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Obese and Allergic Related Asthma Phenotypes Among Children Across the United States

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Abstract

Objectives—Pediatric asthma is heterogeneous with phenotypes that reflect differing underlying inflammation and pathophysiology. Little is known about the national prevalence of certain obesity and allergy related asthma phenotypes or associated characteristics. We therefore assessed the national prevalence, risk factors, and parent-reported severity of four asthma phenotypes: not-allergic-not-obese, allergic-not-obese, obese-not-allergic, and allergic-and-obese.

Methods—We analyzed data from the 2007–2008 National Survey of Children's Health (NSCH) of 10–17 year-olds with parent-reported asthma. We described sociodemographic and health risk factors of each phenotype and then applied logistic and ordinal regression models to identify associated risk factors and level of severity of the phenotypes.

Results—Among 4,427 children with asthma in this NSCH cohort, the association between race and phenotype is statistically significant ($p<0.0001$); white children with asthma were most likely to have allergic-not-obese asthma while black and Hispanic children with asthma were most likely to have the obese-non-allergic phenotype ($p<0.001$). ADD/ADHD was more likely to be present in allergic-not-obese children (OR 1.50, CI 1.14–1.98, $p=0.004$). The phenotype with the highest risk for more severe compared to mild asthma was the obese-and-allergic asthma phenotype (OR 3.34, CI 2.23–5.01, $p<0.001$).

Conclusions—Allergic-not-obese asthma comprised half of our studied asthma phenotypes, while obesity-related asthma (with or without allergic components) comprised one-fifth of asthma phenotypes in this cohort representative of the U.S. population. Children with both obese and allergic asthma are most likely to have severe asthma. Future management of childhood asthma might consider more tailoring of treatment and management plans based upon different childhood asthma phenotypes.

Keywords

Pediatrics; Obesity

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Introduction

Asthma causes substantial morbidity due to poorly controlled symptoms in up to one-third of patients.(1) While many factors contribute to lack of asthma control, one challenge is the variable nature of underlying inflammation of asthma—e.g. eosinophilic, neutrophilic, mixed, or paucigranulocytic.(2) Research on adults and children with asthma has identified several asthma phenotypes using secondary data analysis from previously performed intervention trials; these include allergic-related, obese-related, early-onset, late-onset, viral-induced, symptom-related, smoking-related, exercise-induced, and aspirin-related asthma.(3–11)

Experts believe that some of these phenotypes reflect the underlying pathophysiology of the patients and identifying these phenotypes might allow clinicians to differentiate inflammation types, and thereby tailor optimal medications.(12–15) There are some types of inflammation that do not respond as well to corticosteroids,(16) yet this medication class is typically the first-line approach across-the-board for all children with asthma.(17) While asthma treatment guidelines provide a somewhat uniform approach for all patients in terms of medication use, an even more effective strategy might be to inform treatment choice based on the underlying inflammatory process represented by different phenotypes of asthma.

Two pediatric asthma phenotypes identified through previous clustering work to further study are obese-related and allergic-related phenotypes because they likely represent contrasting underlying inflammation.(18) Allergic-asthma represents eosinophilic inflammation(19) and obese-asthma can represent a non-T helper 2 (Th2) mediated inflammation response (e.g. neutrophilic inflammation).(20–22) Patients with both allergies and obesity can represent a mixed inflammation picture and those with neither can represent paucigranulocytic or different underlying inflammation pattern. A personalized approach to asthma treatment might base treatment on the inflammatory process; thus identifying asthma phenotypes becomes important.(23, 24)

To our knowledge the national prevalence of different combinations of allergic and obese-related pediatric asthma phenotypes are unknown. Similarly, patient characteristics or risk factors related to each phenotype are not well understood. There are an estimated 6.2 million children with asthma,(25) 6.1 million with hay fever, 4.1 million with food allergies, 8.8 million with skin allergies,(26) and 12.7 million with obesity(27) in the United States (U.S.), but it is unknown how many children have concomitant asthma plus obesity and/or allergies. In addition, more information is needed about the relationship of pediatric obese and allergic-related asthma and health-risk factors and asthma severity. For example, factors such as poverty, stressors, and secondhand smoke might be associated with different asthma phenotypes or with different asthma severity.

The goal of this study was to characterize obese and allergic related pediatric asthma phenotypes among older children in a large national cohort of children in the U.S., the National Survey of Children's Health (NSCH). Our specific objectives were to 1) describe the prevalence of obese and allergic pediatric asthma phenotypes, 2) assess

sociodemographic factors associated with each phenotype, and 3) estimate the relationship of obese and allergic related phenotypes and severity of asthma.

Methods

Sample

The NSCH survey is a recurring nationally representative survey of parents of U.S. residents. The survey is conducted in English and Spanish for children ages 0–17, with sampling methods that use the State and Local Area Integrated Telephone Survey created by the National Center for Health Statistics. We analyzed data from the 2007–2008 NSCH, which included a total of 91,642 completed surveys. We used this dataset because it included questions about allergic status; which were not present in the 2011–2012 survey (the most recent publicly available data at the time of this study). Children 10–17 years were included if their parents responded positively to asthma questions, and if body mass index percentile and allergic status were documented. The University of California Los Angeles (UCLA) institutional review board approved a waiver of consent for this secondary data analysis of de-identified data.

Measurements

Asthma presence and severity—Asthma status was determined by a positive response to “Has a doctor or other health care provider ever told you that your child had asthma?” and “Does your child currently have asthma?”(28) The severity of asthma was determined by caregiver response to the question “would you describe (his/her) asthma as mild, moderate, or severe?”(29, 30)

Obese presence—We categorized a child as obese if they met the U.S. Preventive Services Task Force recommendation statement definition of ≥95% body mass index (BMI) percentile for age based upon the Center for Disease Control growth charts.(31, 32) The BMI percentiles in the dataset were predetermined by the Data Resource Center for Child and Adolescent Health from the parent-reported height and weight. They estimated participants were at the midpoint of the year for their reported age. In the NSCH, the height and weigh data is only available to calculate BMI for children aged 10–17 because it has been demonstrated that height is overestimated and weight is underestimated by caregiver report in children less than10-years-old.(33) Therefore our sample was limited to children 10–17 years of age.

