Published in final edited form as:

J Allergy Clin Immunol. 2014 May ; 133(5): 1308–1314.e5. doi:10.1016/j.jaci.2013.09.041.

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

Erick Forno, MD MPH¹, Edna Acosta-Pérez, PhD, MSc², John M. Brehm, MD MPH¹, Yueh-Ying Han, PhD¹, María Alvarez, MD², Angel Colón-Semidey, MD², Glorisa Canino, PhD², and Juan C Celedón, MD DrPH¹

¹ Division of Pediatric Pulmonary Medicine, Allergy, and Immunology, Children's Hospital of Pittsburgh of UPMC, University of Pittsburgh, Pittsburgh, PA.

² Behavioral Sciences Research Institute and Department of Pediatrics, University of Puerto Rico, San Juan, PR

Abstract

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

Objective: To examine the relation 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 body mass index (BMI), percent body fat (PBF), waist circumference (WC), and waist-to-hip ratio (WHR). 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, PBF, and WC were associated with increased odds of asthma. Among cases, all three 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 22-53% of the association with asthma, and sensitization to cockroach mediated 13-20% of the association with FVC and 29-42% of the association with emergency room 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

© 2013 American Academy of Allergy, Asthma and Immunology. Published by Mosby, Inc. All rights reserved

Contact author: Juan C. Celedón, M.D., Dr.P.H. Division of Pediatric Pulmonary Medicine, Allergy and Immunology Children's Hospital of Pittsburgh of UPMC 4401 Penn Avenue, Pittsburgh, PA 15224 Phone: 412.692.8429; Fax 412.692.7636
juan.celedon@chp.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

outcomes. Longitudinal studies are needed to further investigate the causal role, if any, of adiposity distribution and atopy on “obese asthma” in childhood.

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 relation between obesity and asthma in Puerto Rican children.

Capsule Summary: In a cohort of Puerto Rican children, measures of adiposity were associated with asthma, asthma severity/control, and atopy; however, some differences existed depending on the adiposity indicator utilized. Atopy significantly mediated the association between adiposity indicators and asthma.

Keywords

Childhood asthma; obesity; adiposity; body mass index; percent body fat; obesity and asthma; obesity and atopy

INTRODUCTION

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 adults⁽⁴⁻⁸⁾. Compared to 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 (e.g. percent 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, as BMI alone may not adequately characterize the relation 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 (e.g. 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 relation to asthma severity or control, lung function, or markers of allergic sensitization (e.g. allergy skin testing).

In this report, we examine the relation between indicators of adiposity/obesity, allergy markers, and measures of asthma severity or control (e.g. lung function) in Puerto Rican children with asthma living in San Juan, PR. 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**. From March of 2009 to June of 2010, children in San Juan (SJ) were chosen from randomly selected households. In brief, households in the Standard Metropolitan Area of SJ were selected using a multistage probability sample design⁽²²⁾. Primary sampling units (PSUs) were randomly selected neighborhood clusters based on the 2000 U.S. Census, and secondary sampling units were randomly selected households within PSU. A household was eligible if 1 resident was a child 6- 14 years old. A total of 6,401 households selected for inclusion were contacted. Of these, 1,111 households had 1 child who met inclusion criteria other than age (four Puerto Rican grandparents and residence in the same household for 1 year). Of these 1,111 households, 438 (39.4%) had 1 eligible child with asthma (a case, defined as having physician-diagnosed asthma and wheeze in the prior year). From these 438 households, one child with asthma was selected (at random if there was more than one such child). Similarly, only one child without asthma (a control subject, defined as having neither physician-diagnosed asthma nor wheeze in the prior year) was randomly selected from the remaining 673 households. In order to reach our target sample size (~700 children), we attempted to enroll 783 of the 1,111 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, gender, 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 (AST), and collection of blood and house dust samples. Dust samples were obtained from three areas in the home: one in which the child slept (usually his/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]) using monoclonal-antibody Multiplex array assays using the same reagents employed in the established ELISA⁽²³⁾. Allergen levels were analyzed as continuous (after log10-transformation), with non-detectable 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. Percent body fat (PBF) was calculated from tricipital (TC) and subscapular (SS) skin folds⁽²⁴⁾, which were obtained by trained study personnel using calibrated calipers; the averages of three TC and SS measurements were 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 using a program based on the 2000 CDC growth charts⁽²⁵⁾; PBF z-scores were calculated using a recent study on reference equations for U.S. children and adolescents⁽²⁶⁾; and waist circumference (WC) and waist-to-hip ratio (WHR) were standardized 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 (IRBs) of the University of Puerto Rico (SJ [Protocol # 0160507]), Brigham and Women's Hospital (Boston, MA [Protocol # 2007P- 001174]), and the University of Pittsburgh (Pittsburgh, PA [Protocol # PRO10030498]).

