Ferrand: semicontinental climate with large thermal variations, Marseille: Mediterranean climate, Reims: temperate oceanic climate, and Strasbourg: continental climate.

A total of 9,000 children from 108 schools (aged 9–11 years) were initially selected. The parents of 7,432 children provided their consent for the study and 6,471 underwent skin testing.

Skin Prick Testing

Skin prick testing (SPT) for atopy was performed in 6,461 children using Stallergenes Laboratories (Antony, France). The skin tests were performed by the SPT technique according to the ISAAC protocol [7]. Children were tested for common aeroallergens which were encountered in all 6 geographic areas: *Der p*, *Der f*, *Blatta germanica*, cat fur, *Alternaria tenuis*, and mixed grass and birch pollen. Allergenic extracts used in the 6 centers originated from the same batch. Allergic sensitization was defined as at least 1 positive reaction, i.e., wheal size of at least 3 mm and greater than the negative control.

Prior to the study, all field workers performed a proficiency test [8], which was performed by all field workers prior to starting the study and repeated until results were satisfactory.

Table 1. Number of children included in the survey in each city, sex ratios, and age

	Bordeaux	Clermont	Créteil	Marseille	Reims	Strasbourg	Total
Children, <i>n</i>	1,115	1,066	1,369	1,018	876	1,017	6,461
Male/female ratio	1.03	1.00	0.96	1.04	1.02	0.92	0.99
Mean age $\pm$ SD, years	10.26 $\pm$ 0.70	10.57 $\pm$ 0.72	10.22 $\pm$ 0.79	10.47 $\pm$ 0.70	10.52 $\pm$ 0.80	10.49 $\pm$ 0.74	10.41 $\pm$ 0.75

Table 2 Percentage of positive skin tests to each of the airborne allergens tested in each participating city

	Bordeaux	Clermont	Créteil	Marseille	Reims	Strasbourg	Total
<i>Der p 1</i>	26.88	15.9	9.79	18.55	19.6	13.25	16.96
<i>Der f 1</i>	19.93	13.16	7.30	14.53	14.70	9.77	12.96
Cat	5.95	4.75	1.58	4.59	3.05	3.01	3.79
<i>Alternaria</i>	4.14	3.58	1.79	2.96	3.58	1.13	2.81
Birch pollen	3.47	7.41	2.89	1.05	3.05	4.42	3.78
Cockroach	2.89	0.83	1.72	2.49	1.06	0.85	1.68
Grass pollen	12.08	13.65	6.68	7.46	8.48	7.99	9.43

Climatic Variables

Data on mean relative humidity, mean temperature, and mean dew point over the last 10 years were provided by the national meteorological services. Dew point computation involves both mean temperature and mean relative humidity. This parameter expresses the temperature to which air must be cooled to reach saturation and condensate. It is a more accurate way of measuring humidity since it is an absolute measurement (www.meteofrance.com).

Potential Confounding Factors

Potential confounders assessed through the standardized ISAAC questions included age, gender, passive smoking, paternal or maternal history of asthma and allergic diseases, dampness, pet exposure, gas appliance, ethnicity, and socioeconomic status coded using the French Insee (Institut national de la statistique et des études économiques) classification (<http://www.insee.fr>).

Logistics

All elements of the survey protocol obtained approval from the National Ethics Board (CPPRB). All children and their parents/caregivers gave written informed consent.

Statistical Analysis

All continuous variables are presented as means and standard deviations (SD), and the categorical variables as frequencies. To assess associations between SPT reactions, positive or negative, and locations, the Pearson χ^2 test was used for categorical variables, and marginal odds ratios (ORs) were computed.

Logistic regression analyses were performed to assess associations between SPT results as the dependent variable and the study location as the independent variable. The relative risks of a positive skin test were estimated by calculating the adjusted ORs and the corresponding 95% confidence intervals. ORs were adjusted for all the potential confounders to control for increased risk of sensitiza-

tion (defined by whether the father or the mother of the child had ever suffered from asthma, allergic rhinitis, or eczema, gender, parental education, maternal and paternal ethnic origins, and exposure to environmental tobacco smoke/passive smoking). *p* values ≤ 0.2 in bivariate analysis were considered as potential confounding factors and included in the regression analysis.

