

Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults

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Summary

Background Obesity is associated with increased asthma and atopy.

Objective To determine whether or not obesity in inner-city adults is associated with increased asthma prevalence, severity and exacerbations and IgE responses.

Methods This retrospective study involved 246 adults with asthma and other atopic disorders who were seen at an asthma clinic in New York City between 1997 and 2010. Height, weight, asthma diagnosis and symptoms, peak flow (PF), spirometry, serum IgE levels and white blood cell differentials were recorded.

Results Asthmatic patients had higher body mass index than non-asthmatics (median, interquartile range: 30.5, 10.2 vs. 27.8, 8.8; Mann–Whitney *U*-test, $P = 0.0006$). Class I and II/III obesity were associated with increased asthma (I: OR: 2.35, 95% CI: 1.04–5.34, $P = 0.04$; II/III: OR: 3.25, 95% CI: 1.36–7.74, $P = 0.008$). Class I and II/III obesity were associated with worsened asthma severity (ordinal logistic regression; I: OR: 4.23, 95% CI: 1.61–11.06, $P = 0.003$; II/III: OR: 2.76, 95% CI: 1.08–7.09, $P = 0.03$). Class II/III obesity was associated with increased asthma exacerbations requiring oral corticosteroids (repeated measures logistic regression, OR: 1.13, 95% CI: 1.03–1.25; $P = 0.01$) and increased requirement of inhaled corticosteroid for long-term asthma management (OR: 1.45, 95% CI: 1.29–1.62; $P < 0.0001$). In asthmatics, class II/III obesity was associated with decreased PF (general linear model, least squares mean $\pm$ SEM: 333.8 ± 37.4 vs. 396.2 ± 32.1 L/min; $P = 0.007$), forced expiratory volume in 1 s (75.2 ± 4.6 vs. $88.4 \pm 5.6\%$; $P = 0.03$) and forced vital capacity (83.2 ± 4.7 vs. $109.2 \pm 6.0\%$; $P = 0.0002$) and increased serum IgE (480.2 ± 88.3 vs. 269.0 ± 66.6 IU/mL; $P = 0.04$) and neutrophils (66.6 ± 3.7 vs. $60.1 \pm 3.8\%$; $P = 0.02$). Class I obesity was also associated with increased serum IgE (458.7 ± 68.9 , $P = 0.03$).

Conclusion and clinical relevance Obesity in inner-city adults may be both a risk and exacerbating factor for atopic asthma.

Keywords asthma, asthma severity, wheeze, peak flow, pulmonary function test, spirometry, forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), obesity, class I, II and III obesity, overweight, BMI, weight, atopy, immunoglobulin E, white blood cell, leukocyte, lymphocyte, neutrophil, monocyte, eosinophil, basophil

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Introduction

Obesity and asthma are two of the most pervasive public health problems in the United States. Obesity prevalence doubled among US adults between 1980 and 2004 [1, 2]. By 2007, the prevalence of obesity was an alarming 32.2% among adult men and 35.5% among adult

women [3]. Likewise, asthma prevalence increased by 70% since 1986 [4]. In 2009, the current asthma prevalence was 8.2% of the U.S. population, up from 7.3% in 2001, an increase of 12.3%. Prevalence of asthma in the non-Hispanic black population in 2009 was 11.1% [5]. The parallel increases suggest that there may be an association between these two disorders. Further, both

obesity [6] and asthma [7] are disproportionately higher among low-income minority populations.

Several studies have identified an association between obesity and asthma [8–15]. However, the relationship between obesity and IgE responses including atopy has not been determined. Some studies found a significant association between obesity and atopy [8, 16–18], whereas others found no significant association [19–21]. We recently reported that prolonged obesity in early childhood is associated with increased prevalence, severity and health care utilization for atopic dermatitis [22]. It has been suggested that the association between obesity and asthma prevalence is stronger in women than men [23, 24]. A recent cross-sectional study of 86 144 Canadians found that 1 unit of body mass index (BMI) increase was associated with a 6% increase in asthma risk in women and 3% increase in men [16].

However, several questions remain regarding the relationship of obesity and asthma. First, while obesity has been linked to increased asthma, it is unclear what role atopy plays in this association. In particular, previous studies have not examined the role of obesity in atopic asthmatics compared with atopic non-asthmatics. It is possible that obesity merely predisposes to atopy, in general, or any allergic disorders, including, but not limited to, asthma. Previous studies found conflicting results regarding whether or not obesity is a risk factor for atopy. Several studies in the United States and internationally found an association between atopy and obesity as judged by increased BMI and waist circumference [8, 17, 25–27], while others did not [21, 28–31].

Second, it is not known if the effects of obesity on asthma are primarily mediated through changes of systemic and/or airway immune responses or mechanically mediated through restrictive effects on chest wall expansion. Third, the longitudinal effects of obesity on asthma severity and exacerbations have not been well defined. We hypothesized that obesity causes increased allergic inflammation and impaired pulmonary function resulting in increased asthma severity and exacerbations and poor long-term asthma control. The present study examined the effects of obesity on asthma prevalence, severity and exacerbations, as well as on IgE and spirometry, from an inner-city adult asthma/allergy population.

Methods

Subject

The study was approved by the institutional review board at State University of New York Downstate Medical Center, Brooklyn, NY, USA. According to institutional research guidelines, informed consent from patients was not required because of the retrospective nature of the study. Subjects were patients of the adult

asthma and immunology clinic at State University of New York Downstate Medical Center between January 1997 and January 2010.

Inclusion criteria were adults (older than 18 years) who received care at this clinic, men and women, with atopy as judged by at least one positive skin-prick test and/or allergen-specific serum IgE. Exclusion criteria included chronic obstructive pulmonary disease (COPD) as defined by the ATS/ERS Task Force [32], usage of oral corticosteroids (OCS) or immunotherapy at initial encounter, history of autoimmune disorders or immunodeficiency, recent or current history of malignancy and incomplete follow-up. Most patients were followed-up over multiple visits.

