

Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children

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Background: Whether adiposity indicators other than body mass index (BMI) should be used in studies of childhood asthma is largely unknown. The role of atopy in “obese asthma” is also unclear.

Objectives: To examine the relationship among adiposity indicators, asthma, and atopy in Puerto Rican children, and to assess whether atopy mediates the obesity-asthma association.

Methods: In a study of Puerto Rican children with ($n = 351$) and without ($n = 327$) asthma, we measured BMI, percent of body fat, waist circumference, and waist-to-hip ratio. The outcomes studied included asthma, lung function, measures of atopy, and, among cases, indicators of asthma severity or control. We performed mediation analysis to assess the contribution of atopy to the relationship between adiposity and asthma.

Results: BMI, percent of body fat, and waist circumference were associated with increased odds of asthma. Among cases, all 3 measures were generally associated with lung function, asthma severity/control, and atopy; however, there were differences depending on the adiposity indicator analyzed.

Atopy considerably mediated the adiposity-asthma association in this population: allergic rhinitis accounted for 22% to 53% of the association with asthma, and sensitization to cockroach mediated 13% to 20% of the association with forced vital capacity and 29% to 42% of the association with emergency department visits for asthma.

Conclusions: Adiposity indicators are associated with asthma, asthma severity/control, and atopy in Puerto Rican children. Atopy significantly mediates the effect of adiposity on asthma outcomes. Longitudinal studies are needed to further investigate the causal role, if any, of adiposity distribution and atopy on “obese asthma” in childhood. (*J Allergy Clin Immunol* 2013;■■■■:■■■■-■■■■.)

Key words: *Childhood asthma, obesity, adiposity, body mass index, percent of body fat, obesity and asthma, obesity and atopy*

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Abbreviations used

BMI: Body mass index
ED/UC: Emergency department or urgent care
FVC: Forced vital capacity
PBF: Percent of body fat
STR: Skin test reactivity
WC: Waist circumference
WHR: Waist-to-hip ratio

Childhood asthma and obesity are both major public health concerns worldwide, and the prevalence of both diseases has risen markedly in the last several decades.¹⁻³ There is ample and growing evidence of an association between obesity and asthma, both in children and in adults.⁴⁻⁸ Compared with children of normal weight, those who are overweight or obese have a greater risk of incident asthma, more severe or frequent symptoms, and a decreased response to inhaled corticosteroids.⁹ While there is growing evidence for an “obese asthmatic” phenotype,^{10,11} little is known about its specific characteristics.

Body mass index (BMI) has been extensively used as a proxy for overweight or obesity in epidemiologic studies of asthma. Whether other adiposity measures (eg, percent of body fat [PBF] or waist-to-hip ratio [WHR]) provide phenotypic information that differs from or adds to that obtained by measuring BMI for studies of asthma is largely unknown. This is important, because BMI alone may not adequately characterize the relationship between overweight or obesity and complex diseases such as asthma. For example, adults with “normal weight central obesity” (normal BMI but high WHR) may have the highest risk for coronary artery disease.¹²

Several plausible mechanisms have been proposed to explain the observed association between obesity and asthma, including enhanced systemic inflammation.¹³ Given conflicting findings from studies of overweight or obesity (largely assessed by BMI) and atopy or atopic diseases (eg, allergic rhinitis),¹⁴⁻¹⁷ the role of atopy or allergic airway inflammation in the “obese asthmatic” phenotype is currently unclear.

Puerto Ricans share a disproportionate burden of asthma and overweight/obesity.¹⁸⁻²⁰ Very few studies have examined overweight or obesity and childhood asthma in Puerto Ricans,^{7,21} and none has assessed adiposity indicators other than BMI in relationship to asthma severity or control, lung function, or markers of allergic sensitization (eg, allergy skin testing).

In this report, we examine the relationship between indicators of adiposity/obesity, allergy markers, and measures of asthma severity or control (eg, lung function) in Puerto Rican children with asthma living in San Juan, Puerto Rico. We hypothesized that indicators of adiposity other than BMI would help characterize the “obese asthmatic” phenotype in Puerto Rican children,

in whom an association between overweight or obesity and asthma severity or control could be mediated by atopy.

METHODS

Subject recruitment

A detailed description of study methods is provided in the Online Repository at www.jacionline.org. From March 2009 to June 2010, children in San Juan were chosen from randomly selected households. In brief, households in the Standard Metropolitan Area of San Juan were selected by using a multistage probability sample design.²² Primary sampling units were randomly selected neighborhood clusters based on the 2000 US Census, and secondary sampling units were randomly selected households within primary sampling units. A household was eligible if 1 or more resident was a 6- to 14-year-old child. A total of 6401 households selected for inclusion were contacted. Of these, 1111 households had 1 or more child who met inclusion criteria other than age (4 Puerto Rican grandparents and residence in the same household for ≥ 1 year). Of these 1111 households, 438 (39.4%) had 1 or more eligible child with asthma (a case, defined as having physician-diagnosed asthma and wheeze in the previous year). From these 438 households, 1 child with asthma was selected (at random if there was more than 1 such child). Similarly, only 1 child without asthma (a control subject, defined as having neither physician-diagnosed asthma nor wheeze in the previous year) was randomly selected from the remaining 673 households. To reach our target sample size (~ 700 children), we attempted to enroll 783 of the 1111 eligible children selected for inclusion. Parents of 105 (13.4%) of these 783 children refused to participate or could not be reached, leaving 678 study participants (351 cases and 327 control subjects). There were no significant differences in age, sex, or area of residence between eligible children who did ($n = 678$) and did not ($n = 105$) agree to participate.

