

# 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

## Abbreviations used

BMI: Body mass index

EIB: Exercise-induced bronchospasm

FEF<sub>25-75</sub>: 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.<sup>1</sup> There is also evidence for an increase in these conditions in poorer countries,<sup>2,3</sup> but a large difference in prevalence exists between urban and rural areas.<sup>4-6</sup>

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.<sup>7</sup> Previous studies have suggested that children from rural areas with a lower prevalence of atopic disease are shorter and lighter<sup>6</sup> with less body fat<sup>8</sup> 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,<sup>9</sup> 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.<sup>8</sup> 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

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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<sub>1</sub> of  $\geq 15\%$  or a fall in forced expiratory flow at 25% to 75% of forced vital capacity (FEF<sub>25-75</sub>) of  $\geq 26\%$ <sup>10</sup> after 6 minutes of free running.<sup>11</sup> Controls were defined by a fall in spirometry postexercise of no greater than 10% of pre-exercise FEV<sub>1</sub> or 20% of FEF<sub>25-75</sub>, 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).<sup>12</sup> Each child attempted at least 3 expiratory maneuvers. If serial FEV<sub>1</sub> 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 than 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<sup>13</sup> 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  $-20^{\circ}\text{C}$ . A positive test for specific IgE was defined as RAST class  $\geq 1$ .

Height was measured without shoes as described by Falkner and Frank<sup>14</sup> by using a portable free-standing stadiometer. Weight was recorded in indoor clothes without shoes by using a Soehnle 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.<sup>15</sup> 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.<sup>16</sup> 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.<sup>17</sup> 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<sup>18</sup> (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 than 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

**TABLE I.** Summary of results for cases and controls

|                                                               | Case                 | Control              | P value |
|---------------------------------------------------------------|----------------------|----------------------|---------|
| Number                                                        | 380                  | 393                  |         |
| Age, mean (95% CI)                                            | 10.4 (10.3, 10.6)    | 10.5 (10.4, 10.6)    | .36     |
| Gender (male)                                                 | 179 (47.1%)          | 175 (44.5%)          | .47     |
| Skin test positive (SPT; %)                                   | 118 (31.2%)          | 90 (23.9%)           | .02     |
| Geometric mean wheal size: SPT positive subjects, mm (95% CI) | 3.00 (2.71, 3.31)    | 2.38 (2.11, 2.69)    | .004    |
| RAST positive (%)                                             | 233 (62.0%)          | 221 (58.9%)          | .40     |
| Total IgE, IU, geometric mean (95%CI)                         | 426.6 (370.7, 489.8) | 390.8 (338.8, 449.8) | .36     |
| BMI z score, mean (95% CI)                                    | −0.12 (−0.22, −0.02) | −0.37 (−0.47, −0.27) | .0005   |
| Height for age z score, mean (95% CI)                         | −0.74 (−0.84, −0.65) | −0.88 (−0.97, −0.79) | .04     |
| Weight for height z score, mean (95% CI)                      | 0.25 (0.13, 0.38)    | 0.06 (−0.06, 0.17)   | .02     |
| Ascaris infection, N (%)                                      | 250 (66%)            | 207 (56%)            | .003    |
| Parental education (tertiles)                                 |                      |                      |         |
| 1 (0-2 y)                                                     | 104 (30.1%)          | 150 (43.0%)          | .005    |
| 2 (3-6 y)                                                     | 138 (40.7%)          | 127 (36.4%)          |         |
| 3 (7-14 y)                                                    | 97 (28.6%)           | 72 (20.6%)           |         |
| Items owned* (tertiles)                                       |                      |                      |         |
| 1 (0-2 items)                                                 | 135 (39.4%)          | 183 (52.1%)          | .0002   |
| 2 (3-5 items)                                                 | 85 (24.8%)           | 83 (23.6%)           |         |
| 3 (6-9 items)                                                 | 123 (35.9%)          | 85 (24.2%)           |         |

\*Motor vehicle, bicycle, radio, electric stove, gas stove, primus cooker, refrigerator, television, hot water geyser, electric kettle, telephone.

1 positive RAST test did not differ between cases and controls.

