
Obesity, inflammation, and asthma severity in childhood: data from the National Health and Nutrition Examination Survey 2001–2004

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Background: The prevalences of asthma and obesity in children have increased significantly during the past 2 decades. The basis for the relationship between pediatric asthma and obesity is not well established.

Objectives: To explore the association between obesity and asthma severity in children and adolescents and to test whether obesity-induced inflammation, as characterized by serum C-reactive protein (CRP), is associated with increased severity of asthma.

Methods: Retrospective cohort analysis of interview, physical examination, and laboratory test data from participants younger than 20 years in 2 rounds of the National Health and Nutrition Examination Survey (2001–2002 and 2003–2004). We also performed generalized ordered logistic regression to evaluate the effect of body mass index (BMI) *z* score and CRP level on asthma severity, controlling for the impact of age, sex, race, income, insurance, and tobacco smoke exposure.

Results: Of the 77 million individuals younger than 20 years represented by this weighted sample, 19% met the study-defined criteria for asthma; most cases were defined as mild (11%) or moderate (6%); 2% had severe asthma. In multivariable models, elevated BMI *z* scores (odds ratio, 1.12; 95% confidence interval, 1.05–1.21) were associated with worse asthma severity. Elevated CRP level was associated with obesity ($P < .001$) and asthma severity (odds ratio, 1.33; 95% confidence interval, 1.16–1.52).

Conclusions: Higher BMI *z* scores and elevated serum CRP levels are associated with increased asthma severity. These findings highlight the importance of controlling for inflammation when considering the role of obesity and provide support for the hypothesis that obesity-induced inflammation may contribute to greater asthma severity.

Ann Allergy Asthma Immunol. 2009;103:381–385.

INTRODUCTION

Asthma and obesity are concurrently at historic high levels in pediatric populations.¹ These 2 public health epidemics share risk factors (eg, poverty and physical inactivity); asthmatic children also may be at higher risk for obesity due to reduced exercise capacity.^{2,3} Mounting evidence suggests, however, that obesity independently contributes to the incidence and severity of asthma in children and adults.^{4,5} Although controversy persists regarding the exact nature of the relationship, several mechanisms that potentially mediate the relationship between obesity and asthma have been hypothesized, including mechanical factors,^{6–8} gastroesophageal reflux,⁹ and adipose-induced inflammation.¹⁰

Multiple animal and human studies^{11,12} have demonstrated that obesity is a proinflammatory state. Leptin,¹³ tumor necrosis factor, transforming growth factor β , and C-reactive

protein (CRP)^{14,15} are inflammatory molecules that have been demonstrated to be present in the obese state and that are implicated as potential contributors to the respiratory complications seen in obesity.¹⁶ Children with asthma have elevated leptin concentrations that decrease with inhaled corticosteroid therapy.¹⁷ Furthermore, elevated CRP levels have been demonstrated in adults with an elevated body mass index (BMI) and asthma.^{18–20} Nevertheless, information linking systemic inflammation, pediatric obesity, and asthma remains incomplete. We sought to explore the cross-sectional relationship between obesity and asthma in a large national cohort of US children. We also examined the role of systemic inflammation in the association between increased body weight and asthma severity. We hypothesize that children with higher BMIs would have more asthma symptoms and that this relationship would be partially explained by CRP, a nonspecific marker of obesity-induced inflammation.

METHODS

Sample

The National Health and Nutrition Examination Survey (NHANES) is a federally funded data collection effort that combines interviews and physical examinations to survey the health and nutritional status of the US population. Selected individuals participate in a detailed home interview that in-

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Disclosures: Authors have nothing to disclose.

Received for publication December 6, 2008; Received in revised form May 7, 2009; Accepted for publication June 7, 2009.

cludes demographic, socioeconomic, and health-related questions and undergo a comprehensive examination that includes medical, dental, and laboratory analysis at 1 of the mobile examination centers. We used the most recent interview and examination cycles for which complete data were available, years 2001 to 2002 and 2003 to 2004. The only study inclusion criterion was age younger than 20 years.