Study procedures

A detailed description of the study procedures is provided in the Online Repository. Study participants completed a protocol that included questionnaires on respiratory health and household characteristics, spirometry, allergy skin testing, and collection of blood and house dust samples. Dust samples were obtained from 3 areas in the home: one in which the child slept (usually his or her bedroom), living room/television room, and kitchen. The dust was sifted through a 50-mesh metal sieve, and the fine dust was reweighed, extracted, and aliquoted for analysis of allergens from dust mite (*Der p 1*), cockroach (*Blattella germanica* [*Bla g 2*]), and mouse (mouse urinary protein [*Mus m 1*]) by using monoclonal-antibody Multiplex array assays using the same reagents used in the established ELISA.²³ Allergen levels were analyzed as continuous (after log₁₀-transformation), with nondetectable levels assigned a constant (half the lowest detectable value).

Measures of obesity and adiposity

BMI was calculated from weight in kilograms and height in meters. PBF was calculated from tricipital and subscapular skin folds,²⁴ which were obtained by trained study personnel by using calibrated calipers; the average of 3 tricipital and subscapular measurements was used for PBF calculation. All measures were transformed to z scores to obtain standardized/comparable coefficients and odds ratios, as follows: BMI z scores were calculated by using a program based on the 2000 CDC growth charts²⁵; PBF z scores were calculated by using a recent study on reference equations for US children and adolescents²⁶; and waist circumference (WC) and WHR were standardized by using the distribution of our study sample.

Ethics statement

Written parental consent and written assent were obtained for participating children. The study was approved by the institutional review boards of the University of Puerto Rico (SJ [Protocol no. 0160507]), Brigham and Women's Hospital (Boston, Mass [Protocol no. 2007P-001174]), and the University of Pittsburgh (Pittsburgh, Pa [Protocol no. PRO10030498]).

Statistical analysis

Our outcomes of interest included asthma (defined as above), lung function measures (FEV₁, forced vital capacity [FVC], and FEV₁/FVC), allergic rhinitis (defined as current naso-ocular symptoms apart from colds and at least 1 positive skin test result to allergens), allergy markers (skin test reactivity [STR] to allergens and serum total IgE), and other indicators of asthma severity or control, as follows: (1) number of days on oral or intravenous steroids in the previous year (categorized as 0, 1-8, 9-40, and over 40); (2) missed school days because of asthma in the previous year (categorized as 0, 1-2, 3-5, or at least 6); (3) exercise-induced symptoms in the previous year (categorized as never, occasionally, frequently, or always); and (4) number of visits to the emergency department for asthma, ever.

Bivariate analyses were conducted by using Fisher exact tests for binary variables and 2-tailed t tests for pairs of binary and continuous variables. Linear or logistic regression was used to examine the relationship between each adiposity/obesity indicator and the outcomes of interest, while adjusting for potential confounders. All multivariate models included age, sex, household income ($<$ vs \geq \$15,000/year [the median household income for Puerto Rico in 2008-2009²⁷]), parental (maternal or paternal) history of asthma, and percentage of African racial ancestry (determined by using genome-wide genotypic data²⁸; see Online Repository at www.jacionline.org). All analyses of FEV₁ and FVC were additionally adjusted for height and height squared, and analyses of STR were additionally adjusted for levels of indoor allergens (see Online Repository for details).

We performed mediation analysis to assess whether part or all of the association between adiposity indicators (eg, BMI) and outcomes of interest (eg, FEV₁) is explained by atopy via a mediated or "indirect effect" (see Online Repository for details). This analysis was performed via structural equation modeling for continuous and ordinal data, and by using the Karlson-Holm-Breen decomposition method²⁹ for binary outcomes, which adjusts for the rescaling issues that arise from cross-model comparison of nonlinear models.^{30,31} Mediation analysis was performed only on measures of atopy (ie, allergic rhinitis, STR to cockroach) that were associated with both the adiposity indicators and the asthma outcomes. Other indicators of atopy (eg, total IgE) did not meet this criterion and were thus not included in the mediation analysis. All statistical analyses were performed by using SAS statistical software, version 9.3 (SAS Institute; Cary, NC), with the exception of the mediation analysis (which was conducted by using Stata 12.1 [StataCorp; College Station, Tex]).

RESULTS

The characteristics of the 678 study participants are shown in Table I. BMI was significantly associated with increased odds of asthma after adjusting for covariates. PBF and WC were also associated with asthma, but these associations only approached significance ($P = .06$ and $P = .08$, respectively) (Table II). As expected, all 4 obesity/adiposity measurements were significantly correlated with each other ($P < .0001$), although the degree of correlation and the slope of the regression coefficient varied (Fig 1).

