Asthma and Allergy to House-dust Mites in Populations Living in High Altitudes*

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Do subjects living in high altitude where house-dust mites are known to be uncommon exhibit a lower prevalence of asthma and allergy to house-dust mites? To answer this question, we compared the prevalence rates of asthma and skin reactions to house-dust mites in two towns with contrasted environments: Marseille, located on the seashore, and Briançon, 1,350 m in altitude. The study population consisted of a random sample of 4,008 people in Marseille and 1,055 people in Briançon. All subjects received a home questionnaire, and a sample of patients and asymptomatic subjects had a skin-prick test evaluation. The cumulative prevalence of asthma was equal to 4.1 percent in Marseille and 2.4 percent in Briançon, a difference which was significant (p=0.01). The prevalence of positive skin tests to housedust mites in asymptomatic subjects was equal to 27.5 percent in Marseille and 10.2 percent in Briançon (p<0.001). This study supports the hypothesis that exposure to environmental factors may have a major influence on developing allergic diseases.

The importance of house-dust mites (HDM) in house-dust allergy has been recognized since 1964.¹ Their implication in the pathogenesis of asthma is supported by strong epidemiologic arguments. Papua New Guinea populations demonstrated, in recent years, a rapid and parallel increase in asthma prevalence and allergy to HDM. This increase seems to be related to a change in lifestyle, especially the introduction of blankets heavily infested with HDM.² Groups of asthmatic children with HDM allergy show clinical improvement and a fall in total and serum specific IgE levels when they stay in high altitudes³ where HDMs are known to be uncommon.⁴ Sensitivity to HDM is frequent in humid areas and seldom occurs in dry areas.⁵ Thus, one could expect that people born, raised, and living in high altitudes should demonstrate a lower prevalence of asthma and allergy to HDM. To test this hypothesis, we performed a comparative cross-sectional study in two towns, one located at high altitude, the other one at the sea level.

**MATERIAL AND METHODS**

**Material**

The target population consisted of adults, 18 to 65 years old, permanent residents in Marseille or Briançon. Marseille (Fig 1) is a city of 879,000 inhabitants located on the Mediterranean seashore. Briançon (Fig 1) is the highest city in Europe. It is located in the French Alps, at an altitude equal to 1,350 meters. It has two main resources: skiing and medical care, formerly for tuberculosis patients, now for a wide variety of chronic diseases, especially bronchial asthma.

The sampling frame was different in each town. In Marseille, we performed a three-stage cluster sampling. Prior to the sampling, we computed, at a 95 percent confidence level, an estimated sample size, which was based on an estimated prevalence rate for asthma close to 6 percent,⁶ and a standard error equal to 1 percent. Owing to the cluster sampling frame used, we doubled the estimated sample size needed.⁷ Thus, the estimated sample size was roughly equal to 4,000. We chose to select, at random, 40 neighborhoods from all over the city because, as a working rule, from the number 30, the cluster means will tend to have normal distribution.⁸ Thus, we decided to study 100 people in each of the 40 neighborhoods.

![Map of France showing Marseille and Briançon](image-url)
with a probability proportional to their size (systematic sample). In a second step, in each neighborhood, we selected, through random sampling, a group of households or cluster. Then, in a third step, the interviewers in the field selected, at random, in each selected cluster, the corner where to start interviewing people and moved forward step by step. They visited the households only once, mostly in the evening, and proceeded until they had seen 100 people in the selected cluster.

In Briançon, we used a one-stage cluster sampling. The town is divided in 20 sectors. We selected, randomly, 14 of them and tried to interview all adults 18 to 65 years old. As the objective was to assess the long-term influence of living in a low HDM environment, we had to consider separately in the analysis those subjects who were born, grew up, and lived in Briançon, and whose family had always lived in this area. This is especially important, because the climate in Briançon is known to be favorable to asthmatic patients, and some asthmatics have chosen to settle there. The public was informed about the study through radio, local television, newspapers, and picture posters placed in stores and blocks of flats. The interviewers performed home visits. If the person was absent, the interviewers came back later the same day or another day. The interviewer had to visit the house or flat at least three times before the person was considered a nonrespondent. The response rate was equal to 45 percent and provided the interviewer had to visit the house or flat at least three times before the person was considered a nonrespondent. The response rate was assessed by comparing the number of respondents to the total resident population 18 to 65 years old. The latter was obtained from the 1982 Census, which provides, for each cluster, the size of the resident population. To evaluate if nonrespondents could be comparable to respondents, we performed, after the main study, a mail survey. In this survey, we sent letters, including the questionnaire and a stamped envelope for the response, to 100 nonrespondents. The response rate to this letter was equal to 45 percent and provided similar answers to the responses elicited in the main survey.