Dependent Variable

We drew asthma data from the respiratory health questionnaire. We classified a patient as having asthma if the respondent endorsed such questions as, "Has a doctor or other health professional ever told you that your child has asthma?" or "In the past 12 months, have you heard wheezing or whistling in your child's chest?" The data set was based on available criteria, and the definitions were patterned after the National Heart, Lung, and Blood Institute's *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*.²¹

We classified individuals with asthma into 3 categories: mild, moderate, and severe, depending on their reported symptom burden. Specifically, we classified as severe those who endorsed any of the following questions: "Does your child cough on most days for 3 consecutive months or more during the year?" "Is there productive cough with phlegm on most days for 3 consecutive months or more during the year?" or "During the past 12 months, has there been a need to visit an emergency room or urgent care center because of your child's asthma?" Respondents who reported having received medical care for 1 or more attacks of wheezing or whistling in the chest or having a physician prescribe wheezing medication or limiting activities due to wheezing or missing school or work due to wheezing or reporting an episode of asthma or an asthma attack in the past 12 months were classified as having moderate asthma. Participants with asthma but none of these symptoms or health care encounters were classified as having mild asthma.

Independent Variables

We used the physical examination weight, length, and age in months to determine a BMI *z* score, which was the obesity variable. The CRP level is included in the NHANES as a marker of tissue damage or inflammation associated with underlying chronic illnesses. We selected log-transformed blood CRP values as a measure of inflammation. Additional variables included in the model to control for potential sources of confounding included age in years, sex, race or ethnicity (white, black, Mexican, other Hispanic, and all others), health insurance status (insured vs uninsured), annual household income (<\$20,000 vs ≥\$20,000), housing (house, apartment, trailer, or other), current environmental tobacco smoke exposure in the home, and prenatal maternal smoking history. No information regarding coexisting conditions was provided. Physical activity measures were not available for the entire data cohort and were not included.

Statistical Analysis

We categorized the cohort into those without asthma and those with mild, moderate, or severe asthma and explored differences among the 4 groups using logistic regression and χ^2 analysis for categorical variables. Generalized ordered logistic regression was performed to estimate a regression model for ordinal dependent variables. This technique relaxes the parallel lines assumption and, thus, allows the impact of each independent variable to differ across the ordinal outcome categories (no asthma, mild asthma, moderate asthma, and severe asthma).²²

Two separate "cycles" (2001–2002 and 2003–2004) of NHANES data were combined to produce estimates with enhanced statistical reliability. All the analyses were performed using Stata 9.2 (StataCorp, College Station, Texas). The complex sample design and weighting methods were fully reflected in the combination of data cycles using the methods recommended by the NHANES. This study was exempt from institutional review board approval.

RESULTS

The full NHANES sample included 10,140 participants aged 0 to 19 years, representative of 76,805,481 US children. The mean (SD) age of the sample was 9.3 (6.3) years, 49.7% were girls, 30% were white, 31% were black, 34% were Mexican American and other Hispanic, and 5% were "other" racial/ethnic groups, weighted by the NHANES to represent a population with a mean age of 9.5 years, 49.2% girls, 61% white, 14% black, 18% Mexican American and other Hispanic, and 6% other racial/ethnic groups (Table 1). The sample included 1,925 children with asthma (19%; 95% confidence interval [CI], 18%–21%); most cases were mild (*n* = 1,116 [11%; 95% CI, 10%–12%]) or moderate (*n* = 609 [6%; 95% CI, 6%–8%]), although 200 children (2%; 95% CI, 1%–2%) had severe asthma according to the classification described in the "Methods" section.

There were no statistically significant differences in the distribution of age, sex, income, or housing type among the 4 groups; however, there were significant differences in the distribution of individuals with health insurance (*P* < .001) (Table 2). In addition, using multivariate logistic analysis, there were differences in asthma severity in those with higher BMI *z* scores and log serum CRP values (*P* < .001 for both).

Because the differences in asthma severity are ordinal, we used a generalized ordered logistic regression model to evaluate the impact of the independent variables on asthma severity; this model allowed us to evaluate the relative contribution of each variable to an increase in asthma severity. This analysis allows for multiple comparisons between groups: those with severe asthma vs those with no, mild, or moderate asthma; those with moderate and severe asthma vs those with no or mild asthma; and those with mild, moderate, or severe asthma vs those with no symptoms. In this model, contributing factors for those with severe asthma included having an increased serum CRP level (odds ratio [OR], 1.33; *P* < .001)