Statistical analysis

Our outcomes of interest included asthma (defined as above), lung function measures (FEV₁, FVC and FEV₁/FVC), allergic rhinitis (defined as current naso-ocular symptoms apart from colds and at least one positive skin test 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 prior year (categorized as 0, 1-8, 9-40, and over 40); 2) missed school days due to asthma in the prior year (categorized as 0, 1-2, 3-5 or at least 6); 3) exercise-induced symptoms in the prior year (categorized as never, occasionally, frequently, or always); and 4) number of visits to the emergency department (ED) for asthma, ever.

Bivariate analyses were conducted using Fisher's exact tests for binary variables and two-tailed *t* tests for pairs of binary and continuous variables. Linear or logistic regression was used to examine the relation between each adiposity/obesity indicator and the outcomes of interest, while adjusting for potential confounders. All multivariate models included age, sex, household income (< vs. \$15,000/year [the median household income for Puerto Rico in 2008-2009⁽²⁷⁾]), parental (maternal or paternal) history of asthma, and percentage of African racial ancestry (determined using genome-wide genotypic data⁽²⁸⁾, see **Online Repository**). 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 (e.g. BMI) and outcomes of interest (e.g. 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 the Karlson-Holm- Breen decomposition method⁽²⁹⁾ 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 (i.e. allergic rhinitis, STR to cockroach) that were associated with both the adiposity indicators and the asthma outcomes. Other indicators of atopy (e.g. total IgE) did not meet this criterion and were thus not included in the mediation analysis. All statistical analyses were performed using SAS statistical software, version 9.3 (SAS Institute; Cary, NC), with the exception of the mediation analysis (which was conducted using Stata 12.1 [StataCorp, College Station, TX]).

RESULTS

The characteristics of the 678 study participants are shown in **Table 1**. 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 ($p=0.06$ and $p=0.08$, respectively) (**Table 2**). As expected, all four obesity/adiposity measurements were significantly correlated with each other ($P < 0.0001$), although the degree of correlation and the slope of the regression coefficient varied (**Figure 1**).

Table 2 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 ~69 ml higher FEV₁. All adiposity measures were positively associated with FVC, ranging from an ~50mL increment per each z-score in WHR to an ~98mL increment per z-score increment in BMI, with intermediate results obtained for PBF and WC. Of the four adiposity measures, only WC was significantly associated with a decrement in FEV₁/FVC. All adiposity measures except WHR were associated with increased lifetime ED / urgent care (UC) visits for asthma, ranging from ~3 additional ED/UC visits per each z-score increment in BMI to ~4.6 additional ED/UC visits 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 2**), 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.

In order 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 Figure S1 in the **Online Repository**). 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 three indicators of adiposity or obesity (BMI, PBF and WC) and asthma (**Table 3**); the estimated mediation effect explained 22%, 53%, and 43%, respectively, of each association. Among children with asthma, STR to cockroach mediated ~20% and ~13% of the estimated effects of PBF and WC on FVC, respectively. STR to cockroach also mediated ~28-42% 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 relation 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 asthma⁽⁴⁻⁶⁾ or worsened asthma control⁽⁷⁾ in children. In contrast to our findings for asthma, however, limiting our assessment to BMI would have led to non-detection 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 prior studies. Of interest, recent studies have shown that WC predicts total body fat (measured by dual-energy X-ray absorptiometry) more accurately than BMI, which may require different height correction factors depending on age, gender, and race⁽³⁴⁾.

