Prevalence and risk factors for wheezing in children from rural areas of north India

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ABSTRACT

Phase I of the International Study of Asthma and Allergies in Childhood (ISAAC) showed marked variability in the global pattern of allergic disorders. Risk factors for asthma in children from rural areas of developing countries have not been studied. The purpose of this study was to document the prevalence of asthma-associated symptoms in children residing in rural areas and to determine risk factors for its development. We studied 8470 school children, aged 6–7 years and 13–14 years, from 10 villages on the outskirts of Delhi, India, over a 6-month period. The study was performed using the Hindi translated version of Phase III of the ISAAC questionnaires. All of the questionnaires were self-reported by children and/or parents. Frequent passage of trucks through the street near home (odds ratio [OR]: 95% CI, 1.7 [1.2–2.4]), maternal smoking (OR: 95% CI, 1.5, [1.1–2.1]), paternal smoking (OR: 95% CI, 1.3 [1.0–1.8]), total number of cigarettes smoked by both parents of more than seven per day (OR: 95% CI, 1.9 [1.3–2.7]), paracetamol intake of more than once a month (OR: 95% CI, 1.9 [1.4–2.6]), and current exposure to cats (OR: 95% CI, 1.5 [1.1–1.9]) were independently associated with occurrence of recent wheezing (in the last 12 months), whereas fruit intake of more than twice a week had a protective effect (OR: 95% CI, 0.7 [0.5–0.9]). There is a significant burden of asthma-associated symptoms in children of rural areas of north India. Occurrence of wheezing among children from rural areas of Delhi is determined by a complex interplay of environmental agents that induce allergic sensitization and are proinflammatory and environmental agents that supplement the antioxidant stores.

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Key words: Air pollution, asthma, atopic disease, epidemiology, ISAAC, maternal smoking, paracetamol, passive smoking load, questionnaires, risk factors, survey

The Phase I of the International Study of Asthma and Allergies in Childhood (ISAAC), conducted in 155 centers located in 56 countries, has shown marked variability in the global pattern of various allergy-related symptoms.[1] A 20- to 60-fold difference in the prevalence of these symptoms was found between various centers involved in this study. This variation is difficult to explain solely based on the existing hypothesis for development of various allergic disorders. Marked variability in the prevalence of allergic disorders in a population with similar ethnicity or genetic makeup undermines the importance of genetic factors. Likewise, certain environmental factors believed to be important risk factors for the development of allergic disorders such as house-dust mites[2] also do not explain the markedly variable international patterns. Nonetheless, consensus appears to be emerging on the importance of the significance of environmental factors in the development of allergic disorders at a community level.[3]

These findings have prompted a search for novel risk factors associated with the development of allergic disorders. Studies from across the globe have reported variable risk factors for the development of allergic disorders.[4–7] Most studies have evaluated patients from the urban or suburban regions of developed nations. There are few studies describing risk factors for development of asthma in rural populations from developing countries. These populations are difficult to sample because of factors including lack of proper infrastructure for travel to geographically remote areas. In addition, people residing in these regions are usually illiterate and lack the motivation to participate in these studies. Elucidation of the risk factors for development of asthma from these regions can form the basis of unique public health measures, which may promote prevention of exposure to these environmental factors. Such measures may eventually help to re-