Table II shows the results of the multivariate analysis of each measure of obesity/adiposity and indicators of asthma severity or control in children with asthma ($n = 351$). In this analysis, each 1.0 z -score increment in BMI was significantly associated with an approximately 69 mL higher FEV₁. All adiposity measures were positively associated with FVC, ranging from an approximately 50-mL increment per each z score in WHR to an approximately 98-mL increment per z -score increment in BMI, with intermediate results obtained for PBF and WC. Of the 4 adiposity measures, only WC was significantly associated with a decrement in FEV₁/FVC. All adiposity measures except WHR were associated with increased lifetime emergency department or urgent care (ED/UC) visits for asthma, ranging from approximately 3 additional ED/UC visits per each z -score increment in BMI to approximately 4.6 additional ED/UC visits

TABLE I. Characteristics of study participants

Demographic characteristics	Cases (N = 351)	Controls (N = 327)
Sex: male, n (%)	201 (57.3%)*	159 (48.6)
Age (y), mean ± SD	10.0 ± 2.59*	10.5 ± 2.73
Parental asthma history (%)	68.1*	33.1
Household income ≥ \$15,000/y (%)	34.6	37.2
African ancestry (%), mean ± SD	25.2 ± 11.7	24.8 ± 12.5
Household dust allergen levels†		
Dust mite (μg/g)	2.42 (4.5-9.6)	1.97 (4.4-9.3)
Cockroach (U/g)	0.73 (1.3-4.3)	0.71 (1.2-2.7)
Mouse (ng/g)	2.0 (7.0-31.0)	2.0 (7.0-28.0)
Obesity/adiposity measures, mean ± SD‡		
BMI	0.69 ± 1.19*	0.51 ± 1.12
PBF	0.29 ± 0.86§	0.22 ± 0.77
WC	0.03 ± 1.04§	-0.03 ± 0.95
WHR	0.001 ± 0.85	-0.001 ± 1.13
Pulmonary function tests, mean ± SD		
FEV ₁ (L)	1.88 ± 0.67*	2.05 ± 0.74
FVC (L)	2.33 ± 0.82*	2.47 ± 0.88
FEV ₁ /FVC (%)	80.9% ± 9.0%*	83.5% ± 8.9%
Asthma severity		
No. of ED/UC visits for asthma†	10 (5-20)	NA
Severity scores, past year†		
Prednisone courses (0-4)	2 (1-2)	NA
Exercise symptoms (0-3)	1 (1-3)	NA
Missed school days (0-3)	1 (0-2)	NA
Atopy measures		
Total serum IgE level (IU/mL)†	346 (116-881)*	158 (44-600)
Allergic rhinitis (%)	53.6*	19.2
STR to (%)		
Dust mite	55.4*	41.6
Cockroach	39.4*	26.3
Alternaria	25.2	24.8
Mold	12.2%	14.4
Mouse	26.2	21.2
Any STR+	69.0*	56.0

IQR, Interquartile range; NA, not applicable.

* $P < .05$.

†Numbers for continuous variables represent mean ± SD, except median (IQR).

‡All transformed to z scores.

§ $P < .10$.

||Defined as history of allergic rhinitis plus current symptoms plus STR to at least 1 allergen.

per z-score increase in PBF. Similar results were obtained for the analysis of school absences due to asthma. BMI and PBF (but not WC or WHR) were also associated with an increased number of courses of systemic steroids for asthma in the previous year. In addition, PBF, WC, and WHR (but not BMI) were associated with increased exercise-induced asthma symptoms.

In the multivariate analysis of allergic rhinitis and allergy markers (Table II), PBF and WC were each associated with increased odds of allergic rhinitis and WC was associated with increased total IgE. In this analysis, all indicators of obesity/adiposity were associated with increased odds of STR to cockroach and *Alternaria* and all measures except WHR were also associated with increased odds of STR to mold and mice. There was no significant association between any of the adiposity measures and STR to dust mite.

To assess whether the observed association between obesity/adiposity and asthma-related outcomes is mediated through atopy, we performed a mediation analysis (see Methods

and Fig E1 in the Online Repository at www.jacionline.org). On the basis of their high prevalence in our study population and their association both with indicators of adiposity and with asthma outcomes, we examined allergic rhinitis as a mediator for asthma and STR to cockroach as a mediator for FVC and ED/UC visits. Allergic rhinitis significantly mediated the associations between each of 3 indicators of adiposity or obesity (BMI, PBF, and WC) and asthma (Table III); the estimated mediation effect explained 22%, 53%, and 43%, respectively, of each association. Among children with asthma, STR to cockroach mediated approximately 20% and approximately 13% of the estimated effects of PBF and WC on FVC, respectively. STR to cockroach also mediated approximately 28% to 42% of the association between indicators of adiposity/obesity (BMI, PBF, and WC) and the number of ED/UC visits for asthma. While mediation does not imply causation, these results demonstrate a significant contribution of atopy to the obesity-asthma relationship.

DISCUSSION

In this study we show that BMI, PBF, and WC are each significantly associated with asthma and indicators of asthma severity or control in Puerto Rican children. We also report that atopy may be an important mediator of the relationship between adiposity or obesity and asthma morbidity in these children.

Although BMI has been the most widely used proxy of adiposity, its usefulness and predictive value have been questioned in studies of cardiovascular disease and diabetes.^{32,33} Our results for PBF or WC are consistent with those of several studies showing an association between BMI and asthma⁴⁻⁶ or worsened asthma control⁷ in children. In contrast to our findings for asthma, however, limiting our assessment to BMI would have led to nondetection of significant associations between obesity/adiposity (measured by PBF or WC) and exercise-induced asthma symptoms, allergic rhinitis, and total IgE. Our results thus suggest that sole reliance on BMI may partly explain inconsistent findings for asthma severity or atopy in previous studies. Of interest, recent studies have shown that WC predicts total body fat (measured by dual-energy x-ray absorptiometry) more accurately than does BMI, which may require different height correction factors depending on age, sex, and race.³⁴

To our knowledge, the only previous study that examined PBF and asthma control³⁵ found an association in adolescent girls but not boys. WHR, which has been touted as an important marker of cardiovascular disease,^{12,33} demonstrated the fewest associations with asthma outcomes in Puerto Rican children.

