# Prevalence of asthmatic phenotypes and bronchial hyperresponsiveness in Turkish schoolchildren: an International Study of Asthma and Allergies in Childhood (ISAAC) phase 2 study

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**Background:** Numerous epidemiologic studies have revealed that bronchial asthma affects populations without regard to frontiers. However, standardized methodological approaches are necessary to compare these populations.

**Objective:** To investigate objective markers of childhood asthma on an epidemiologic basis and to include Turkish children in international comparisons.

**Methods:** Parental questionnaires were collected and skin prick tests performed on fourth grade primary schoolchildren, aged 8 to 11 years, residing in Ankara, Turkey. Pulmonary function tests and bronchial challenge with hypertonic saline (HS) were conducted in children selected from this cohort with a stratified random sampling according to the presence of current wheezing.

**Results:** A total of 3,041 questionnaires were included in the evaluation. Skin prick tests were performed on 2,774 children (97.1%). A total of 347 children from this cohort underwent pulmonary function and bronchial challenge tests. In 18 (5.1%) of the 347 children, bronchial challenge tests could not be successfully completed. The prevalence values were 11.5% for current wheezing, 6.9% for physician-diagnosed asthma, and 7.7% for physician-diagnosed recurrent bronchitis. Population-based weighted prevalence of bronchial hyperresponsiveness (BHR) was 21.8%. Frequency of responses to HS was 38.6% among physician-diagnosed asthma cases and 30.5% among patients with current wheezing. Skin test positivity was present in 38.7% of the children with a diagnosis of asthma or asthmatic bronchitis, 35.0% of current asthmatic patients, and 19.2% of patients with current wheezing.

**Conclusions:** Objective markers, in addition to the questionnaire-based prevalence figures, need to be used in epidemiologic surveys for asthma, especially in countries with inadequate health care facilities or problems with interpretation of the wheeze concept.

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## INTRODUCTION

The striking increase in the prevalence rates of asthma in the last 2 decades has led researchers to investigate the possible causes of this trend. Although many in vivo and in vitro laboratory studies have been conducted to highlight the etiopathogenesis of asthma, the complex and multifactorial nature of the disease makes it obligatory to see what is occurring in real-life scenarios. In this respect, there is a need for a significant contribution of epidemiology to the study of chronic disorders.[1]

During the past decade, numerous epidemiologic studies have revealed that bronchial asthma is a disease that affects populations without regard to frontiers. However, standardized methodological approaches are necessary to compare populations and highlight the similarities and dissimilarities between them. The International Study of Asthma and Allergies in Childhood (ISAAC) is a global epidemiologic project aimed at gaining new insights into the epidemiology of asthma and allergic diseases through standardized comparisons of different childhood populations worldwide.[2] Phase 1 of this study, which was conducted in 155 centers around the world, revealed differences of more than 20-fold in asthma prevalence figures from different countries.[3] The ISAAC phase 2 study was planned to evaluate the prevalence of

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objective markers of asthma and atopic diseases and to evaluate the role of possible risk factors in representative childhood populations.[4] The first cross-sectional study using the ISAAC phase 2 protocol was performed in East and West Germany in 1995 and 1996.[5] Recently, the ISAAC phase 2 study has been completed in more than 30 centers in different parts of the world. The present study was conducted according to the ISAAC phase 2 protocol as a collaborating center and, to our knowledge, is the only study in Turkey that investigates the objective markers of childhood asthma on an epidemiologic basis.

## MATERIALS AND METHODS

### *Study Area and Population*

The study was conducted in Ankara, the capital city of Turkey, between October 1999 and April 2000. Ankara is located in central Anatolia and is the second most crowded city in Turkey, with slightly more than 4,000,000 inhabitants according to the 2000 national census. There are many neighborhoods within the central urban districts that harbor thousands of people of low socioeconomic class. The climate is dry, with hot summers and snowy winters. In the last few years, air pollution has substantially increased, especially in some underprivileged districts of the city, owing to the use of poor-quality charcoal for indoor heating. Additionally, heavy car traffic with motor vehicle exhaust emission, still including much from leaded gasoline, contributes greatly to the air pollution during the entire year. According to official data provided by the Refik Saydam Hygiene Center in Ankara, the mean annual (1999) concentrations of sulfur dioxide ($SO_2$) and particulate matter were 57.8 and 76.4 $\mu$g/mL, respectively, for Ankara as a whole, with those annual figures reaching 77.7 and 98.7 $\mu$g/mL, respectively, in some heavily polluted districts of the city.

The sampling method for this study was 2-stepped, in accordance with option B of the ISAAC phase 2 protocol.[4] As a first step, all schoolchildren attending the fourth grade in 22 schools were selected, primary schools being the sampling unit. To be representative, the 8 administrative districts of Ankara were accepted as the strata, and a weighted number of schools were selected in a stratified random manner from a complete list of primary schools in Ankara. A self-administered parental questionnaire and skin prick tests were obtained in this population. In the second step, the children were stratified according to the presence or absence of wheezing in the last 12 months, based on questionnaire responses. Children from the current wheezers and current nonwheezers stratums were randomly selected by the block randomization method. These children were recruited for spirometric measurements and bronchial challenge tests using hypertonic saline (HS).

