

Asthma control, adiposity, and adipokines among inner-city adolescents

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This project has been funded in whole or in part with Federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, under contract numbers NO1-AI-25496 and NO1-AI-25482 and from the National Center for Research Resources, National Institutes of Health, under grants RR00052, M01RR00533, M01RR00071, 5UL1RR024992-02, and 5M01RR020359-04.

Disclosure of potential conflict of interest: J. Kumar has received research support from the National Heart, Lung, and Blood Institute; is President of the Illinois Society of Allergy, Asthma, and Immunology; and is a member of the American Thoracic Society. G. R. Bloomberg has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases. H. Mitchell has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases. C. M. Kerckmar is on the Speakers' Bureau for Merck; and has received research support from Sepracor. E. Matsui has received research support from the National Institutes of Health. S. Steinbach has received research support from the National Institutes of Health/National Institute of Allergy and Infectious Diseases; and has served as an expert witness on the topic of bronchiolitis. S. J. Szeffler is a Consultant for GlaxoSmithKline, Genentech, Merck, Boehringer-Ingelheim, Novartis, and Schering Plough; has received research support from the NIH/NHLBI Childhood Management Program (CAMP), NHLBI Childhood Asthma Research and Education (CARE), NIH/NHLBI Asthma Clin Res Network (ACRN), NIH/NIAID Inner City Asthma Consortium (ICAC), GlaxoSmithKline, NJH/NHLBI Asthma Net, and NEEHS/EPA Childhood Environmental Health Center Grant. C. A. Sorkness is on the Advisory Board for GlaxoSmithKline, Schering Plough, AstraZeneca, and Novartis; and has received research support from Schering Plough and Sanofi. W. J. Morgan is a consultant for, and Chair of the Data Safety Monitoring Board for the Cystic Fibrosis Foundation; is a Consultant and Chair of the North American Scientific Advisory Group for the Epidemiologic Study of Cystic Fibrosis for Genentech; is a Consultant for Novartis; has received research support from the NIH/University of Wisconsin and Novartis. S. J. Teach has received research support from Novartis; has served as an expert witness on the topics of wheezing, pneumonia, and dehydration; and is a volunteer for the NIAID Food Allergy Guidelines. V. N. Gan has received research support from Baylor College of Medicine/Texas Department of State Health Services. The other authors declare they have no conflicts of interest.

Received for publication September 17, 2009; revised December 22, 2009; accepted for publication January 29, 2010.

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0091-6749/00.00

Published by Elsevier, Inc. on behalf of the American Academy of Allergy, Asthma & Immunology

doi:10.1016/j.jaci.2010.01.053

Background: There is an association between adiposity and asthma prevalence, but the relationship to asthma control is unclear.

Objectives: We sought to understand the relationships among adiposity, sex, and asthma control in inner-city adolescents with asthma.

Methods: We prospectively followed 368 adolescents with moderate-to-severe asthma (ages 12-20 years) living in 10 urban areas for 1 year. Asthma symptoms and exacerbations were recorded, and pulmonary function and exhaled nitric oxide levels were measured every 6 weeks. Adiposity measures (body mass index [BMI] and dual-energy X-ray absorptiometric scans) were made, and blood was collected for measurement of allergy markers, adiponectin, leptin, TNF- α , IL-6, and C-reactive protein levels.

Results: More than 60% of female subjects and 50% of male subjects were above the 85th percentile of BMI for age.

Higher BMI was associated with more symptom days ($R = 0.18$, $P = .02$) and exacerbations ($R = 0.18$, $P = .06$) among female subjects only. Adiponectin was inversely related to asthma symptoms ($R = -0.18$, $P < .05$) and exacerbations ($R = -0.20$, $P < .05$) and positively with FEV₁/forced vital capacity ratio ($R = 0.15$, $P < .05$) in male subjects only independent of body size. There was no relationship between adiposity or adipokines and total IgE levels, blood eosinophil counts, and exhaled nitric oxide levels. Dual-energy X-ray absorptiometry provided little additional value in relating adiposity to asthma outcome in this population of adolescents.

Conclusion: Adiposity is associated with poorer asthma control in female subjects. Adiponectin is associated with improved asthma control in male subjects. (*J Allergy Clin Immunol* 2010;125:584-92.)

Key words: Obesity, asthma, adipokines, leptin, adiponectin

In the past several decades, obesity has increased dramatically, especially among low-socioeconomic-status minority populations.¹⁻³ Epidemiologic studies have shown that being overweight serves as a risk factor for the development of asthma. The plausibility of a causal relationship is supported by prospective studies in both adults and children suggesting that being overweight and obesity can precede the onset of asthma⁴⁻⁶ and studies in adults demonstrating improvement in asthma symptoms with weight loss.^{7,8} In light of a growing literature showing an association between obesity and asthma, detailed study of children with asthma living in these areas might shed light on this relationship.