Atopic non-asthmatics were selected as controls because they allowed for more specific study of the effects of atopic asthma *per se*, and not atopy overall. Non-asthmatic control subjects were treated for other atopic disorders, including urticaria, atopic dermatitis as defined by Hanifin and Rajka criteria [33], and allergic rhinoconjunctivitis as defined by the ARIA workshop report [34].

Data collection

At each visit, patients were interviewed about signs and symptoms of atopic diseases, smoking status and medication history and examined by a single physician (RJ); height and weight were measured.

Serial chart review was performed for this retrospective study by a researcher who was not aware of the *a priori* hypothesis. Some of the analyses used single measure data from the initial visit while others used repeated measures data from multiple visits (Fig. 1). Therefore, data were collected for all visits.

Asthma monitoring and classification

Asthmatic patients were instructed to monitor the presence and frequency of daytime and nighttime symptoms, such as cough and wheeze and were asked about symptoms at each visit. Peak flow (PF) was measured in-office at each visit using Vitalograph® (Ennis, Ireland). Clinical diagnosis and classification of asthma severity was based upon the 1997 National Heart, Lung and Blood Institute guidelines [35]: 0 = no asthma; 1 = mild intermittent asthma; 2 = mild persistent asthma; 3 = moderate persistent asthma; and 4 = severe persistent asthma. Methacholine challenge tests were not used for the diagnosis of asthma.

Atopy assessment

Atopy was defined by either *in vivo* or *in vitro* evidence of sensitization to a panel of aeroallergens common to

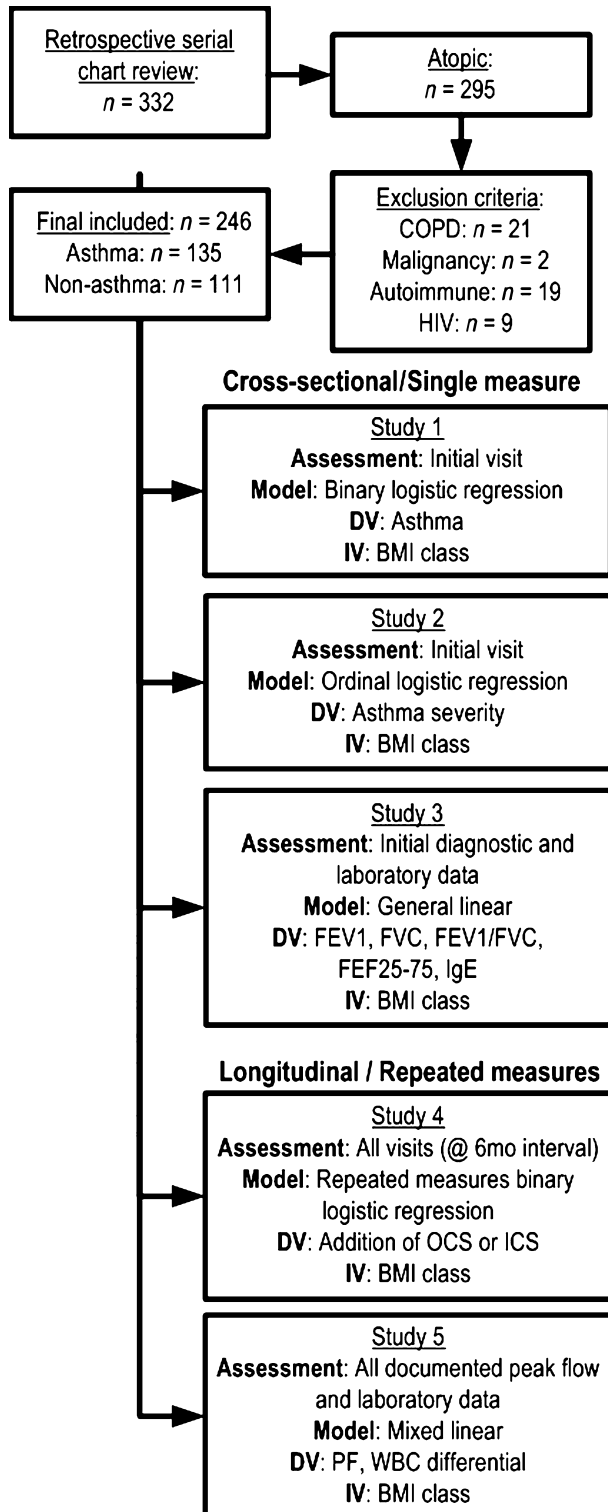


Fig. 1. Flowchart of study design.

the Northeastern United States. All epicutaneous skin-prick tests (Dermapik method; Greer Labs, Lenoir, NC, USA) were performed by RJ and induration present at 15 min was compared to histamine and saline controls.

This routine followed the same standard of care for all patients. *In vivo* evidence involved demonstration of at least one positive epicutaneous skin prick test to an aeroallergen. *In vitro* evidence involved at least one positive aeroallergen result from testing of serum using allergen-specific serum IgE (Immunocap; Quest Diagnostics, Syosset, NY, USA).

Body mass index

Weight (lb) and height while standing (in) were measured at each visit. BMI was calculated by $[\text{weight (lb)} \times 703] / \text{height (in)}^2$. BMI was found to be non-monotonic and was therefore treated as an ordinal variable where 0 = normal weight (BMI: <25), 1 = overweight (BMI: 25–30), 2 = class I obese (BMI: 30–35), and 3 = class II/III obese (BMI: >35) [36]. Waist circumference was not measured as part of routine clinical practice.

Pulmonary function testing (PFTs)

Spirometry was performed at initial asthma visit in the pulmonary function testing laboratory at State University of New York Downstate Medical Center using the KoKo Spirometer model 313100 (Ferraris CardioRespiratory, Louisville, CO, USA). All tests were performed by a dedicated technician and read/interpreted by a pulmonologist. Forced expiratory volume in 1 s (FEV1%), forced vital capacity (FVC%) and forced expiratory flow 25–75% (FEF25–75%) were recorded. Diffusing capacity of carbon monoxide was also used to aid in the diagnosis of asthma vs. COPD. In some instances, spirometry was performed prior to initial evaluation at another centre and was excluded from analysis.