Allergic presence—Allergic status was determined by a positive response to the question “During the past 12 months, have you been told by a doctor or other health care provider that your child had a) hay fever or any kind of respiratory allergy, b) any kind of food or digestive allergy, or c) eczema or any kind of skin allergy”?(34)

Sociodemographic and Health Risk Factors (Covariates)—Demographic features assessed from this dataset included age, sex, race, and urban setting. We included additional socioeconomic risk factors based upon the previous literature that might be independently associated with greater asthma severity or obesity.(35–39) Factors included in our analysis

were family income, caregiver education, family structure, parental mental illness (stressor), insurance status (with uninsured as a marker for access), unsafe neighborhood (stressor), and caregiver's overall rating of the child's health status. Risk factors such as parental asthma status were not available in this dataset.

Analysis

We divided the cohort into four phenotypes based on prior literature and that represents different underlying inflammation: Not-allergic-not-obese, allergic-not-obese, obese-not-allergic, and obese-and-allergic. We used descriptive statistics to describe sociodemographic and health risk factors among the cohort. We used chi-square tests of association/analysis of variance (ANOVA) to examine the association between categorical/continuous sociodemographic and health risk factors related to pediatric phenotypes.

Next, in order to evaluate the sociodemographic and health risk factors associated with each asthma type, we modeled the four phenotypes as dependent variables in a nominal multivariable logistic regression model, keeping the not-allergic-not-obese phenotype as the reference group. Since all of the children in the cohort had asthma, we chose this group as the comparison because we found that in an ordinal logistic regression model, obesity and allergy were associated with more severe asthma individually and combined.

We included the variables of age (< or ≥12 years old), sex (male or female), race/ethnicity (white, black, Hispanic, or other), federal poverty level (FPL) <300% family income level, highest caregiver education (high school or greater than high school), insurance status (none, public, private or unknown type), family structure (single mother, two parents, or other), divorced parent, smoker in household, emotional health of parent (fair/good or poor), >2 hours screen time/day, presence of television in child's room, exercise <3 times per week, unsafe neighborhood, presence of a mental health/behavioral diagnosis (attention-deficit disorder (ADD)/attention-deficit hyperactivity disorder (ADHD), depression, anxiety, conduct or behavior disorder, or autism), and presence of other chronic illness (diabetes or seizures) in the child. We also included the interaction between a) poverty and family structure, and b) poverty and insurance status and both of the interaction terms were not statistically significant. We included variables that were statistically significant ($p<0.05$) and used Bayesian information criterion (BIC) to select a model with the best fit.

Finally, we performed partial proportional odds ordinal logistic regression to identify the sociodemographic and health risk features associated with the outcome of more severe asthma (categories being mild, moderate, or severe). We first performed the model selection procedure using variables of age (< or ≥12years old), sex, race, obese status, allergy status, family income, caregiver education, family structure, secondhand smoke exposure, emotional health of parent, screen time, exercise, type of neighborhood, insurance status, and mental health/behavioral diagnosis as independent covariates. To determine the final set of covariates, we selected those with a p-value <0.05, which led to the most parsimonious model with the best fit using BIC. The interaction between FPL <300% and insurance type was significant, which means the effect of insurance was modified by income level. Pairwise interactions between FPL<300% and unsafe neighborhood; FPL <300% and race; race and insurance status; race and obesity; caregiver education and obesity/allergy/FPL<300%/

unsafe neighborhood/mental health behavior diagnosis; and obesity and allergies were not statistically significant. Obesity and caregiver education did not meet the proportionality odds assumption. We performed statistical analysis using Statistical Analysis System (SAS) 9.4; Cary, North Carolina.

Results

Of the 91,642 children in the NSCH 2007–2008 survey cohort, there were 4,562 (4.9%) children ages 10–17 years old in the analytic dataset with asthma. Of these children, 145 (3.1%) were excluded because they did not have a documented allergy, asthma severity or a BMI percentile. Therefore, our final analysis comprised 4,427 children.

Prevalence of Asthma Phenotypes

Of the children ages 10–17 years old with asthma in the 2007–2008 NSCH survey cohort, the most common group was the allergic-not-obese (49.4%), followed by not-allergic-not-obese (30.8%), obese-and-allergic (12.2%), and obese-not-allergic (7.6%) phenotypes.

Sociodemographic and Health Risk Factors Associated with Asthma Phenotypes

Overall, males comprised a significantly higher proportion of all the phenotypes, more so in the obese-and-allergic phenotype. Across all race/ethnicities, allergic asthma was more prevalent than other phenotypes. The largest proportion of white children with asthma had the allergic-not-obese phenotype and the largest proportions of black and Hispanic children with asthma had the obese-and-allergic phenotype (Table 1). The two phenotypes that included obese children (obese-allergic and obese-not-allergic) had a higher proportion (vs. the two non-obese phenotypes combined) of families with the following characteristics: <300% of the FPL, less educated caregivers, more single mother households, more secondhand tobacco smoke exposure, less than three hours per week of physical activity, and perceived as having less overall good health (Table 2).

Features Associated with Asthma Phenotypes

The results of the multinomial logistic regression analysis are presented in Table 3. As compared to non-allergic-non-obese asthma, children of black or Hispanic race/ethnicity, (versus white), males, younger (age <12 years), low-income family, and less exercise (<3 times per week) were all significantly associated with the two phenotypes that include obesity (obese-not-allergic and obese-and allergic) and are overall consistent with risk factors for obesity except for age. The only feature significantly associated with the allergic-related phenotypes (allergic-not-obese and obese-and-allergic) was a mental health/behavioral diagnosis in the child. In particular, among children with both asthma and ADD/ADHD, ADD/ADHD was more likely to be present in allergic-not-obese children (odds ratio (OR) 1.50, confidence interval (CI) 1.14–1.98, p=0.004) than other phenotypes as compared to not-allergic-not-obese children.

Asthma Severity

There was a significant association between severity of asthma and phenotypes (p<0.001)—allergic-related phenotypes were more likely to have more severe asthma. Severe asthma was

most prevalent in the obese-and-allergic phenotype (7.7%) and least prevalent in the not-allergic-not-obese phenotype (1.6%) as shown in Figure 1.