Cases came from homes that had more educated heads of household and owned more items.

An effort was made to ensure that exercise tests were comparable between subjects. It was found that urban children ran slightly further than rural children but did not have as large a change in heart rate (see Table E1 in the Online Repository in the online version of this article at [www.jacionline.org](http://www.jacionline.org)).

### Association of EIB with BMI

Before adjustment for confounders, EIB was associated with increasing BMI, increasing mean skin wheal diameter, and increasing affluence (Table II). Age, sex, and other variables such as exposure to tobacco smoke and source of domestic fuel were not associated with EIB after adjustment for place of residence. After mutual adjustment for atopy and urban residence, increasing BMI was independently associated with increasing risk of EIB. However, atopy and BMI alone did not completely explain urban-rural differences in risk of EIB. After inclusion of variables describing affluence in the model, the OR for risk of EIB in urban versus rural areas was no longer significant ( $P = .17$ ). Pre-exercise FEV<sub>1</sub> and FEF<sub>25-75</sub> were associated with BMI, but pre-exercise lung function was not associated with the results of exercise testing.

Sex, skin test sensitivity, specific IgE, and place of residence did not modify the relation between EIB and BMI. Adjustment for the presence of ascaris infection made no substantive difference to the association.

Exercise-induced bronchospasm was more common in those with greater mean skin wheal diameters and in those

with the largest number of positive skin test results. Those subjects with the highest tertile of wheal size (4.1-7 mm) had a 3-fold greater risk (OR, 2.65; 95% CI, 1.43-4.89;  $\chi^2$  test for trend,  $P < .0001$ ) of a positive exercise test compared with subjects with no positive skin test results. Similarly, comparing those with 3 or more skin tests with subjects with no positive skin test results, there was a 75% increase in risk of EIB in the sensitized subjects (OR, 1.76; 95% CI, 1.19-2.60;  $\chi^2$  test for trend,  $P = .005$ ).

### Atopy and BMI

Urban children were twice as likely to have a positive skin test result compared with rural children (OR, 2.06; 95% CI, 1.41-3.01;  $P = .001$ ). As expected, children with IgE specific for an allergen were more likely to have a positive skin test result (see Table E2 in the Online Repository in the online version of this article at [www.jacionline.org](http://www.jacionline.org)), with the exception of cat allergen. The highest risk of a positive skin test result occurred in children with specific IgE and a higher BMI compared with children with low BMI. Subjects were stratified into 2 groups: lighter subjects with a standardized BMI score of less than the mean value for the study population (−0.25 SD) and heavier subjects with greater standardized scores. With the exception of *Aspergillus*, to which very few were sensitized, there was a trend toward a greater risk of a positive skin test result in subjects with the corresponding specific IgE in heavier compared with lighter children (Table III).

The effect of body weight on the association between specific IgE and corresponding SPT responses was analyzed further by looking at the association between specific IgE and skin tests for *D pteronyssinus*. Among children with IgE against *D pteronyssinus*, the risk of a