### *Questionnaires and Definitions*

The ISAAC phase 2 questionnaire modules, including questions about demographic characteristics and respiratory disorders, were used.[4] The questionnaires were translated into Turkish by a translator familiar with asthma and allergy terms and then translated back into English by another translator. To find the most appropriate translation for the word *wheeze*, which does not have an equivalent in Turkish, an earlier Turkish translation of the ISAAC phase 1 questionnaires was used. In that study, the most appropriate word for wheeze had been found through interviews with families of children with known asthma and validated in a large group of children.[6]

Since it is common practice among Turkish physicians to label asthma as allergic bronchitis or asthmatic bronchitis, the prevalence of the diseases was sought with the following question: "Has a doctor ever diagnosed one of the following diseases in your child, and if yes, how many times? (a) asthma, (b) asthmatic bronchitis, (c) allergic bronchitis, (d) bronchitis." Children whose parents reported at least one diagnosis of asthma, asthmatic bronchitis, or allergic bronchitis were classified as having physician-diagnosed asthma. These children were further categorized as having current asthma if wheezing in the last 12 months was also reported. Physician-diagnosed asthma or asthmatic bronchitis cases were analyzed separately to evaluate the effects of labeling. Children were classified as having bronchitis if they had been diagnosed as having bronchitis more than once and the definition criteria for asthma were not met. These children were further categorized as having current bronchitis if wheezing had also occurred in the last 12 months. Current wheeze was defined as a positive response to "Has your child had wheezing or whistling in the chest during the past 12 months?" and former wheeze as a positive response to "Has your child ever had wheezing or whistling in the chest at any time in the past?" but a negative response to "Has your child had wheezing or whistling in the chest during the past 12 months?" Chronic cough with phlegm was defined as a positive response to "Does your child seem congested in the chest or cough up phlegm on most days (4 or more days a week) for as many as 3 months of the year?" Children without any diagnostic label of asthma, asthmatic bronchitis, allergic bronchitis, bronchitis, or hay fever and without a history of wheezing, dyspnea, or chest tightness were classified as asymptomatic.

### *Skin Prick Tests*

Skin prick tests were performed with 6 core allergen extracts recommended in the ISAAC phase 2 module[4]: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, *Alternaria alternata*, cat epithelium, mixed grasses (*Phleum pratense*, *Poa pratensis*, *Dactylis glomerata*, *Lolium perenne*, *Festuca pratensis*, *Avena eliator)*, and mixed trees (*Betula verrucosa*, *Alnus glutinosa*, *Coryllus avellena*). Seven additional allergens of local relevance were added to those 6: *Parieteria officinalis*, *Cladosporium herbarum*, *Olea europea*, mixed feathers, mixed weeds (*Artemisia vulgaris*, *Chenopodium*, *Plantago*, *Salsola kali)*, mixed local trees (*Quercus alba*, *Ulmus americana*, *Platanus*, *Salix*, *Populus)*, and *Blatella germanica* (as cockroach). Histamine, 10 mg/mL, and diluent were used as positive and negative controls, respectively. The

standardized core allergen extracts and controls were provided by ALK-Abello (Horsholm, Denmark), and standardized local allergens were provided by ALK-Abello, Allergopharma (Reinbek, Germany), and Center Laboratories (Port Washington, NY).

Skin prick tests were performed in a manner similar to that recommended in the ISAAC phase 2 module.[4] All antihistaminic drugs were withheld 10 days before skin testing. One drop of each skin prick testing solution was placed on the volar surfaces of the right and left forearms and penetrated with separate ALK lancets. Reactions to skin test solutions were measured after 15 minutes. The contours of each wheal were outlined with a fine filter tip pen and then transferred to the record sheet by means of translucent tape. The size of each wheal was documented as the mean of the longest diameter and the diameter perpendicular to it. A positive skin reaction was defined as a wheal size of 3 mm or more after subtraction of the negative control. Cases were considered atopic if they had at least one positive skin reaction to common allergens.

*Spirometry and Bronchial Challenge Test With HS*

Spirometry and bronchial challenge test with HS were performed according to the standardized protocols[4] of ISAAC phase 2. The following drugs were withheld before the test by telephone calls to the parents: antihistamines, 48 hours; cromoglycate, nedocromil sodium, and short-acting $\beta$-agonists, 8 hours; theophyllines, 12 hours; and long-acting $\beta$-agonists and leukotriene antagonists, 24 hours. Before testing, the children were examined for signs of respiratory infections, and these data were recorded along with the time and the names of recently used medications. Lung function was measured by a portable spirometer (Masterscope Version 4.1; Jaeger-Toennis, Hoehberg, Germany). Baseline and postchallenge forced expiratory volume in 1 second ($FEV_1$) measurements were made until 2 successive readings did not differ by more than 5%, and the highest $FEV_1$ value was recorded as the baseline. Patients were excluded from the bronchial challenge test if the baseline $FEV_1$ value was less than 75% of the predicted value or in the case of noncompliance. Predicted values of The European Community for Coal and Steel were used for spirometric measurements.