We then modeled the severity of asthma (dependent variable) using multivariable ordinal logistic regression controlling for obesity, allergy, race, poverty level, caregiver education level, insurance status, neighborhood safety, and mental health/behavioral diagnosis. There were 4,047 complete cases included in the model. All the covariates except obesity and caregiver education satisfied the proportionality odds assumption.

In regard to phenotype characteristics, obesity-related phenotypes were independently associated with a 1.59 higher odds of more severe asthma as compared to mild asthma (CI 1.09–2.30, p=0.015), adjusting for the above-mentioned covariates. Allergy-related phenotypes were independently associated with a 2.11 higher odds of more severe asthma as compared to mild asthma (CI 1.79–2.47, p<0.001). Furthermore, the presence of both obesity and allergies (obese-and-allergic phenotype) was associated with a 3.34 higher odds of more severe versus mild asthma (CI 2.23–5.01, p<0.001), Table 4.

Apart from asthma phenotypes, several sociodemographic factors were independently associated with more severe asthma: being black and Hispanic vs. white race/ethnicity, poverty, no health insurance, and the presence of a mental health/behavioral diagnosis. There was a significant interaction between income level and insurance (p=0.044), which implies that the risk of severe asthma was higher for those without insurance who are also below poverty level (Table 4).

Discussion

In the 2007 NSCH cohort, 61.6% of children have allergic related asthma, and about one-fifth of older children with asthma have obesity-related asthma. Further, allergy-related phenotypes were associated with more severe asthma than phenotypes without allergies. Children who have asthma and are obese with allergies were reported to have the most severe asthma.

Our multivariable analysis determined that the risk factors most associated with an obese-related asthma phenotype were largely the same as some of the risk factors for pediatric obesity-- parental obesity, >8 hours of television per week, more weight gain in the first year of life, heavier birth weight, less sleep, lower socioeconomic status, being male, black or Hispanic race/ethnicity, and increased sedentary time.(40, 41)

We do not have a clear explanation for why the risk factor that was the most independently associated with an allergic-related asthma phenotype (when compared to the not-allergic-not-obese group) was the presence of a mental health/behavior diagnosis. Although numbers were small, when we analyzed children with only ADD/ADHD we found that it was significantly associated with the allergic-not-obese phenotype. We also noted that among children with asthma in this dataset, a mental health/behavioral diagnosis was associated with more severe asthma. Perhaps children with behavior or mental health issues are less adherent to medications, and therefore have less controlled symptoms. In addition, stress itself can be a trigger for asthma symptoms. Interestingly, a relationship between mental

health and/or behavioral diagnoses such as ADHD and asthma/allergic disorders has been reported previously in the literature, although the underlying mechanism is unclear. Hypotheses include possible genetic and environmental influences, the release of nerve growth factor (NGF) by mast cell activation or abnormal NGF regulation causing persistent inflammation.(42–44) Studies investigating histamine function's role has had mixed results, some with negative findings (45, 46), and further research is underway.(47) We did not find that exposure to tobacco smoke was significantly associated with any asthma phenotype or with asthma severity. This may be due to collinearity with other risk factors included in the models.

The obese-and-allergic phenotype was associated with the highest risk of more severe asthma. This relationship has been described in the adult literature and mouse models without a unified explanation. Possible explanations are that obesity increases allergic-related airway hyperreactivity and serum IgE, changes in eosinophil location in the airway, adipokines (adiponectin and leptin) affect allergic inflammation, and alteration of pathways such as chitinase 3-like-1 affect both obesity and allergic inflammation.(48–51)

Our study has several strengths. We analyzed a large national survey that included parent-reported height and weight (allowing for an estimated BMI), detailed questions about asthma and allergies, and a rich set of covariates. We attempted to control for covariates likely to be related to asthma prevalence and severity. Nevertheless, there are some limitations to this work. First, the survey data is based upon caregiver report and may not be completely accurate. Caregivers may underestimate the diagnosis of asthma when self-reporting, so that our estimates of the national prevalence of asthma and different asthma phenotypes might be conservative. A report of physician-diagnosed asthma can prevent reporting errors; however, there is still potential for misclassification. Allergic status was determined based upon a question that inferred the child had discussed allergies with a physician in the past year. While this question was used to determine allergic status in previous studies, this may underestimate the number of children with allergies. Asthma severity was also parent-reported rather than derived from an objective measure such as forced expiratory volume in 1 second (FEV1). Parent-reported asthma severity has been used in prior asthma studies,(29, 30) but studies have shown that parents are not always accurate and tend to underestimate the severity and control of their child's asthma.(52–54) We were unable to include children <10 years old because the parent-reported BMI in this age group is less accurate.(33) Of note, self-reported BMI for older children can also be at risk of height overestimation and weight underestimation.(55) Finally, we studied an older dataset and pediatric asthma phenotypes may have changed over the past ten years; however, there was not a newer NSCH dataset available that captured data about allergic status of children and these phenotypes have been identified in recent literature.

Despite these limitations, we feel our findings have immediate implications for the management of childhood asthma. The risk of asthma severity based on obesity and allergic status highlights the importance of incorporating the concept of asthma phenotypes into the management strategy of children with asthma to achieve a more individualized care plan. Our findings highlight the importance of identifying and treating co-morbidities and

addressing modifiable patient or family risk factors such as children's behavioral or mental health conditions.

Our findings also have implications for the future management of childhood asthma. There is some literature to suggest that medication treatment could be tailored based on a child's asthma phenotype and underlying inflammation. Allergic inflammation is related to Th2 pathways and it has been demonstrated that corticosteroids are more effective for eosinophilic inflammation.(56) Whereas, obese inflammation may be related to other inflammatory pathways including those related to neutrophils and Th17(22) and may benefit from treatment with other medications. One report suggests that adults with obese-and-allergic asthma respond favorably to montelukast, a leukotriene receptor antagonist.(57) In terms of children who are both obese and allergic, it has been postulated that mast cells may be involved in obese asthma; therefore mast cell stabilizers may have potential as an additional therapy for this phenotype.(58, 59) While it is too early to recommend tailored asthma medications at this point, further studies of treatment for different asthma phenotypes may elucidate helpful strategies to personalize asthma treatment.

