Effect of body mass on exercise-induced bronchospasm and atopy in African children

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Background: Sensitization to allergen is common in rural populations in less affluent countries, but atopic disease is less frequent than in richer countries. Variables explaining this dichotomy may provide insight into underlying mechanisms of atopic diseases like asthma.

Objective: To test whether risk of exercise-induced bronchospasm (EIB) in urbanized African populations is increased in association with greater skin sensitivity or increased body mass.

Methods: A total of 3322 children were enrolled in a prevalence survey of EIB in urban and rural South Africa. Children responding positively to an exercise challenge and a random sample of children responding negatively were recruited into a case-control study (393 controls, 380 cases). Subjects were investigated by using allergen skin prick testing, anthropometry, and assay of IgE. Stools were analyzed for parasite infestation.

Results: The prevalence of EIB was higher in urban (14.9%) than rural (8.9%) areas ($P < .0001$). The difference in risk of EIB between urban and rural subjects was associated with atopy (odds ratio [OR] for upper tertile of skin wheal diameter, 2.65; 95% CI, 1.43-4.89; $P < .0001$), increasing weight (OR for upper tertile of body mass index [BMI], 2.17; 95% CI, 1.45-3.26; $P = .001$), and affluence. Increasing BMI was also associated with a greater strength of association between specific IgE and the corresponding skin test (*Dermatophagoides pteronyssinus*, OR for a positive skin test result in presence of specific IgE: heavier subjects, OR, 34.6; 95% CI, 0.9-109.3; $P < .0001$; lighter subjects, OR, 8.05; 95% CI, 2.74-23.6; $P < .001$).

Conclusion: Increases in BMI of rural children in subsistence economies may lead to an increased prevalence of atopic disease. This observation merits further investigation in prospective studies. (J Allergy Clin Immunol 2005;116: 773-9.)

Key words: *Epidemiology, nutritional status, asthma, exercise-induced, prevalence comparative study, rural/urban health, South Africa*

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Abbreviations used

BMI:	Body mass index
EIB:	Exercise-induced bronchospasm
$FEF_{25\text{-}75}$:	Forced expiratory flow at 25% to 75% of forced vital capacity
OR:	Odds ratio
SPT:	Skin prick test

Atopic disease has increased in more affluent countries over the period of the last 3 decades.[1] There is also evidence for an increase in these conditions in poorer countries,[2,3] but a large difference in prevalence exists between urban and rural areas.[4-6]

In the face of rapid urbanization, it is important to understand the reasons for these observations. Even in rural areas with low levels of atopic disease, there is a substantial prevalence of IgE to common allergens.[7] Previous studies have suggested that children from rural areas with a lower prevalence of atopic disease are shorter and lighter[6] with less body fat[8] than urban children with a higher prevalence of atopic disease. Low levels of allergic skin test responses are found in those with protein calorie malnutrition,[9] and the strong association between skin test response to dust mite and exercise-induced bronchospasm (EIB) found in a study of heavier urban children in Kenya was not found in rural children with less body fat.[8] The effect of malnutrition on the expression of allergic disease in human beings has not been investigated. In this study, we explore the effects of body mass on EIB and skin test response in Xhosa children in urban and rural areas of South Africa.

METHODS

Subjects

The prevalence of EIB was established in a cross-sectional survey of 1671 children in 18 rural schools in the Kentani district of the rural Eastern Cape of South Africa and 1651 children in 6 urban schools in Khayelitsha, an informal urban settlement in the Western Cape. Schools in the urban area were contacted in order of construction, and all schools approached agreed to participate in the study. This permitted recruitment of children from families who had recently migrated from the area of residence of the rural population studied. In the rural area, all 22 schools reachable within an hour's drive from the study base were approached and invited to participate in the study, and 18 agreed. Children were age 8 to 12 years and were exclusively from the African population. The sample was selected to ensure that subjects reflected a general, community-based population. Access to medical services was poor in rural and urban areas. This is reflected in the observation that none of the children studied used asthma medications or had received a doctor's diagnosis of asthma despite the fact that a proportion of subjects recruited had asthma on the basis of symptoms and response to exercise. Rural and urban areas were visited alternately 4 times each for a month at a time to minimize the effect of seasonality on data collection.

Those with EIB and a random sample of subjects with a normal response to exercise were enrolled in a case-control study to examine factors that might explain rural-urban differences in the prevalence of asthma and allergy. EIB was defined as a fall in FEV_1 of $\geq$15% or a fall in forced expiratory flow at 25% to 75% of forced vital capacity ($FEF_{25\text{-}75}$) of $\geq$26%[10] after 6 minutes of free running.[11] Controls were defined by a fall in spirometry postexercise of no greater than 10% of pre-exercise FEV_1 or 20% of $FEF_{25\text{-}75}$, and were selected in each school as a proportion of the number of children available as control subjects. Spirometric measurements were performed according to European Respiratory Society guidelines by using a portable spirometer (Vitalograph 2120; Vitalograph Ltd, Buckinghamshire, United Kingdom).[12] Each child attempted at least 3 expiratory maneuvers. If serial FEV_1 and forced vital capacity readings agreed to within 5%, no further measurements were made. Where readings did not correspond, as many as 2 further attempts were permitted.