Adipose tissue may be related to inflammation and immune responses through the production of cytokines/adipokines and macrophage activation.¹³ However, distinct types of adiposity may differentially affect various diseases in children and adults. For example, visceral fat has been associated with cardiovascular disease in adults but not with insulin sensitivity in children.³⁶ Similarly, large subcutaneous adipocytes may be more important than visceral fat for glucose/insulin regulation in obese women.³⁷ Alternatively, one cannot rule out that measures of adiposity other than BMI may better reflect poor fitness rather than just asthma. Our results highlight the importance of determining which indicator(s) of obesity/adiposity should be used in future studies of obesity and asthma,^{38,39} particularly as we characterize obese asthmatic phenotypes (eg, nonatopic vs atopic).

TABLE II. Indicators of adiposity, allergy markers, and indicators of asthma severity or control

	BMI	PBF	WC	WHR
Asthma status	1.27 (1.1-1.5)*	1.24 (0.99-1.6)†	1.18 (0.98-1.4)†	1.12 (0.93-1.35)‡
Lung function in cases				
FEV ₁ (mL)§	68.8 (34.7-103.0)*	37.5 (−10.5 to 84.5)‡	20.1 (−18.3 to 60.2)‡	27.3 (−19.4 to 74.0)‡
FVC (mL)§	98.0 (59.0-137.1)*	63.4 (8.9-117.8)*	61.1 (15.9-106.2)*	50.1 (−4.0 to 104.3)†
FEV ₁ /FVC (%)	−0.6 (−1.5 to 0.5)‡	−0.6 (−1.9 to 0.7)‡	−1.0 (−2.1 to 0.0)†	−0.7 (−2.1 to 0.7)‡
Asthma severity				
Urgent care visits, ever	3.0 (0.01-6.1)*	4.6 (0.50-8.79)*	3.4 (−0.01 to 6.8)†	2.4 (−2.0 to 6.9)‡
>1 urgent care visit, last year	1.23 (0.96-1.59)†	1.40 (0.99-1.97)*	0.99 (0.75-1.31)‡	1.01 (0.70-1.45)‡
Severity scores				
Prednisone courses	0.08 (−0.01 to 0.17)†	0.15 (0.03-0.28)*	0.07 (−0.03 to 0.14)‡	0.07 (−0.05 to 0.20)‡
Missed school days	0.13 (0.02-0.25)*	+0.17 (0.01-0.33)*	0.13 (0.005-0.26)*	0.10 (−0.05 to 0.26)‡
Exercise symptoms	0.09 (−0.02 to 0.11)‡	0.15 (0.03-0.29)*	0.18 (0.07-0.29)*	0.18 (0.04-0.32)*
Atopy measures in cases				
Allergic rhinitis	1.19 (0.96-1.49)‡	1.33 (0.97-1.81)†	1.36 (1.05-1.77)*	1.31 (0.95-1.90)†
Total IgE level (IU/mL)	0.99 (0.84-1.18)‡	1.04 (0.83-1.31)‡	1.2 (1.002-1.45)*	1.03 (0.83-1.29)‡
STR to¶				
Dust mite	0.97 (0.77-1.23)‡	1.17 (0.85-1.61)‡	1.07 (0.83-1.39)‡	0.95 (0.70-1.30)‡
Cockroach	1.37 (1.04-1.79)*	1.57 (1.11-2.24)*	1.49 (1.11-2.01)*	1.41 (0.99-2.01)†
Alternaria	1.46 (1.08-1.97)*	1.80 (1.20-2.70)*	1.76 (1.26-2.45)*	1.44 (1.01-2.06)*
Mold	2.54 (1.54-4.19)*	2.08 (1.23-3.52)*	1.80 (1.20-2.71)*	1.17 (0.73-1.88)‡
Mouse	1.36 (1.02-1.83)*	1.70 (1.15-2.51)*	1.38 (1.01-1.88)*	1.21 (0.85-1.74)‡
Any STR+	1.30 (1.02-1.64)*	1.54 (1.10-2.17)*	1.36 (1.03-1.78)*	1.35 (0.96-1.91)†

Note. Results for adjusted regression analysis in asthmatic children. All models adjusted for sex, age, parental history of asthma, household income, and percent African ancestry. Numbers represent β coefficients for continuous/ordinal outcomes and odds ratio for binary outcomes (with 95% CI in parentheses) per 1.0 z-score increment in each adiposity measure. Values in boldface are considered statistically significant ($P < .05$).

* $P < .05$.

† $P < .10$.

‡ $P > .10$.

§Analyzed as absolute values because of lack of predictive equations for Puerto Ricans; adjusted additionally for sex, age, height, and height squared.

||Analyzed as \log_{10} .

¶All STR models additionally adjusted for dust mite allergen level, except those for STR to cockroach or mouse, which were adjusted for levels of the respective allergens.

Obese asthmatic phenotypes may differ between children and adults. Whereas obese adults with asthma have been shown to have a restrictive ventilatory deficit (low FVC and FEV₁ but normal FEV₁/FVC),⁴⁰ obese children with asthma tend to have either an obstructive ventilatory deficit or dysanaptic lung growth, representing a mismatch between growth of the airway and that of the lung parenchyma (normal or high FVC and FEV₁ but decreased FEV₁/FVC).⁴¹⁻⁴⁴ In general but not complete agreement with these findings, we show that BMI is associated with higher FEV₁, that all adiposity measures are associated with higher FVC, and that WC is associated (albeit nonsignificantly) with a lower FEV₁/FVC in Puerto Rican children.