The HS challenge test was performed with 4.5% saline delivered via an ultrasonic nebulizer (De Vilbiss, Langen, Germany). During the challenge, the nebulizer output was kept constant at 1.2 mL/min, and the dose of the saline was increased by repeated doublings of the inhalation time (0.5, 1, 2, 4, and 8 minutes). The challenge was stopped after the $FEV_1$ had decreased by at least 15% or when a total inhalation period of 15.5 minutes had been completed. The contents of the nebulizer canister plus tubing were measured before and after the final step of the challenge to determine the total amount of saline nebulized and nebulizer output. A decrease of 15% or more in $FEV_1$ from the baseline was defined as a positive response to the HS challenge. The amount of saline (in milliliters) delivered to the patient causing a decrease in $FEV_1$ of 15% ($PD_{15}$ $FEV_1$) was calculated from dose-response curves with the percent change in $FEV_1$ on a linear scale and the cumulative dose of saline delivered on a logarithmic scale. The severity of bronchial hyperresponsiveness (BHR) was classified according to the $PD_{15}$ $FEV_1$ value: mild BHR ($PD_{15}$, $>6.0$ mL), moderate BHR ($PD_{15}$, 2.01–6.0 mL), and severe BHR ($PD_{15}$, $<2.0$ mL).

*Field Work and Quality Control*

The parental questionnaires were distributed throughout the schools. During the 6-month study period, all the tests were conducted in the schools by 3 teams of field workers. All the field workers were trained by one of the principal investigators (S.K.) and also supervised by the same investigator throughout the field work. Reproducibility of skin prick tests was monitored by the coefficient of variation of histamine reaction sizes, which was expected to be less than 20% for each field worker. Reproducibility of spirometric measurements was considered to be achieved with a variation in $FEV_1$ of less than 5% for children of the same height and weight.

*Statistical Analysis*

All study methods were approved by the Ethics Committee of the Turkish Ministry of Health and the Ethics Committee of Hacettepe University Faculty of Medicine. Informed written consent was obtained from the parents on a single occasion for all tests. Data entry and analyses were made using SPSS 10.0 statistical software (SPSS Inc, Chicago, IL). The $\chi^2$ tests were performed to compare prevalence values. *t* tests were used for the comparison of continuous variables. Cases recruited for spirometric measurements and bronchoprovocation tests were not a randomized sample of the 8- to 11-year-old population. They were selected in equal numbers from current wheezer and nonwheezer subpopulations. Hence, weighted values were calculated to correct for the stratified sampling method and to find the prevalence value for the population. However, other figures for BHR were frequency values in a limited population of patients. Sensitivity and specificity of the HS challenge used to identify different definitions of asthma were calculated from cross tables.

## RESULTS

The questionnaire was distributed to 3,426 children. Parents of 3,056 children (89.2%) returned the completed questionnaire. Of those returned, 3,041 questionnaires (88.7%) were included in the evaluation. Written consent for the tests was obtained for 2,858 children (92.5%). Of the eligible children, skin prick tests were performed on 2,774 (97.1%). From these 2,774 children, 350 were stratified according to the presence or absence of wheezing in the last 12 months (175 in each group). Lung function tests were performed on 347 (99.1%) of the 350 children selected. In 18 (5.1%) of the 347 participating children, bronchial challenge tests could not be successfully completed due to nausea or vomiting ($n = 6$), cough ($n = 1$), limited cooperation ($n = 5$), baseline $FEV_1$ less than 75% ($n = 3$), and technical problems ($n = 3$).

Table 1. Demographic Characteristics of the Study Population

| Characteristics | Study population, % (N = 3,041) |
|---|---|
| Age, y | |
| 8 | 5.6 |
| 9 | 76.4 |
| 10 | 16.8 |
| 11 | 1.2 |
| Mean ± SD | 9.14 ± 0.5 |
| Sex, M/F | 50.5/49.5 |
| Maternal education | |
| Primary school | 51.9 |
| University | 12.8 |
| Paternal education | |
| Primary school | 30.7 |
| University | 22.0 |
| Monthly family income, $ | |
| <350 | 83.0 |
| ≥350 | 14.2 |

Demographic characteristics of the study population (n = 3,041) are shown in Table 1. Most (94.4%) of the study population were aged 9 to 11 years, and the remaining (5.6%) were 8 years old.