Abbreviations used

ACE: Asthma Control Evaluation
ACT: Asthma Control Test
BMI: Body mass index
CRP: C-reactive protein
DEXA: Dual-energy X-ray absorptiometry
FENO: Fraction of exhaled nitric oxide
FVC: Forced vital capacity

In contrast to the consistent evidence linking obesity to the incidence and prevalence of asthma, studies on the association between asthma control and obesity have been less consistent.⁹⁻¹³ Additionally, many of the studies that focused on obesity and asthma morbidity lacked detailed phenotypic characterization of asthma and have not carefully assessed control of asthma symptoms using a standardized guidelines-based approach.¹⁴⁻¹⁸ Even fewer studies have evaluated the interaction of sex and obesity on asthma morbidity.^{15,18} This interaction is of importance in view of the variable effect that sex has had in studies of the relationship between obesity and asthma.^{19,20}

Several hypotheses to explain the asthma-obesity association have been proposed, including the effects of obesity on chest wall mechanics, low-grade systemic inflammation, and changes in serum concentrations of adipose tissue–derived proteins (adipokines).²⁰ Adipose tissue of the obese expresses increased amounts of proinflammatory proteins, such as TNF- α , IL-6, and C-reactive protein (CRP). These cytokines can modify airway inflammation,²¹ increase airway contractility,²² and modify the response to glucocorticoids.²³ The adipokine leptin increases with increased adiposity and has proinflammatory effects.²⁴ In contrast, levels of another adipokine, adiponectin, decrease with increasing adiposity, and it has anti-inflammatory properties.²⁵ Notably, adipokines can mediate the association between obesity and asthma in a sex-specific fashion.^{26,27}

The variability of the sex influence on the effect of adiposity on asthma might be due to the use of body mass index (BMI) as a measure of adiposity. BMI does not differentiate between lean body mass and fat mass,²⁸ and therefore for a given BMI value, female subjects have a higher proportion of body fat than male subjects.²⁹ It is reasonable to conjecture that the stronger association between BMI and asthma seen in female subjects could be due to the fact that the relationship between BMI and body fat is sex dependent.³⁰⁻³⁶ The use of a direct measure to characterize adiposity, such as dual-energy X-ray absorptiometry (DEXA), is needed to resolve this issue.

As part of a larger randomized trial examining the utility of measuring exhaled nitric oxide levels to improve asthma control in adolescents residing in inner-city neighborhoods (the Asthma Control Evaluation [ACE] study),³⁷ we designed a prospective study to examine the effect of weight and body fat on asthma morbidity as measured by symptom report and exacerbations. In this sample of inner-city adolescents with careful guidelines-based management of asthma, we evaluated the sex-specific association between asthma morbidity and adiposity using traditional BMI and DEXA scan measures of body fat. To further investigate the mechanisms involved in the relationship of adiposity measures and sex, we also assessed inflammatory biomarkers and adipokines. Some of the results of this study have been previously reported in the form of an abstract.³⁸

METHODS

Study design and population

The Asthma Adiposity Study included 368 adolescents 12 to 20 years of age enrolled from among ACE study participants in 10 major urban areas of the United States. All appropriate institutional review boards approved this study. Written informed consent and assent were obtained. The ACE study was a randomized, double-blind, parallel-group trial with a 3-week run-in period to characterize participants, establish treatment, and evaluate adherence.³⁷ The main objective of the ACE study was to determine whether the addition of exhaled nitric oxide measurement to a guidelines-based approach to selecting therapy improved asthma outcomes over guidelines-based therapy alone. At the recruitment, randomization, and follow-up visits, symptoms, rescue medication use, pulmonary function, and adherence were used to assign a medication regimen based on standardized treatment guidelines across sites. In the intervention group exhaled nitric oxide levels were additionally considered when assigning medications. There were 6 follow-up visits approximately 2 months apart for 1 year. Treatment recommendations were derived from protocol-defined treatment steps based on asthma control and adherence.³⁷ With each step-up in treatment, the intensity of the controller medication regimen increased, as reflected by either an increase in inhaled corticosteroid dose or the addition of a leukotriene modifier or long-acting β -agonist.

Asthma morbidity outcomes

The primary morbidity outcomes were maximum symptom days and exacerbations during the follow-up period.³⁷ Maximum symptom days recalled over the previous 2 weeks were assessed every 6 to 8 weeks and averaged over the 46-week treatment period after randomization. Exacerbations over the previous 2 months were determined at every visit and summed over the 46-week treatment period. *Maximum symptom days* were defined as the largest value among number of days with wheezing, chest tightness, or cough; number of nights of sleep disturbance; and number of days when activities were affected. An *asthma exacerbation* was defined as a hospitalization, unscheduled visit, or prednisone course for asthma during the treatment period. The Asthma Control Test (ACT) was administered at each visit, and the score was averaged over the 46-week treatment period after randomization. A score equal to or less than 19 on the ACT suggests that asthma is not well controlled.