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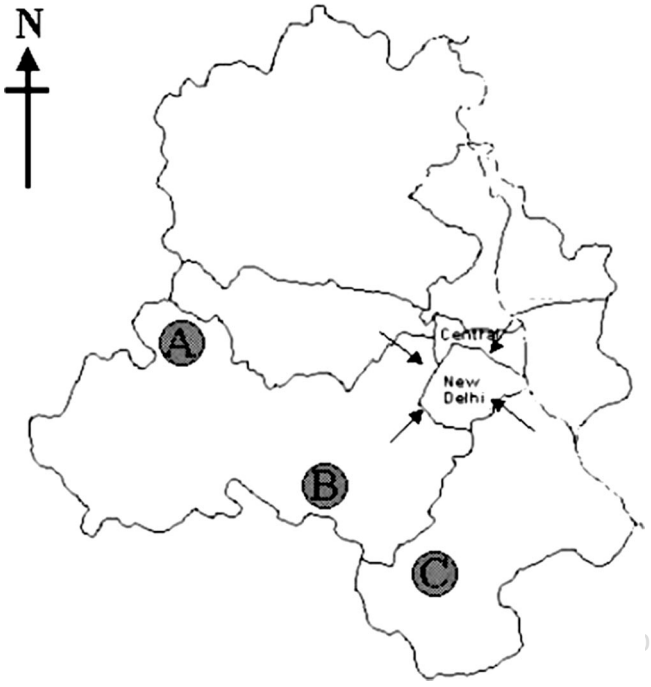

Figure 1. Map of Delhi, India, showing the geographical area surveyed. Urban areas including the New Delhi city are present in the central area of the state (shown by arrows). The three rural areas on the outskirts of state of Delhi are shown by gray circles, (A) Najafgarh, (B) Mehrauli, and (C) Tuglakabad.

duce the incidence of these diseases in the future. This study was conducted to determine the prevalence of asthma-associated symptoms in children residing in rural areas and to determine risk factors for its development.

SUBJECTS AND METHODS

The institutional Ethics Committee approved the study protocol. The study was conducted as a part of the multicentric ISAAC Phase III. The All India Institute of Medical Sciences hospital, New Delhi, a tertiary health care institute in north India, was one of the centers for ISAAC Phase III study for which schools were included from various urban regions.[8] Permission was procured from the ISAAC Steering Committee and the ISAAC Phase III study group (ISAAC International Data Center, Auckland, New Zealand) to extend the survey from urban to rural areas.

This study was performed from September 2004 to February 2005. The sampling frame was determined mainly by the geographical areas. Broadly, three regions were identified on the outskirts of the state of Delhi, India (Fig. 1). All of these regions are known to have a predominantly rural background. A total of 10 villages were identified from these three regions. Subsequently, a random sample of schools from these areas was selected.

Permission to conduct the study was obtained from the Director of Education of the state of Delhi. A letter of intent, detailing purpose and methodology of the study, was written and sent to 34 schools in these three regions. Twenty-nine schools expressed desire to participate in the study. A survey team consisting of trained physicians and technical staff visited each of these schools. The survey team members remained the same throughout the period of study.

This study used a simple, standard, noninvasive tool for collection of data to ensure a high response rate. The study was performed using the standard questionnaires used for Phase III of the ISAAC. All questionnaires were initially translated into local language (Hindi). Separate questionnaires were used for children of the 6- to 7-year and 13- to 14-year age groups. The details of the questionnaire have been elaborated elsewhere.[1]

Initially, questions were asked to ascertain the prevalence of symptoms associated with asthma along with those to assess its severity (number of episodes of wheezing and awakening at night per week because of wheezing). This was followed by an "environmental questionnaire" section that was comprised of questions regarding education, diet, breastfeeding, drug intake, exercise, pets and contact with other animals, fuel used in the house, air pollution, and passive smoking to determine the prevalence of possible risk factors. The video questionnaire was not used for this study because most of the schools that were included did not have a provision of electricity.

Class teachers were initially sensitized to the protocol and their help was sought to assist in distribution of the questionnaires. Children of the 13- to 14-year age group were questioned directly; parents completed the questionnaires distributed among the children of 6- to 7-year age group. Throughout the survey process, it was ensured that all children attending the school were residing in the local villages and not traveling to or from any other area that could have been urban.

Questionnaires received from children were initially screened for completeness and consistency. Wherever applicable, dubious responses were corrected by a discussion with the child or parent. Incomplete questionnaires were excluded from the analysis (n = 430, 4.8%). Finally, questionnaires from 8470 (male/female ratio, 3717:4753) children were analyzed. Response rates were different for the two age groups. In the 13- to 14-year age group 98.3% of children returned completed questionnaires; the response rate was lower (73.9%) in children of the 6- to 7-year age group.