To our knowledge, the only previous study that examined PBF and asthma control⁽³⁵⁾ 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 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 for glucose/insulin regulation than visceral fat 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 (e.g. non-atopic vs. atopic, etc.).

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 non-significantly) 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, interleukin (IL)-5, and eosinophilia⁽⁴⁷⁾. Cluster analysis in adults has shown that certain “obese asthmatic” phenotypes have increased IgE⁽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 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 utilizing 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 non-significant (data not shown). Our results are in contrast with those of a prior study showing that, while BMI was associated with total IgE, BMI was only associated with asthma in non-atopic 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 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, as hormonal differences before and after puberty may affect the relation among gender, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of funding: This work was supported by grant HL079966 from the US National Institutes of Health (NIH)

Abbreviations

AST	Allergy skin testing
BMI	Body mass index
ED/UC	Emergency department or urgent care visit
FVC	Forced vital capacity
FEV1	Forced expiratory volume in one second
IgE	Immune globulin E
IL	Interleukin
PBF	Percent of body fat
PSU	Primary sampling unit
SD	Standard deviation
SS	Subscapular
STR	Skin test reactivity (positive AST)

TC	Tricipital
WC	Waist circumference
WHR	Waist-to-hip ratio

REFERENCES

1. Wang Y, Lobstein T. Worldwide trends in childhood overweight and obesity. *International journal of pediatric obesity. IJPO : an official journal of the International Association for the Study of Obesity*. 2006; 1(1):11–25.
2. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity in the United States, 1999–2004. *JAMA : the journal of the American Medical Association*. 2006; 295(13):1549–55. [PubMed: 16595758]
3. Akinbami LJ, Moorman JE, Garbe PL, Sondik EJ. Status of childhood asthma in the United States, 1980–2007. *Pediatrics*. 2009; 123(Suppl 3):S131–45. Journal Article. [PubMed: 19221156]
4. Papoutsakis C, Priftis KN, Drakouli M, Prifti S, Konstantaki E, Chondronikola M, et al. Childhood overweight/obesity and asthma: is there a link? A systematic review of recent epidemiologic evidence. *Journal of the Academy of Nutrition and Dietetics*. Jan; 2013 113(1):77–105. PubMed PMID: 23260726. [PubMed: 23260726]
5. Flaherman V, Rutherford GW. A meta-analysis of the effect of high weight on asthma. *Archives of Disease in Childhood*. 2006; 91(4):334–9. [PubMed: 16428358]
6. Stream AR, Sutherland ER. Obesity and asthma disease phenotypes. *Curr Opin Allergy Clin Immunol*. Feb; 2012 12(1):76–81. PubMed PMID: 22157152.
7. Borrell LN, Nguyen EA, Roth LA, Oh SS, Tcheurekdjian H, Sen S, et al. Childhood Obesity and Asthma Control in a Diverse Sample: Examining age and Racial/Ethnic Differences. *Am J Respir Crit Care Med*. Feb 7.2013 PubMed PMID: 23392439.
8. Rzehak P, Wijga AH, Keil T, Eller E, Bindslev-Jensen C, Smit HA, et al. Body mass index trajectory classes and incident asthma in childhood: Results from 8 European Birth Cohorts-a Global Allergy and Asthma European Network initiative. *J Allergy Clin Immunol*. Feb 9.2013 PubMed PMID: 23403049.
9. Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedon JC. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol*. Mar; 2011 127(3): 741–9. PubMed PMID: 21377042. Pubmed Central PMCID: 3056233. Epub 2011/03/08. eng. [PubMed: 21377042]
10. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS One*. 2012; 7(5):e36631. PubMed PMID: 22606276. Pubmed Central PMCID: 3350517. [PubMed: 22606276]
11. Lugogo NL, Kraft M, Dixon AE. Does obesity produce a distinct asthma phenotype? *Journal of applied physiology (Bethesda, Md: 1985)*. 2010; 108(3):729–34.
12. Coutinho T, Goel K, Correa de Sa D, Carter RE, Hodge DO, Kragelund C, et al. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of "normal weight central obesity". *Journal of the American College of Cardiology*. Feb 5; 2013 61(5):553–60. PubMed PMID: 23369419. [PubMed: 23369419]
13. Lam YY, Mitchell AJ, Holmes AJ, Denyer GS, Gummeson A, Caterson ID, et al. Role of the gut in visceral fat inflammation and metabolic disorders. *Obesity*. Nov; 2011 19(11):2113–20. PubMed PMID: 21881620. [PubMed: 21881620]
14. Cibella F, Cuttitta G, La Grutta S, Melis MR, Bucchieri S, Viegi G. A cross-sectional study assessing the relationship between BMI, asthma, atopy, and eNO among schoolchildren. *Ann Allergy Asthma Immunol*. Oct; 2011 107(4):330–6. PubMed PMID: 21962093. [PubMed: 21962093]

15. Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth cohort. *Am J Respir Crit Care Med*. Mar 1; 2005 171(5):440–5. PubMed PMID: 15557135. [PubMed: 15557135]
16. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, et al. Association of childhood obesity with atopic and nonatopic asthma: results from the National Health and Nutrition Examination Survey 1999–2006. *J Asthma*. Sep; 2010 47(7):822–9. PubMed PMID: 20707763. Pubmed Central PMCID: 2975947. Epub 2010/08/17. eng. [PubMed: 20707763]
17. Van Gysel D, Govaere E, Verhamme K, Doli E, De Baets F. Body mass index in Belgian schoolchildren and its relationship with sensitization and allergic symptoms. *Pediatr Allergy Immunol*. May; 2009 20(3):246–53. PubMed PMID: 18798801. [PubMed: 18798801]
18. Cohen RT, Canino GJ, Bird HR, Shen S, Rosner BA, Celedon JC. Area of residence, birthplace, and asthma in Puerto Rican children. *Chest*. 2007; 131(5):1331–8. [PubMed: 17494783]
19. Homa DM, Mannino DM, Lara M. Asthma mortality in U.S. Hispanics of Mexican, Puerto Rican, and Cuban heritage, 1990–1995. *Am J Respir Crit Care Med*. 2000; 161(2 Pt 1):504–9. [PubMed: 10673193]
20. CDC. Prevalence and Trends Data - Overweight and Obesity (BMI) - 2011 2011 [03/07/2013]. Available from: <http://apps.nccd.cdc.gov/brfss/list.asp?cat=OB&yr=2011&qkey=8261&state=All>
21. Vangeepuram N, Teitelbaum SL, Galvez MP, Brenner B, Doucette J, Wolff MS. Measures of obesity associated with asthma diagnosis in ethnic minority children. *Journal of obesity*. 2011;517417. 2011. PubMed PMID: 21773007. Pubmed Central PMCID: 3136214. [PubMed: 21773007]
22. Forno E, Cloutier MM, Datta S, Paul K, Sylvia J, Calvert D, et al. Mouse allergen, lung function, and atopy in puerto rican children. *PLoS ONE*. 2012; 7(7):e40383. PubMed PMID: 22815744. Pubmed Central PMCID: 3398035. Epub 2012/07/21. eng. [PubMed: 22815744]
23. Luczynska CM, Arruda LK, Platts-Mills TA, Miller JD, Lopez M, Chapman MD. A two-site monoclonal antibody ELISA for the quantification of the major *Dermatophagoides* spp. allergens, Der p I and Der f I. *J Immunol Methods*. 1989; 118(2):227–35. [PubMed: 2926155]
24. Monyeki KD, Kemper HC, Makgae PJ. Relationship between fat patterns, physical fitness and blood pressure of rural South African children: Ellisras Longitudinal Growth and Health Study. *Journal of human hypertension*. May; 2008 22(5):311–9. PubMed PMID: 18273041. Epub 2008/02/15. eng. [PubMed: 18273041]
25. CDC. A SAS Program for the CDC Growth Charts 2011 [January 10, 2013]. Available from: <http://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm>
26. Laurson KR, Eisenmann JC, Welk GJ. Body fat percentile curves for U.S. children and adolescents. *Am J Prev Med*. Oct; 2011 41(4 Suppl 2):S87–92. PubMed PMID: 21961617. Epub 2011/10/14. eng. [PubMed: 21961617]
27. Bureau UC. Household Income for the States: 2008 and 2009 2010 [January 10, 2013]. Available from: <http://www.census.gov/prod/2010pubs/acsbr09-2.pdf>
28. Brehm JM, Acosta-Perez E, Klei L, Roeder K, Barmada MM, Boutaoui N, et al. African ancestry and lung function in Puerto Rican children. *J Allergy Clin Immunol*. Jun; 2012 129(6):1484–90. e6. PubMed PMID: 22560959. Pubmed Central PMCID: 3367038. Epub 2012/05/09. eng. [PubMed: 22560959]
29. Karlson K, Holm A. Decomposing primary and secondary effects: A new decomposition method. *Research in Social Stratification and Mobility*. 2011; 29(2):221–37.
30. Kohler U, Karlson K, Holm A. Comparing coefficients of nested nonlinear probability models. *The Stata Journal*. 2011; 11(3):420–38.
31. Breen, R.; Karlson, K.; Holm, A. Total, Direct, and Indirect Effects in Logit and Probit Models. *Sociological Methods & Research* [Internet]. Apr. 2011 2011. Available from: <http://ssrn.com/abstract=1730065>
32. Kodama S, Horikawa C, Fujihara K, Heianza Y, Hirasawa R, Yachi Y, et al. Comparisons of the strength of associations with future type 2 diabetes risk among anthropometric obesity indicators, including waist-to-height ratio: a meta-analysis. *Am J Epidemiol*. Dec 1; 2012 176(11):959–69. PubMed PMID: 23144362. [PubMed: 23144362]