SPTs were considered separately, then grouped as “indoor allergens,” including house dust mite (HDM), cat, and cockroach allergens, or “outdoor allergens,” namely grass pollen and birch pollen, with *Alternaria* being in between. Besides, we considered nonallergic, monosensitized, and polysensitized children. Cities were considered separately, then grouped into 2 categories, namely coastal cities, Bordeaux and Marseille, and inland cities, Créteil, Reims, Clermont-Ferrand, and Strasbourg.

All reported *p* values were based on two-sided tests, and a *p* value < 0.05 was considered statistically significant. All analyses were performed with R v.17.

Results

The overall sex ratio was equal to 0.99, and mean age was 10.4 years (Table 1).

Table 2 provides the results of skin tests in the 6 participating cities. The highest rate of sensitization was encountered for HDM allergens in all participating cities, with sensitization to *Der p 1* being higher than for *Der f 1*.

All potential confounding factors did not show a statistically significant distribution across study centers, apart from passive smoking, ethnicity, and socioeconomic status. Thus, only the latter 3 variables were introduced

Table 3. Logistic regression analysis including sensitization to each airborne allergen as the dependent variable and, as independent variables, the cities where the children live and potential confounding variables

	Bordeaux	Clermont	Créteil	Reims	Strasbourg
<i>Der p 1</i>	1.61*** (1.25–2.09)	0.85 (0.65–1.13)	0.48*** (0.35–0.66)	1.26 (0.94–1.69)	0.73* (0.55–0.97)
<i>Der f 1</i>	1.42* (1.07–1.89)	0.90 (0.66–1.22)	0.44*** (0.31–0.62)	1.11 (0.80–1.54)	0.66* (0.48–0.91)
Cat dander	1.57 (0.98–2.59)	0.95 (0.56–1.62)	0.35** (0.17–0.67)	0.79 (0.41–1.47)	0.77 (0.44–1.35)
<i>Alternaria</i>	1.48 (0.84–2.72)	1.17 (0.65–0.32)	0.65 (0.32–1.31)	1.04 (0.52–2.08)	0.42* (0.19–0.91)
Birch pollen	3.46** (1.55–9.22)	7.85*** (3.68–20.36)	3.00* (1.30–8.15)	3.35* (1.39–9.30)	4.33*** (1.95–11.49)
Cockroach	2.11 (0.94–5.37)	0.65 (0.23–1.86)	0.85 (0.34–2.33)	0.91 (0.31–2.68)	0.4 (0.12–1.26)
Grass pollen	1.79** (1.25–2.60)	2.10*** (1.47–3.03)	1.05 (0.70–1.59)	1.26 (0.82–1.94)	1.13 (0.77–1.69)
Indoor	1.41** (1.12–1.79)	0.74* (0.57–0.95)	0.49*** (0.37–0.64)	1.01 (0.77–1.33)	0.65** (0.50–0.85)
Outdoor	1.04 (0.78–1.40)	1.20 (0.90–1.60)	0.58** (0.42–0.82)	0.65* (0.45–0.93)	0.72* (0.52–0.98)
Polysensitization	1.77** (1.26–2.53)	1.53* (1.08–2.20)	0.55** (0.36–0.85)	1.25 (0.83–1.88)	0.83 (0.56–1.24)

Marseille acts as the reference. Results are expressed as odds ratios (95% confidence intervals). Sensitivity to indoor allergens as well as to outdoor allergens was also considered as a group. Statistically significant differences are presented in italics. *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$.

in the logistic regression analysis as potential confounding factors.