Overall, in Marseille we interviewed 4,008 adults, 18 to 65 years old, and in Briançon, 1,055 subjects from the same age range. The distribution of the studied population according to gender and age is listed on Table 1. The mean (±SD) age was equal to 40.80 ± 14.5 in Marseille and 39.3 ± 14.2 in Briançon.

Methods

Each subject had to answer a standardized questionnaire on past or present history of wheezing in the chest, attacks of wheezing, attacks of shortness of breath with wheezing in chest, asthma attacks, asthma diagnosed by a doctor, and seasonal or perennial rhinitis. In addition, the questionnaire included other items not directly related to atopic diseases: local or systemic reactions following hymenoptera stings, chronic cough and sputum, and smoking habits.

Then, the interviewers performed, in a sample of the respondents, skin tests to HDM. One person out of two among those answering yes to the question about a history of asthma attacks was tested, as well as one person out of three among those who answered yes to the question about seasonal rhinitis, and one control subject (no asthma, no seasonal rhinitis, no childhood eczema) out of 20. The skin tests were performed on the volar surface of the forearm, using the prick testing method. The allergen used was a standardized extract of Dermatophagoides pteronyssinus, containing 100 reactivity units per ml of HDM. Such an extract has been standardized to induce, by prick-testing, in a group of subjects known to be sensitized to such an allergen, a wheal measuring 6 mm in diameter. The diameter of the wheal was measured 20 minutes later, and the test was considered positive if the wheal had at least a 3 mm diameter. We also performed a test using a 9 percent codeine phosphate solution as a positive control.

Statistical Analysis

In Marseille, the estimates of the mean and standard deviation were computed using the Horvitz-Thompson equations. These estimates have to be used when the probability to be included in the sample is not the same for all individuals of the target population. In Briançon, we used simplified estimates which suppose that the size of the various clusters is not different. Actually, its coefficient of variation was equal to 10 percent.

Because of a slightly different distribution of the study population according to age, we performed a direct standardization of the prevalence rates, using as a standard the combined populations.

RESULTS

The response rate in Briançon was equal to 63 percent. There was a 5 percent refusal rate. The high percentage of nonrespondents is related to the large number of persons who were away from Briançon at the time of the study (1985, autumn). Indeed, the ski season starts at Christmas and ends at Easter. We had chosen to perform the study in autumn because at that time, there are very few tourists. In Marseille, the response rate cannot be assessed because we paid a single home visit and did not try to perform an exhaustive study.

Comparison of Asthma and Allergic Diseases

Prevalence in Both Towns

Table 2 shows that the cumulative standardized prevalence rate of asthma and related symptoms were significantly lower in Briançon. This difference remained unchanged when considering the Marseille sample, only those subjects who had been living in this town for at least 10 years. For example, the prevalence of asthma in Marseille for those subjects who had been living in Briançon for at least 10 years. For example, the prevalence of asthma in Marseille for those subjects was equal to 4.0 percent. In Briançon, the 25 asthmatic subjects recorded were not evenly distributed all over

| Table 1—Distribution of Studied Population, in Each Town, According to Age and Gender |
|-----------------|-----------------|-----------------|-----------------|
| Age Range       | Marseille M     | Marseille F     | Briançon M      | Briançon F     |
| 18-34           | 756             | 847             | 205             | 232            |
| 35-49           | 431             | 623             | 148             | 170            |
| 50-65           | 540             | 610             | 131             | 169            |
| Total           | 4,008           | 4,938           | 1,055           |                |

| Table 2—Prevalence of Asthma and Related Symptoms in Marseille and Briançon |
|-----------------|-----------------|-----------------|-----------------|
|                 | Briançon        | Marseille       |
| Attacks of wheezing | 2.8 ± 0.5      | 3.9 ± 0.4      |
| Attacks of shortness of breath with wheezing | 1.8 ± 0.4      | 3.1 ± 0.3      |
| Asthma attacks   | 2.4 ± 0.5      | 3.8 ± 0.7      |
| Positive answers to the above three questions | 1.3 ± 0.3      | 2.6 ± 0.2      |
| Asthma diagnosed by a doctor | 2.1 ± 0.4      | 3.4 ± 0.3      |
### Table 3—Number of Persons Having Skin Test*

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<tr>
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<th>Briançon</th>
<th>Marseille</th>
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<tbody>
<tr>
<td>Overall</td>
<td>120 (10%)</td>
<td>398 (44.5%)</td>
</tr>
<tr>
<td>Asymptomatic subjects</td>
<td>78 (10.2%)</td>
<td>127 (27.5%)</td>
</tr>
<tr>
<td>Asthmatic subjects</td>
<td>11 (18.2%)</td>
<td>147 (49.6%)</td>
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* Hay fever patients are not mentioned. In parentheses is the percentage of positive skin test to HDM—p values refer to the comparison of the proportion of positive skin test to HDM in the two towns.