Laboratory tests

All laboratory tests were conducted in the Clinical Diagnostic Laboratory at SUNY Downstate Medical Center. For analysis of serum IgE, blood was collected into red top Monoject tubes (Sherwood Medical, Deland, FL, USA) and allowed to clot for 30 min at room temperature. Serum IgE levels were determined using the UniCAP Total IgE fluoroenzyme immunoassay (Pharmacia and Upjohn Diagnostics, Freiburg, Germany) and was performed according to the manufacturers' recommendations. To evaluate test results, the response for a subject's sample was compared directly to the response of the IgE calibrators. Data are expressed as IU/mL (normal IgE range 20–100 IU/mL).

For complete blood counts with routine white blood cell (WBC) differentials, blood was collected into purple top Monoject tubes containing EDTA. WBC and differential counts were measured using the Cell-Dyn 4000

automated system (Abbott, Santa Clara, CA, USA). Data are expressed as cells/mm³.

Statistical analysis

The baseline characteristics of those patients with asthma and those without were examined. BMI, age at visit, PF and PFT parameters did not violate assumptions of normality, as judged by analysis of residuals and Shapiro–Wilk and Kolmogorov–Smirnov tests ($P < 0.05$) [37, 38]. Data are presented as mean $\pm$ standard deviation or least squares means (LSM) $\pm$ standard error. WBC and differential counts and serum IgE did violate assumptions of normality. Therefore, log-transformed variables were modelled since they did not violate assumptions of normality. Data are presented as exponentiated or LSM $\pm$ standard error. All data processing and statistics were done in SAS version 9.2 (SAS Institute, Cary, NC, USA).

A two-sided P -value < 0.05 was taken to indicate statistical significance for all estimates. However, the multiple dependent tests ($k = 26$) performed in this study increase the risk of falsely rejecting the null hypothesis. Therefore, P -values near 0.05 should be interpreted with caution.

Statistical models

Analysis 1: Logistic regression. The investigation was divided into five distinct analyses based on statistical design. The first analysis was cross-sectional using logistic regression to determine whether overweight, class I obesity and class II/III obesity were associated with asthma prevalence when compared with normal weight. The dependent variable was diagnosis of asthma (binary) and the independent variable was BMI, which was modelled both as a continuous and as an ordinal variable where 0 = normal weight (BMI < 25), 1 = overweight (BMI: 25–30), 2 = class I obesity (BMI: 30–35) and 3 = class II/III obesity (BMI: > 35). Adjusted odds ratio (aOR) and 95% confidence interval (CI) was calculated by including sex (binary), age at visit (continuous), race (categorical), and/or current smoking status (binary) in the model.

Analysis 2: Ordinal logistic regression. The second analysis was cross-sectional using ordinal logistic regression to determine whether or not overweight and obesity were associated with increased severity of asthma. Asthma severity was based on symptoms at the initial visit. The dependent variable was encoded as an ordinal variable where 0 = no asthma, 1 = mild intermittent asthma, 2 = mild persistent asthma, 3 = moderate persistent asthma, and 4 = severe persistent asthma, respectively. The independent variable was BMI, which was modelled

as an ordinal variable as above. OR for ordinal logistic regression were generated which represent the relationship between BMI (or other independent variables) with asthma severity across all four severity classes regardless of the threshold for severity. This approach was used because the models satisfied the proportional odds assumption as judged by Score test ($P > 0.05$). The aOR were calculated by including sex, age at visit, race and current smoking status in the model.

Analysis 3: Repeated measures logistic regression. The third analysis of asthma control was longitudinal (albeit retrospective) using repeated measures binary logistic regression to determine whether or not overweight and obesity were associated with fluctuations of requirement for oral OCS or inhaled corticosteroids (ICS) in asthmatics. This approach was used to model asthma exacerbations and long-term control as a function of BMI, respectively. Medication history was clinically assessed at each visit, in particular, usage of OCS or ICS and adherence to treatment regimen. Documented medication histories were collected by retrospective chart review.

Binary variables were constructed for requirement of oral or ICS at each visit. For oral steroids, 1 = addition of oral prednisone to the therapeutic regimen for asthma exacerbation, defined as significant disruption of activities of daily living or asthma affecting sleep for more than one night in a week and 0 = either oral prednisone was not part of the therapeutic regimen, patients were non-adherent to previously prescribed regimen, or patients were previously prescribed and using oral prednisone but there was no change or a decrease of the dosing. That is, the binary variable was set to 1 only when oral prednisone was newly prescribed. For inhaled steroids, 1 = requirement of ICS and 0 = either ICS were not prescribed or patients were non-adherent to previously prescribed regimen. Of note, the majority of asthmatic patients had persistent disease and required long-term usage of ICS during their treatment course. The independent variable was BMI, which was modelled as an ordinal variable as above. The aOR were calculated by including sex, age at each visit, race and current smoking status in the models.

As this was a retrospective clinical study, visits were subject-specific and were unbalanced across subjects. Therefore, these variables were modelled using repeated measures at 6 month intervals limited to the first 5 years of follow-up. If a subject had > 1 test in a given interval, the test with the closest date to the midpoint of that interval was selected. Thus, no subject had > 1 test per interval; however, some subjects had no tests per interval, which were treated as missing values. Missing values were encountered in $< 5\%$ of subjects for both OCS and ICS usage. Several imputation approaches were considered to address the missing values, including

interpolation and carrying over previous values. There were no significant differences between the results of the three approaches. Therefore, final models did not involve data imputation. Compound symmetry correlation structures were selected based on the quasi-likelihood information criterion.

Analysis 4: Generalized linear models. The fourth analysis of serum IgE levels and spirometric parameters used generalized linear models to determine whether or not there was an association with overweight and obesity; these were all modelled as continuous variables. Serum IgE levels and spirometry were tested during initial workup. Therefore, the first values were modelled as the dependent variables, and any subsequent values were not included in the models. Selection of the best-fitting intra-subject correlation structure was made by residual analysis and minimizing the Akaike's Information Criterion. Outliers were excluded using studentized residual and Cook's distance measures. LSM and standard errors were calculated for each variable at normal weight, overweight, class I obesity and class II/III obesity BMI intervals, while adjusting for sex, age and current smoking status. Post-hoc comparisons were done using Tukey's pair-wise comparisons. *P*-values are presented for comparison between class II/III obesity and normal weight.