Mean relative humidity over the last 5 years was lowest in Marseille (68.5%) and highest in Créteil (82.1%), whereas mean temperature was lowest in Reims (7.9°C) and highest in Marseille (14.8°C). Dew point was highest in Bordeaux (11.5°C) and lowest in Reims (2.2°C).

Concerning cat mean allergens, there were few between-city contrasts, except for a lower sensitization rate in Créteil compared to Marseille.

The logistic regression analyses included skin reactivity to each aeroallergen as the dependent variable and each set of 2×2 comparisons of cities as the independent variables, after adjusting for potential confounding variables. Compared to Marseille taken as the reference, children from Bordeaux had a higher prevalence of sensitization to HDM allergens, whereas children from Créteil and Strasbourg showed a lower rate (Table 3). *Alternaria* sensitization was not statistically different between cities, except for a lower rate in Strasbourg compared to Marseille. As far as birch sensitization is concerned, children from all cities displayed a higher rate than those from Marseille. No differ-

ence could be found for cockroach allergens. Finally, sensitization to grass pollen allergens was significantly higher in Bordeaux and Clermont-Ferrand than Marseille. Compared to children living in Marseille, those living in Bordeaux had a higher prevalence of sensitization to indoor allergens, whereas those living in Clermont-Ferrand and Créteil had a lower prevalence. As regards sensitization to outdoor allergens, compared to children living in Marseille, those living in Créteil, Reims, and Strasbourg had a lower prevalence of positive skin tests. Prevalence of children polysensitized to airborne allergens was significantly higher in Bordeaux than in Marseille, but children living in Créteil, Reims, and Strasbourg had a lower rate of polysensitization than those living in Marseille.

Compared to children living in inland cities, those living in coastal cities had a higher rate of sensitization to both indoor and pollen allergens. The difference is more striking for indoor allergens (Table 4). Results were unchanged if *Alternaria* was considered as outdoor allergen (data not shown).

As far as monosensitization to each of the airborne allergen tested is concerned, the hierarchy of sensitization

across cities was comparable to the one obtained for polysensitization.

Table 5 shows that children living inland had a statistically higher prevalence of monosensitization to birch pollen and a lower rate of monosensitization to HDM, cat dander, and *Alternaria* allergens.

Discussion

This large, multicenter, cross-sectional, epidemiological survey revealed statistically significant differences in skin test reactivity between children living in 6 French cities with different climatic conditions. The strengths of this survey lie in the large sample of children selected in cities scattered around France and the standardization of the study protocol. The panel of allergens tested was quite limited because we chose not to include allergens of local interest such as cypress, olive, and *Parietaria* pollen. We also discarded dog allergen because of its low diagnostic value. For statistical analysis, we only considered passive smoking, ethnic group, and education as confounding factors because all other potential confounding factors had no statistically significant relationship ($p > 0.2$) to the variables explained.

Overall, the prevalence of atopy was 28.3%. It is difficult to compare this result to data from the literature because study groups, allergenic extracts, and field workers were not homogeneous. However, this result was similar to what has been reported in studies performed in Western Europe for the same age group: 37.1, 25.2, 32.3, and 29.5% in the studies by Linehan et al. [9], Ronchetti et al. [10], Jögi et al. [11], and van Amsterdam et al. [12], respectively.

A statistically significant male predominance was found in all studies. This may help to explain the higher prevalence of asthma in boys.

Large geographical differences in allergic sensitization have been reported in the literature. Regarding HDM sensitization, these differences might be accounted for by the hygiene hypothesis in Eastern versus Western countries [5, 6] or to climatic differences in countries with similar socioeconomic background.