33. Chrysant SG, Chrysant GS. New insights into the true nature of the obesity paradox and the lower cardiovascular risk. *Journal of the American Society of Hypertension : JASH*. Jan; 2013 7(1):85–94. PubMed PMID: 23321407. [PubMed: 23321407]
34. Heo M, Kabat GC, Gallagher D, Heymsfield SB, Rohan TE. Optimal scaling of weight and waist circumference to height for maximal association with DXA-measured total body fat mass by sex, age and race/ethnicity. *International journal of obesity*. Dec 4.2012 PubMed PMID: 23207404.
35. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *The Journal of allergy and clinical immunology*. 2010; 125(3):584–92. [PubMed: 20226295]
36. Maffei C, Manfredi R, Trombetta M, Sordelli S, Storti M, Benuzzi T, et al. Insulin sensitivity is correlated with subcutaneous but not visceral body fat in overweight and obese prepubertal children. *J Clin Endocrinol Metab*. Jun; 2008 93(6):2122–8. PubMed PMID: 18397988. [PubMed: 18397988]
37. Hoffstedt J, Arner E, Wahrenberg H, Andersson DP, Qvist V, Lofgren P, et al. Regional impact of adipose tissue morphology on the metabolic profile in morbid obesity. *Diabetologia*. Dec; 2010 53(12):2496–503. PubMed PMID: 20830466. [PubMed: 20830466]
38. Garcia-Marcos L, Valverde-Molina J, Ortega ML, Sanchez-Solis M, Martinez-Torres AE, Castro-Rodriguez JA. Percent body fat, skinfold thickness or body mass index for defining obesity or overweight, as a risk factor for asthma in schoolchildren: which one to use in epidemiological studies? *Matern Child Nutr*. 2008; 4(4):304–10. [PubMed: 18811794]
39. Fenger RV, Gonzalez-Quintela A, Vidal C, Gude F, Husemoen LL, Aadahl M, et al. Exploring the obesity-asthma link: do all types of adiposity increase the risk of asthma? *Clin Exp Allergy*. Aug; 2012 42(8):1237–45. PubMed PMID: 22805471. [PubMed: 22805471]
40. Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. Sep; 2006 130(3):827–33. PubMed PMID: 16963682. [PubMed: 16963682]
41. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Childhood Asthma Management Program Research G. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003; 58(12):1036–41. [PubMed: 14645968]
42. Vo P, Makker K, Matta-Arroyo E, Hall CB, Arens R, Rastogi D. The association of overweight and obesity with spirometric values in minority children referred for asthma evaluation. *J Asthma*. Feb; 2013 50(1):56–63. PubMed PMID: 23189981. [PubMed: 23189981]
43. Sidoroff V, Hyvarinen M, Piippo-Savolainen E, Korppi M. Lung function and overweight in school aged children after early childhood wheezing. *Pediatr Pulmonol*. Dec 30.2010 PubMed PMID: 21194138.
44. Rastogi D, Canfield SM, Andrade A, Isasi CR, Hall CB, Rubinstein A, et al. Obesity-associated asthma in children: a distinct entity. *Chest*. Apr; 2012 141(4):895–905. PubMed PMID: 21980061. [PubMed: 21980061]
45. Vieira VJ, Ronan AM, Windt MR, Tagliaferro AR. Elevated atopy in healthy obese women. *Am J Clin Nutr*. Sep; 2005 82(3):504–9. PubMed PMID: 16155260. [PubMed: 16155260]
46. Beuther DA, Weiss ST, Sutherland ER. Obesity and asthma. *Am J Respir Crit Care Med*. Jul 15; 2006 174(2):112–9. PubMed PMID: 16627866. Pubmed Central PMCID: 2662903. Epub 2006/04/22. eng. [PubMed: 16627866]
47. Dietze J, Bocking C, Heverhagen JT, Voelker MN, Renz H. Obesity lowers the threshold of allergic sensitization and augments airway eosinophilia in a mouse model of asthma. *Allergy*. Dec; 2012 67(12):1519–29. PubMed PMID: 23005257. [PubMed: 23005257]
48. Celedon JC, Sredl D, Weiss ST, Pisarski M, Wakefield D, Cloutier M. Ethnicity and skin test reactivity to aeroallergens among asthmatic children in Connecticut. *Chest*. 2004; 125(1):85–92. [PubMed: 14718425]
49. Visness CM, London SJ, Daniels JL, Kaufman JS, Yeatts KB, Siega-Riz AM, et al. Association of obesity with IgE levels and allergy symptoms in children and adolescents: results from the National Health and Nutrition Examination Survey 2005-2006. *J Allergy Clin Immunol*. May; 2009 123(5):1163–9. PubMed PMID: 19230960. Pubmed Central PMCID: 2748319. [PubMed: 19230960]