Analysis 5: Mixed linear models. The fifth analysis of laboratory, spirometric, and PF parameters used mixed linear models to determine whether or not overweight and obesity were associated with altered values for PF and WBC count with differential; these were all modelled as continuous variables.

Peak flow was tested at each visit and WBC count with differential was tested repeatedly, but less frequently. As this was a retrospective clinical study, visits were subject-specific and were unbalanced across subjects. Therefore, these variables were modelled using repeated measures at 1 year intervals for the first 2 years of follow-up. If a subject had >1 test in a given interval, the test with the closest date to the midpoint of that interval was selected. Thus, no subject had >1 test per interval; however, some subjects had no tests per interval, which were treated as missing values. Missing values were encountered in <2% of subjects for PF and <20% for WBC with differential.

As mentioned above, several imputation approaches were considered to address the missing values, including interpolation and carrying over previous values. For both PF and WBC with differential, the results were similar between models using imputation approaches vs. not, although *P*-values were more significant with the use of imputation approaches. Models using the carry over method of data imputation are presented.

Compound symmetry correlation structures were selected based on the quasi-likelihood information criterion.

Retention of covariates in multivariate models was based on consideration of confounding and effect modification. Sex, age at visit, race, current smoking status, season of birth and other disease parameters were evaluated individually and in combination with BMI classification as predictors. Any variable that had a *P*-value <0.1 or changed the parameter estimate for BMI classification by more than 10% was retained as a covariate in that model.

Results

Population characteristics

Three hundred and thirty-two patients with complete follow-up were serially selected for the study; 37 were non-atopic and were not included in the study. Twenty-one were excluded due to COPD, 2 for malignancy, 19 for comorbid autoimmune disease, and 9 for HIV infection. Of the remaining 246 subjects, 135 were diagnosed with asthma; 111 were never diagnosed with asthma, but were diagnosed with other allergic disorders, including urticaria (*n* = 44), angioedema (*n* = 20), rhinitis (*n* = 58), conjunctivitis (*n* = 42), food allergies (*n* = 25), and/or atopic dermatitis (*n* = 7). One hundred and ninety were women (77.2%), 203 were African-American/Afro-Caribbean (86.0%), 17 were smokers (8.1%), with a mean age $\pm$ standard deviation of 42.9 ± 15.0 years.

Logistic regression models were constructed with demographic variables as independent variables. Diagnosis of asthma was significantly associated with current smoking status (OR: 3.75, 95% CI: 1.04–13.47; *P* = 0.04). There were marginally significant associations with female sex (OR: 1.71, 95% CI: 0.94–3.11; *P* = 0.08) and African-American/Afro-Caribbean race (OR: 1.31, 95% CI: 0.99–1.73; *P* = 0.06), but not age or season of birth (*P* = 0.28–0.93) (Table 1). Therefore, smoking status, sex and race were retained in the final models. Age was also retained in the final model because of effect-modification of BMI parameter estimate >10%.

Association of class I and class II/III obesity with asthma and asthma severity

Asthmatic patients had significantly higher BMI when compared with non-asthmatics [median (IQR, range): 30.5 (10.2, 42.7) vs. 27.8 (8.8, 29.2), respectively; Mann–Whitney *U*-test, *P* = 0.0006]. In the non-asthmatic group, 34.2% of subjects were obese, which is comparable to recent estimates of obesity prevalence

Table 1. Characteristics of the patients

Variable	Asthma (<i>n</i> = 135)	Control (<i>n</i> = 111)	Odds ratio (95% CI)	<i>P</i> -value*
Age (years) [†] – mean ± std	42.9 ± 14.6	43.0 ± 15.6	1.00 (0.98–1.02)	0.93
Female sex – <i>n</i> (%)	110 (81.5)	80 (72.1)	1.71 (0.94–3.11)	0.08
Season of birth – <i>n</i> (%) [‡]				
Winter	28 (20.7)	28 (25.3)	1.00	–
Spring	33 (24.4)	25 (22.5)	1.32 (0.63–2.76)	0.46
Summer	44 (32.6)	30 (27.0)	1.47 (0.73–2.95)	0.28
Autumn	30 (22.2)	28 (25.2)	1.07 (0.51–2.23)	0.85
Race – <i>n</i> (%)				
African-American/Afro-Caribbean	115 (87.1)	88 (84.6)	1.31 (0.99–1.73)	0.06
Other	17 (12.9)	16 (15.4)	1.00	–
Current smoker – <i>n</i> (%)	14 (11.6)	3 (3.4)	3.75 (1.04–13.47)	<u>0.04</u>

*Logistic regression was used for all dependent (outcome) variables.

[†]Age range – asthma: 18.5–77.5 years, control: 19.0–81.7 years.

[‡]Season of birth: Winter, December through February; Spring, March through May; Summer, June through August; Autumn, September through November.

Underlined *P*-values represent significant values where *P* < 0.05.

Table 2. Association of asthma with class I and class II/III obesity

Independent variable	Asthma* (<i>n</i> = 135)	Control* (<i>n</i> = 111)	Odds ratio (95% CI)	<i>P</i> -value	Adjusted odds ratio (aOR) (95% CI)	<i>P</i> -value [†]
Body mass index (BMI) – <i>n</i> (%)						
<25	26 (19.3)	38 (34.2)	1.00	–	1.00	–
25–30	36 (26.7)	35 (31.5)	1.50 (0.76–2.97)	0.24	1.57 (0.75–3.29)	0.23
30–35	35 (25.9)	24 (21.6)	2.13 (1.04–4.38)	<u>0.03</u>	2.35 (1.04–5.34)	<u>0.04</u>
≥35	38 (28.2)	14 (12.6)	3.97 (1.80–8.74)	<u>0.0006</u>	3.25 (1.36–7.74)	<u>0.008</u>

Median BMI (interquartile range, range) was 30.5 (10.2, 42.7) for asthmatics and 27.8 (8.8, 29.2) for controls.

