

Effect of area of residence on patterns of aeroallergen sensitization in atopic patients

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ABSTRACT

Background: An association with sensitization to inhaled allergens and allergic rhinitis and asthma has been established. A recent study concluded that the disparity in allergen sensitization might primarily be caused by environmental factors rather than genetic differences. The primary objective was to identify potential differences in sensitization among subjects with the same ethnicity in South India who reside in different environments.

Methods: Five hundred forty-six patients presenting to a tertiary allergy center with allergic rhinitis and/or asthma underwent evaluation using a structured questionnaire, skin-prick testing to common aeroallergens, and spirometry and were categorized according to area of residence.

Results: The most common allergens causing sensitization were house-dust mite (range, 65–70%), trees (range, 52–56%), and cockroaches (range, 39–53%). There was lower risk of sensitization to cockroach allergens for subjects <21 years old living in suburban (odds ratio [OR], 0.32; 95% confidence interval [CI], 0.12–0.81) and rural environments (OR, 0.33; 95% CI, 0.11–0.96) compared with subjects <21 years old living in urban areas. There was higher risk of sensitization to fungi in subjects <21 years old living in suburban areas (OR, 1.51; 95% CI, 0.60–3.77) and rural environments (OR, 2.71; 95% CI, 0.98–7.48) compared with subjects <21 years old living in urban environments.

Conclusion: Sensitization patterns are similar in different areas of residence except in younger subjects. Sensitization to fungi was higher in younger subjects from the rural area and cockroach sensitization were higher in younger subjects from urban areas. Sensitization is an important precursor of clinical allergic disease and further studies to unravel the complex gene–environment interactions of aeroallergen sensitization in different environments are needed.

(Am J Rhinol Allergy 24, e98–e103, 2010; doi: 10.2500/ajra.2010.24.3529)

Allergic rhinitis and asthma are IgE-mediated chronic inflammatory diseases of the respiratory tract and have been increasing in frequency in many parts of the world.¹ Studies^{1–3} have revealed an association with sensitization to inhaled allergens for both allergic rhinitis and asthma. The prevalence of rhinitis and asthma varies widely in different countries. The International Study of Asthma and Allergies in Childhood study⁴ revealed a prevalence of allergic rhinitis from 3.2 to 66% in 13- to 14-year old children and of asthma² in 8- to 12-year old children from 2.5 to 35.6%. A recent study in Jordan did not show differences in the prevalence of asthma in urban school children in Amman and the Bedouin children living in a desert environment.⁵ The prevalence of allergic sensitization in the International Study of Asthma and Allergies in Childhood study² in children varied from 1.7% in Ghana to 43% in Norway. An eightfold variation in the prevalence of wheeze and significant variation in the prevalence of atopic sensitization between countries were shown in the European Community Respiratory Health Survey⁶ in adults. Recently, Yang *et al.*⁷ showed that the disparity in allergy sensitization might primarily be caused by environmental factors rather than genetic differences.

Allergens are important sensitizing agents in asthma and studies have shown that atopic asthma is more common than nonatopic asthma.^{8,9} Differences in allergic sensitization in varied geographical areas have been established in earlier studies. Indoor allergens such as house-dust mites and cockroaches was the most common allergen noted in different geographic regions such as Hong Kong (adults⁸ and children¹⁰), United States (children¹¹), Qatar (adults¹²), Africa (children¹³), and Israel (children and adults¹⁴), whereas outdoor allergens such as pollens were the most common allergens noted in Turkey (adults⁹), the United Arab Emirates (adults¹⁵), and the United King-

dom (children¹⁶). Different ethnicities with similar environmental exposures showed similar patterns of sensitization to indoor and outdoor allergens in United States (children¹⁷), whereas significant racial–ethnic differences in allergen sensitization with different environments was shown in a study in the United States (children¹⁸), suggesting that disparities in housing, community, and environmental influences can lead to differing sensitization patterns. In a study in Israel,¹⁴ subjects residing in the coastal Mediterranean compared with the inland desert area showed higher weed sensitivity in the desert area. Association with asthma was observed with house-dust mites in the coastal area and with fungi in the desert area. A study in Turkey⁹ has not shown differences between urban and rural populations of the same ethnicity for cockroach sensitization. Sensitization to house-dust mites in both adults and children and sensitization to trees in adults was found to be independently associated with the development of asthma in patients suffering from allergic rhinitis.¹⁹

The study presented here was conducted to evaluate whether areas of residence could result in differences in sensitization among subjects of the same ethnicity in South India. The primary objective was to identify if there are differences in sensitization in subjects' residence in different environments. We hypothesized that urban subjects would be more sensitized to house-dust mites and cockroaches and would be less allergic to pollens and fungi in comparison with subjects living in rural regions. We also wanted to investigate whether potential associations between area of residence and being sensitized to these allergens were different between younger and older subjects.