As with asthma and obesity, there are clinical and experimental data linking obesity and atopy: adipose tissue contains high concentrations of aromatase and can increase circulating levels of estrogen in obese women, and estrogen has been shown to enhance eosinophil function and modulate IL-4 and IL-13 production by monocytes.^{45,46} Obesity in mouse models of asthma has been shown to lower the threshold for allergic sensitization, measured by IgE, IL-5, and eosinophilia.⁴⁷ Cluster analysis in adults has shown that certain “obese asthmatic” phenotypes have increased IgE levels.¹⁰

We have previously shown that atopy is common in Puerto Rican children with asthma.^{22,48} In this study, we report that BMI, PBF, and WC are each consistently associated with increased odds of STR to cockroach, STR to mold, and STR to mouse in Puerto Rican children with asthma. In addition, we show that WC is associated with higher total IgE levels and

allergic rhinitis in these children. Previous studies have reported conflicting results for BMI and atopy, with some studies showing a positive association with allergic sensitization in all children (independently of asthma status)^{14,49} or in girls only^{15,50} and others yielding negative results.¹⁷ Discrepancies among reports, including ours, may be explained by differences in genetic and environmental/lifestyle factors across study populations.

Whether atopy mediates or modifies the association between obesity and asthma is unclear. To our knowledge, this is the first report using mediation analysis to address this question. Findings from our analysis suggest that a significant proportion of the association between adiposity indicators and asthma-related outcomes in Puerto Rican children is mediated by atopy. Up to 22% of the increased asthma risk associated with BMI was explained by allergic rhinitis, with consistent results for WC and PBF (up to 42% and 53%, respectively). Among cases, atopy also mediated a significant proportion of the associations between obesity indicators, FVC, and ED/UC visits for asthma. Of interest, when structuring the models in the opposite direction (to answer the question “is the association between atopy and asthma mediated by obesity?”), most indirect effects were nonsignificant (data not shown). Our results are in contrast with those of a previous study showing that while BMI was associated with total IgE levels, BMI was associated only with asthma in nonatopic children.¹⁶ Our results also contrast with those of a previous study that concluded that PBF provided no additional information to that given by BMI with regard to asthma severity.³⁵ This suggests

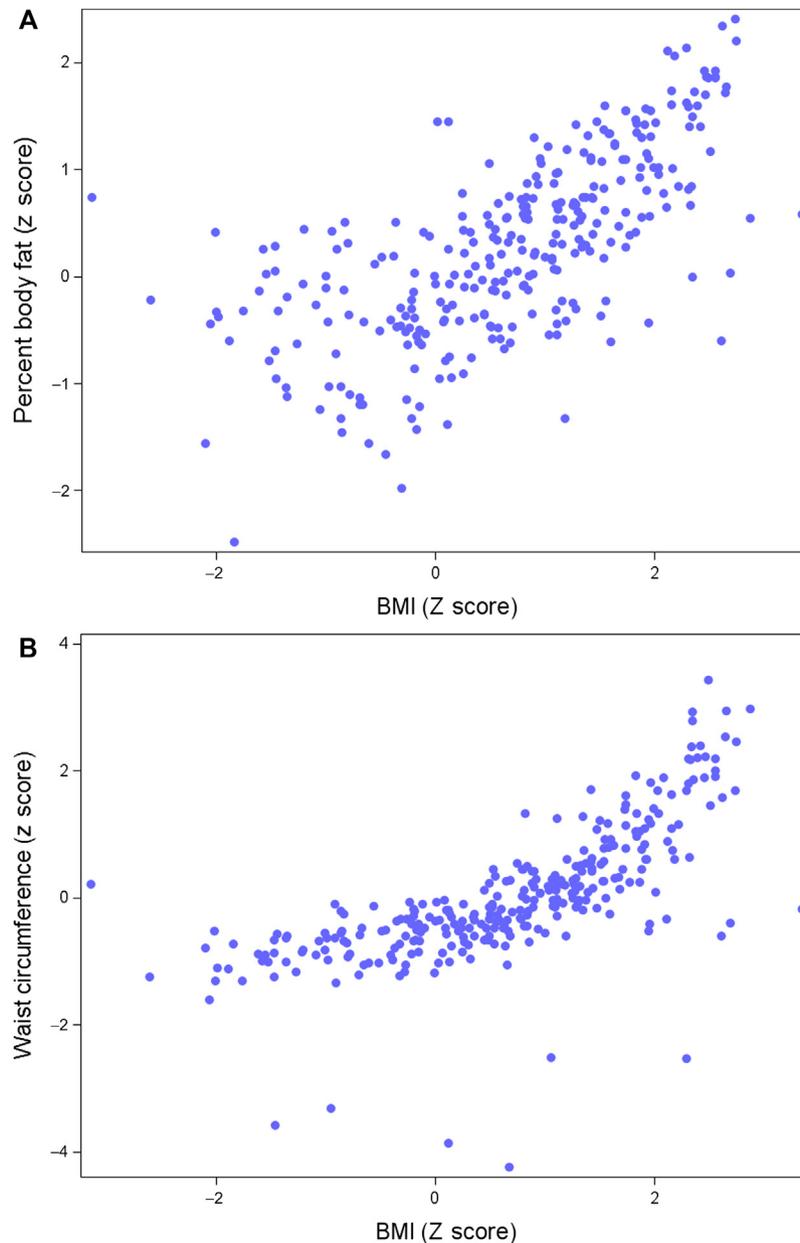


FIG 1. Correlation between BMI and indicators of adiposity.

that adiposity or obesity may be more likely to influence asthma through atopy in Puerto Rican children than in children in other ethnic groups.