Procedures

At each study visit, pulmonary function tests were performed according to American Thoracic Society guidelines³⁹ and overread for quality control. Skin testing was performed by means of the puncture method on the volar surface of the forearm with a Multi-Test II device (Lincoln Diagnostics, Decatur, Ill). Serum total IgE levels were measured with the UniCap System (Phadia, Uppsala, Sweden). Fraction of exhaled nitric oxide (FENO) was measured (flow rate, 50 mL/s) with a rapid-response chemiluminescent analyzer (NIOX System, Aerocrine, Sweden) according to American Thoracic Society guidelines.⁴⁰

Height and weight measurement

At baseline, subjects were weighed twice to the nearest 0.1 kg by using a digital or balance scale that was calibrated daily. Height was measured 3 times to the nearest 0.1 cm with a stadiometer (Harpender model no. 602VR; Holtain, Ltd, Dyfed, United Kingdom) that was calibrated daily. Weight and height measurements were averaged, and BMI was calculated.

Body composition assessments

DEXA scans were completed for 300 participants across 9 sites. Participants who weighed more than 136.4 kg (300 lbs) were not eligible for a DEXA scan ($n = 4$). There was no significant difference in BMI between participants with DEXA measurements and those without (data not shown). Total body fat, fat-free mass, and lean soft tissue and bone mineral content (in kilograms) were assessed.

Adipokines and biomarkers

Serum leptin, adiponectin, and CRP levels were measured by Northwest Lipid Research Laboratories (Seattle, Wash). Leptin and adiponectin levels

TABLE I. Characteristics of the 368 Asthma Adiposity Study participants by sex

Characteristics	Female subjects (n = 169)	Male subjects (n = 199)	P value*
Age at recruitment (y)	14.5 ± 2.1	14.0 ± 1.9	.02
Racial/ethnic group (%)			
African American	62.7	62.3	.99
Hispanic	22.5	22.6	
Other or mixed	14.8	15.1	
Caretaker completed high school (%)	75.0	80.1	.27
Household income <\$15,000 (%)	48.4	51.1	.62
≥1 Household member employed (%)	78.1	85.9	.05
No. of positive skin test responses (of 14 performed)	4.1 ± 3.2	5.3 ± 3.2	<.001
Total IgE (kU/L)	178 (62–567)	315 (120–723)	.002
Blood eosinophils (per μL)	168 (84–301)	268 (180–437)	<.001
Asthma status, pulmonary function, and use at recruitment†			
Maximum symptom days (no. of days/last 2 wk)	6.1 ± 4.5	4.9 ± 4.3	.002
ACT score in the last month	17.2 ± 4.3	19.2 ± 3.7	<.001
FEV ₁ (% predicted)	93.7 ± 16.5	91.3 ± 16.6	.18
FEV ₁ /FVC ratio	79.2 ± 10.1	77.3 ± 9.1	.03
FENO (ppb)	22.2 (11.8–52.3)	40.6 (17.8–72.0)	<.001
≥1 Exacerbation (%)	72.8	75.4	.57
Asthma status, pulmonary function, and use during 1-y follow-up			
Maximum symptom days (no. of days/last 2 wk)	2.1 ± 1.5	1.8 ± 1.7	.01
ACT score in the last month	21.5 ± 2.3	22.1 ± 2.1	.01
FEV ₁ (% predicted)	97.2 ± 14.8	93.9 ± 14.9	.03
FEV ₁ /FVC ratio	81.3 ± 8.0	79.3 ± 8.1	.01
FENO (ppb)	21.6 (11.0–45.6)	33.6 (18.5–59.8)	<.001
≥1 Exacerbation (%)	38.5	41.2	.59

Values are shown as means ± SDs, where applicable. Interquartile ranges are included in parentheses with median values.

*P value for χ^2 tests (categorical variables) or Wilcoxon tests (continuous variables) for the differences between female and male subjects.

†Maximum symptom days are defined as the largest value among the following variables reported over the prior 2 weeks: (1) number of days with wheezing, chest tightness, or cough; (2) number of nights of sleep disturbance; and (3) number of days when activities were affected. An asthma exacerbation was defined as a hospitalization, unscheduled visit (including emergency department visits), or prednisone course for asthma.

were measured with an RIA (Linco Research, Inc, St Charles, Mo). CRP levels were measured immunochemically. Serum IL-6 and TNF- α levels were measured by means of ELISA assay (R&D Systems, Minneapolis, Minn), and total serum eosinophil counts were performed by local clinical laboratories. Only IL-6 had a number (n = 56) of undetectable results. These were assigned a value of half the lower limit of detection.

Statistical analyses

Partial Pearson correlations were calculated for the entire study population to measure the strength of the relationships between baseline adiposity measures and outcomes during the year of follow-up while controlling for the effects of site, race, and age. Effect modification by sex was examined, and a large number of interactions were significant (especially those related to asthma status and DEXA-determined percentage body fat); thus analyses were stratified by sex. Data for FENO, total IgE, blood eosinophil, CRP, IL-6, and TNF- α values were log-transformed to better approximate a normal distribution before analysis. A P value of less than .05 was considered statistically significant. All statistical analyses were performed with SAS statistical software version 9.2 (SAS Institute, Inc, Cary, NC) and the R system for statistical computing version 2.10.0 (R Development Core Team).