METHODOLOGY

Design and Subjects

In this cross-sectional study, all of the patients presenting with allergic rhinitis and/or asthma to a tertiary allergy center (Mysore, India) during the period January 1999 to April 2001 were included. A total of 546 subjects aged 9–55 years underwent evaluation using a structured questionnaire, skin-prick testing to common aeroallergens, and spirometry. All of the subjects were from the Mysore district with subjects belonging to middle and upper socioeconomic classes and differing areas of residence. The institutional ethics committee approved the study.

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Measurements

The structured questionnaire collected data on demographics and a detailed clinical history including rhinitis and asthma. Medical doctors administered the questionnaires in person. The attending physician based the classification of patients as having allergic rhinitis and asthma on the Allergic Rhinitis and Its Impact on Asthma²⁰ and the Global Initiative for Asthma²¹ guidelines. Spirometry to confirm the diagnosis of asthma was performed according to American Thoracic Society guidelines.²² The subjects were classified based on their area of residence and according to administrative demarcations as urban, semiurban, and rural. The classification of area of residence included the place of their occupation (adults) or schooling (children) along with their place of residence. The state is divided into districts, districts into taluks, and taluks into villages. The district headquarters forms the urban area (areas with a population of above 200,000, administered by the city corporation), the taluk headquarters forms the semiurban area (areas with a population of 10,000 to 200,000, administered by taluk municipality), and the villages form the rural areas (areas with a population of 5000–15,000, administered by village panchayat (body of locally elected village members who run the administration of the villages)). The subjects were classified based on their occupation as student, unemployed, employed, self-employed, retired, or child.

Assessment of Sensitization

Skin-prick tests (SPT) were performed by the same medical person, using prick Lancetter (Hollister Stier, Spokane, WA) on the flexural aspect of the forearm according to standard guidelines,²³ using standardized glycerinated extracts from ALK ABELLO (1:10 to 1:20 w/v) and the following categories of allergens were evaluated: weeds, grasses, shrubs, trees, fungi, mites, and insects. Histamine phosphate (10 mg/mL; ALK ABELLO) and glycerinated saline (ALK ABELLO) were used as positive and negative control, respectively. The SPT to the antigen was considered positive if the wheal size was >3 mm when compared with saline control. The aeroallergens tested under the category of “weeds” were *Amaranthus*, *Artemisia*, *Chenopodium*, common weed mix, *Parthenium*, ragweed, *Xanthium*, and zeamays; aeroallergens tested under “grasses” were *Cynodon*, grassmix i, grassmix ii, mustard pollen, and wheat cultivated; aeroallergens tested under “shrubs” were Castrobeapollen, *Morus alba*, and *Helianthus annuus*; aeroallergens tested under “trees” were Australian pine, eucalyptus, *Prosopis juliflora*, and tree of heaven; and aeroallergens tested under “fungi” were *Alternaria*, *Aspergillus*, *Candida*, *Curvularia*, *Helminthosporium*, and *Penicillium*. The other aeroallergens included pets such as dogs, cats, and mixed feathers, house-dust mites, cockroaches, mosquitos, cattle epithelium, and fire ants.

Statistical Analyses

The relationship between area of residence and sensitization to different allergens was evaluated in all subjects first and stratified for age (younger and older than 21 years) in a second analysis. Unadjusted associations were examined using logistic regression analysis. Multivariate logistic regression models were used to control for potential confounders (sex, age, and family history of allergy) by including them in the regression models simultaneously. Results are presented as unadjusted and adjusted odds ratios (OR) with corresponding 95% confidence interval (CI). Statistical analyses were performed using the statistical software package Stata Version 10.1 (STATA Corp., College Station, TX).

RESULTS

Approximately one-quarter of the study population was <21 years old; two-thirds lived in urban areas, and one-half of them had a family history of allergy. These results and other characteristics of the study subjects are presented in Table 1. The most common allergen

Table 1 Characteristics of patients enrolled in a study conducted in an asthma/allergy private clinic in Mysore, India (n = 546)