Conclusion

Pediatric asthma can be classified into distinct phenotypes related to obesity and allergies. In older children across the U.S., allergic-not-obese asthma comprises half of all asthma phenotypes, while obesity-related asthma (with or without allergic components) comprises one-fifth of asthma phenotypes. Children with the phenotype associated with both obesity and allergies are at greater risk for severe asthma than children without either obesity or allergies. A next step toward personalized asthma management is increased consideration of asthma phenotypes and their risk factors in the treatment plan for children with asthma.

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References

1. Sullivan SD, Rasouliyan L, Russo PA, Kamath T, Chipps BE, Group TS. Extent, patterns, and burden of uncontrolled disease in severe or difficult-to-treat asthma. Allergy. 2007;62(2):126–33. doi: 10.1111/j.1398-9995.2006.01254.x. PubMed PMID: 17298420. [PubMed: 17298420]
2. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. Respirology. 2006;11(1):54–61. doi: 10.1111/j.1440-1843.2006.00784.x. PubMed PMID: 16423202. [PubMed: 16423202]
3. Henderson J, Granell R, Heron J, Sherriff A, Simpson A, Woodcock A, et al. Associations of wheezing phenotypes in the first 6 years of life with atopy, lung function and airway responsiveness in mid-childhood. Thorax. 2008;63(11):974–80. doi: 10.1136/thx.2007.093187. PubMed PMID: 18678704; PubMed Central PMCID: PMCPMC2582336. [PubMed: 18678704]
4. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218–24. doi: 10.1164/rccm.200711-1754OC. PubMed PMID: 18480428; PubMed Central PMCID: PMCPMC3992366. [PubMed: 18480428]

5. Weatherall M, Travers J, Shirtcliffe PM, Marsh SE, Williams MV, Nowitz MR, et al. Distinct clinical phenotypes of airways disease defined by cluster analysis. Eur Respir J. 2009;34(4):812–8. doi: 10.1183/09031936.00174408. PubMed PMID: 19357143. [PubMed: 19357143]
6. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315–23. doi: 10.1164/rccm.200906-0896OC. PubMed PMID: 19892860; PubMed Central PMCID: PMCPMC2822971. [PubMed: 19892860]
7. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. J Allergy Clin Immunol. 2011;127(2):382–9 e1–13. doi: 10.1016/j.jaci.2010.11.015. PubMed PMID: 21195471; PubMed Central PMCID: PMCPMC3060668. [PubMed: 21195471]
8. Lotvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. J Allergy Clin Immunol. 2011;127(2):355–60. doi: 10.1016/j.jaci.2010.11.037. PubMed PMID: 21281866. [PubMed: 21281866]
9. Siroux V, Basagana X, Boudier A, Pin I, Garcia-Aymerich J, Vesin A, et al. Identifying adult asthma phenotypes using a clustering approach. Eur Respir J. 2011;38(2):310–7. doi: 10.1183/09031936.00120810. PubMed PMID: 21233270. [PubMed: 21233270]
10. Depner M, Fuchs O, Genuneit J, Karvonen AM, Hyvarinen A, Kaulek V, et al. Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med. 2014;189(2):129–38. doi: 10.1164/rccm.201307-1198OC. PubMed PMID: 24283801. [PubMed: 24283801]
11. Newby C, Heaney LG, Menzies-Gow A, Niven RM, Mansur A, Bucknall C, et al. Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. PLoS One. 2014;9(7):e102987. doi: 10.1371/journal.pone.0102987. PubMed PMID: 25058007; PubMed Central PMCID: PMCPMC4109965. [PubMed: 25058007]
12. Anderson GP. Endotyping asthma: new insights into key pathogenic mechanisms in a complex, heterogeneous disease. Lancet. 2008;372(9643):1107–19. doi: 10.1016/S0140-6736(08)61452-X. PubMed PMID: 18805339. [PubMed: 18805339]
13. Wenzel S Severe asthma: from characteristics to phenotypes to endotypes. Clin Exp Allergy. 2012;42(5):650–8. doi: 10.1111/j.1365-2222.2011.03929.x. PubMed PMID: 22251060. [PubMed: 22251060]
14. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J. 2014;43(2):343–73. doi: 10.1183/09031936.00202013. PubMed PMID: 24337046. [PubMed: 24337046]
15. Ramratnam SK, Bacharier LB, Guilbert TW. Severe Asthma in Children. J Allergy Clin Immunol Pract. 2017;5(4):889–98. doi: 10.1016/j.jaip.2017.04.031. PubMed PMID: 28689839. [PubMed: 28689839]
16. Gelfand EW, Alam R. The other side of asthma: Steroid-refractory disease in the absence of TH2-mediated inflammation. J Allergy Clin Immunol. 2015;135(5):1196–8. doi: 10.1016/j.jaci.2015.01.032. PubMed PMID: 25772592. [PubMed: 25772592]
17. National Asthma E, Prevention P. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. J Allergy Clin Immunol. 2007;120(5 Suppl):S94–138. doi: 10.1016/j.jaci.2007.09.043. PubMed PMID: 17983880. [PubMed: 17983880]
18. Sampson AP. The role of eosinophils and neutrophils in inflammation. Clin Exp Allergy. 2000;30 Suppl 1:22–7. PubMed PMID: 10849470. [PubMed: 10849470]
19. Humbles AA, Lloyd CM, McMillan SJ, Friend DS, Xanthou G, McKenna EE, et al. A critical role for eosinophils in allergic airways remodeling. Science. 2004;305(5691):1776–9. doi: 10.1126/science.1100283. PubMed PMID: 15375268. [PubMed: 15375268]
20. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594–602. doi: 10.1183/09031936.00139810. PubMed PMID: 21310876. [PubMed: 21310876]