**TABLE II.** Analysis of risk factors associated with EIB

|                                   | Unadjusted odds ratio | P      | Mutually adjusted* OR | P      | Mutually adjusted† OR (including income) | P      |
|-----------------------------------|-----------------------|--------|-----------------------|--------|------------------------------------------|--------|
| Place of residence                |                       |        |                       |        |                                          |        |
| Rural                             | 1.00                  | >.0001 | 1.00                  | .06    | 1.00                                     | .17    |
| Urban                             | 1.76 (1.47-2.10)      |        | 1.31 (0.99-1.74)      |        | 0.67 (0.38-1.20)                         |        |
| Atopy (SPT)                       |                       |        |                       |        |                                          |        |
| Quantiles for mean wheal diameter |                       |        |                       |        |                                          |        |
| 0 (0 mm)                          | 1.00                  |        | 1.00                  |        | 1.00                                     |        |
| 1 (0.75-2.3 mm)                   | 1.08 (0.68-1.71)      | <.0001 | 1.09 (0.69-1.72)      | <.0001 | 1.19 (0.72-1.98)                         | <.0001 |
| 2 (2.4-4 mm)                      | 1.34 (0.75-2.38)      |        | 1.22 (0.67-2.24)      |        | 1.27 (0.74-2.17)                         |        |
| 3 (4.1-7 mm)                      | 3.06 (2.14-4.37)      |        | 3.04 (1.74-5.30)      |        | 2.65 (1.43-4.89)                         |        |
| BMI z score tertile               |                       |        |                       |        |                                          |        |
| 1 (-7.0, -0.16)                   | 1.00                  | <.0001 | 1.00                  | <.0001 | 1.00                                     | .001   |
| 2 (-0.60, 0.16)                   | 1.37 (0.95-1.96)      |        | 1.29 (0.88-1.89)      |        | 1.31 (0.87-1.98)                         |        |
| 3 (0.17, 2.77)                    | 2.32 (1.73-3.11)      |        | 2.19 (1.56-3.08)      |        | 2.17 (1.45-3.26)                         |        |
| Education of head of house        |                       |        |                       |        |                                          |        |
| 1 (0-2 y)                         | 1.00                  | .002   | —                     | —      | 1.00                                     | .08    |
| 2 (3-6 y)                         | 1.63 (1.15-2.30)      |        | —                     |        | 1.37 (0.89-2.11)                         |        |
| 3 (7-14 y)                        | 2.10 (1.36-3.24)      |        | —                     |        | 1.44 (0.94-2.22)                         |        |
| Household items owned‡            |                       |        |                       |        |                                          |        |
| 1 (0-2 items)                     | 1.00                  | <.0001 | —                     | —      | 1.00                                     | .07    |
| 2 (3-5 items)                     | 1.58 (1.06-2.36)      |        | —                     |        | 1.46 (0.72-2.96)                         |        |
| 3 (6-9 items)                     | 2.23 (1.51-3.29)      |        | —                     |        | 2.04 (0.91-4.55)                         |        |

\*Adjusted for residence, atopy, BMI, and ascaris infestation.

†Adjusted for residence, atopy, BMI, ascaris infestation, education, and household items.

‡Motor vehicle, bicycles, radio, electric stove, gas stove, primus cooker, fridge, television, hot water geyser, electric kettle, telephone.

P values refer to  $\chi^2$  test for trend.**TABLE III.** Strength of association between specific IgE and skin testing for the corresponding allergen stratified by BMI\*

| Allergen (RAST)        | Heavier/lighter (N) | P for interaction | OR (95% CI)       | P      |
|------------------------|---------------------|-------------------|-------------------|--------|
| <i>D pteronyssinus</i> | Heavier (126)       |                   | 34.6 (0.9-109.3)  | <.0001 |
|                        | Lighter (110)       | .05               | 8.05 (2.74-23.6)  | .001   |
| <i>B tropicalis</i>    | Heavier (118)       |                   | 23.7 (11.1-50.8)  | <.0001 |
|                        | Lighter (131)       | .75               | 21.3 (5.6-80.9)   | <.0001 |
| Timothy grass          | Heavier (82)        |                   | 35.2 (4.6-269.5)  | .001   |
|                        | Lighter (71)        | .17               | 6.85 (2.02-23.2)  | .003   |
| <i>Aspergillus</i>     | Heavier (24)        |                   | 6.8 (0.68-68.4)   | .1     |
|                        | Lighter (27)        | .29               | 68.8 (5.96-794.6) | .007   |
| Cat                    | Heavier (104)       |                   | 8.24 (2.63-25.8)  | .001   |
|                        | Lighter (142)       | .47               | 1.22 (0.14-10.9)  | .85    |
| Atopy (RAST)           | Heavier (216)       |                   | 37.9 (8.44-171)   | <.0001 |
| (Composite)            | Lighter (218)       | .02               | 3.94 (1.11-14.01) | .04    |

\*Heavier = BMI z score &gt; -0.25 SD; lighter = BMI z score &lt; -0.25. Interaction term and ORs for stratified analyses were controlled for urban living, and income was measured by using educational level of head of household and number of items owned.

positive skin test result increased in a linear manner with increasing BMI. This is demonstrated graphically for successive quintiles of BMI standardized score (see Fig E1 in the Online Repository in the online version of this article at [www.jacionline.org](http://www.jacionline.org)).