*Diagnosis of asthma was the binary dependent (outcome) variable where 1 = Asthma and 0 = no asthma.

[†]aORs were calculated by logistic regression with the diagnosis of asthma as the dependent (outcome) variable and BMI as an independent (predictor) variable, including sex, age, race, and smoking status as fixed covariates. There were no significant interactions between independent variables. Underlined *P*-values represent significant values where *P* < 0.05.

in the United States [3]. However, in the asthmatic group, greater than 50% of subjects were obese (Table 2). In unadjusted models, class I and class II/III obesity were associated with increased odds of asthma (logistic regression; class I: OR = 2.13, 95% CI = 1.04–4.38, *P* = 0.03; class II/III: OR = 2.35, 95% CI = 1.04–5.34, *P* = 0.0006) (Table 2). These associations remained significant in confounding models that included sex, age, race, and smoking status (class I: OR = 2.35, 95% CI = 1.04–5.34, *P* = 0.04; class II/III: OR = 3.25, 95% CI = 1.36–7.74, *P* = 0.008) (Table 2).

Class I and II/III obesity were associated with greater asthma severity when compared with normal weight (class I: OR: 4.23, 95% CI: 1.61–11.06; *P* = 0.003, class II/III: OR: 2.76, 95% CI: 1.08–7.09; *P* = 0.03). However, overweight was not significantly associated with asthma severity (*P* = 0.09) (Table 3). There were no significant linear interaction terms between BMI or BMI intervals and sex, age, race and smoking status (*P* = 0.13–0.96); therefore, interaction terms were not included in the final models. Sex, race, age and smoking status were retained in final models because of

significant effects or effect modification of BMI parameter estimates.

Class II/III obesity was associated with requirement of oral and inhaled corticosteroids

Class II/III obesity was associated with increased asthma exacerbations requiring OCS when compared with normal weight (repeated measures logistic regression, aOR: 1.13, 95% CI: 1.03–1.25; *P* = 0.01). The association remained significant even when controlling for asthma severity (*P* = 0.04). However, overweight and class I obesity were not significantly associated with OCS requirement (*P* = 0.22 and 0.29, respectively) (Table 4).

Class II/III obesity was associated with increased requirement for ICS for long-term asthma management when compared with normal weight (aOR: 1.45, 95% CI: 1.29–1.62; *P* < 0.0001). The association remained significant even when controlling for asthma severity (*P* < 0.0001). However, overweight and class I obesity were not significantly associated with ICS requirement (*P* = 0.11 and 0.06, respectively) (Table 4).

Table 3. Association of asthma severity classification with class I and II/III obesity

Body mass index (BMI) – n (%)	Intermittent (n = 35)	Mild persistent (n = 22)	Moderate persistent (n = 39)	Severe (n = 39)	Adjusted odds ratio (aOR) (95% CI)*	P-value
>25	12 (34.3)	4 (18.2)	6 (15.4)	4 (10.3)	1.00	–
25–30	9 (25.7)	6 (27.3)	13 (33.3)	8 (20.5)	2.22 (0.88–5.63)	0.09
30–35	7 (20.0)	4 (18.2)	9 (23.1)	15 (38.5)	4.23 (1.61–11.06)	<u>0.003</u>
>35	7 (20.0)	8 (36.4)	11 (28.2)	12 (30.8)	2.76 (1.08–7.09)	<u>0.03</u>

Using ordinal logistic regression modelling, a single OR is generated which represents the trend of asthma severity across all four possibilities in the asthma severity scale. A significant OR >1 in this model refers to an increased odds of more severe asthma for a particular BMI classification.

*aORs were calculated by ordinal logistic regression with asthma severity (1 = intermittent, 2 = mild persistent, 3 = moderate persistent and 4 = severe) as the dependent (outcome) variable and BMI classification as an independent (predictor) variable, including sex, race, age and smoking status as fixed covariates.

Underlined P-values represent significant values where $P < 0.05$.

Table 4. Association of severe asthma exacerbation requiring oral corticosteroids (OCS) and long-term asthma control requiring inhaled corticosteroids (ICS) with class I and class II/III obesity

Body mass index (BMI) – n (%)*	OCS [†]	Adjusted odds ratio (aOR) (95% CI) [‡]	P-value
<25	4 (10.5)	1.00	–
25–30	0 (0.0)	0.97 (0.93–1.02)	0.22
30–35	81 (6.7)	0.95 (0.85–1.05)	0.29
≥35	20 (20.6)	1.13 (1.03–1.25)	<u>0.01</u>

BMI – n (%)*	ICS [§]	aOR (95% CI) [‡]	P-value
<25	25 (65.8)	1.00	–
25–30	25 (65.8)	1.17 (0.96–1.43)	0.11
30–35	776 (63.8)	1.09 (0.99–1.21)	0.06
≥35	84 (86.6)	1.45 (1.29–1.62)	<u><0.0001</u>

n = 135 asthmatics. The analyses were restricted to the first 5 year period of follow-up with repeated measures at 6 month intervals. For the overweight group ($25 \leq \text{BMI} < 30$), there were no episodes of poor long-term asthma control requiring ICS. Therefore, comparisons were only made between class I ($30 \leq \text{BMI} < 35$) and class II/III ($35 \leq \text{BMI}$) obesity compared with normal weight ($\text{BMI} < 25$). Compound symmetry correlation structures were selected based on the quasi-likelihood information criterion.

*Percentages are of encounters stratified by BMI class at each visit.

[†]Asthma exacerbations requiring oral prednisone was encoded as a binary variable where 1 = exacerbation requiring oral steroids and 0 = no, decreased or stable requirement of OCS.

[‡]aORs were calculated by repeated measures logistic regression with severe asthma exacerbations requiring prednisone therapy or long-term asthma control requiring ICS as the binary dependent variable and BMI as an independent variable, including sex, race, age, smoking status, asthma severity and the interval of follow-up as fixed covariates.

[§]Long-term asthma control requiring ICS was encoded as a binary variable where 1 = the requirement of ICS and 0 = no requirement of ICS.

Underlined P-values represent significant values where $P < 0.05$.