21. Telenga ED, Tideman SW, Kerstjens HA, Hacken NH, Timens W, Postma DS, et al. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy. 2012;67(8):1060–8. doi: 10.1111/j.1398-9995.2012.02855.x. PubMed PMID: 22686834. [PubMed: 22686834]
22. Kim SH, Sutherland ER, Gelfand EW. Is there a link between obesity and asthma? Allergy Asthma Immunol Res. 2014;6(3):189–95. doi: 10.4168/aair.2014.6.3.189. PubMed PMID: 24843792; PubMed Central PMCID: PMCPMC4021235. [PubMed: 24843792]
23. Lang JE. Obesity and asthma in children: current and future therapeutic options. Paediatr Drugs. 2014;16(3):179–88. doi: 10.1007/s40272-014-0069-1. PubMed PMID: 24604125; PubMed Central PMCID: PMCPMC4355012. [PubMed: 24604125]
24. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. J Allergy Clin Immunol. 2015;135(2): 299–310; quiz 1. doi: 10.1016/j.jaci.2014.12.1871. PubMed PMID: 25662302. [PubMed: 25662302]
25. Control TCfD. Most Recent Asthma Data 2015 [January 27, 2018]. Available from: https://www.cdc.gov/asthma/most_recent_data.htm.
26. Control TCfD. Summary Health Statistics: National Health Interview Survey 2015 2015 Available from: https://ftp.cdc.gov/pub/Health_Statistics/NCHS/NHIS/SHS/2015_SHS_Table_C-2.pdf.
27. Control TCfD. Childhood Obesity Facts 2014 [January 27, 2018]. Available from: https://www.cdc.gov/obesity/data/childhood.html.
28. Services USDoHaH. Summary Health Statistics for U.S. Children: National Health Interview Survey, 2012: National Center for Health Statistics; 2012 Available from: https://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf.
29. Brachlow AE, Ness KK, McPheeters ML, Gurney JG. Comparison of indicators for a primary care medical home between children with autism or asthma and other special health care needs: National Survey of Children's Health. Arch Pediatr Adolesc Med. 2007;161(4):399–405. doi: 10.1001/archpedi.161.4.399. PubMed PMID: 17404138. [PubMed: 17404138]
30. Rojanasarot S, Carlson AM. The Medical Home Model and Pediatric Asthma Symptom Severity: Evidence from a National Health Survey. Popul Health Manag. 2017. doi: 10.1089/pop.2017.0066. PubMed PMID: 28805507.
31. Control TCfD. About Child and Teen BMI 2015 [January 27, 2018]. Available from: https://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf.
32. Force USPST, Grossman DC, Bibbins-Domingo K, Curry SJ, Barry MJ, Davidson KW, et al. Screening for Obesity in Children and Adolescents: US Preventive Services Task Force Recommendation Statement. JAMA. 2017;317(23):2417–26. doi: 10.1001/jama.2017.6803. PubMed PMID: 28632874. [PubMed: 28632874]
33. Akinbami LJ, Ogden CL. Childhood overweight prevalence in the United States: the impact of parent-reported height and weight. Obesity (Silver Spring). 2009;17(8):1574–80. doi: 10.1038/oby.2009.1. PubMed PMID: 19629061. [PubMed: 19629061]
34. Strom MA, Silverberg JI. Associations of Physical Activity and Sedentary Behavior with Atopic Disease in United States Children. J Pediatr. 2016;174:247–53 e3. doi: 10.1016/j.jpeds.2016.03.063. PubMed PMID: 27156181. [PubMed: 27156181]
35. Bloomberg GR, Banister C, Sterkel R, Epstein J, Bruns J, Swerczek L, et al. Socioeconomic, family, and pediatric practice factors that affect level of asthma control. Pediatrics. 2009;123(3): 829–35. doi: 10.1542/peds.2008-0504. PubMed PMID: 19255010; PubMed Central PMCID: PMCPMC2723164. [PubMed: 19255010]
36. Halfon N, Larson K, Slusser W. Associations between obesity and comorbid mental health, developmental, and physical health conditions in a nationally representative sample of US children aged 10 to 17. Acad Pediatr. 2013;13(1):6–13. doi: 10.1016/j.acap.2012.10.007. PubMed PMID: 23200634. [PubMed: 23200634]
37. Bethell CD, Newacheck P, Hawes E, Halfon N. Adverse childhood experiences: assessing the impact on health and school engagement and the mitigating role of resilience. Health Aff (Millwood). 2014;33(12):2106–15. doi: 10.1377/hlthaff.2014.0914. PubMed PMID: 25489028. [PubMed: 25489028]