The proportion of heavy and light subjects with a positive skin test result for dust mite was also considered

according to class of dust mite RAST. Numbers were small in RAST classes 4 to 6, but children in these categories almost all had positive skin test results. However, in RAST classes 1 to 3, the heavier children were more likely to have a positive skin test result compared with the lighter, thinner children (see Fig E2 in the Online Repository in the online version of this

**TABLE IV.** ORs for a positive skin test for dust mite in heavier and lighter subjects, in whom IgE specific for dust mite was detected stratified by place of residence\*

|                         | Urban               |                     | Rural               |                     |
|-------------------------|---------------------|---------------------|---------------------|---------------------|
|                         | Heavier OR (95% CI) | Lighter OR (95% CI) | Heavier OR (95% CI) | Lighter OR (95% CI) |
| Dust mite RAST positive |                     |                     |                     |                     |
| No                      | 1                   | 1                   | 1                   | 1                   |
| Yes                     | 48.5 (9.13-257.2)   | 13.1 (3.24-53.2)    | 16.4 (1.99-134.8)   | 6.1 (1.12-33.1)     |

\*ORs are controlled for age, sex, and income. Heavier subjects had a BMI z score > -0.25 SD, and lighter subjects had a BMI z score < -0.25 SD.

article at [www.jacionline.org](http://www.jacionline.org)). Finally, a stratified analysis was performed that showed a greater strength of association between specific IgE and the corresponding skin test for dust mite in heavier compared with lighter residents in both the rural and urban areas (Table IV).

Specific measurements of dust mite allergen were not made in subjects' homes for logistical reasons. However, there was no difference in the proportion of urban and rural subjects in whom specific IgE for dust mite was detected ( $P = .81$ ), and there was also no difference in the median level of specific IgE to dust mite measured ( $P = .20$ ). It would therefore be difficult to infer that there was a difference in exposure to dust mite between urban and rural subjects, even though we have no specific information on this. The presence of cats in the home was also evenly distributed between the rural and urban areas (urban, 46.3%; rural, 54.4%;  $P = .07$ ).

## DISCUSSION

In this population with few overweight children, increasing BMI and the presence of a positive skin test result were associated with increasing risk of EIB. The association between specific IgE and the corresponding skin test was much stronger in heavier subjects with a higher BMI. The effect of body weight on the relationship between IgE and the corresponding allergen skin test was linear over the range of standardized BMI studied for dust mite allergen. This was only observed in subjects with RAST classes 1 to 3, suggesting that at higher concentrations of specific IgE, nutritional status has less effect on the relationship between specific IgE and the corresponding allergen SPT.

The data presented here come from a population-based survey with objective outcomes measured by trained fieldworkers using a standard protocol. The adjusted and unadjusted associations between EIB and BMI are strong, significant, and dose-dependent. Others have shown the airway response to exercise to be more common<sup>19</sup> or more severe<sup>20</sup> in the overweight, both in patients with asthma and others without asthma.<sup>21</sup> Several large population-based surveys of children have also shown a relation between symptoms of asthma and measured BMI.<sup>22</sup> The current study has extended these observations into a relatively underweight population and has not shown a lower threshold effect.

The mechanism that links raised BMI with asthma is not yet understood.<sup>23</sup> In this study, the effect of body

weight was partly independent of atopy. Although it is recognized that obesity can reduce lung function<sup>24</sup> and thereby increase the possibility of a positive exercise challenge test, the heavier children in this study had higher lung function at baseline, making this an unlikely explanation. It has also been argued that if obesity led to a lack of exercise, this could in turn lead to deconditioning of the lung and to greater airway responsiveness.<sup>25</sup> In this study, the rural children had a greater increase in heart rate and did not run as far as the urban children, which argues against the urban children, who had the greater airway responsiveness, having a more sedentary lifestyle or being less fit.