Race, sex, age, smoking status, asthma severity and interval of follow-up were retained in models of OCS or ICS usage because of significant effects or effect modification of BMI parameter estimates.

Class II/III obesity was associated with decreased peak expiratory flow rate

Class II/III obesity was associated with decreased PF when compared with normal weight (general linear model, $\text{LSM} \pm \text{SE}$: 333.8 ± 37.4 vs. 396.2 ± 32.1 L/min; $P = 0.03$) (Table 5). However, there were no significant differences of PF in overweight and class I obesity patients ($P = 0.70$ and 0.19 , respectively). Race, sex, age, smoking status and current use of inhaled or OCS were retained in models because of significant effects or effect modification of BMI parameter estimates.

Class II/III obesity was associated with decreased FEV1 and FVC

Class II/III obesity was also associated with decreased FEV1 (75.2 ± 4.6 vs. $88.4 \pm 5.6\%$; $P = 0.03$) and FVC (83.2 ± 4.7 vs. $109.2 \pm 6.0\%$; $P = 0.0002$) compared with normal weight (Table 6). Moreover, overweight and class I obesity were associated with decreased FVC ($P = 0.0008$ and 0.001 , respectively). However, there were no significant differences of FEV1 in overweight or class I obesity, when compared with normal weight ($P = 0.32$ – 0.80). Further, there were no differences of FEV1 : FVC ratio or FEF25–75% in overweight, class I and II/III obese patients compared with normal weight ($P = 0.16$ – 0.8052). FEV1 and FVC were not assessed for non-asthmatic control subjects. Race, sex and smoking status were retained in models because of significant effects or effect modification of BMI parameter estimates.

Class I and II/III obesity were associated with increased serum IgE

Class I and II/III obesity were associated with increased serum IgE levels when compared with normal weight (general linear model, $\text{LSM} \pm \text{SE}$: 458.7 ± 68.9 and

Table 5. Association of peak flow (PF) with class II/III obesity in asthmatics

PF (L/min) (<i>n</i> = 134*)	Body mass index (BMI)				<i>P</i> -value [†]
	≤25	25–30	30–35	≥35	
<i>n</i> (%)	38 (2.7)	38 (2.7)	1217 (87.6)	97 (7.0)	
LSM ± SE [‡]	396.2 ± 32.1	375.2 ± 33.4	344.6 ± 33.4	333.8 ± 37.4	<u>0.03</u>

There were no significant differences of PF values between overweight (BMI 25–30) or class I obesity (BMI 30–35) compared with normal weight (BMI ≤ 25) (*P* > 0.05). Compound symmetry correlation structure was selected based on the quasi-likelihood information criterion.

*111/135 asthmatics had no missing PF values, 23 had some missing values (<50% per subject) that were filled-in using the carry over method from prior visit, one had no PF values and was therefore excluded.

[†]*P*-values are for statistical comparisons between class II/III obesity (BMI ≥ 35) and normal weight (BMI ≤ 25), adjusting for sex, race, age, smoking status and current use of inhaled or oral steroids.

[‡]General linear models were constructed with PF at all encounters at 6 month intervals for the first 5 years of follow-up as dependent variables and BMI as an independent variable, including sex, age, smoking status, race and current use of inhaled or oral steroids as covariates. Outliers were excluded using residuals, studentized residuals and cook's distance. Least squares means and standard errors (SE) were calculated for each BMI group, adjusting for sex, age, race, smoking status and current use of inhaled or oral corticosteroids.

Underlined *P*-values represent significant values where *P* < 0.05.

Table 6. Association of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) with class II/III obesity in asthmatics

Spirometry (<i>n</i> = 90)	Body mass index (BMI)				<i>P</i> -value*
	<25	25–30	30–35	≥35	
<i>n</i> (%)	14 (15.6)	25 (27.8)	25 (27.8)	26 (28.9)	
FEV1 (%) [†]	88.4 ± 5.6	79.2 ± 5.1	82.8 ± 5.2	75.2 ± 4.6	<u>0.03</u>
FVC (%) [†]	109.2 ± 6.0	85.2 ± 5.2	91.4 ± 5.2	83.2 ± 4.7	<u>0.0002</u>
FEV1/FVC (%) [†]	78.5 ± 4.4	73.1 ± 3.9	79.1 ± 3.9	81.0 ± 3.5	0.61
Forced expiratory flow 25–75% (FEF25–75%) (%) [†]	56.0 ± 10.2	44.1 ± 9.0	60.3 ± 9.0	55.1 ± 8.3	0.59

There were no significant differences of FEV1, FEV1/FVC ratio or FEF25–75% parameter values between overweight (BMI 25–30) or class I obesity (BMI 30–35) and normal weight (BMI ≤ 25) (*P* > 0.05).

**P*-values are for Tukey post-hoc comparisons between class II/III obese (BMI ≥ 35) and normal weight (BMI ≤ 25), adjusting for sex, race and smoking status.

[†]General linear models were constructed with spirometry parameters at initial encounter as dependent (outcome) variables and BMI as an independent (predictor) variable, including sex, race and smoking status as covariates. Outliers (*n* = 3) were excluded using residuals, studentized residuals and Cook's distance. Least squares means and standard errors were calculated for each BMI group, adjusting for sex, race and smoking status.

Underlined *P*-values represent significant values where *P* < 0.05.

Table 7. Association of serum IgE with class I and II/III obesity in asthmatics

Serum IgE (IU/mL) (<i>n</i> = 196*)	Body mass index (BMI)				<i>P</i> -value [†]
	≤25	25–30	30–35	≥35	
<i>n</i> (%)	45 (23.0)	48 (24.5)	73 (37.2)	35 (17.9)	
LSM ± SE [‡]	269.0 ± 66.6	382.7 ± 69.6	458.7 ± 68.9	480.2 ± 88.3	<u>0.04</u>

There were also a significant difference of serum IgE levels between class I obesity (BMI 30–35) compared with normal weight (BMI ≤ 25) (*P* = 0.03), but not overweight (BMI 25–30) (*P* = 0.21).

*196/246 subjects had no missing serum IgE values, 50 had missing values either for serum IgE levels or BMI and were therefore excluded.