Characteristics	n (%)
Male gender	293 (54)
Age group (yr)	
<21	132 (24)
21–30	138 (25)
31–45	144 (27)
>45	132 (24)
Residence	
Urban	359 (66)
Suburban	90 (16)
Rural	97 (18)
Occupation	
Child	23 (4)
Student	113 (21)
Unemployed*	148 (27)
Employed	152 (28)
Self-employed	72 (13)
Retired	38 (7)
Smoking	
Ex- or current smoker	52 (10)
Passive smoker	72 (13)
Never smoked	422 (77)
Family history of allergy (yes)	295 (54)
Pets	142 (26)
Asthma	389 (71)
Skin disease	43 (8)
Allergic symptoms related to the nose	418 (77)
Allergic symptoms related to the sinuses	380 (70)
Allergic symptoms related to the eye	233 (43)
Allergic symptoms related to the ear	175 (32)

*Except for n = 4 these were all housewives.

that subjects were sensitized to was house-dust mites (range, 65–70% for the three groups) followed by trees (range, 52–56%), cockroaches (range, 39–53%), fungi (range, 46–53%), grasses (range, 45–48%), and shrubs (range, 29–35%).

In total, 250 (70%) of the 359 subjects who lived in an urban area were SPT positive for house-dust mites: 61 (68%) for the suburban group and 63 (65%) for the rural residents (Table 1). These rates were very similar in the three groups and there was no association between area of residence and sensitization to house-dust mites: the adjusted OR and 95% CI were 0.91 (0.55–1.49) for the suburban residents and 0.79 (0.49–1.27) for the rural residents (Table 2) when these groups were compared with subjects living in urban areas. Similarly, there were also no differences in sensitization level to cockroaches, grasses, shrubs, tree pollen, and fungi in subjects living in different environments. In additional exploratory statistical analyses we found that this was also true for all of the other groups of allergens and for all of the allergens tested individually (not in groups). Similar results were found when we stratified for gender.

Statistical analyses stratified for age (<21 years versus ≥21 years) showed similar results also, except for sensitization to cockroaches and fungal allergens (Tables 3 and 4). We found a lower risk of sensitization to cockroach allergens for subjects <21 years old living in suburban (OR, 0.32; 95% CI, 0.12–0.81) and rural environments (OR, 0.33; 95% CI, 0.11–0.96) compared with subjects <21 years living in urban areas, but not for subjects ≥21 years. It was also found that there was a higher risk of sensitization to fungi allergens in subjects <21 years old living in suburban areas (OR, 1.51; 95% CI, 0.60–3.77) and rural subjects <21 yrs (OR, 2.71; 95% CI, 0.98–7.48) compared with subjects <21 years old living in urban environments, but not for subjects ≥21 years old living in different environments. The finding

Table 2 Associations between area of residence and sensitization to different allergens

Sensitization	Urban (n = 359)		Suburban (n = 90)			Rural (n = 97)		
	n (%)	OR (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
House-dust mite	250 (70)	1.00 Reference	61 (68)	0.92 (0.58–1.51)	0.91 (0.55–1.49)	63 (65)	0.81 (0.50–1.30)	0.79 (0.49–1.27)
Trees	202 (56)	1.00 Reference	47 (52)	0.85 (0.53–1.35)	0.87 (0.54–1.38)	53 (55)	0.93 (0.60–1.47)	0.95 (0.60–1.50)
Cockroaches	192 (53)	1.00 Reference	35 (39)	0.55 (0.34–0.88)	0.53 (0.33–0.86)	46 (47)	0.78 (0.50–1.23)	0.78 (0.50–1.23)
Fungi	171 (48)	1.00 Reference	41 (46)	0.91 (0.58–1.46)	0.97 (0.60–1.55)	51 (53)	1.22 (0.78–1.91)	1.22 (0.78–1.93)
Grasses	171 (48)	1.00 Reference	40 (44)	0.88 (0.55–1.40)	0.89 (0.56–1.42)	44 (45)	0.91 (0.58–1.43)	0.94 (0.60–1.47)
Shrubs	124 (35)	1.00 Reference	26 (29)	0.77 (0.46–1.28)	0.79 (0.47–1.31)	31 (32)	0.89 (0.55–1.44)	0.91 (0.56–1.14)

*Adjusted for sex, age, and family history of allergy.

CI = confidence interval; OR = odds ratio.

Table 3 Associations between area of residence and sensitization to cockroaches, stratified by age

Sensitization	Urban (n = 85 children, n = 274 adults)		Suburban (n = 27 children, n = 63 adults)			Rural (n = 20 children, n = 77 adults)		
	n (%)	OR (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Cockroaches								
<21 yr	49 (58)	1.00 Reference	9 (33)	0.37 (0.15–0.91)	0.32 (0.12–0.81)	6 (30)	0.31 (0.11–0.90)	0.33 (0.11–0.96)
≥21 yr	142 (52)	1.00 Reference	26 (41)	0.64 (0.37–1.12)	0.64 (0.37–1.12)	40 (52)	0.99 (0.60–1.64)	0.99 (0.60–1.65)

*Adjusted for sex and family history of allergy.