Table 1 **Prevalence of asthma-associated symptoms in the study population**

Symptom	Overall	6–7 yr	13–14 yr	OR (95% CI)
Total no. of children	8470	4128 (48.7%)	4342 (51.3%)	—
Sex (male/female ratio)	3717:4753	2116:2012	1601:2741	—
Height (cm)#	131.4 ± 25.8	107.8 ± 12.6	153.8 ± 10.7	—
Weight (kg)#	30.6 ± 12.9	19.1 ± 3.8	41.6 ± 8.2	—
BMI (kg/m^2)#	17.2 ± 3.6	16.9 ± 4.2	17.5 ± 2.8	—
No. of children with history of wheezing ever	437 (5.16%)	232 (5.6%)	205 (4.7%)	1.2 (0.9–1.4)
No. of children with history of wheezing in last 12 mon	300 (3.5%)	181 (4.4%)	119 (2.7%)	1.6 (1.3–2.0)***
No. of children with more than three episodes of wheezing per week in last 12 mon	92 (1.1%)	66 (1.6%)	26 (0.6%)	2.7 (1.7–4.2)***
No. of children with awakening due to wheezing one or more nights per week	67 (0.8%)	46 (1.1%)	21 (0.5%)	2.3 (1.4–3.8)**
No. of children diagnosed with asthma	259 (3.0%)	150 (3.6%)	109 (2.5%)	1.4 (1.1–1.8)**
No. of children with wheezing during exercise	310 (3.6%)	181 (4.2%)	129 (3.1%)	1.3 (1.1–1.7)*

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.
#Data are presented as mean and SD.
BMI = body mass index.

Statistical Analysis

Data were entered into a computer on a Microsoft Excel spreadsheet (Microsoft Corp., Redmond, WA). Data were double entered to minimize error. The ISAAC Steering Committee and the ISAAC Phase III study group, Auckland, New Zealand, supervised data collection and data entry for the urban schools. The same guidelines were followed for rural areas. Inconsistencies in data were checked by running Epi Info 6.01 (Division of Public Health Surveillance and Informatics, Center for Disease Control, Atlanta, GA) and verification was done by three persons independently. Analysis was done using the statistical software SPSS version 10.0 (SPSS, Inc., Chicago, IL). Prevalence of symptoms associated with asthma was described separately for the two age groups. The differences in the prevalence between the two age groups were compared by applying Fisher's exact test and odds ratio (OR) was determined (Table 1). We then sought to determine the environmental factors associated with the occurrence of wheezing. Wheezing in the last 12 months (referred to as recent wheezing) was taken as the dependent variable. Continuous variables and categorical variables were analyzed using Student's *t*-test and Fisher's exact test, respectively. In addition to age, sex, and body mass index, variables that were statistically significant on univariate analysis at $p < 0.1$ were selected as covariates. Multivariate logistic regression analysis (backward stepwise) was applied to define independent risk factors for recent wheezing. Statistical significance was considered at $p < 0.05$.

RESULTS

The study group consisted of an equal proportion of children from the two age groups. Gender difference was minimal for the 6- to 7-year age group but in the 13- to 14-year age group a higher number of female children were included. Prevalence of asthma-associated symptoms has been elaborated in Table 1. All of the symptoms were either more prevalent in the 6- to 7-year age group or similar in the two age groups. The prevalence of severe asthma as estimated by more than three episodes of wheezing per week and one or more awakening at night per week due to wheezing also was higher in 6- to 7-year age