50. Schachter LM, Peat JK, Salome CM. Asthma and atopy in overweight children. *Thorax*. Dec; 2003 58(12):1031–5. PubMed PMID: 14645967. Pubmed Central PMCID: 1746556. [PubMed: 14645967]

Figure 1.
Correlation between BMI and indicators of adiposity.

Table 1

Characteristics of study participants

Demographics	Cases N=351	Controls N=327
Male gender	201 (57.3%)**	159 (48.6%)
Age (years)	10.0 (2.59)**	10.5 (2.73)
Parental asthma history	68.1%**	33.1%
Household income \$15,000/yr	34.6%	37.2%
African ancestry (%)	25.2 (11.7)	24.8 (12.5)
Household dust allergen levels ¹ :		
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 measures²		
Body mass index (BMI)	0.69 (1.19)**	0.51 (1.12)
Percent body fat (PBF)	0.29 (0.86)*	0.22 (0.77)
Waist circumference (WC)	0.03 (1.04)*	-0.03 (0.95)
Waist-to-hip ratio (WHR)	0.001 (0.85)	-0.001 (1.13)
Pulmonary function tests		
FEV1 (L)	1.88 (0.67)**	2.05 (0.74)
FVC (L)	2.33 (0.82)**	2.47 (0.88)
FEV1/FVC (%)	80.9% (9.0%)**	83.5% (8.9%)
Asthma severity		
No. of ED/UC visits for asthma ¹	10 [5-20]	n/a
Severity scores, past year ¹ :		
- Prednisone courses (0-4)	2 [1-2]	n/a
- Exercise symptoms (0-3)	1 [1-3]	n/a
- Missed school days(0-3)	1 [0-2]	n/a
Atopy measures		
Total serum IgE (IU/mL) ¹	346 [116-881]**	158 [44-600]
Allergic rhinitis ³	53.6%**	19.2%
Skin-test reactivity (STR) to:		
- Dust mite	55.4%**	41.6%
- Cockroach	39.4%**	26.3%
- Alternaria	25.2%	24.8%
- Mold	12.2%	14.4%