Children living in coastal cities, i.e., Bordeaux and Marseille, presented with a higher prevalence of positive SPTs to HDM allergens than children living inland. The difference was quite large, with a 69–74% increase in sensitization to HDM for children living on the coast. Such difference is likely due to different climatic conditions. Colloff [13] stated that mite development, apart from the microclimate of the house, is governed by 2 outdoor fac-

Table 4. Logistic regression analysis including sensitization to each airborne allergen tested as the dependent variable and living near the sea (Bordeaux and Marseille) or inland (Clermont-Ferrand, Créteil, Reims, and Strasbourg) as the independent variables after controlling for potential confounding variables

	OR	95% CI
<i>Der p 1</i>	1.74***	1.49-2.04
<i>Der f 1</i>	1.69***	1.42-2.02
Cat dander	1.90***	1.40-2.58
<i>Alternaria</i>	1.59*	1.11-2.27
Birch pollen	0.51***	0.35-0.73
Cockroach	2.43***	1.45-4.06
Grass pollen	1.04	0.84-1.27
Indoor	1.80***	1.56-2.09
Outdoor	1.26*	1.05-1.51
Polysensitization	1.04	0.82-1.32

Inland cities were used as a reference. OR, marginal odds ratio; CI, confidence interval. *** $p < 0.001$, * $p < 0.05$.

Table 5. Comparison of monosensitization to each aeroallergen tested in children living inland or on the coast

	Inland	Coast	Total	<i>p</i>
<i>Der p 1</i>	13.91	23.02	16.96	<0.001
<i>Der f 1</i>	10.71	17.43	12.96	<0.001
Cat dander	3.02	5.32	3.79	<0.001
<i>Alternaria</i>	2.42	3.59	2.81	<0.01
Birch pollen	4.50	2.35	3.78	<0.001
Cockroach	1.16	2.71	1.68	<0.001
Grass pollen	9.17	9.93	9.43	ns

tors: latitude and coastal location. According to regression equations, for beds, with every 10° increase in latitude from the equator, there is a 1.6-fold decrease in the mean mite population density. This is due to the lower amplitude of diurnal and seasonal variations in temperature close to the equator [13]. However, this phenomenon is most unlikely to explain differences demonstrated in our survey. Besides, according to Colloff [13], coastal locations have 5 times the median number of mites in beds and 8 times the number in floors than inland localities, because of evaporation from sea surfaces. Here, skin reactivity in children was in agreement with these results, except for those living in Créteil (Table 2). Such difference in skin reactivity was exemplified in the GA²LEN survey, which revealed a 67% prevalence of positive skin tests to *Der p* in outpatients from Australia, whereas it was only 23% in outpatients from Northern Europe [4]. How-

ever, these data are not representative of the general population and, as the authors acknowledged, could reflect patterns of referral and differences in local health services. Other studies on samples from the general population in Europe, reviewed previously [4], are available, but the comparison of percentage of positive tests to HDM allergens is difficult because the protocols of these studies were not similar. Large international epidemiological surveys [1–3] did not provide data about climate in various centers and did not assess the relationship between location, climate, and skin test responses.

Some surveys included the comparison of 2 geographical areas with very contrasting climatic conditions. For example, a Canadian study evaluated asthmatic children living in humid and warm areas and an area in a semiarid continental region [5]. Children living in houses with a relative humidity under 50% had a significantly lower prevalence of positive skin tests to HDM. A French, cross-sectional, comparative epidemiological survey in school-children living in altitude or at sea level demonstrated a much higher prevalence of positive skin tests to HDM allergen in children living at sea level. In Mexico, Larenas-Linnemann et al. [14] demonstrated large differences in sensitization to HDM allergen, with the highest rate in humid semihot area and the lowest in dry and temperate climates. In contrast, our survey included several cities within a country without such drastic meteorological differences.

Large differences in the prevalence rates of sensitization to pollen were demonstrated in our survey. They are

quite trivial, accounted for by climatic differences. For example, there are very few birch trees and few grass pollen under the Marseille Mediterranean climate.

In conclusion, large differences in prevalence of sensitization to HDM allergens were demonstrated, with high rates in coastal than inland cities, a difference most likely related to outdoor mean humidity. Whether this allergic sensitization is a risk factor for asthma incidence is a matter of debate.

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Disclosure Statement

The authors declare no conflict of interest.

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