There are several potential limitations to our study. As with any cross-sectional study, the temporality of the observed associations cannot be ascertained, and we cannot thus exclude “reverse causation.” However, a link between obesity and asthma has been established in several longitudinal studies of children.^{5,8} Similarly, a mediation analysis allows for “decomposition” of an association into a “direct” effect and a “mediated” effect but cannot determine causality. Of note, we did not assess puberty staging. However, we obtained very similar findings after additional adjustment for age as a proxy for puberty onset (set at ≥ 12 years for boys and at ≥ 11 years for girls) in our multivariate models (data not

shown). Future studies should include Tanner staging because hormonal differences before and after puberty may affect the relationship among sex, obesity, and asthma. Finally, we may have been underpowered to detect small effects of adiposity measures on certain asthma-related outcomes. However, such effects may not be clinically relevant.

In summary, we report that measures of obesity/adiposity are associated with asthma, asthma severity/control, and atopy in Puerto Rican children. While our results were generally consistent, there were several differences according to the adiposity indicator analyzed. In this group of children, atopy was a significant mediator of the effect of adiposity on asthma and asthma-related outcomes. Future studies should aim to elucidate the roles of adiposity distribution and atopic sensitization on “obese asthma” in childhood.

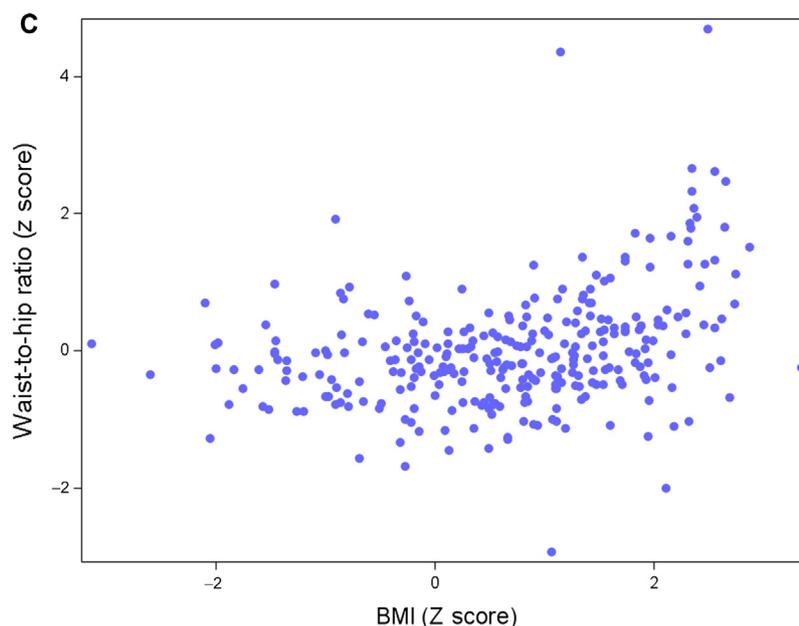


FIG 1. (Continued)

TABLE III. Estimated mediation of the association between obesity/adiposity indicators and asthma outcomes by atopy

	BMI	PBF	WC
Asthma status by allergic rhinitis			
Total effect	1.32 (1.11-1.58), .002	1.26 (0.99-1.61), .06	1.20 (0.99-1.46), .067
Direct effect	1.24 (1.04-1.48), .015	1.12 (0.87-1.42), .38	1.11 (0.92-1.35), .29
Indirect effect	1.06 (1.01-1.13), .032	1.13 (1.04-1.23), .004	1.08 (1.01-1.16), .022
Percent mediated	22.3	52.9	42.6
Total/direct effect	1.29	2.12	1.74
FVC by STR+ to cockroach in cases			
Total effect (mL)	97 (56-138), <.001	60 (3-117), .04	75 (26-125), .003
Direct effect	90 (49-131), <.001	48 (-8 to 105), .09	65 (17 to 114), .008
Indirect effect	7 (-2 to 16), .11	12 (-1 to 26), .08	10 (-1 to 22), .08
Percent mediated	7.5	20.1	13.3
Total/direct effect	1.08	1.25	1.15
Number of ED/UC visits by STR+ to cockroach			
Total effect	2.8 (-0.3 to 6), .08	4.7 (0.5 to 9), .03	2.7 (-0.9 to 6), .14
Direct effect	2.0 (-1 to 5), .21	3.4 (-1 to 8), .13	1.6 (-2 to 5), .39
Indirect effect	.8 (-0.08 to 2), .07	1.4 (0.01 to 3), .048	1.1 (0.01 to 2), .048
Percent mediated	28.7	28.9	41.9
Total/direct effect	1.40	1.41	1.72

Note. Results from decomposition (binary outcomes) or structural equation modeling (continuous outcomes). Table shows odds ratios (binary outcomes) or β coefficients (continuous outcomes), 95% CIs, and *P* values. Indirect effect: Mediation of allergic rhinitis in the relationship between adiposity measure and outcome. Percent mediated: Percentage of the total effect explained by the mediation of atopy. Values in boldface are considered statistically significant (*P* < .05).

Clinical implications: Assessment of adiposity rather than sole reliance on BMI may be important in studies of childhood asthma. Atopy is an important mediator of the relationship between obesity and asthma in Puerto Rican children.