Atopy was defined as either the presence of at least 1 positive skin prick test (SPT; atopy [SPT]) greater then the negative control or the presence of specific IgE to at least 1 of the allergens measured (atopy [RAST]).

Assessment

Skin prick testing adapted the method described for the European Community Respiratory Health Study[13] by using plain lancets and the allergens *D pteronyssinus*, *D farinae*, *Blomia tropicalis* (supplied by Dr E. Fernandez-Caldas), cockroach, Timothy grass, Bermuda grass, *Aspergillus*, *Cladosporium*, *Alternaria*, cat, dog, a negative saline control, and a positive histamine control (Allergy Therapeutics, Worthing, United Kingdom). A positive test was defined as the presence of any skin wheal greater than 0 after deduction of the size of the negative control. Blood was drawn for assay of specific IgE to 5 allergens (*D pteronyssinus*, *B tropicalis*, cat, Timothy grass, *Aspergillus*; CAP-IgE System, Pharmacia, Uppsala, Sweden). Serum was chilled immediately and separated from clotted blood within 4 hours and stored at −20°C. A positive test for specific IgE was defined as RAST class $\geq$1.

Height was measured without shoes as described by Falkner and Frank[14] by using a portable free-standing stadiometer. Weight was recorded in indoor clothes without shoes by using a Soenhle digital scale (CMS Weighing equipment, London, United Kingdom). Calibration of scales was checked weekly with an object of fixed weight.

The Department of Microbiology, Tygerberg Hospital, analyzed stools for the presence of geohelminth eggs by using an ether sedimentation technique.[15] One investigator (J. C.) performed all skin tests in both the rural and urban areas. Native Xhosa speakers collected data on potential confounders by using a questionnaire administered in the local language. Number of years of education of the head of household and number of items from a standard list owned by the household were recorded and used as a proxy for affluence.[16] Trained fieldworkers made all measurements by using standardized techniques. Laboratory staff, interviewers, and investigators were blind to the clinical outcome during testing.

Analysis

Recruitment into the study was based on response to exercise, stratified by rural-urban place of residence. All subjects with a positive exercise test, together with a random sample of subjects with negative exercise tests, were enrolled. Subjects' probabilities of being recruited were recorded. Analyses used standard methods for the analysis of surveys, in which participants' responses are weighted according to the inverse of the probability of selection.[17] This method makes reconstruction of the control group possible, allowing for the effects of oversampling of atopic subjects occurring as a result of use of EIB as a criterion for entry into the case-control study. Odds ratios (ORs) were calculated by using weighted logistic regression. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. Variance of BMI increased with age, so SD (*z*) scores were calculated by using sex-specific reference curves for children in the United Kingdom[18] (in the absence of reference curves specific for the study population). Geometric means were calculated for log normal data and compared by using the Student *t* test. CIs allowed for the clustered study design.

Consent and ethical approval were obtained from the University of Cape Town Medical Research Ethics Committee. Parents or guardians of all study participants provided informed consent before testing.

RESULTS

Distribution of variables

In total, 3322 children underwent exercise testing. EIB was identified in 8.9% of rural and 14.9% of urban children (P = .004). Further examinations were undertaken of 773 children (380 cases, 393 controls), with 754 consenting to skin prick testing and providing blood samples and 743 providing stool samples. Parents of 696 children (370/436 urban and 326/337 rural) completed questionnaires. Children not providing samples did not differ from children providing samples in respect of age, sex, or airways responsiveness after exercise. Information on migration was available for 697 subjects; 341 (48.9%) reported moving from their place of birth for a period greater then 3 months. The majority of people migrated within the area in which they were born; however, 95 subjects migrated from an urban to a rural area and 69 from a rural to an urban area. Overall, the range of urban residence in study subjects was from 1 to 156 months, with a mean of 73 months. After mutual adjustment for age and current urban residence, risk associated with increasing lifetime urban residence was nonsignificant (OR, 1.03; 95% CI, 0.99-1.07; P = .17).

Table I compares results for cases and controls. Controls were lighter and shorter than cases and had a significantly lower BMI. Using a definition derived from centiles of English and Scottish children equivalent to a BMI at age 19.5 years of >30 (obese), >25 (overweight), and <18.5 (underweight), 9.4% of children were underweight (urban, 6.7%; rural, 13.1%), 4.5% were overweight (7.1%, urban; 1.2%, rural), and 0.6% were obese (urban, 0.9%; rural, 0.03%). Using World Health Organization criteria, 2 cases and 2 controls were stunted (height for age *z* score >2 SD below mean; P for difference, .96) and 34 cases and 42 controls wasted (weight for height *z* score, >2 SD below mean; P for difference, .42). Cases were more likely to have a positive skin test result, but the proportion of subjects with at least