Table 1. Characteristics of the NHANES Pediatric Cohort, 2001–2004

Characteristic (sample No./weighted sample No.)	Sample	Weighted sample
Age, range (median), y (10,140/77,000,000)	0–19 (9.5)	0–19 (9.51)
Sex, No. (%) (10,140/77,000,000)		
Male	5,045 (49.8)	38,000,000 (49.4)
Female	5,095 (50.2)	39,000,000 (50.6)
Ethnicity, No. (%) (10,140/77,000,000)		
Non-Hispanic white	3,067 (30.3)	47,000,000 (60.6)
Non-Hispanic black	3,124 (30.8)	11,000,000 (14.4)
Mexican	3,011 (29.7)	9,500,000 (12.4)
Other Hispanic	448 (4.4)	4,900,000 (6.4)
Other	490 (4.8)	4,800,000 (6.3)
Health insurance, No. (%) (10,072/77,000,000)		
Yes	8,444 (83.8)	67,000,000 (87.0)
No	1,628 (16.2)	9,700,000 (13.0)
BMI z score, mean (range) (7,856/60,000,000)	0.51 (–27.0 to 4.6)	0.46 (0.41 to 0.51 ^a)
Smokers in the home, No. (%) (10,072/77,000,000)		
Yes	2,113 (21.0)	17,000,000 (22.1)
No	7,959 (79.0)	59,000,000 (77.9)
Smoking in pregnancy, No. (%) (7,861/60,000,000)		
Yes	1,179 (15.0)	11,000,000 (18)
No	6,682 (85.0)	50,000,000 (82)
Housing characteristics, No. (%) (10,072/77,000,000)		
House	6,540 (64.9)	56,000,000 (73)
Apartment	2,529 (25.1)	12,000,000 (16)
Trailer	825 (8.2)	6,600,000 (9)
Other	178 (1.8)	1,600,000 (2)
Household income ≤\$20,000/y, No. (%) (9,485/73,000,000)		
Yes	2,744 (0.29)	15,000,000 (20.5)
No	6,741 (0.71)	58,000,000 (79.5)
Log C-reactive protein, mean (range) (7,035/58,000,000)	–3.0 (–4.6 to 2.1)	–3.08 (–3.13 to –3.03 ^a)

Abbreviations: BMI, body mass index; NHANES, National Health and Nutrition Examination Survey.

^a 95% confidence interval.

Table 2. Characteristics of the NHANES Pediatric Cohort, by Asthma Severity, 2001–2004

Characteristic	Overall sample (N = 10,140)	No asthma (n = 8,215)	Mild asthma (n = 1,116)	Moderate asthma (n = 609)	Severe asthma (n = 200)	P value ^a
Male sex, %	50.8	49.9	55.7	50.6	55.5	.06
Ethnic group, %						
White	60.6	60.8	58.0	63.9	53.1	.002
Black	14.4	13.6	19.0	13.8	22.7	
Insurance, %	87.3	86.6	88.2	92.2	95.5	<.001
Smoke exposure at home, %	22.4	21.5	25.5	28.6	25.1	.01
Type of home, %						
House	73.2	73.7	70.0	74.0	68.3	.26
Apartment	16.0	16.0	17.4	12.8	20.2	

Abbreviation: NHANES, National Health and Nutrition Examination Survey.

^a Pearson χ^2 test between asthma severity and listed categorical variables.

and an increased BMI z score (OR, 1.12; $P = .002$). Furthermore, having increased CRP levels seemed to be particularly important in the development of severe asthma, whereas the effect of BMI was uniform across all levels of asthma severity (Table 3). When analyzing the remaining variables in the multivariable model, male sex was observed with increased asthma at all levels of severity (OR, 1.19; $P = .04$), and

having health insurance (OR, 4.01; $P = .009$) was observed in those with severe asthma (Table 3).

DISCUSSION

Asthma severity is associated with an elevated BMI and a higher serum CRP level in a representative national cohort of 0- to 19-year-olds studied between 2001 and 2004. Further-

Table 3. Odds Ratios (ORs) of Independent Variables and Asthma Severity

	Mild asthma ^a		Moderate asthma ^b		Severe asthma ^c	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Sex ^d	1.185 (1.005–1.397)	.04	1.185 (1.005–1.397)	.04	1.185 (1.005–1.397)	.04
BMI z score ^d	1.124 (1.046–1.208)	.002	1.124 (1.046–1.208)	.002	1.124 (1.046–1.208)	.002
Insurance status	1.666 (1.355–2.049)	<.001	2.884 (1.949–4.268)	<.001	4.010 (1.458–11.025)	.009
Log CRP	1.076 (1.015–1.142)	.02	1.077 (1.005–1.156)	.04	1.327 (1.159–1.520)	<.001

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein.