Table 2. Prevalences of Respiratory Symptoms and Diagnoses

| Symptom or diagnosis | Boys, % (n = 1,535) | Girls, % (n = 1,506) | Total, % (n = 3,041) |
|---|---|---|---|
| Cumulative ("ever") symptoms | | | |
| Wheeze | 23.7* | 20.6 | 22.2 |
| Chest tightness | 5.7 | 6.4 | 6.1 |
| Breathlessness | 8.9 | 8.1 | 8.5 |
| Chronic cough with phlegm | 6.5 | 8.2 | 7.4 |
| Current (last 12 months) symptoms | | | |
| Wheeze | 12.2 | 10.8 | 11.5 |
| ≥4 attacks of wheezing | 2.0 | 2.1 | 2.0 |
| Exercise-induced wheezing | 4.0 | 4.0 | 4.0 |
| Wheezing with pollen, fur, or dust | 4.7 | 5.1 | 4.9 |
| Nocturnal cough | 25.7 | 26.5 | 26.1 |
| Cough with phlegm | 12.0 | 14.2 | 13.1 |
| Physician diagnosis | | | |
| Asthma† | 7.2 | 6.6 | 6.9 |
| Bronchitis‡ | 7.8 | 7.5 | 7.7 |
| Current asthma§ | 3.1 | 2.6 | 2.9 |

* Significantly different from girls, $P < .05$.

† Children who had been diagnosed as having asthma, asthmatic bronchitis, or allergic bronchitis by a physician at least once.

‡ Children who had been diagnosed as having bronchitis by a physician more than once but the definition criteria for asthma were not met.

§ Wheezing in the last 12 months was reported in addition to physician-diagnosed asthma.

Prevalences of the respiratory symptoms and diagnoses are presented in Table 2. The prevalence of ever wheezed was significantly higher in boys than in girls ($P = .04$). However, there was no difference between the sexes for current wheezing. Chronic cough with phlegm was slightly higher in girls than boys, although the difference did not reach statistical significance ($P = .07$).

Weighted mean basal $FEV_1$ and forced vital capacity (FVC) values in boys were significantly higher than in girls. However, the girls' mean $FEV_1$/FVC and maximal expiratory flow at 25% of the thoracic vital capacity values were significantly higher than the boys'. The calculated weighted prevalence of BHR to HS was 21.8% for the whole population. No significant difference was found between the weighted prevalences of BHR for boys and girls (Table 3).

The frequency of BHR in respiratory disorders according to atopic status is presented in Table 4. The highest rate of BHR was found in the physician-diagnosed asthma group. Of those with a previous diagnosis of asthma or asthmatic bronchitis, 50.0% showed a positive BHR result. Among atopic patients, BHR was significantly higher in physician-diagnosed asthmatic patients ($P = .007$), current asthmatic patients ($P = .03$), and those with nocturnal cough ($P = .04$) and chronic cough with phlegm ($P = .04$) when compared with nonatopic patients, whereas ever and current wheezing, physician-diagnosed bronchitis, and current bronchitis did not show a significant relation with atopic status ($P = .05$). BHR was present in 17.6% of atopic asymptomatic children and 23.3% of nonatopic asymptomatic children. The difference was insignificant ($P = .47$).

The sensitivity of the HS challenge was 38.6% in physician-diagnosed asthmatic patients and 30.5% in those with current wheezing. The specificity of HS for these patients was 77.4% and 79.5%, respectively. When asthma cases were confined to those who had received a diagnosis of asthma and/or asthmatic bronchitis, excluding the allergic bronchitis cases, the sensitivity of HS was 50.0% and the specificity 77.0%.

Table 5 shows the distribution of the level of BHR within symptom and diagnosis groups and asymptomatic children. Physician-diagnosed asthmatic patients and current asthmatic patients showed higher rates of moderate degree BHR ($PD_{15}$, 2.01–6.0 mL) than patients with current and former wheezing and bronchitis. When asthma cases were confined to those who had been diagnosed as having asthma and/or asthmatic bronchitis, excluding the allergic bronchitis cases, 35.8% showed a moderate-to-severe degree ($PD_{15}$, ≤2.0 mL) of BHR. In other groups, mild-degree ($PD_{15}$, > 6 mL) BHR was predominant. Of the children without a respiratory disorder (asymptomatic), 19.4% showed BHR, 76.4% of them to a mild degree.