RESULTS

The average age of the Asthma Adiposity Study participants was 14.2 (± 2.0) years, and slightly more than half were male (54.1%). Nearly two thirds were African American (62.5%), and the remainder were predominantly Hispanic (22.6%). Family income levels were low, with approximately 50% having incomes of less than \$15,000 per year. Because most research

TABLE II. Baseline weight status of the Asthma Adiposity Study participants by sex

Characteristic	Female subjects n = 169	Male subjects n = 199	P value*
Adiposity measurements			
Height (cm)	159.9 ± 7.0	166.1 ± 10.6	<.001
Height percentile	49.3 ± 27.5	56.0 ± 30.2	.024
Weight (kg)	70.6 ± 21.3	70.0 ± 22.9	.61
Weight percentile	79.7 ± 24.1	74.3 ± 27.5	.24
BMI (kg/m ²)	27.4 ± 7.1	25.0 ± 6.5	<.001
BMI percentile	82.0 ± 22.3	75.6 ± 25.9	.055
Percentage body fat†	35.4 ± 8.9	21.9 ± 10.2	<.001
Adipokines and biomarkers			
Adiponectin (μg/mL)	13.9 ± 6.0	11.9 ± 4.5	.003
Leptin (ng/mL)	20.7 ± 12.0	8.6 ± 9.5	<.001
CRP (mg/dL)	0.09 (0.03–0.21)	0.05 (0.02–0.14)	.005
IL-6 (pg/mL)	0.93 (0.40–2.10)	0.68 (0.30–1.64)	.02
TNF- α (pg/mL)	2.00 (1.37–3.49)	1.74 (1.27–2.78)	.24

Values are shown as means ± SDs where applicable. Interquartile ranges are included in parentheses with median values.

*P value for χ^2 tests (categorical variables) or Wilcoxon tests (continuous variables) for the differences between female and male subjects.

†The number with DEXA measurements is 136 for female subjects and 164 for male subjects.

investigations have found effects of obesity to differ between male and female subjects, the initial characteristics table (Table I) presents all variables by sex. The population is highly atopic, with 4 to 5 positive skin test responses on average (from a panel of 14);

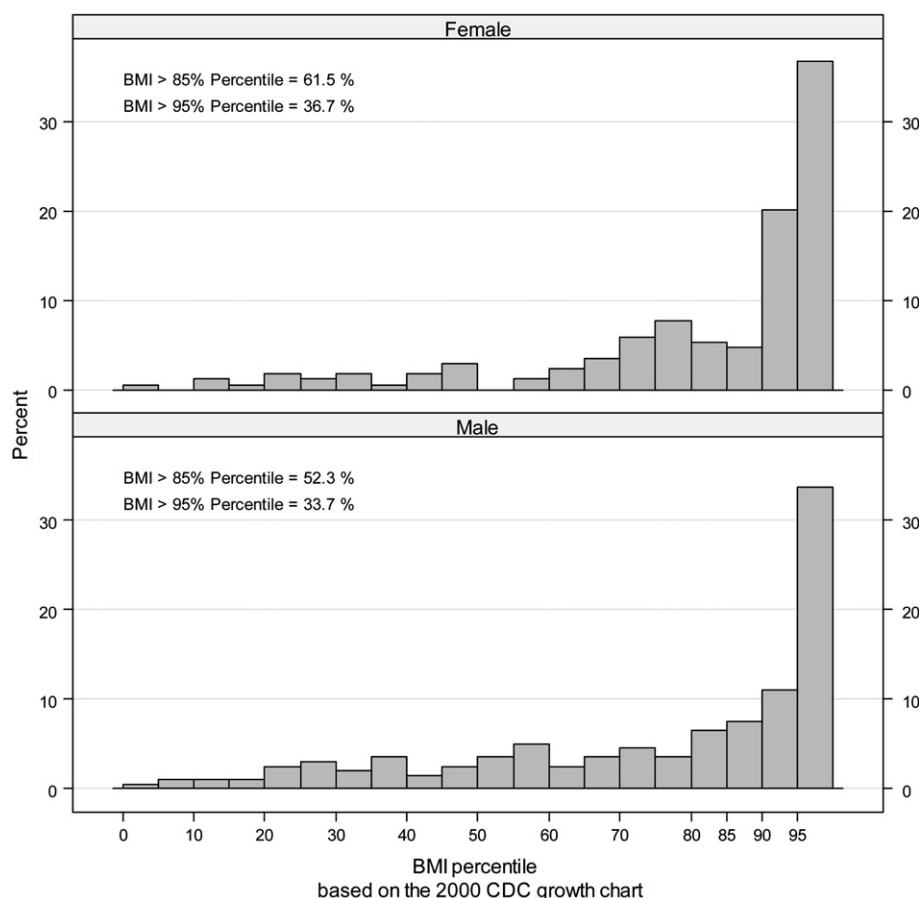


FIG 1. Distribution of BMI among female and male subjects in the Asthma Adiposity Study. CDC, Centers for Disease Control and Prevention.

male subjects had a higher number of positive skin test responses ($P < .001$) and total IgE levels ($P = .002$). At recruitment, male subjects had slightly worse lung function and higher exhaled nitric oxide levels than female subjects (median, 40.6 vs 22.2 ppb; $P < .001$). Asthma symptoms, however, were significantly greater among female subjects compared with those of male subjects for symptom days (6.1 vs 4.9 per 2 weeks, $P = .002$) and ACT scores (17.2 vs 19.2, $P < .001$). This same pattern of worse lung function and higher FENO value for male subjects but worse asthma symptoms for female subjects persisted throughout the 1-year follow-up period.