The prevalence of seasonal rhinitis was comparable in Marseille (14.8 ± 0.5 percent) and Briançon (12.9 ± 1.0 percent). By contrast, the prevalence of perennial rhinitis (ie, lasting more than three months for two consecutive years) was lower in Briançon (4.3 ± 0.6 percent) than in Marseille (12.2 ± 0.5 percent), a difference which was statistically significant (p<0.001).

#### Comparison of Skin Reactions to Housedust Mites in Both Towns (Table 3)

Overall, among persons who had a skin test evaluation, in Briançon 12 of 120 (10 percent) had a significant reaction to HDM, while in Marseille, 177 out of 398 (44.5 percent) had such a reaction.

In Briançon, 78 asymptomatic subjects had a skin test to HDM, and in Marseille, 127. Their distribution, according to gender and age, was comparable in both settings. All had a positive reaction to codeine phosphate. The percentage of significant skin reactions to HDM was lower in Briançon (10.2 percent) than in Marseille (27.5 percent), a difference which was statistically significant (p<0.001).

Among the 11 asthmatics from Briançon (ie, subjects who provided a positive answer to the question: “Have you ever had asthma?”), only two (18.2 percent) had a positive test to HDM, whereas in Marseille, 73 out of 147 (49.6 percent) had such a positive answer.

### Discussion

The difference we have observed in asthma and allergic disease prevalence, as well as in prevalence of positive skin test results to HDM, are unlikely to be spurious. These diseases do not usually involve hospitalization or absence from home so that the low response rate should not have biased the estimates. Biased responses could have been obtained from the people in Briançon because of their willingness to support the health benefits of its climate or because of a lack of health education. However, the prevalence of symptoms not related to atopy (ie, local and systemic reaction to hymenoptera stings, chronic cough and sputum in smokers) was comparable in both settings. This fact does not support this latter hypothesis.

The lower prevalence of asthma and allergic diseases could be related to several environmental factors including specific meteorologic conditions and low air pollution. Among the former, low temperatures and low humidity are known to inhibit the growth of HDM. In Briançon, the highest monthly mean relative humidity indoors, encountered in summertime, is around 75 percent. In wintertime, monthly mean relative humidity is around 35 percent indoors, because of the heating. Now, it is known that there are six times fewer HDM at 75 percent relative humidity than at 80 percent. Besides, experimental data have shown that below the critical equilibrium humidity (70 percent), the mite can no longer maintain its body and progressively loses water until it succumbs to desiccation. Moreover, the influence of altitude on HDM has been illustrated by studies including counts of mites at different altitudes. Such studies have been conducted in Switzerland, Italy, and France. In this latter county, Vervloet et al studied, in each season for one year, 218 mattress-dust samples taken from the Briançon region in the Alps, 900 to 3,170 meters in altitude. The percentage of positive samples and the concentration of mites were inversely correlated to altitude. Recently, Pauli et al using a new standardized kit measuring semiquantitatively gramine, a major and specific component of the mites, confirmed these data in the Northern Alps (Chamonix). From a clinical standpoint, Vervloet et al have shown, in a group of 42 asthmatic children with HDM allergy, a very consistent decrease in total and mite specific IgE, as well as a clinical improvement, as a result of a stay in altitude. Murray et al, studying children with respiratory symptoms coming from cities throughout British Columbia, a province with both humid and semiarid regions, demonstrated that skin prick tests to HDM were positive in 40 percent of those children from the humid areas, whereas in those children from dry areas, tests were positive in 2 percent. Moreover, there was a marked difference in the degree of sensitivity.

From a broader standpoint, our study also points out the influence of environment on the development of allergy, illustrated by skin reactions to HDM and respiratory symptoms. The modification of skin reactions to acro-allergens resulting from exposure to an allergen, is exemplified by a Finnish study showing that infants exposed to a cat during the first six months of life have a significantly higher prevalence of positive skin test to cat dander than infants who had a cat later in their life or did not have a cat. Some articles suggest that infants born during the pollen season or during the humid season, when the concentrations of pollens...
or mites, respectively, are higher, have an increased risk of developing allergic disease to these allergens. However, the development of allergic diseases under the influence of aero-allergens can also occur later in life. Maternowski and Mathews have shown that the prevalence of ragweed polinosis, low in foreign students arriving in United States, steadily increases. After two years in United States, this prevalence rate is the same as in American students. In a like manner, an Australian group performed several prevalence studies in the last decade in village communities within the Papua New Guinea highlands. They demonstrated a dramatic rise in the prevalence of asthma in adults over the last decade and attributed this change to modifications in lifestyle and especially the recent introduction of blankets and changes in sleeping habits which promote a more fertile environment for growth and multiplication of mites.

All these studies support the hypothesis that exposure to environmental factors in infancy, but also later in life, may have a major influence on developing allergic diseases. Traits which are traditionally put forward to back-up the importance of genetics in allergy (ie, high prevalence of allergic diseases in some areas, positive skin tests to aero-allergens) may well be the result of exposure to allergens.

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