[†]*P*-values are for statistical comparisons between class II/III obesity (BMI ≥ 35) and normal weight (BMI ≤ 25), adjusting for sex, age and race.

[‡]General linear models were constructed with serum IgE levels at initial encounter as dependent (outcome) variables and BMI as an independent (predictor) variable, including sex, age and race as covariates. Outliers were excluded using residuals, studentized residuals and cook's distance. Least squares means and standard errors (SE) were calculated for each BMI group, adjusting for sex, age and race.

Underlined *P*-values represent significant values where *P* < 0.05.

480.2 ± 88.3 vs. 269.0 ± 66.6 IU/mL; *P* = 0.03 and 0.04, respectively) (Table 7). However, there were no significant differences in serum IgE levels in overweight

patients (*P* = 0.21). Race, age and sex were retained in models because of significant effects or effect modification of BMI parameter estimates.

Table 8. Association of leukocyte numbers with class I and II/III obesity in atopics

Variable*	Body mass index (BMI)				P-value†
	<25	25–30	30–35	≥35	
n (%)	101 (21.7)	133 (28.5)	152 (32.6)	80 (17.2)	
WBC‡ ($\times 10^3/\text{mm}^3$)	8.0 $\pm$ 0.7	8.4 $\pm$ 0.7	8.7 $\pm$ 0.7	9.3 $\pm$ 0.7	<u>0.01</u>
Neutrophils‡	5.0 $\pm$ 0.6	4.7 $\pm$ 0.6	5.4 $\pm$ 0.6	5.9 $\pm$ 0.6	<u>0.03</u>
Lymphocytes‡	2.1 $\pm$ 0.2	2.4 $\pm$ 0.2	2.5 $\pm$ 0.2	2.3 $\pm$ 0.2	0.20
Monocytes‡	0.5 $\pm$ 0.06	0.5 $\pm$ 0.06	0.6 $\pm$ 0.06	0.5 $\pm$ 0.06	0.41
Eosinophils‡	0.2 $\pm$ 0.07	0.3 $\pm$ 0.06	0.3 $\pm$ 0.07	0.2 $\pm$ 0.07	0.54
Basophils‡	0.03 $\pm$ 0.007	0.03 $\pm$ 0.007	0.03 $\pm$ 0.008	0.03 $\pm$ 0.007	0.55
Neutrophils : eosinophils	22.1 $\pm$ 5.9	18.7 $\pm$ 5.2	17.3 $\pm$ 5.8	24.1 $\pm$ 5.7	0.66

*n = 466 values for 246 subjects at 1 year intervals for the first 2 years of clinical follow-up. Missing values were filled-in using a carry-over method.

†P-values are for *t*-test comparisons between class II/III obese (BMI $\geq$ 35) and normal weight (BMI $\leq$ 25), adjusting for sex, age, race, smoking status, diagnosis of asthma and time of follow-up (year), and current use of oral and inhaled corticosteroids (ICS).

‡General linear models were constructed with leukocyte numbers and neutrophil : eosinophil ratio as dependent (outcome) variables and BMI as an independent (predictor) variable, including sex, age, race, smoking status, diagnosis of asthma and the time of follow-up (years), and current use of oral and ICS as covariates. Outliers (range *n* = 1–6 per cell type) were excluded using residuals, studentized residuals and Cook's distance. Least squares means and standard errors were calculated for each BMI group, adjusting for sex, age, race, smoking status, diagnosis of asthma and time of follow-up (year), and current use of OCS and ICS.

Underlined P-values represent significant values where *P* < 0.05.

Class I and II/III obesity were associated with increased peripheral blood neutrophils

In all subjects, class II/III obesity when compared with normal weight was associated with increased peripheral blood WBC counts (general linear model, 9.3 ± 0.7 vs. $8.0 \pm 0.7 \times 10^3/\text{mm}^3$; *P* = 0.01), in particular increased percentage of neutrophils (66.6 ± 3.7 vs. $60.1 \pm 3.8\%$; *P* = 0.02) (Table 8), but overweight and class I obesity were not (*P* = 0.14–0.78). In contrast, class II/III obesity when compared with normal weight was associated with decreased percentage of lymphocytes (23.5 ± 3.2 vs. $29.3 \pm 3.4\%$; *P* = 0.02), but overweight and class II/III obesity were not (*P* = 0.54–0.82). Interestingly, overweight when compared with normal weight was associated with increased percentage of eosinophils (5.1 ± 1.0 vs. $3.2 \pm 1.2\%$, *P* = 0.006), but not class I and II/III obesity (*P* = 0.14 and 0.99, respectively). In contrast, numbers of monocytes and basophils were not associated with any BMI classification (*P* = 0.27–0.99). Race, sex, smoking status, diagnosis of asthma, interval of follow-up and current use of oral or ICS were retained in models because of significant effects or effect modification of BMI parameter estimates.

Discussion

The present investigation demonstrates a strong association between obesity and multiple asthma disease parameters including IgE and peripheral blood leukocyte counts. We found that class I and II/III obesity are associated with (1) increased asthma prevalence, (2) worse asthma severity, (3) increased serum IgE levels,

and (4) increased peripheral blood neutrophils. Class II/III obesity is associated with (5) increased asthma exacerbations requiring OCS, (6) increased requirement of ICS for long-term asthma management, (7) decreased PF and (8) decreased FEV1 and FVC. These findings suggest that obesity may be both a predisposing and exacerbating factor for asthma.

Using a longitudinal (albeit retrospective) analysis of clinical data on asthma severity, the present study found that obesity is associated with more severe asthma and more frequent exacerbations. This study is in agreement with previous cross-sectional studies that also found an association between obesity and increased asthma. Sharma et al. [14] found that a one unit increase of BMI was associated with increased airway hyperactivity risk. In two separate cross-sectional studies, obese adults were more likely to report poor asthma-specific quality of life, poor asthma control and have more asthma-related hospitalizations, as well as more emergency department and urgent care utilizations [39, 40]. In contrast, a questionnaire-based study of asthma control in primary care clinics demonstrated no significant association with obesity [41]. That study had several differences from the present study, including regional differences, a higher proportion of patients with private insurance, and questionnaire-based design. Previous studies found a stronger association between obesity and asthma prevalence in women than in men [23, 24]. However, the present study found no differences between the effects of obesity in men vs. women as indicated by the lack of significant interaction terms between BMI and sex. Thus, the results of the present study indicate that obesity is associated with a higher

prevalence of and more severe asthma in both men and women alike.