BMI and percentage body fat measured by means of DEXA are presented in Table II, along with adipokines and biomarkers related to obesity. Male subjects were taller than female subjects on average, but weight was similar. Both BMI and percentage body fat were significantly higher for female subjects. This inner-city population of adolescents with asthma was considerably heavier than the US population,³ with distributions of BMI for female subjects showing 61.5% above the 85th percentile of BMI for age and 36.7% above the 95th percentile. More than half the male subjects (52.3%) were above the 85th percentile, and 33.7% were heavier than the 95th percentile of BMI for age (Fig 1). Serum levels of adipokines and weight-related biomarkers (CRP and IL-6) were higher for female than male subjects, but TNF- α levels did not differ (Table II).

The correlations of BMI and DEXA percentage body fat with asthma symptoms, atopy, and biomarkers are shown separately

for male and female subjects in Table III. Among female subjects, but not male subjects, higher levels of symptoms were associated with higher BMI and even more strongly associated with a higher percentage body fat. Both male and female subjects exhibited a reduced FEV₁/forced vital capacity (FVC) ratio with higher BMI and body fat. Levels of leptin, CRP, and IL-6 all increased with increased adiposity, and levels of adiponectin were reduced. Levels of TNF- α were not related to adiposity. Female subjects above the 85th percentile of age-adjusted BMI had 0.56 more symptom days per 2 weeks (95% CI, 0.10-1.01) than female subjects of normal weight and were nearly 2½ times more likely to have an exacerbation (odds ratio, 2.49; 95% CI, 1.25-5.14). Fig 2 shows this marked difference in the relationship between percentage body fat and asthma symptoms and exacerbations for female subjects compared with male subjects (interaction P values $< .01$ and $< .05$, respectively). The trunk/peripheral fat ratio, as measured by means of DEXA, was not associated with symptoms or exacerbations (data not shown). In models sequentially examining BMI and percentage body fat, percentage body fat did not add to the percentage of variance explained for maximum symptom days or exacerbations once BMI was accounted for (data not shown). We were prevented from examining pulmonary function outcomes in this manner because of collinearity.

The relationship of adiponectin and leptin to asthma morbidity for both male and female subjects is shown in Table IV. For male subjects, adiponectin levels were inversely related to asthma symptoms and exacerbations (Fig 3, both interaction P values

TABLE III. Correlations of asthma status, adipokines, and biomarkers with BMI and percentage body fat (DEXA) by sex

Characteristic	BMI		Percentage body fat	
	Female subjects	Male subjects	Female subjects	Male subjects
Asthma status				
Maximum symptom days	0.18*	0.00	0.27†	−0.04
Asthma Control Test	−0.11	−0.04	−0.22†	0.02
Any exacerbations	0.18	0.13	0.35‡	0.11
Lung function, atopy, and FENO				
FEV ₁ (% predicted)	0.10	0.18*	0.02	−0.02
FEV ₁ /FVC ratio	−0.26‡	−0.18*	−0.13	−0.20†
Total IgE (kU/L)	0.03	0.03	−0.08	0.00
Blood eosinophils (per μ L)	0.14	−0.03	0.08	−0.02
FENO (ppb)	−0.05	−0.08	−0.10	−0.08
Adipokines and biomarkers				
Adiponectin (μ g/mL)	−0.41‡	−0.22†	−0.31‡	−0.27‡
Leptin (ng/mL)	0.70‡	0.82‡	0.73‡	0.87‡
CRP (mg/dL)	0.64‡	0.58‡	0.64‡	0.58‡
IL-6 (pg/mL)	0.22†	0.20†	0.18*	0.18*
TNF- α (pg/mL)	−0.11	0.01	−0.10	0.03

Values are Pearson correlation coefficients, except for any exacerbation in which a polyserial correlation was calculated. All values are adjusted for site, race, age, and group assignment.

* $P < .05$.

† $P < .01$.

‡ $P < .001$.

< .10) and were positively associated with ACT scores and FEV₁/FVC ratios. Leptin levels were positively related to asthma symptoms in female subjects. The effect of adiponectin was maintained in models adjusting for BMI (data not shown). We were unable to control the leptin models for BMI because of substantial collinearity. There was no association seen between CRP or IL-6 levels and maximum symptom days or exacerbations.

DISCUSSION

In this study of inner-city adolescents with asthma, we have provided an extensive analysis of the relationship between obesity and asthma morbidity using a prospective, well-characterized, and closely monitored cohort. Our major finding is that, as in the case between asthma prevalence and obesity,^{19,20} sex has substantial influence on the relationship of adiposity to asthma morbidity. In female adolescents only, increased BMI and body fat were associated with worse asthma control, more asthma exacerbations, and lower FEV₁/FVC ratio. In male subjects we report another novel finding, a protective role of serum adiponectin on the same parameters independent of adiposity. Notably, these effects were observed despite good adherence to guidelines-based management.³⁷ Our study is also the first to provide information on the relationship between adiposity measures other than BMI and asthma morbidity and to examine the relationship of serum adipokines to asthma control and measures of airway inflammation.