Atopy prevalence was 20.6% for the study population as a whole. The prevalences of skin test reactivity to at least one allergen ($P < .001$), pollen ($P < .001$), cat epithelium ($P = .004$), cockroach ($P = .02$), and *D farinae* ($P = .03$) were significantly higher in boys than in girls. Skin test positivity was present in 38.7% of the children with a diagnosis of

Table 3. Lung Function Measurements and Prevalence of BHR to Hypertonic Saline in an 8- to 11-Year-Old Student Population*

| | Boys (n = 182) | | Girls (n = 165) | | *P* value |
|---|---|---|---|---|---|
| | Mean | Percent predicted | Mean | Percent predicted | |
| Spirometry | | | | | |
| FVC, L | 2.37 | 111.4 | 2.14 | 107.3 | < .001 |
| $FEV_1$, L | 1.99 | 111.8 | 1.86 | 108.5 | < .001 |
| $FEV_1$/FVC, % | 84.6 | | 87.5 | | < .001 |
| PEFR, L/s | 4.17 | 101.7 | 4.04 | 97.7 | > .05 |
| $MEF_{75}$, L/s | 3.76 | 101.6 | 3.74 | 100.4 | > .05 |
| $MEF_{50}$, L/s | 2.45 | 93.6 | 2.50 | 94.9 | > .05 |
| $MEF_{25}$, L/s | 0.95 | 70.8 | 1.10 | 82.2 | < .01 |
| MMEF, L/s | 1.98 | 87.2 | 2.10 | 92.2 | > .05 |
| BHR to hypertonic saline | | | | | > .05 |
| Hyperresponsiveness, % | 22.0 | | 21.3 | | |

Abbreviations: BHR, bronchial hyperresponsiveness; $FEV_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; $MEF_{75}$, maximal expiratory flow at 75% of the thoracic vital capacity; $MEF_{50}$, MEF at 50%; $MEF_{25}$, MEF at 25%; MMEF, maximal midexpiratory flow; PEFR, peak expiratory flow rate.

* Data are weighted mean and prevalence values to correct for the stratified sampling method.

Table 4. Distribution of Bronchial Hyperresponsiveness in Respiratory Disorders According to Atopic Status

| Symptom or diagnosis* | Bronchial hyperresponsiveness, % (n = 329) | |
|---|---|---|
| | Atopic† | Nonatopic |
| Cumulative wheezing | 41.9 | 26.7 |
| Current wheezing | 46.2 | 27.6 |
| Physician-diagnosed asthma | 63.6‡ | 30.3 |
| Diagnosed asthma or asthmatic bronchitis | 66.6‡ | 37.5 |
| Current asthma | 62.5‡ | 25.0 |
| Physician-diagnosed bronchitis | 37.5 | 24.3 |
| Current bronchitis | 42.9 | 26.7 |
| Nocturnal cough | 42.9‡ | 23.8 |
| Chronic cough with phlegm | 45.4‡ | 12.7 |
| Asymptomatic§ | 17.6 | 23.3 |

* For definitions of diagnoses, see Table 2.

† Atopy was defined as a positive response to 1 or more of the 13 allergens tested. A reaction was considered positive if a wheal reaction of 3 mm or greater was present, after subtraction of the reaction to negative control.

‡ $P < .05$ when compared with nonatopic children.

§ Children without wheezing, dyspnea, or physician's diagnosis of a respiratory disorder.

asthma or asthmatic bronchitis, 35.0% of current asthmatic patients, and 19.2% of current wheezers (Table 6). The prevalence of atopy was significantly higher in those with a physician's diagnosis of asthma or asthmatic bronchitis and in current asthmatic patients. Ever and current wheezing and bronchitis were not associated with atopy.

## DISCUSSION

Diagnosis of bronchial asthma depends mostly on clinical findings, and lack of a gold standard diagnostic method makes it difficult to evaluate the real prevalence of asthma in epidemiologic surveys.[7] The subjective features of questionnaires have led researchers to seek more objective epidemiologic markers of asthma, such as BHR.[4,8] In the present study, the prevalence values were 11.5% for current wheezing, 6.9% for physician-diagnosed asthma, and 21.8% for BHR in 8- to 11-year-old Turkish children. To our knowledge, this is the only epidemiologic study to date that investigates BHR prevalence in children living in Turkey. Hence, it is not possible to compare the BHR prevalence or to establish trends for these children. The only other data about BHR prevalence in Turkish children come from a German study conducted in 1990, in which prevalence of BHR to cold air hyperventilation challenge was found to be 3.9% in 9- to 11-year-old Turkish immigrant children living in Munich, which was almost half of the figure for their German counterparts.[9] However, this value cannot be compared with the present data because of different methods.