38. Chaudry A, Wimer C. Poverty is Not Just an Indicator: The Relationship Between Income, Poverty, and Child Well-Being. Acad Pediatr. 2016;16(3 Suppl):S23–9. doi: 10.1016/j.acap.2015.12.010. PubMed PMID: 27044698. [PubMed: 27044698]
39. Hughes HK, Matsui EC, Tschudy MM, Pollack CE, Keet CA. Pediatric Asthma Health Disparities: Race, Hardship, Housing, and Asthma in a National Survey. Acad Pediatr. 2017;17(2):127–34. doi: 10.1016/j.acap.2016.11.011. PubMed PMID: 27876585; PubMed Central PMCID: PMCPMC5337434. [PubMed: 27876585]
40. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. Early life risk factors for obesity in childhood: cohort study. BMJ. 2005;330(7504):1357. doi: 10.1136/bmj.38470.670903.E0. PubMed PMID: 15908441; PubMed Central PMCID: PMCPMC558282. [PubMed: 15908441]
41. O'Dea JA. Gender, ethnicity, culture and social class influences on childhood obesity among Australian schoolchildren: implications for treatment, prevention and community education. Health Soc Care Community. 2008;16(3):282–90. doi: 10.1111/j.1365-2524.2008.00768.x. PubMed PMID: 18328051. [PubMed: 18328051]
42. Kwon HJ, Lee MY, Ha M, Yoo SJ, Paik KC, Lim JH, et al. The associations between ADHD and asthma in Korean children. BMC Psychiatry. 2014;14:70. doi: 10.1186/1471-244X-14-70. PubMed PMID: 24606878; PubMed Central PMCID: PMCPMC3975298. [PubMed: 24606878]
43. Holmberg K, Lundholm C, Anckarsater H, Larsson H, Almqvist C. Impact of asthma medication and familial factors on the association between childhood asthma and attention-deficit/hyperactivity disorder: a combined twin- and register-based study: Epidemiology of Allergic Disease. Clin Exp Allergy. 2015;45(5):964–73. doi: 10.1111/cea.12529. PubMed PMID: 25772649. [PubMed: 25772649]
44. Ferro MA, Van Lieshout RJ, Ohayon J, Scott JG. Emotional and behavioral problems in adolescents and young adults with food allergy. Allergy. 2016;71(4):532–40. doi: 10.1111/all.12829. PubMed PMID: 26715290. [PubMed: 26715290]
45. Esbenshade TA, Browman KE, Bitner RS, Strakhova M, Cowart MD, Brioni JD. The histamine H3 receptor: an attractive target for the treatment of cognitive disorders. Br J Pharmacol. 2008;154(6):1166–81. doi: 10.1038/bjp.2008.147. PubMed PMID: 18469850; PubMed Central PMCID: PMCPMC2483387. [PubMed: 18469850]
46. Weisler RH, Pandina GJ, Daly EJ, Cooper K, Gassmann-Mayer C, Investigators ATTS. Randomized clinical study of a histamine H3 receptor antagonist for the treatment of adults with attention-deficit hyperactivity disorder. CNS Drugs. 2012;26(5):421–34. doi: 10.2165/11631990-000000000-00000. PubMed PMID: 22519922. [PubMed: 22519922]
47. Tiligada E, Kyriakidis K, Chazot PL, Passani MB. Histamine pharmacology and new CNS drug targets. CNS Neurosci Ther. 2011;17(6):620–8. doi: 10.1111/j.1755-5949.2010.00212.x. PubMed PMID: 22070192. [PubMed: 22070192]
48. Michelson PH, Williams LW, Benjamin DK, Barnato AE. Obesity, inflammation, and asthma severity in childhood: data from the National Health and Nutrition Examination Survey 2001–2004. Ann Allergy Asthma Immunol. 2009;103(5):381–5. doi: 10.1016/S1081-1206(10)60356-0. PubMed PMID: 19927535. [PubMed: 19927535]
49. 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. doi: 10.1371/journal.pone.0036631. PubMed PMID: 22606276; PubMed Central PMCID: PMCPMC3350517. [PubMed: 22606276]
50. Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. J Allergy Clin Immunol. 2014;133(6):1549–56. doi: 10.1016/j.jaci.2013.10.006. PubMed PMID: 24315502. [PubMed: 24315502]
51. Dixon AE, Poynter ME. Mechanisms of Asthma in Obesity. Pleiotropic Aspects of Obesity Produce Distinct Asthma Phenotypes. Am J Respir Cell Mol Biol. 2016;54(5):601–8. doi: 10.1165/rcmb.2016-0017PS. PubMed PMID: 26886277; PubMed Central PMCID: PMCPMC4942199. [PubMed: 26886277]
52. Halterman JS, Yoos HL, Kaczorowski JM, McConnochie K, Holzhauer RJ, Conn KM, et al. Providers underestimate symptom severity among urban children with asthma. Arch Pediatr Adolesc Med. 2002;156(2):141–6. PubMed PMID: 11814375. [PubMed: 11814375]

53. Yoos HL, Kitzman H, McMullen A, Sidora K. Symptom perception in childhood asthma: how accurate are children and their parents? J Asthma. 2003;40(1):27–39. PubMed PMID: 12699209. [PubMed: 12699209]

54. Silva CM, Barros L. Asthma knowledge, subjective assessment of severity and symptom perception in parents of children with asthma. J Asthma. 2013;50(9):1002–9. doi: 10.3109/02770903.2013.822082. PubMed PMID: 23859138. [PubMed: 23859138]

55. Long MW, Ward ZJ, Resch SC, Cradock AL, Wang YC, Giles CM, et al. State-level estimates of childhood obesity prevalence in the United States corrected for report bias. Int J Obes (Lond). 2016;40(10):1523–8. doi: 10.1038/ijo.2016.130. PubMed PMID: 27460603. [PubMed: 27460603]

56. Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies. Proc Am Thorac Soc. 2009;6(3):256–9. doi: 10.1513/pats.200808-087RM. PubMed PMID: 19387026. [PubMed: 19387026]

57. Farzan S, Khan S, Elera C, Akerman M. Montelukast Is a Better Controller in Obese Atopic Asthmatics. J Allergy Clin Immun.137(2):AB210. doi: 10.1016/j.jaci.2015.12.1274.

58. Wang J, Shi GP. Mast cell stabilization: novel medication for obesity and diabetes. Diabetes Metab Res Rev. 2011;27(8):919–24. doi: 10.1002/dmrr.1272. PubMed PMID: 22069285; PubMed Central PMCID: PMCPMC3318912. [PubMed: 22069285]

59. Sismanopoulos N, Delivanis DA, Mavrommati D, Hatziagelaki E, Conti P, Theoharides TC. Do mast cells link obesity and asthma? Allergy. 2013;68(1):8–15. doi: 10.1111/all.12043. PubMed PMID: 23066905; PubMed Central PMCID: PMCPMC3515712. [PubMed: 23066905]