Adiponectin is produced exclusively by adipocytes; however, circulating levels decrease with increasing adiposity.²⁵ This protein has anti-inflammatory properties.⁴¹⁻⁴³ It acts on macrophages and monocytes to inhibit production of proinflammatory cytokines and to augment IL-10 and IL-1 receptor antagonist expression.⁴⁴ Despite higher serum levels of adiponectin in female subjects, the protective effect was seen in male subjects only. The sex-specific effect of adiponectin was not explained by the ratio of leptin to adiponectin, which is significantly different in

male and female subjects. A possible explanation might be that adiponectin receptors are downregulated with increased adiposity in adolescent female subjects. In a study evaluating asthma prevalence, adiponectin was found to be protective against current asthma prevalence in premenopausal women independent of BMI.²⁷ The reported protective effects of adiponectin in human studies are consistent with murine studies in which exogenous administration of adiponectin resulted in an almost complete suppression of allergen-induced airway hyperreactivity, airway inflammation, and T_H2 cytokine expression in the lung.⁴⁵ In contrast, leptin was associated with poorer asthma control, but an independent effect could not be demonstrated because of the high correlation between adiposity measures and leptin. The role of adiponectin in asthma warrants further study and might have implications for therapy.

Adipocytes and macrophages that infiltrate adipose tissue are important sources of inflammatory cytokines.⁴⁶ It has been hypothesized that high levels of proinflammatory molecules released from adipose tissue into the systemic circulation could contribute to airway inflammation and increase asthma severity.⁴⁷ However, Sutherland et al⁴⁸ found that although systemic and airway inflammation were present in obesity and asthma, there was no evidence of interaction between the two. In our study the markers of systemic inflammation generally increased with increasing BMI or percentage body fat in subjects of both sexes, with female subjects having higher levels than male subjects. However, the markers did not correlate with asthma morbidity. In the absence of bronchial lavage to directly measure cytokines, we cannot determine the association of adiposity with these markers of airway inflammation. However, we demonstrated no correlation of adiposity and serum leptin with FENO. This supports the possibility that adipokines might be related to asthma through a mechanism unrelated to inflammation.

The relationship between obesity and asthma severity as classified in published asthma guidelines is controversial. Obesity was associated with severity as classified by Global Initiative for

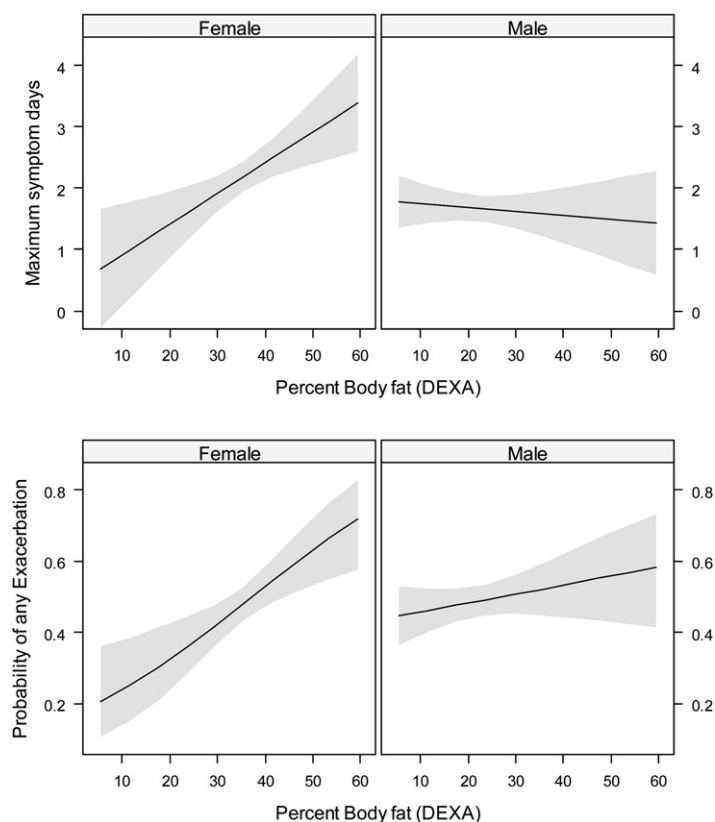


FIG 2. Relationships between percentage body fat (DEXA) and asthma outcomes by sex. Relationship of percentage body fat with maximum symptom days (*top row*) and with exacerbations (*bottom row*) is shown. All models are adjusted for site, race, age, and group assignment (*black lines*) with 95% CIs (*light gray areas*).