The first reported results of the ISAAC phase 2 study revealed a BHR prevalence to HS of 18.6% in German children living in Munich.[5] In that study, the ratio of the prevalence of BHR to current wheezing was fairly similar to the ratio of the prevalence of BHR to physician-diagnosed asthma. Another study, which also used HS bronchoprovocation testing, found that the prevalences of current wheezing, physician-diagnosed asthma, and BHR were nearly the same (approximately 20%–25%) in 12- to 15-year-old Australian children.[10] However, in the present Turkish study, the former ratio (BHR to current wheezing) was 1.5 times lower than the latter ratio (BHR to diagnosed asthma). This finding may have 3 explanations. First, the threshold for the use of asthma as a diagnosis is high among Turkish physicians (especially pediatricians) and parents. Instead, diagnoses such as allergic bronchitis, asthmatic bronchitis, or just bronchitis are in general use. In the present study, physician-diagnosed asthma was defined as a diagnosis of asthma, asthmatic

Table 5. Distribution of BHR and its Severity in Relation to Asthma Symptoms and Diagnosis*

| Symptom or diagnosis | None (n = 246) | BHR to hypertonic saline, % mild (n = 60)† | Saline, % moderate (n = 16)† | Severe (n = 7) |
|---|---|---|---|---|
| Former wheeze | 79.3 | 12.5 | 4.1 | 4.1 |
| Current wheeze | 69.5 | 21.5 | 8.4 | 0.6 |
| Frequent wheeze (≥4 attacks yearly) | 67.9 | 25.0 | 7.1 | 0 |
| Exercise-induced wheeze | 63.6 | 26.9 | 7.6 | 1.9 |
| Nocturnal cough | 72.5 | 18.4 | 7.0 | 2.1 |
| Physician-diagnosed asthma | 61.4 | 22.7 | 13.7 | 2.2 |
| Diagnosed asthma or asthmatic bronchitis | 50.0 | 14.2 | 28.6 | 7.2 |
| Current asthma | 66.8 | 19.4 | 13.8 | 0 |
| Physician-diagnosed bronchitis | 73.5 | 17.7 | 8.8 | 0 |
| Asymptomatic children | 80.6 | 14.9 | 1.1 | 3.4 |

Abbreviation: BHR, bronchial hyperresponsiveness.

* For definitions of diagnoses, see Table 2.

† Mild BHR was defined as a provocative dose of saline causing a 15% fall in forced expiratory volume in 1 second ($PD_{15}$ $FEV_1$) of greater than 6 mL; moderate BHR, $PD_{15}$ $FEV_1$ of 2.01 to 6.0 mL; and severe BHR, $PD_{15}$ $FEV_1$ of 2 mL or less.

Table 6. Prevalence of Atopy among Asthma-Related Symptoms and Diagnosis Groups*

| Symptom or diagnosis | Atopy positive (n = 563) | Atopy negative (n = 2160) | *P* value |
|---|---|---|---|
| Cumulative wheezing | 20.5 | 20.7 | .87 |
| Current wheezing | 19.2 | 21.0 | .56 |
| Physician-diagnosed asthma | 25.4 | 21.1 | .23 |
| Diagnosed asthma or asthmatic bronchitis | 38.7 | 21.0 | .02 |
| Current asthma | 35.0 | 20.9 | .009 |
| Physician-diagnosed bronchitis | 17.0 | 21.9 | .13 |
| Asymptomatic children | 22.2 | 19.0 | .12 |

* For definitions of diagnoses, see Table 2. Atopy was defined as a positive response to 1 or more of the 13 allergens tested. A reaction was considered positive if a wheal reaction of 3 mm or greater was present after subtraction of the reaction to negative control.

bronchitis, or allergic bronchitis at least once in the child's lifetime. We preferred to evaluate recurrent bronchitis cases separately, since they may represent an asthmatic phenotype different from clinically important asthma cases. Second, the study population, with its low socioeconomic characteristics, may have insufficient access to specialized health care facilities, which may add to underdiagnosis of asthma. However, this is the least likely reason, since Ankara has a large number of physicians and specialized hospitals for people with every type of health insurance and for those without insurance. Third, current wheeze may not be a good and specific marker for current asthma in the Turkish population.

Wheeze is regarded as a highly sensitive and specific epidemiologic marker for asthma in English-speaking countries.[7,11] However, in non–English-speaking countries, current wheezing was not found to be a good indicator of current asthma when both questionnaire and bronchoprovocation testing were used.[12] A recent ISAAC phase 2 study revealed a rather low rate of BHR and atopy among wheezing children in Estonia when compared with their Swedish counterparts.[13] Furthermore, an excellent cohort study conducted in 108 schoolchildren in England showed that questionnaire-reported wheeze was not a good marker of significant respiratory disease when compared with a physician's diagnosis of asthma and was little better than cough at identifying important asthma cases.[14] A physician's diagnosis of asthma had an independent and stronger predictive value than wheeze, atopy, BHR, or combinations of these variables. These findings are in accord with our results, which revealed that among current wheezers only 19.2% were atopic and 30.5% showed BHR, most of which was of a mild degree. These values were not significantly different from asymptomatic cases. However, these rates rose to 38.7% and 50.0% among physician-diagnosed asthma and asthmatic bronchitis cases, with a predominance of moderate-to-severe BHR. Thus, physician-diagnosed asthma, with or without wheeze, is a rather sensitive and specific epidemiologic indicator of persistent atopic asthma for this community.