CI = confidence interval; OR = odds ratio.

Table 4 Associations between area of residence and sensitization to fungi, stratified by age

Sensitization	Urban (n = 85 children, n = 274 adults)		Suburban (n = 27 children, n = 63 adults)			Rural (n = 20 children, n = 77 adults)		
	n (%)	OR (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)	n (%)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Fungi								
<21 yr	29 (34)	1.00 Reference	11 (41)	1.32 (0.55–3.23)	1.51 (0.60–3.77)	12 (60)	2.90 (1.06–7.88)	2.71 (0.98–7.48)
≥21 yr	142 (52)	1.00 Reference	30 (48)	0.85 (0.49–1.45)	0.85 (0.49–1.46)	39 (51)	0.95 (0.58–1.58)	0.96 (0.57–1.57)

*Adjusted for sex and family history of allergy.

CI = confidence interval; OR = odds ratio.

in the suburban subjects who were <21 years old was, however, not statistically significant.

DISCUSSION

This cross-sectional study in high-risk subjects shows that subjects <21 years old living in Indian suburban and rural areas have a lower risk of sensitization to cockroach allergens and a higher risk of sensitization to fungal allergens. There were no such differences for subjects >21 year of age. There were also no differences in level of sensitization to house-dust mite, tree, grass, and shrub allergens between residents living in different urbanization areas.

Increased prevalence of allergic sensitization has been shown in urban dwellers when compared with rural dwellers with or without a farming background.²⁴ To explain these differences, notably, the “hygiene hypothesis”^{25–27} and the effect of air pollution are described.²⁸ Asthma and allergic diseases are unevenly distributed in Europe with higher levels observed with increasing urbanization or westernization. This encompasses complex lifestyle-associated factors including lower rates of microbial contact in early childhood leading to impaired immune regulation.^{29,30} The hygiene hypothesis alone is

unable to explain all of the variations observed in different parts of the world.³¹ Outdoor air pollution has been shown to increase the prevalence of aeroallergen sensitization. Diesel exhaust particles, in particular, can potentiate the sensitizing potential of aeroallergens.³² The effect of air pollution alone in increasing allergic sensitization is called into question by the study in Sweden and Poland,³³ which showed both higher allergen sensitization and higher air pollution levels in urban Sweden when compared with a rural population in Sweden. However, lower allergen sensitization was observed in urban Poland with even higher levels of air pollution than urban Sweden. Another important factor affecting the rates of sensitization includes the dose of the allergen exposure. Children exposed to allergens of house-dust mites, cockroaches, molds, cats, or dogs in the Childhood Asthma Management Program³⁴ in United States were found to have a higher prevalence of sensitization to the same allergens.

Few studies have examined the pattern of sensitization between urban and rural residents with variable results. Studies examining the effect of area of residence and allergic sensitization have revealed a strong association, with some studies showing higher

allergen sensitization rates in urban residents, some in rural residents, and others showing no difference. Yang *et al.*⁷ evaluated whether genetic ancestry, self-reported race, and area of residence affected pattern of allergic sensitization and indicated that current location of residence (urban versus semiurban) was strongly predictive of allergic sensitization when compared with geographic ancestry. They also observed higher rates of sensitization to cockroaches in the urban residents, but not to cats, dogs, dust mites, pollen, or fungi. A study in Portugal³⁵ observed similar prevalence of sensitization to dust mites, molds, cats, and dogs among urban and rural residents, but higher pollen (grass, *Parietaria*) sensitization in urban residents when compared with rural residents. A study in Turkish children³⁶ found higher rates of sensitization to *Candida*, sheep dander, and pollens in rural children than in urban children. German rural dwellers³⁷ were found to have higher rates of sensitization to storage mites than urban dwellers, and another study in Germany³⁸ found urban residents had higher rates of sensitization to pollens and lower rates of sensitization to house-dust mites compared with the rural population. Korean children in the rural areas were found to have higher rates of sensitization to citrus red mites and Japanese cedar pollen than in the urban areas.³⁹ Crimi *et al.*⁴⁰ observed that pet sensitization was more common in the urban residents and pollen sensitization was more common in rural subjects and a good correlation between degree of pollen exposure and sensitization. A study in Turkey⁹ did not find any differences in rates of sensitization to cockroaches in rural and urban residents, and others did not observe any differences in the rates of sensitization to house-dust mites⁴¹ or to pollens⁴² between rural and urban groups. Different patterns of sensitization are thus observed in different geographic areas. Either indoor or outdoor allergen sensitization could predominate in either rural or urban areas. Many of the studies are limited by the unavailability of aerobiological data and allergen concentrations in the environment.