TABLE IV. Correlations of asthma status with adipokines

Characteristic	Adiponectin		Leptin	
	Female subjects	Male subjects	Female subjects	Male subjects
Asthma status				
Maximum symptom days	−0.06	−0.18*	0.16*	−0.08
Asthma Control Test	0.00	0.19†	−0.13	0.03
Any exacerbations	−0.00	−0.20*	0.11	0.11
Lung function, atopy, and FENO				
FEV ₁ (%predicted)	−0.04	−0.04	0.02	0.03
FEV ₁ /FVC ratio	0.14	0.15*	−0.12	−0.13
Total IgE (kU/L)	−0.04	0.07	−0.05	−0.02
Blood eosinophils (per μ L)	−0.14	−0.05	0.09	−0.02
FENO (ppb)	−0.01	0.04	−0.11	−0.07

Values are Pearson correlation coefficients, except for any exacerbation in which a polyserial correlation was calculated. All values are adjusted for site, race, age, and group assignment.

* $P < .05$.

† $P < .01$.

Asthma guidelines among adults in the National Asthma Survey in the United States¹⁷ but not in the European Community Respiratory Health Survey⁴⁹ or a Canadian sample of asthmatic subjects.¹¹ The effect of increasing body weight on asthma control or response to therapy is not consistently reported in the literature. Increased BMI has been associated with increased symptoms or health care use for asthma attacks among 3- to 5-year-olds in Head Start,⁵⁰ inner-city children 4 to 9 years old,⁹ and adults in

the National Asthma Survey.¹⁷ In the Childhood Asthma Management Program cohort there was no correlation between BMI and markers of asthma control. However, these children were prepubertal, and median BMI was much lower than in our study.⁵¹ A cross-sectional study of urban adults with asthma found no differences in asthma control as measured by using 4 validated asthma control questionnaires with changes in BMI.⁵² In a recent study comparing obese and nonobese adult asthmatic subjects

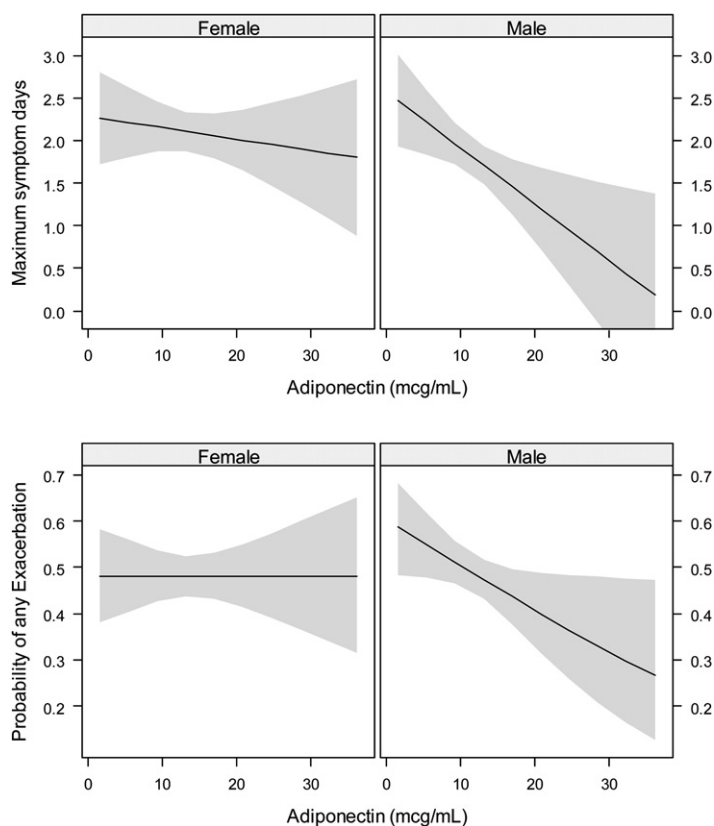


FIG 3. Relationships between adiponectin and asthma outcomes by sex. Relationship of adiponectin with maximum symptom days (*top row*) and with exacerbations (*bottom row*) is shown. All models are adjusted for site, race, age, and group assignment (*black lines*) with 95% CIs (*light gray areas*).

presenting to emergency departments, the severity of the asthma exacerbations was found to be similar.¹² Responsiveness to asthma treatment shows a similar ambiguity. Secondary analyses performed on participants 18 years of age and older from 5 clinical trials found obese asthmatic subjects (BMI ≥ 40) have a lower response to inhaled corticosteroids or inhaled corticosteroids combined with a long-acting β -agonist.⁵³ In a study of 18- to 50-year-olds seeking treatment in an emergency department, heavier patients (BMI ≥ 25) had more residual wheezing and a higher hospitalization rate.⁵⁴ A review of the hospitalization course for asthmatic subjects 2 to 18 years of age admitted to an intensive care unit found obese subjects (BMI ≥ 95 th percentile) had longer treatment and hospital stays despite similar severity at presentation.⁵⁵ In contrast, for inner-city asthmatic subjects 2 to 18 years of age participating in the Breathmobile project, obesity (BMI ≥ 95 th percentile) had no effect on the ability to achieve or maintain asthma control.⁵⁶ Failure to adequately measure or standardize therapy limits the interpretability of these studies. The design of the ACE study included guidelines-based standardized treatment for all participants and therefore addressed these limitations of previous studies.