^a The OR of each independent variable on having mild asthma vs having no asthma.

^b The OR of each independent variable on having moderate asthma vs having mild asthma or no asthma.

^c The OR of each independent variable on having severe asthma vs having moderate, mild, or no asthma.

^d Sex and BMI z score did not have statistically significant differences in effect between the levels of outcome (ie, they did not require relaxation of the straight-line assumption), and so the coefficients were held fixed for each outcome.

more, when participants with the most severe symptoms of asthma are compared with the rest of the cohort, the association with elevated CRP levels is at its most pronounced.

Leptin, adiponectin, chemokines, and cytokines have been suggested as causes of the inflammation seen in the obese state.²³ In fact, low-level systemic inflammation, as evidenced by elevated CRP and IL-6 levels, has been linked to an increased risk of cardiovascular disease and type 2 diabetes in overweight individuals.²⁴ Other inflammatory disorders, including asthma, inflammatory bowel disease, and rheumatoid arthritis,²⁵ also have been described to have consistently elevated measures of inflammation associated with increased adiposity,²⁶ but no causal association has been documented. In the present analysis of children with asthma, we demonstrated not only that a higher BMI is observed in children with increased asthma severity but also that some of the seeming association between obesity and asthma is significantly mitigated when we control for serum CRP level.

We also found that asthma prevalence is worse in males. Although there is conflicting previous evidence on the role of sex in the association between asthma and obesity,⁶ we showed that males were almost 20% more likely to have asthma symptoms across all levels of asthma severity, even after controlling for inflammation and obesity. Gilliland et al²⁷ found that the risk of new-onset asthma was worse in overweight males, which we confirmed in the present sample. Because of potential confounders, such as muscle mass and physical activity, further studies on the role of sex in asthma severity are needed.

Generalized ordered logistic regression was used in this analysis to determine the impact of different variables across levels of asthma severity. Whereas ordered logistic regression assumes that the relationship between each pair of outcome groups is the same, generalized ordered logistic regression allows for the estimate of the independent variable effect to differ by the level of the ordinal outcome. Using this design, we showed that an elevated CRP level and an elevated BMI z score are significantly associated with the existence and severity of asthma and that for CRP, this effect is most pronounced in individuals with the most severe symptoms of

asthma. Although male sex and having health insurance were also associated with more severe asthma symptoms, no other variable (ie, tobacco smoke exposure, housing, or household income) contributed to determining differences in the existence or severity of asthma.

The positive association we observe between health insurance and asthma severity may be due to a variety of factors. For example, patients who are high “utilizers,” particularly those with frequent emergency department visits, may have been offered the opportunity by hospital staff to enroll in a public insurance program for uninsured children (ie, SCHIP [State Children’s Health Insurance Program]). Alternatively, parents of insured children may be more likely to seek treatment, especially if their children are more symptomatic. Although the sources of this positive association may be worthy of further investigation, it is beyond the scope of this discussion.

There is a growing literature supporting the hypothesis that the impact of obesity on increased asthma prevalence is by the generation of inflammatory mediators.^{23–25} The present findings are consistent with this hypothesis. Although causality cannot be definitively demonstrated using this model, the suggestion that CRP is a biomarker linked to asthmatic patients with an elevated BMI seems worthy of further investigation.

This analysis is the first, to our knowledge, to use a large pediatric population cohort to associate increased asthma severity with being overweight or obese and to present statistical evidence demonstrating the importance of controlling for inflammation when examining the link between obesity and asthma. We acknowledge the limitations of a retrospective database analysis, but we hope that these compelling findings can be hypothesis generating. We support the promotion of prospective multicenter studies that examine the effect of obesity on pediatric asthma and that monitor asthma symptoms and serum CRP levels during weight loss. Future studies that examine the role of obesity-specific markers of inflammation, such as leptin, adiponectin,²³ and resistin, will further the understanding of the role of elevated BMI z scores in the development and severity of asthma in children.

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