There is no clear association between socioeconomic class and asthma. In a study in Germany higher prevalence of more severe asthma was observed in children of lower socioeconomic class.⁴³ Black and poor children in the United States⁴⁴ were observed to have higher rates of asthma that can be accounted for by social and environmental characteristics, whereas a Brazilian study specifically addressing the issue of socioeconomic class in children and asthma observed a higher prevalence of asthma and allergic rhinitis in children of higher socioeconomic class.⁴⁵ The opposing effects of class in developed and developing countries have been attributed to poverty-associated risk factors in developed countries leading to higher asthma such as smoking, passive smoking, large family size, high indoor and outdoor pollution, and dietary characteristics in subjects with lower socioeconomic class and in developing countries higher rates of asthma in higher socioeconomic class because of the hygiene hypothesis.^{45,46} In Jordan, however, there was no difference in the prevalence of asthma between urban and Bedouin school children living in the desert with lower socioeconomic class.⁵

The discrepancies observed in the aforementioned studies are likely to be caused by gene–environment interactions. Studies exploring gene–environment interactions in asthma and sensitization have observed that the genetic susceptibility is complex and is context dependent and asthma-related polymorphisms have a complex interaction with the environment, other genes, and host-related factors such as age and phase of disease.^{47,48} Lower prevalence of asthma and allergic sensitization in children who live on farms, consume farm milk, or rural areas during childhood has been observed, which is hypothesized to be caused by environmental exposure to noninfectious microbial agents such as endotoxin,⁴⁹ higher bacterial and viral infections,⁵⁰ or higher omega-3 dietary fatty acids in milk of cows that are exclusively fresh grass fed.⁵¹ Studies reinforcing the hygiene hypothesis have found that genes encoding pattern recognition receptors such as CD14; Toll-like receptors such as TLR-2, TLR-4, and TLR-9; Caspase recruitment domain protein 4 and others such as

Neuropeptide S receptor 1; and chitinase 3-like 1 gene polymorphisms have complex interactions with the environment to determine the presence of asthma and allergic sensitization.^{50–55} In black infants, interaction of environmental tobacco smoke and IL-4 C598 T polymorphisms increased the risk of “wheeze without a cold” by 10-fold. The childhood origin of asthma cohort observed that dog and not cat exposure was associated with an increased IL-10 in children with a CD14/–159 T/T polymorphism indicating an important gene–environment interaction.⁵⁶ However, a static model in which the gene polymorphism is associated with asthma in a linear fashion does not consider the interdependence of various asthma risk factors⁵⁷ and therefore apparently contradictory effects may sometimes be observed for the same single nucleotide polymorphism in different studies involving different age groups,⁴⁷ different populations,⁵⁸ or different levels of exposures to endotoxin.⁵⁹

In our study we observed similar patterns of both indoor and outdoor allergen sensitization among different areas of residence with different environmental exposures except in the younger age group, where cockroach sensitization was more common than in the urban residents and mold sensitization in the rural dwellers. It is unclear from our study why this difference in sensitization was noted in younger subjects. This could be related to the degree of exposure in which urban residents have higher exposure to cockroaches, whereas a greater exposure to molds is present in the rural environment because of exposure to hay and organic cow dung manures and factors associated with sensitization may be different in younger subjects compared with older subjects. These observations could suggest that although it is possible that the degree of environmental exposures to these allergens may vary, the pattern of sensitization may be similar and some allergens are more likely to cause sensitization than others.

Our study has certain limitations. One of the important limitations of our study was that we did not measure the environmental exposure levels of these indoor and outdoor allergens in which the presence of sensitization in relation to their dose of exposure could be studied and put these findings in proper perspective. Another limitation is that the data have been collected from a tertiary referral center and may not be reflective of sensitization in the general population.

Overall, we have shown that younger subjects in the rural area have higher sensitization to fungi and younger subjects in the urban area have a higher sensitization to cockroaches. Sensitization patterns are similar in older subjects in both the urban and the rural areas. It is probable that so far unidentified factors are involved in determining the pattern and prevalence of sensitization in allergic subjects. Since sensitization is an important precursor of clinical allergic disease, it is important that further studies are undertaken to unravel the complex gene–environment interactions of aeroallergen sensitization in different environmental settings.

ACKNOWLEDGMENTS

The authors acknowledge the help of Peter Burney, Professor, Imperial College, London, U.K., for his critical comments and suggestions on the article.

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