Stein et al[15] identified different wheezing phenotypes in childhood according to objective markers associated with asthma. Other reports supporting this concept showed that, within the asthma syndrome, a subgroup of children show recurrent episodes of infection-induced wheezing (wheezy bronchitis) with a favorable outcome, a reduced risk of BHR and atopy, and a familial tendency.[16,17] In our study, questionnaire-elicited physician-diagnosed recurrent bronchitis cases, 59.7% of which had wheeze in the last year (data not shown), showed a lower rate of BHR, mostly of mild degree

and not associated with atopic status. These children (7.7% of the 8- to 11-year-old population) presumably correspond to the nonatopic wheezing or wheezy bronchitis groups defined in the literature.[15–17] Undoubtedly, longitudinal follow-up will elicit the prognosis and outcome of these different subgroups.

Another interesting finding of the present study was the unexpectedly high prevalence (19.4%) of BHR among asymptomatic children. There are a number of conditions other than asthma that may result in BHR: atopy, allergic rhinitis, upper and lower respiratory tract infections, ethnic background, and air pollution.[18–20] In accordance with the ISAAC phase 2 protocol, children with current respiratory infections but well enough to attend school were allowed to participate in the present study to overcome standardization problems. Frequent occurrence of common colds and other upper respiratory tract infections in Turkish schoolchildren during the study period (from October to April) may have contributed to a high rate of BHR in these children.

There is a well known relation between BHR and atopy.[12,15,19] The use of sensitization and degree of sensitization to the individual allergens may be more informative in explaining the variations in BHR than the use of any skin test positivity for atopy definition.[21,22] In the Childhood Asthma Management Program, Nelson et al[21] showed a strong direct correlation between increased sensitivity to pollen, mold, and animal dander allergens and BHR in children with mild-to-moderate asthma. The presence of atopic sensitization and a previous diagnosis of hay fever (data not shown) had no effect on the BHR rate in asymptomatic children of our study population. However, among the asthmatic and asthma-related symptom groups, the BHR rate increased in the presence of atopy. The relative importance of individual allergen sensitivities in the development of BHR will be the subject of a further report.

The official air pollution data (Refik Saydam Hygiene Center) for Ankara in 1999 to 2000 showed that, especially in winter months, mean annual $SO_2$ and particulate matter concentrations were high when compared with World Health Organization nomograms. In a cohort study conducted in Hong Kong, BHR prevalence among symptomatic and asymptomatic 9- to 12-year-old children was found to be higher in those living in polluted ($SO_2$) areas than in children living in unpolluted areas.[20] The authors also showed that 1 year after the introduction of a government air-quality intervention program BHR prevalence declined from 29% to 16%, almost half of the basal values, with the decrease in air pollution. Soyseth et al[23] have shown that exposure to low concentrations of airway irritants, such as $SO_2$ and fluoride, during infancy was associated with an increased prevalence of BHR in schoolchildren. Interestingly, the 8- to 11-year-old children included in the present survey were infants in the early 1990s, when air pollution by $SO_2$ had increased near to fatal levels due to widespread use of unlicensed charcoal in Ankara (Refik Saydam Hygiene Center, oral communication, July 2000). Although clearcut conclusions cannot be drawn relevant to the role of present and previous air pollution in the development of BHR in asymptomatic children, we think that it may be one of the contributing factors.

In a natural history of asthma study, Hopp et al[24] and Townley[25] found that 52% of nonasthmatic patients and 47% of nonallergic patients among a pediatric population had a positive response to methacholine inhalation challenge. They also showed that age had a significant effect on the methacholine response. Children and elderly people showed increased bronchial responses that may falsely suggest hyperreactive airway disease when compared with adults.[24] The unexpectedly high prevalence of BHR among asymptomatic schoolchildren in Ankara needs to be addressed in terms of prognosis. Zhong et al[26] have shown that approximately 45% of 11- to 17-year-old children with asymptomatic BHR developed asthma in the following years. An important epidemiologic cohort study by Carey et al[27] included the prospective follow-up of 5- to 9-year-old children with BHR. They found that for patients with BHR but no history of wheeze or asthma, the risk of subsequently developing wheeze was 3.9 times higher than for controls without BHR. Hence, a longitudinal cohort study is necessary to elucidate the prognosis of our asymptomatic responders to bronchoprovocation with HS.

In conclusion, the present study showed that the prevalence of BHR to HS was much higher than questionnaire-elicited prevalences of diagnosed asthma and current wheezing in Turkish schoolchildren. Furthermore, the relations of these 2 epidemiologic definition groups to atopy and BHR were distinctly different. This finding points to the necessity of using objective markers, in addition to the questionnaire-based prevalence figures, in epidemiologic surveys for asthma, especially in countries with inadequate health care facilities or where there are problems with language or interpretation of the wheeze concept. Although an underdiagnosis or unawareness of asthma and asthmatic symptoms could have contributed to this discrepancy, an evaluation of different risk factors relevant to BHR seems necessary in Turkish children.