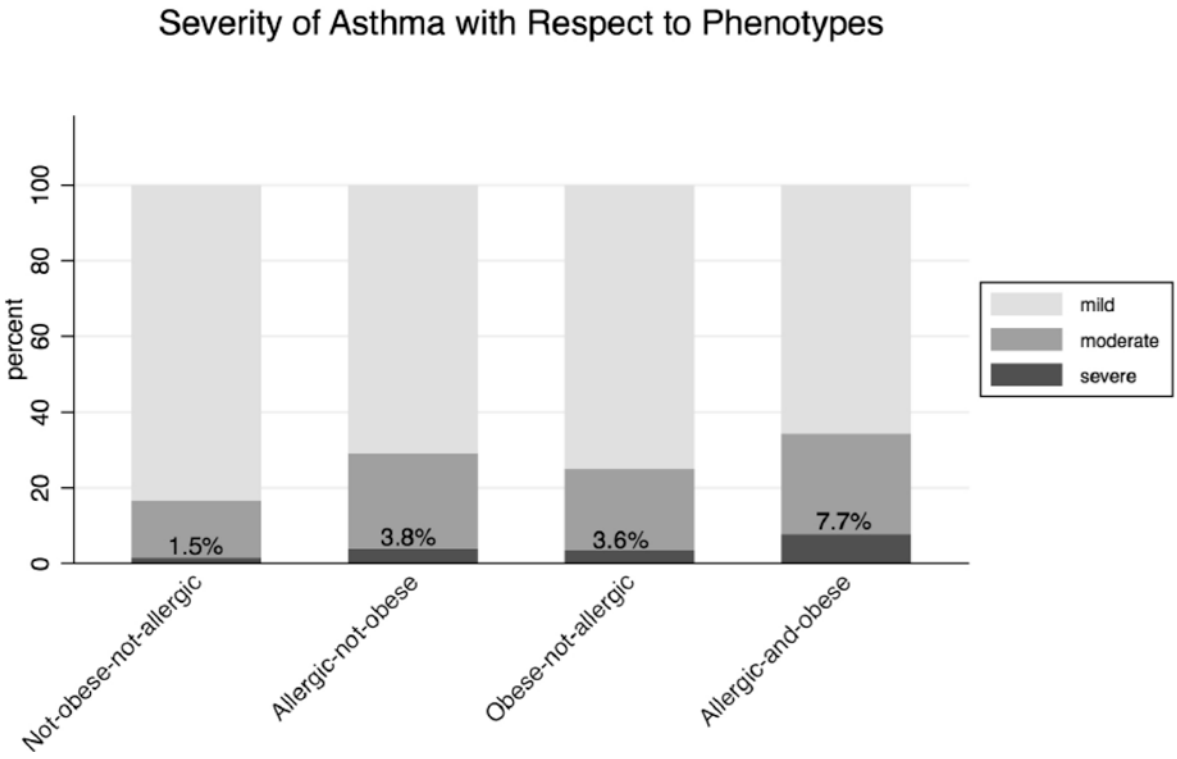

Figure 1.
Asthma severity (in percentage) distributed by phenotype.

Table 1.

Cohort demographic descriptive statistics of children ages 10–17 years with each of the four asthma phenotypes.

Demographics	Sample Size (N)	Not-allergic-not-obese N (%)	Allergic-not-obese N (%)	Obese-not-allergic N(%)	Allergic-and-obese N(%)
	4427	**1363 (30.8%)**	**2186 (49.4%)**	**336 (7.6%)**	**542 (12.2%)**
Age yr, Mean (sd) ***§	13.8(2.3)	14(2.3)	13.8(2.3)	13.4 (2.3)	13.3(2.4)
Sex ***					
Female	2025	668 (49.0%)	1016 (46.5%)	123 (36.6%)	218 (40.3%)
Male	2402	695 (51.0%)	1170 (53.5%)	213 (63.4%)	324 (59.7%)
Race ***					
White, non-Hispanic	2863	900 (66.0%)	1502 (68.7%)	161 (47.9%)	300 (55.3%)
Black, non-Hispanic	695	198 (14.5%)	287 (13.1%)	84 (25.0%)	126 (23.3%)
Hispanic	412	118 (8.7%)	185 (8.5%)	46 (13.7%)	63 (11.6%)
Multiracial/Other	387	119 (8.7%)	187 (8.6%)	41 (12.2%)	41 (7.6%)
Missing/unknown	69	28 (2.1%)	25 (1.1%)	4 (1.2%)	12 (2.2%)
Geographic ***					
Metropolitan	2396	706 (51.8%)	1207 (55.2%)	184 (54.8%)	299 (55.2%)
Non-metropolitan	2031	657 (48.2%)	979 (44.8%)	152 (45.2%)	243 (44.8%)

*** p-value<.001, **p-value<.01, *p-value<.05.

§ ANOVA, the rest by Chi-square test

Table 2.

Cohort sociodemographics and health risk factors of the four phenotypes.

Sociodemographic and Health Risk Factors	Sample Size (N) 4427	Not-allergic-not-obese N (%) 1363 (30.8%)	Allergic-not-obese N (%) 2186 (49.4%)	Obese-not-allergic N (%) 336 (7.6%)	Allergic-and-obese N (%) 542 (12.2%)
Family Income ***					
<300% FPL	1266	350 (25.7%)	529 (24.2%)	160 (47.7%)	227 (41.9%)
>300% FPL	2823	903 (66.2%)	1510 (69.1%)	150 (44.6%)	267 (49.2%)
Missing/unknown	331	110 (8.1%)	147 (6.7%)	26 (7.7)%	48 (8.9%)
Highest Caregiver Education ***					
HS or less	1152	355 (26.1%)	458 (21.0%)	167 (49.7%)	172 (31.7%)
More than HS	3223	986 (72.3%)	1711 (78.3%)	165 (49.1%)	361 (66.6%)
Insurance Status ***			488 (22.3%)	146 (43.5%)	212 (39.1%)
Public insurance	1172	326 (23.9%)			
Uninsured	239	90 (6.6%)	93 (4.3%)	26 (7.7%)	30 (5.5%)
Private insurance	2974	938 (68.8%)	1584 (72.5%)	161 (47.9%)	291 (53.7%)
Family Structure ***					
Single mother	1032	270 (19.8%)	484 (22.1%)	103 (30.7%)	175 (32.3%)
Two bio/adopted parents	3012	953 (69.9%)	1563 (71.5%)	186 (55.3%)	310 (57.2%)
Other (including step-family)	361	132 (9.7%)	130 (6.0%)	45 (13.4%)	54 (9.9%)
Divorced Parent					
Yes	542	159 (11.7%)	258 (11.8%)	48 (14.3%)	77 (14.2%)
No	3853	1190 (87.3%)	1916 (87.7%)	286 (85.1%)	461 (85.1%)
Smoker (any household member) ***					
Yes	1310	400 (29.4%)	588 (26.9%)	137 (40.8%)	185 (34.1%)
No	3087	951 (69.8%)	1586 (72.6%)	197 (58.6%)	353 (65.1%)
Fair/poor Emotional Health (parent) **					
Yes	548	153 (11.2%)	244 (11.2%)	54(16.1%)	97 (17.9%)
No	3847	1197 (87.8%)	1928 (88.2%)	279 (83.0%)	443 (81.7%)
Screen Time					
>2hrs/day	1861	579 (42.5%)	890 (40.7%)	154 (45.8%)	238 (43.9%)
<2hrs/day	2562	784 (57.5%)	1296 (59.3%)	182 (54.2%)	304 (56.1%)
TV in room ***					
Yes	2520	776 (56.9%)	1140 (52.2%)	243 (72.3%)	361 (66.6%)
No	1895	581 (42.6%)	1043 (47.7%)	92 (27.4%)	179 (33.0%)
Physical activity ***					
Exercise (< 3times/week)	1669	474 (34.8%)	790 (36.1%)	149 (44.4%)	254 (47.2%)
Exercise (> 3days/week)	2758	889 (65.2%)	1396 (63.9%)	187 (55.6%)	286 (52.8%)
Neighborhood ***					