Table 2 **Determinants of recent wheezing (last 12 mon) on bivariate analysis**

Variable	Wheezing (last 12 mon; $n = 300$)	No Wheezing ($n = 8170$)	Unadjusted OR (95% CI)
Age group (6 yr/13 yr)	181:119	3947:4223	0.6 (0.5–0.8)***
Sex (male/female)	154:146	3563:4607	1.4 (1.1–1.7)**
Fruit intake more than twice per week	67.8%	73.6%	0.7 (0.6–1.0)*
Cereal intake	62.6%	69.0%	0.7 (0.6–1.0)*
Milk intake	61.1%	67.7%	0.7 (0.6–1.0)*
Current paracetamol use more than once a month	78.5%	64.6%	2.0 (1.5–2.7)***
Antibiotic intake during infancy	48.9%	38.1%	1.6 (1.1–2.1)**
Passage of trucks through the street	86.3%	78.8%	1.7 (1.2–2.4)**
Exposure to cats during infancy	32.3%	22.5%	1.6 (1.2–2.2)**
Current exposure to cats	30.4%	21.4%	1.6 (1.2–2.1)***
Exposure to dog during infancy	25.8%	16.4%	1.8 (1.3–2.5)**
Current exposure to dogs	27.4%	21.6%	1.4 (1.1–1.8)*
Regular contact with farm animals during infancy	35.3%	22.6%	1.9 (1.4–2.6)***
Regular contact of mother during pregnancy with farm animals	33.9%	24.6%	1.6 (1.1–2.1)**
History of maternal smoking	18.0%	10.3%	1.9 (1.4–2.6)***
History of paternal smoking	59.3%	45.5%	1.7 (1.4–2.2)***
History of maternal smoking during infancy	7.4%	3.9%	2.0 (1.1–3.5)*
Total number cigarettes smoked by both parent of more than seven per day#	17%	8.0%	2.4 (1.7–3.2)***

Current indicated use during the last 12 mon.
**p < 0.05; **p < 0.01; ***p < 0.001.*
#Choice of cutoff of seven cigarettes per day for the cumulative number of cigarettes smoked by either parent was arbitrary.

group ($p < 0.001$). Prevalence of diagnosed asthma also was higher in the 6- to 7-year age group ($p = 0.003$).

Variables associated with recent wheezing on bivariate analysis have been enumerated in Table 2. The list also includes a variable derived from the usual parameters included in the questionnaire, *i.e.*, the "total number of cigarettes smoked by both parents of more than seven per day."

As a part of the original questionnaire, number of cigarettes smoked by either parent had been recorded separately. Smoking by either parent, total number of cigarettes smoked by both parents of more than seven per day, frequent passage of trucks through the street near home, current paracetamol intake (last 12 months) more than once every month, and current exposure to cats at home (last 12 months) were found to have an independent association with the occurrence of wheezing, whereas fruit intake of more than twice a week had an independent protective effect (Table 3).

DISCUSSION

A majority of the Indian population still lives in rural areas and data on the burden of allergic diseases in these areas are scarce. This study used a well-standardized instrument to provide useful insights into the prevalence of asthma-associated symptoms in these areas. Both age groups (6–7 years/13–14 years, 4128:4342) were equally represented in the study sample although the number of girls was higher (male/female, 3717:4753). The major share of this uneven representation came from the 13- to 14-year age group (male/female, 1601:2741). In India, most of the secondary schools in rural areas do not have a coeducation structure and separate shifts are run for boys and girls with shifts for girls in the first half. Because the survey team visited mostly in the morning or early afternoon, girls were encountered more frequently. On the other hand, children of the 6- to 7-year age group were recruited from the primary schools, which usually have a coeducation structure. Higher prevalence of asthma in the younger age group is consistent with the widely believed concept of "children growing out of allergic diseases."[9]

Among the independent risk factors, frequent passage of trucks through the street near the residence was a strong risk factor for recent wheezing. Earlier studies[10–13] also have found that vehicular pollution plays an important role in allergic sensitization