Reported differences between male and female subjects in the effect of body size on asthma have been called into question because of methodological and statistical concerns about the studies.^{57,58} Our findings demonstrate that in female subjects asthma control, asthma exacerbations, and FEV₁/FVC ratio are adversely affected by increasing BMI and percentage body fat. The increased morbidity and subsequent treatment found in obese

female subjects was not associated with increased atopy or FENO values. Our results are consistent with studies in adults.^{48,59} This raises 2 potential explanations, namely that increased asthma morbidity is a result of a mechanism other than atopy and inflammation or that there is a difference in the perception of asthma symptoms among obese female subjects.

Other studies have suggested a difference in perception and reporting of symptoms among obese asthmatic subjects to account for the increased asthma severity. Asthmatic children ages 8 to 12 years who were obese or overweight as defined by BMI reported greater limitation of physical activity than their normal-weight peers, yet they had similar maximum aerobic power and levels of habitual activity.⁶⁰ Despite similar levels of severity, obese asthmatic subjects reported lower quality-of-life scores.¹¹ Secondary analyses from clinical trial participants found obese asthmatic subjects report a lower response to placebo.⁶¹ Further supporting the possibility of perception differences, bronchial reactivity to methacholine has been found to be equivalent^{51,62} or less⁶³ among obese asthmatic subjects when compared with that seen in lower-weight subjects. These studies do not find that this difference in perception is limited to female subjects, and therefore they do not provide an explanation for the sex differences found in this study.

Among children and adolescents, previous studies have reported that an increase in BMI is accompanied by a higher FEV₁ and FVC but a lower FEV₁/FVC ratio in both nonasthmatic^{64,65} and asthmatic⁵¹ subjects. This effect might reflect the failure of airway size to increase proportionately to lung volume.

The effect of increasing body size on pulmonary function seen in this study is consistent with the previous literature.

The question that arises from previous studies that examined the relationship between asthma and obesity is whether BMI, the most commonly used index of adiposity, is an adequate measure. A similar BMI represents a differing level of percentage body fat depending on the sex, race, or sexual maturity of the child/adolescent.⁶⁶ Our study provides a unique opportunity to examine the relationship between BMI and DEXA measurements of overweight status and body fat. The measures were highly correlated in both male and female subjects. Although BMI alone has limitations in assessing the true degree of adiposity of an individual child,²⁹ more sophisticated measures provided little additional value in studies relating adiposity to asthma outcomes in African American and Hispanic adolescents.

The strength of this study is that it combines multiple measures of adiposity with adipokines and prospectively evaluates asthma outcome. By limiting our study to adolescents, it addresses the criticism that conflicting sex effects found in obesity studies do not take into account overlapping periods of development.⁵⁸ The effects of BMI in female subjects and adiponectin in male subjects on asthma control were seen despite optimal guideline-based management.

Our study has a number of limitations. We measured circulating, but not airway, measures of adipokines and cytokines. It is possible that levels in bronchoalveolar lavage fluid would provide additional information on the relationship between asthma morbidity and adiposity. Second, the improved control of asthma over the 42-week study period would tend to minimize the differences between obese and nonobese asthmatic subjects. Finally, despite the design of the ACE study, with its uniform comprehensive follow-up, data collection, and standardized treatment, it does not eliminate the possibility that perceptual differences in symptom reporting influenced our results.

In summary, our data support a sex-specific role for adipokines produced by adipose tissue in asthma morbidity, as measured by symptoms, pulmonary function, and exacerbations but not reflected in other indicators of airway inflammation. Asthma outcome is adversely affected by adiposity in female subjects, but not male subjects, whereas for male subjects, but not for female subjects, adiponectin has a protective effect independent of adiposity.

The implications of this study are highlighted by the high prevalence of those at risk for being overweight in this inner-city population of predominantly black and Hispanic adolescents. Future therapeutic approaches for asthma are more likely to succeed if sex and body size are taken into account. Further investigations into the roles of adipokines in asthma morbidity might have particular relevance to the high-risk inner-city populations.

The ACE study was a collaboration of the following institutions and investigators (principal investigators are indicated by asterisks): **Johns Hopkins University, Baltimore, Md**—P. Eggleston,* E. Matsui, R. Wood, K. Callahan, M. Mensa, L. Campbell, R. Merrill, P. Huffman, D. Bunce, and H. Brady; **Boston University School of Medicine, Boston, Mass**—G. O'Connor,* S. Steinbach, and N. Kozlowski; **Children's Memorial Hospital, Chicago, Ill**—J. Pongracic,* R. Kumar, J. Kim, R. Story, A. Donnell, S. Desai, A. Murthy, S. Boudreau-Romano, K. Koridek, T. Kearney, S. Pohlman, J. Milam, H. Negron, and I. Flexas; **Case Western Reserve University School of Medicine, Cleveland, Ohio**—C. Kercsmar,* J. Chmiel, M. Hart, T. Myers, T. Dillard, J. Juricka, C. Kane, V. Lockhart-Blue, M. Rogers, K. Ross, and P. Vavrek; **UT Southwestern Medical Center at Dallas, Tex**—R. Gruchalla,*

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Clinical implications: In an urban adolescent population with moderate-to-severe asthma, there is a dose-response relationship of adiposity to symptom days and exacerbations in female subjects.

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