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METHODS

Subject recruitment

From March 2009 to June 2010, children in San Juan were chosen from randomly selected households. Households in the Standard Metropolitan Area of San Juan were selected by using a multistage probability sample design.^{E1} Primary sampling units were randomly selected neighborhood clusters based on the 2000 US Census, and secondary sampling units were randomly selected households within primary sampling units. A household was eligible if 1 or more resident was a 6- to 14-year-old child. A total of 6401 households selected for inclusion were contacted. Of these, 1111 households had 1 or more child who met inclusion criteria other than age (4 Puerto Rican grandparents and residence in the same household for ≥ 1 year). Of these 1111 households, 438 (39.4%) had 1 or more eligible child with asthma (a case, defined as having physician-diagnosed asthma and wheeze in the previous year). From these 438 households, 1 child with asthma was selected (at random if there was more than 1 such child). Similarly, only 1 child without asthma (a control subject, defined as having neither physician-diagnosed asthma nor wheeze in the previous year) was randomly selected from the remaining 673 households. To reach our target sample size (~ 700 children), we attempted to enroll 783 of the 1111 eligible children selected for inclusion (391 of the 438 cases and 392 of the 673 control subjects). Parents of 105 (13.4%) of these 783 children (40 [10.2%] of the 391 cases and 65 [16.6%] of the 392 control subjects) refused to participate or could not be reached, leaving 678 study participants (351 cases and 327 control subjects). There were no significant differences in age, sex, or area of residence between eligible children who did ($n = 678$) and did not ($n = 105$) agree to participate.

The main recruitment tool was a screening questionnaire given to parents of children aged 6 to 14 years to obtain information about the child's respiratory health and Puerto Rican ancestry. All participants (cases and controls) had to have 4 Puerto Rican grandparents and be living in the same household for 1 year or more. We selected as cases children with physician-diagnosed asthma and wheeze in the previous year, and as controls children with no physician-diagnosed asthma and no wheeze in the previous year.

Study procedures

The parents of each participant completed a questionnaire used in the Genetics of Asthma in Costa Rica Study.^{E2} Spirometry was conducted with an EasyOne (nidd Medical Technologies, Andover, Mass) spirometer following American Thoracic Society recommendations.^{E3} All subjects had to be free of respiratory illnesses for at least 4 weeks before spirometry, and they were also instructed to avoid use of inhaled short- and long-acting bronchodilators for at least 4 and 12 hours before testing, respectively. The best FEV₁ and FVC were selected for data analysis of FEV₁ and FEV₁/FVC.

Dust samples were obtained from 3 areas in the home: the one in which the child sleeps (usually a bedroom), living room/television room, and kitchen. The dust was sifted through a 50-mesh metal sieve, and the fine dust was reweighed, extracted, and aliquoted for analysis of allergens from *Dermatophagoides pteronyssinus* (Der p 1), *Blattella germanica* (Bla g 2), and mouse urinary protein (Mus m 1) by using monoclonal antibody Multiplex array assays using the same reagents used in the established ELISA.^{E4} Internal controls were run in each assay to ensure interassay reproducibility.

Allergen levels were analyzed as continuous (after log₁₀-transformation), with nondetectable levels assigned a constant (half the lowest detectable value), and included in the adjusted analyses of STR, as follows: STR to dust mite, cockroach, and mouse was adjusted (in addition to all other covariates) by the indoor levels of the respective allergens; STR to *Alternaria*, mold, and "any positive STR" were adjusted by levels of dust mite allergen because the primary allergen levels were not available. We performed additional analyses for *Alternaria*, mold, and "any positive STR" adjusting for levels of cockroach and mouse allergens, with no significant changes in the estimates ($>10\%$) or significance levels of the main covariates (adiposity indicators) (data not shown).

Serum total IgE level was measured by using the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, Mich). STR to aeroallergens was assessed by using a Multi Test device (Lincoln Diagnostics, Decatur, Ill) in a site free of eczema: in addition to histamine (positive control) and saline solution (negative control), allergen extracts from house-dust mite mix (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), German cockroach (*Blattella germanica*), cat dander, dog dander, mixed grass pollen, mugwort sage, ragweed, mixed tree pollen, mold mix, *Alternaria tenuis*, and mouse pelt were applied to the skin of the forearm (ALK-Abelló, Round Rock, Tex). A test was considered positive if the maximum diameter of the wheal was 3 mm or more after subtraction of the maximum diameter of the negative control.

Genotyping and estimation of racial ancestry

Genotyping of approximately 2.5 million markers was conducted in DNA from study subjects by using the HumanOmni2.5 BeadChip (Illumina, Inc, San Diego, Calif). Single nucleotide polymorphisms that were not in Hardy-Weinberg equilibrium ($P < .05$) in control subjects and had minor allele frequencies of less than 1% or failure rates of greater than 2% were removed. Ancestry was estimated by using the Local Ancestry in admixed Populations method and software^{E5} with 85,059 single nucleotide polymorphisms that were present in all 3 ancestral populations and that were not in tight linkage disequilibrium. The algorithm uses ancestral proportions from previous studies (in this case Tang et al^{E6}) and data from reference panels to estimate ancestral proportions for racially admixed populations. Puerto Rican subjects are an admixture of European, African, and Native American populations; to approximate this admixture, we used reference panels from HapMap^{E7} for European (CEU [Utah residents with Northern and Western European Ancestry collected by the Centre d'Etude du Polymorphisme Humain] and TSI [Toscans in Italy]) and African (YRI [Yoruba in Ibadan, Nigeria]) subjects and from the Human Genome Diversity Project for Native American subjects.^{E8}

Mediation analysis

Mediation analysis (see Fig E1) is a type of structural equation modeling or effect decomposition that evaluates whether part or all of an association between an independent variable "X" and an outcome of interest "Y" is explained by a mediator variable "M" (the "indirect effect"). In mediation, there is a significant association between a predictor or independent variable X and the dependent variable or outcome Y ("X-Y" association). When the mediator variable M is introduced in the model, the X-Y association markedly decreases or becomes nonsignificant, while the M-Y association is significant. The difference between the X-Y association without and with M represents the indirect effect, or the proportion of the total X-Y effect that is mediated by M (which can vary from insignificant to 100% in complete mediation).