Table 3 **Independent determinants of recent wheezing (last 12 mon)**

Variable	Adjusted OR (95% CI)	*p*-Value
History of maternal smoking	1.5 (1.1–2.1)	0.008
History of paternal smoking	1.3 (1.0–1.8)	0.031
Total number cigarettes smoked by both parent of more than seven per day	1.9 (1.3–2.7)	<0.001
Current exposure to cats	1.5 (1.1–1.9)	0.004
History of passage of trucks through the street	1.7 (1.2–2.4)	0.005
Current paracetamol use of more than once a month	1.9 (1.4–2.6)	<0.001
Fruit intake of more than twice per week	0.7 (0.5–0.9)	0.044

Current indicated use during the last 12 mon.

and/or persistence of asthma in children. Among the various types of vehicular pollutants, diesel exhaust has been strongly implicated in allergic sensitization.[14–17]

Parental smoking also is known to be associated with childhood asthma.[18–20] In addition, it also has been found that, although household smoking appears to increase the incidence of wheezing, it mostly leads to nonallergic "wheezy bronchitis"[21] rather than classic atopic asthma. Moreover, maternal smoking, in comparison with paternal smoking, is a stronger risk factor for asthma.[22] In this study, a novel parameter, *i.e.*, total number of cigarettes smoked by both parents of more than seven per day, was entered as a covariate in the multivariate equation. The prevalence of smoking (10.6% versus 45.5%) as well as the mean number of cigarettes smoked per day was markedly lower in mothers when compared with fathers. We hypothesized that the total number of cigarettes smoked by both parents, in other words the "passive smoking load," also could have a bearing on the development of wheezing. To test this, we combined the number of cigarettes smoked by the two parents and derived this parameter. Interestingly, the association of this parameter with wheezing, as judged by the adjusted OR, was the strongest among the smoking exposure–related questions. Therefore, it is pertinent to emphasize the importance of parental smoking in quantitative terms as well.

The subject of furred pets leading to allergic sensitization and a consequent development of asthma has been debated for long time and variable results have been reported.[6,23–32] Among these studies, Melen *et al.*,[23] in a systematically conducted 2-year study, confirmed the importance of early cat exposure in causing allergic sensitization and development of asthma. Our data also support the view that exposure to cats is associated with development of asthma in children.

A strong association between current paracetamol intake (more than once a month) and recent wheezing appears surprising. It is possible that such findings may be caused by reverse causation because patients with asthma or other allergic disorders may be taking paracetamol more frequently when compared with nonsteroidal anti-inflammatory drugs. Moreover, children with allergic disorders may have more frequent headaches and/or fever and take paracetamol for the same. Nonetheless, a graded association between paracetamol use and occurrence of asthma has been established in adults.[33] The possible mechanism of this association is largely speculative. Because paracetamol is an over-the-counter drug, it is almost ubiquitously used and the presence of such an association could have widespread ramifications. The evidence linking paracetamol use with asthma in children is minimal and further epidemiological and clinical studies should be planned in the future to evaluate this association.

A protective effect of moderate fruit intake probably is related to its antioxidant effects. It has been shown that children who consume fresh fruits more than once a day had better lung functions compared with children who never consume fresh fruits.[34] This effect may be related partly to vitamin C content of fruits,[35] which has significant antioxidant properties.

Because this is an epidemiological study, the results of the present analysis should, at best, be considered preliminary and the associations can not be presumed as causal. Such analyses can be confounded by many factors including unmeasured variables and recall bias. In addition, because of the nature of the study, only limited information regarding the associations between various independent risk factors and recent wheezing was collected.

Information on family history, an important aspect of asthma and related disorders, was not available for analysis because the same was not part of the

ISAAC questionnaire. Future studies would be required to evaluate these associations further. Nonetheless, the possibility of a causal association should be considered, because all of the environmental factors having an independent association with recent wheezing seemed scientifically valid.

It is concluded that there is a significant burden of asthma-associated symptoms in children of rural areas of north India and the prevalence is higher in younger children. It appears that development of wheezing among children from rural areas of Delhi, India, is determined by a complex interplay of environmental agents that induce allergic sensitization and are proinflammatory, on one hand, and agents that supplement the antioxidant stores, on the other hand. Findings of the present study need to be confirmed and further evaluated in future studies.

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