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## REFERENCES

1. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 1985;14:32–33.

2. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies–ISAAC: rationale and methods. *Eur Respir J*. 1995;8:483–491.
3. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). *Eur Respir J*. 1998;12:315–335.
4. ISAAC Steering Committee. *Phase II Modules of the International Study of Asthma and Allergies in Childhood (ISAAC).* Münster, Germany: ISAAC Steering Committee; 1998.
5. Weiland SK, Von Mutius E, Hirch T, et al. Prevalence of respiratory and atopic disorders among children in East and West Germany five years after unification. *Eur Respir J*. 1999; 14:862–870.
6. Saraçlar Y, Şekerel BE, Kalaycı Ö, et al. Prevalence of asthma symptoms in school children in Ankara, Turkey. *Respir Med*. 1998;92:203–207.
7. Britton J, Lewis S. Objective measures and the diagnosis of asthma. *BMJ*. 1998;17:227–228.
8. Toelle BG, Peat JX, Salome CM, et al. Toward a definition of asthma for epidemiology. *Am Rev Respir Dis*. 1992;146: 633–637.
9. Kabesch M, Schaal W, Nicolai T, von Mutius E. Lower prevalence of asthma and atopy in Turkish children living in Germany. *Eur Respir J*. 1999;13:577–582.
10. Riedler J, Read T, Salton M, et al. Hypertonic saline challenge in an epidemiologic survey of asthma in children. *Am J Respir Crit Care Med*. 1994;150:1632–1639.
11. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol*. 1996;25:609–616.
12. Riedler J, Gamper A, Eder W, Oberfeld G. Prevalence of bronchial hyperresponsiveness to 4.5 saline and its relation to asthma and allergy symptoms in Austrian children. *Eur Respir J*. 1998;11:355–360.
13. Annus T, Bjorksten B, Mai XM, et al. Wheezing in relation to atopy and environmental factors in Estonian and Swedish school children. *Clin Exp Allergy*. 2001;31:1846–1853.
14. Pattemore PK, Lsampe FC, Smith S, et al. Asthma survey items as predictors of respiratory problems in children 2 years later: a longitudinal study. *Eur Respir J*. 1999;14:650–658.
15. Stein RT, Holberg CJ, Morgon WJ, et al. Peak flow variability, methacholine responsiveness and atopy as markers for detecting different wheezing phenotypes in childhood. *Thorax*. 1997;52: 946–952.
16. von Mutius E, IIIi S, Hirsch T, et al. Frequency of infections and risk of asthma, atopy and airway hyperresponsiveness in children. *Eur Respir J*. 1999;14:4–11.
17. Christie GL, Helms PJ, Godden DJ, et al. Asthma, wheezy bronchitis, and atopy across two generations. *Am J Respir Crit Care Med*. 1999;159:125–129.
18. Williams PV. Inhalation bronchoprovocation in children. *Immunol Aller Clin North Am*. 1998;18:149–164.
19. Spahn JD, Szefler SJ. The etiology and control of bronchial hyperresponsiveness in children. *Curr Opin Pediatr*. 1996;8: 591–596.
20. Wong CM, Lam TH, Peters J, et al. Comparison between two districts of the effects of an air pollution intervention on bronchial hyperresponsiveness in primary school children in Hong Kong. *J Epidemiol Community Health*. 1998;52:571–578.
21. Nelson HS, Szefler S, Jacobs J, et al. The relationships among environmental allergen sensitization, allergen exposure, pulmonary function and bronchial hyperresponsiveness in the Childhood Asthma Management Program. *J Allergy Clin Immunol*. 1999;104:775–785.
22. Chinn S, Burney P, Sunyer J, et al, on behalf of the European Community Respiratory Health Survey. Sensitization to individual allergens and bronchial responsiveness in the ECRHS. *Eur Respir J*. 1999;14:876–884.
23. Soyseth V, Kongerud J, Haarr D, et al. Relation of exposure to airway irritants in infancy to prevalence of bronchial hyperresponsiveness in school children. *Lancet*. 1995;345:217–220.
24. Hopp RJ, Bewtra AK, Nair NM, et al. Methacholine inhalation challenge studies in a selected pediatric population. *Am Rev Respir Dis*. 1986;134:994–998.
25. Townley GR. What factors cause bronchial hyperresponsiveness? Airway inflammation and eosinophilia are only part of the puzzle. *Ann Allergy Asthma Immunol*. 2003;90:176–178.
26. Zhong NS, Chen RC, Yang MO, et al. Is asymptomatic bronchial hyperresponsiveness an indication of potential asthma? a two-year follow-up of young students with bronchial hyperresponsiveness. *Chest*. 1992;102:1104–1109.
27. Carey VJ, Weiss ST, Tager IB, et al. Airways responsiveness, wheeze onset, and recurrent asthma episodes in young adolescents. *Am J Respir Crit Care Med*. 1996;153:356–361.

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