The mediation analysis was performed via classical structural equation modeling for continuous and ordinal data. However, structural equation modeling cannot be used for binary outcomes because in nonlinear models coefficients may vary not only secondary to mediation itself but also because of rescaling of the models with and without the mediator. The decomposition method described by Karlson-Holm-Breen^{E9} for binary outcomes adjusts for the rescaling issues that arise from cross-model comparisons.^{E10,E11} Therefore, we used the Karlson-Holm-Breen procedure in Stata (StataCorp, College Station, Tex) for the mediation analysis of binary outcomes such as asthma status.

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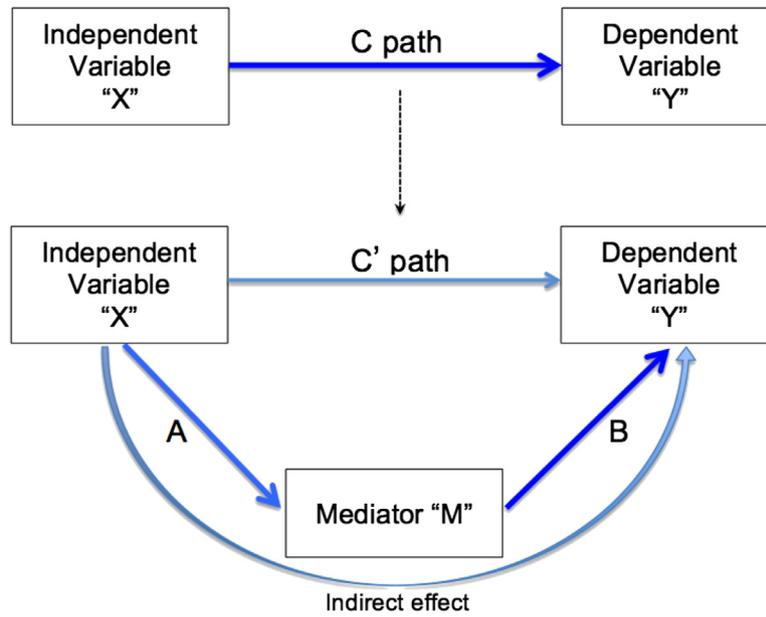


FIG E1. Mediation analysis. In mediation/decomposition analysis, the original association (X - Y or C path) is significant. When a mediator M is introduced, the direct effect (C') is markedly reduced or becomes nonsignificant. The difference between C and C' is explained by B (eg, the indirect effect via M explains a significant proportion or all the effect of X on Y).

TABLE E1. Indicators of obesity/adiposity and asthma in Puerto Rican children

	BMI	PBF	WC	WHR
Odds of asthma*	1.27 (1.1-1.5), .004	1.24 (0.99-1.6), .06	1.18 (0.98-1.4), .08	NS

Note. Values in boldface are considered statistically significant ($P < .05$).

NS, Nonsignificant.

*Adjusted for sex, age, parental history of asthma, household income, and percent African ancestry. Numbers represent odds ratios with 95% CIs in parentheses, followed by P values.

TABLE E2. Indicators of obesity/adiposity, lung function, and allergy markers in controls

	BMI	PBF	WC	WHR
Pulmonary function tests				
FEV ₁ (mL)*	NS†	NS†	NS†	NS†
FVC (mL)*	NS†	NS†	NS†	NS†
FEV ₁ /FVC (%)	NS†	NS†	NS†	NS†
Atopy measures				
Allergic rhinitis	NS†	1.6 (1.04-2.5)‡	NS†	NS†
Total IgE (IU/mL)§	NS†	1.32 (1.02-1.7)‡	1.32 (1.07-1.58)‡	NS†
STR to				
Dust mite	NS†	NS†	NS†	NS†
Cockroach	NS†	1.5 (0.99-2.3)	NS†	NS†
Alternaria	NS†	NS†	NS†	NS†
Mold	NS†	NS†	NS†	NS†
Mouse	NS†	NS†	.71 (0.49-1.05)	NS†
Any STR+	NS†	1.4 (0.96-1.9)	NS†	NS†

Note. Results for adjusted regression analysis in nonasthmatic children. All models adjusted for sex, age, household income, and for house-dust allergen levels when relevant. Numbers represent β coefficients for continuous/ordinal outcomes and odds ratio for binary outcomes (with 95% CI in parentheses) per 1.0 z-score increment in each adiposity measure. Values in boldface are considered statistically significant ($P < .05$).

NS, Not significant.

*Analyzed as absolute values because of lack of predictive equations for Puerto Ricans; adjusted additionally for sex, age, height, and height squared.

† $P > .10$ not displayed (NS).

‡ $P < .05$.

§Analyzed as \log_{10} .

|| $P < .10$.