In this study, the odds of having a positive skin test result in those with specific IgE to *D pteronyssinus* increased with increasing body weight, and the relation was strong and significant. The same relation was seen for grass and cat, but the numbers were small, and the interaction was not statistically significant. A difference in cat exposure is unlikely to be an explanation, as rural/urban prevalence of cats in the home was similar. For *Aspergillus*, the relation appeared to be reversed, but the numbers are small. Sensitization to *Blomia* was more common, but the relation was also weak overall. However, looking at RAST classes 1 to 3, in which the effect of body weight is seen for *D pteronyssinus*, the same effect was seen for *Blomia*, with 42% of heavier children but only 21% of lighter children having positive skin test results ( $P < .01$ ).

Surveys of children have not shown strong and consistent associations between atopy and BMI, although von Mutius showed a marginal association in the National Health and Nutrition Examination Survey III study,<sup>26</sup> and surveys in Taiwan,<sup>27</sup> Australia,<sup>28</sup> and Sweden<sup>29</sup> have reported associations in girls.

In extreme circumstances, the relation between poor nutrition and atopic markers has been more marked. Abbassy et al<sup>9</sup> found no positive SPTs in children with marasmus or kwashiorkor, despite normal responses to histamine. Animal studies also support the view that undernutrition can reduce atopic responses. A low-protein diet in balb/c mice reduces the skin responses to a histamine liberator, histamine,<sup>30</sup> and allergens.<sup>31</sup> Defects in humoral immunity have also been shown in mice after both acute<sup>32</sup> and chronic starvation,<sup>33</sup> and rats have shown a reduction in IgE binding sites on mast cells,<sup>34</sup> reduction in IgE, and inhibition of anaphylaxis in the lungs of sensitized animals,<sup>35</sup> and reduction in IL-4 and mast cells<sup>36</sup> when nutritional intake was reduced. Conversely,

several proinflammatory cytokines and mediators, including IL-6 and TNF- $\alpha$ , are associated with increased adipose tissue,<sup>23</sup> and in a model of overfed mice, obesity was associated with enhanced responses to ovalbumin, without increases in either IL-4 or immunoglobulins.<sup>37</sup>

The lower degree of allergen skin test sensitivity in thinner children was most notable in those with low and intermediate levels of specific IgE and was not seen in those with high levels. An effect of body weight or nutrition on the relation between specific IgE and skin testing would be one explanation for the variable results reported in previous studies. Chinn and Rona<sup>38</sup> showed that the association between asthma symptoms and BMI was of recent origin and that the increase in obesity could not explain the increase in asthma symptoms in spite of the strong cross-sectional association between the 2 and an increasing prevalence of each. They suggested that this might be because the association became obvious only as mean body weight increased. Fig E1, however, suggests no threshold, at least for EIB, below the mean weight of many Western populations (see the Online Repository in the online version of this article at [www.jacionline.org](http://www.jacionline.org)). A combination of lower mean body weight and lower levels of sensitization in earlier years might provide a more plausible explanation, because there is increasing evidence that sensitization to common allergens has increased.<sup>39,40</sup>

In this study, lighter children did not have markedly less IgE, although there were fewer children with RAST class 6 (data not shown). They did, however, have a lower prevalence of skin sensitivity for any given RAST (particularly in classes 1-3). Experimental studies on rodents show that similar effects can be induced by calorie restriction (described earlier), supporting a causal explanation for this association. Associations between body weight and atopy have not been consistently noted elsewhere, but the interactive effects between body weight and sensitization shown in this study would produce less consistent main effects.

The strong association noted here and the evidence from animal experiments suggest that these effects may be directly causal, but we cannot exclude the possibility of confounding by some other factor. The most likely of these is diet, several aspects of which have been associated with asthma, and which is clearly likely to be linked to body weight.

In the poor and rapidly urbanizing populations of the world, it is important to understand what drives the current epidemic of atopic disease. Improving nutrition is a high priority for these populations, yet there is now good evidence that improved nutrition is associated with more atopy, that this extends to relatively malnourished populations, and that this represents a causal association of some sort. Although it seems likely that adiposity itself is important in this relation, we cannot be sure on the basis of the current evidence that other factors, particularly other aspects of the diet, are not responsible for the association. Understanding these mechanisms better will be important in averting a coming epidemic that poor countries can ill afford.

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