Demographics	Cases N=351	Controls N=327
- Mouse	26.2%	21.2%
- Any STR+	69.0% **	56.0%

Numbers for continuous variables represent mean (SD), except

ED/UC: Emergency department / urgent care.

¹ median [IQR].

² All transformed to z-scores.

³ Defined as history of allergic rhinitis plus current symptoms plus STR to at least one allergen.

* P<0.10,

** P<0.05.

Table 2

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

	Body mass index (BMI)	Percent body fat (PBF)	Waist circumference (WC)	Waist-to-hip ratio (WHR)
Asthma status	1.27 (1.1-1.5)**	1.24 (.99-1.6)*	1.18 (.98-1.4)*	1.12 (.93-1.35)
Lung function in cases				
FEV1 (mL) ^I	+68.8 (34.7 – 103.0)**	+37.5 (-10.5 – 84.5)	+20.1 (-18.3 – 60.2)	+27.3 (-19.4 – 74.0)
FVC (mL) ^I	+98.0 (59.0 – 137.1)**	+63.4 (8.9 – 117.8)**	+61.1 (15.9 – 106.2)**	+50.1 (-4.0 – 104.3)*
FEV1/FVC (%)	-0.6 (-1.5 – 0.5)	-0.6 (-1.9 – 0.7)	-1.0 (-2.1 – 0.0)*	-0.7 (-2.1 – 0.7)
Asthma severity				
Urgent care visits, ever	+3.0 (0.01 – 6.1)**	+4.6 (0.50 – 8.79)**	+3.4 (-0.01 – 6.8)*	+2.4 (-2.0 – 6.9)
>1 urgent care visit, last yr	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 – 0.17)*	+0.15 (0.03 – 0.28)**	+0.07 (-0.03 – 0.14)	+0.07 (-0.05 – 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 – 0.26)
- Exercise symptoms	+0.09 (-0.02 – 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 (IU/mL) ²	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 ³ :				
- 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)*

Results for adjusted regression analysis in asthmatic children. All models adjusted for gender, age, parental history of asthma, household income, and percent African ancestry. Numbers represent β coefficients for continuous/ordinal outcomes and OR for binary outcomes (with 95%CI in parentheses) per 1.0 z-score increment in each adiposity measure.

* P<0.10,

** P<0.05. P>0.10 dimmed in gray.

^I Analyzed as absolute values due to lack of predictive equations for Puerto Ricans; adjusted additionally for gender, age, height, and height squared.

² Analyzed as log₁₀.

³ 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.

Table 3

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

	Body mass index (BMI)	Percent body fat (PBF)	Waist circumference (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 – 105) .09	+65 (17 – 114) .008	
Indirect effect	+7 (–2 – 16) .11	+12 (–1 – 26) .08	+10 (–1 – 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 (–.3 – 6) .08	+4.7 (0.5 – 9) .03	+2.7 (–0.9 – 6) .14	
Direct effect	+2.0 (–1 – 5) .21	+3.4 (–1 – 8) .13	+1.6 (–2 – 5) .39	
Indirect effect	+.8 (–0.08 – 2) .07	+1.4 (0.01 – 3) .048	+1.1 (0.01 – 2) .048	
Percent mediated	28.7%	28.9%	41.9%	
Total/direct effect	1.40	1.41	1.72	

Results from decomposition (binary outcomes) or structural equation modeling (continuous outcomes). Table shows odds ratios (binary outcomes) or beta coefficients (continuous outcomes), 95% confidence intervals, 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. ED/UC: Emergency department / urgent care.