Sociodemographic and Health Risk Factors	Sample Size (N) 4427	Not-allergic-not-obese N (%) 1363 (30.8%)	Allergic-not-obese N (%) 2186 (49.4%)	Obese-not-allergic N (%) 336 (7.6%)	Allergic-and-obese N (%) 542 (12.2%)
Unsafe	592	158 (11.6%)	267 (12.2%)	64 (19.1%)	103 (19.0%)
Safe	3792	1190 (87.3%)	1902 (87.0%)	269 (80.1%)	431 (79.5%)
Mental health/behavior diagnosis ***					
Yes	1556	381 (28.0%)	809 (37.0%)	120 (35.7%)	246 (45.4%)
No	2871	982 (72.1%)	1337 (63.0%)	216 (64.3%)	296 (54.6%)
Other medical diagnosis ***					
Yes	4298	1335 (98.0%)	2138 (97.8%)	317 (94.4%)	508 (93.7%)
No	129	28 (2.0%)	48 (2.2%)	19 (5.65%)	34 (6.3%)
Overall in good health ***					
No	348	60 (4.4%)	160 (7.3%)	37 (11.0%)	91 (16.8%)
Yes	4078	1303 (95.6%)	2025 (92.6%)	299 (89.0%)	451 (83.2%)

*** p-value<.001, ** p-value<.01, *p-value<.05. Values may not add up to 100% because missing values of <2% not reported in table.

Table 3.

Multivariable analysis of risk factors associated with each phenotype (reference is not-allergic-not-obese phenotype).

Risk factors		Allergic-not-Obese	Obese-not-Allergic	Obese-and-Allergic
		OR (95% Cl)	OR (95% Cl)	OR (95% Cl)
Ethnicity	Black vs. White	0.98 (0.78–1.23)	1.90(1.34–2.69) ***	1.62(1.20–2.18) **
	Hispanic vs. White	0.95 (0.74–1.24)	1.64(1.10–2.48) *	1.37 (0.96–1.96)
	Other vs. White	0.98(0.76–1.26)	1.73 (1.14–2.62) *	0.94 (0.63–1.41)
Gender (M vs. F)		1.09 (0.94–1.26)	1.83 (1.40–2.39) ***	1.55 (1.24–1.94) ***
Age (<12 vs. >12)		1.13 (0.95–1.36)	1.71 (1.27–2.30) ***	2.21(1.73–2.83) ***
Income FPL <300% (Y vs. N)		0.95 (0.79–1.15)	1.64(1.21–2.24) **	1.70(1.31–2.21) ***
Caregiver education (HS or less vs more)		0.77 (0.64–0.93) **	1.84(1.37–2.47) ***	0.90 (0.70–1.17)
Family structure	Single mother vs. Two Parents	1.11 (0.92–1.35)	1.04 (0.76–1.44)	1.32 (1.01–1.73) *
	other vs. Two Parents	0.57 (0.43–0.76) ***	0.99 (0.65–1.51)	0.92 (0.63–1.35)
Mental Health/Behavior (Y vs. N)		1.75 (1.45–2.10) ***	1.30 (0.95–1.78)	1.85 (1.43–2.40) ***
Smoker, any household member (Y vs. N)		0.88 (0.75–1.04)	1.31 (1.00–1.72)	1.08 (0.86–1.37)
Exercise (<3 vs. >3 days per week)		1.11(0.96–1.30)	1.59(1.22–2.07) ***	1.68(1.35–2.10) ***

*** p-value<.001, **p-value<.01, *p-value<.05

Table 4.

Partial proportional odds ordinal multivariable regression model of risk factors associated with a higher severity of asthma (mild, moderate, severe)

		OR	95% CI	p-value
Obesity (yes vs. no)	Severe vs. mild asthma	1.59	1.09–2.30	0.015
	Moderate vs. mild asthma	1.10	0.92–1.32	0.311
Allergy (yes vs. no)	Severe vs. mild-mod asthma	2.11	1.79–2.47	<0.001
Black vs. white	Severe vs. mild-mod asthma	1.41	1.14–1.74	0.001
Hispanic vs. white	Severe vs. mild-mod asthma	1.46	1.15–1.86	0.002
Other vs. white	Severe vs. mild-mod asthma	0.98	0.75–1.27	0.857
Unsafe neighborhood (yes vs. no	i Severe vs. mild-mod asthma	1.23	1.00–1.53	0.052
Behavioral Diagnosis (yes vs. no)	Severe vs. mild-mod asthma	1.38	1.17–1.64	<0.001
Guardian education	Severe vs. mild asthma	1.91	1.33–2.74	<0.001
(HS or less vs more than HS)	Moderate vs. mild asthma	1.10	0.92–1.32	0.295
Comparisons: when obesity and allergy are both present				
Obese-and-allergic vs	Severe vs. mild asthma	3.34	2.23–5.01	<.001
Not allergic-not-obese[§]	Moderate vs. mild asthma	2.31	1.81–2.95	<.001
Income FPL <3OO%9[#]	None vs. government insurance	1.99	1.62–2.44	<.001
	Government vs. private insurance	3.40	2.24–5.15	<.001
Income FPL >3OO%9[#]	None vs. government insurance	1.26	0.93–1.71	0.130
	Government vs. private insurance	0.85	0.51–1.41	0.530

[§]The covariates did not meet the proportionality odds assumption hence, two separate ORs are reported comparing severe vs. mild and moderate vs. mild level of asthma. Other covariates in the model have one OR for having a more severe level of asthma.

[#]The interaction between Income<300%FPL and the insurance status is significant therefore, the OR for each level is reported separately.