We have found that obesity is associated with both increased serum IgE levels and greater asthma severity. This is consistent with previous studies that showed a correlation between serum IgE levels with degree of airway hyper-responsiveness [42]. Atopy is a well established risk factor for development of asthma [43]. However, some controversy exists regarding the relationship between obesity and atopy. Data from the 2005–2006 NHANES reports show a higher total serum IgE level and an increased OR of atopy in obese children and adolescents [17]. Yoo *et al.* [18] demonstrated an increased OR of atopy in obese subjects, compared with normal weight, even after adjusting for sex, age and other covariates. In contrast, several other studies found no significant association between obesity and atopy [19–21, 28–31]. In particular, Chen *et al.* [20] demonstrated that obesity is a greater risk factor for developing asthma in non-allergic than allergic subjects. Several factors may explain the differences in results between the present and prior conflicting studies, including different regions and environmental exposures, racial and ethnic populations, socio-economic status, etc. Moreover, non-atopic subjects were not assessed in this study. Nevertheless, the higher IgE levels observed in this study suggest that the association between obesity and atopic asthma may be mediated by more severe atopy.

The etiopathogenic reason for an association between obesity and serum IgE levels in atopic asthma has not been determined. Obesity may predispose individuals towards a pro-inflammatory state. Adipose tissue in obese patients has higher expression of the pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α [44, 45]. IL-6 is increased in sputum of asthmatics [46] and has been shown to increase secretion of pro-inflammatory mediators and contribute to airway remodelling [47], as well as expansion of pro-inflammatory Th2 cells [48]. IL-1 involvement in eosinophilic lung inflammation and airway hyper-reactivity is supported by studies showing that IL-1 stimulates release of IL-5 from airway smooth muscle cells and induces endothelial cell production of ICAM-1 and VCAM-1 [49–51]. TNF- α acts as an initial inflammatory cytokine that subsequently regulates both early neutrophil infiltration and eosinophil recruitment into the lung and airspace [52]. Moreover, both IL-1 and TNF- α can stimulate production of granulocyte-, granulocyte-macrophage- and macrophage-colony stimulating factors, which cause the proliferation of neutrophil and monocyte precursors and their release into circulation [53–56]. Increased production of IL-1 and TNF- α by adipose tissue may explain the significantly higher numbers of neutrophils in obese subjects demonstrated in the present study. Together, the results

suggest that obesity in adults has specific effects on systemic immune responses that favor the development of atopy and perhaps atopic asthma.

Adipokines may also play an important role in asthma and atopy. Adiponectin, an anti-inflammatory adipokine, is decreased in obesity, while leptin, a pro-inflammatory adipokine, is increased in obesity with a linear relation [57–59]. Medoff *et al.* [57] found that adiponectin knockout mice had greater eosinophilic airway inflammation than wild-type mice and had a decrease in dynamic lung compliance both at baseline and in response to methacholine challenge. Knockout mice also displayed increased CCL-3, CCL-7, CCL-11 and CCL-12 production, which was reversible by pre-treatment with adiponectin [57]. Wong *et al.* [58] found that leptin had significant anti-apoptotic effects on eosinophils and significantly upregulated surface expression of ICAM-1 and CD-18, which are necessary for recruitment and transmigration of inflammatory cells into airways in asthma. Further, leptin also induced synthesis of IL-1 and IL-6 [58]. Some authors have postulated that leptin increases the risk of asthma [60, 61]. However, recent studies found that serum adipokine levels and BMI do not correlate with exhaled nitric oxide or other markers of airway inflammation [62, 63]. Further research is required to elucidate the complex relationship between obesity and asthma.

In the present study, class II/III obesity was associated with decreased PF, FEV1 and FVC compared with normal weight, which suggests that obesity may worsen asthma by both an obstructive and restrictive/mechanical effect. Pakhale *et al.* [64] showed that obese asthmatics had lower FEV1 when compared with normal weight asthmatics. Obese patients were found to have decreased FEV1, residual volume, functional residual capacity and expiratory reserve volume that were reversed by substantial weight loss from bariatric surgery [65]. The authors suggested that impairment of lung function was mediated by splinting of the diaphragm by intra-abdominal fat [65]. Lessard *et al.* [66] recently demonstrated an association between increased BMI, waist circumference and body fat distribution with impaired lung function, which appeared to be mediated by mechanical rather than inflammatory factors. Aggressive weight reduction was also associated with significantly decreased PF variability and increased FEV1 and FVC [67]. Together, these studies suggest that weight loss can contribute to improved lung function and asthma control.

It is interesting that class II/III obesity but not class I obesity or overweight were associated with increased corticosteroid usage, decreased PF, FEV1 and FVC. It may be that class II/III obesity specifically, but not class I obesity, has pro-inflammatory effects or mechanically impairs breathing. Alternatively, class I obesity may

affect these outcomes less profoundly than class II/III obesity, but such effects were not strong enough to be detected in the study.

This study has several strengths, including clinical evaluation of asthma by a physician, baseline and longitudinal (albeit retrospective) assessment of asthma control, and the use of multiple statistical methodologies. The data used in this study are less likely to be affected by subjective patient interpretation and recall bias, as diagnoses and other clinical information were obtained by a physician during clinical encounter, and were not questionnaire-based. Further, the use of a clinical study allowed for the accurate longitudinal assessment of asthma severity, exacerbations, changes of weight and medication histories. PF, spirometry and laboratory tests were obtained consistently from single providers, thereby limiting potential variability. Moreover, the use of atopic non-asthmatic control subjects, as opposed to non-atopic healthy subjects, allows for more specific study of the effects of atopic asthma *per se* and not atopy overall. Finally, the repeatedly demonstrated association between obesity and clinical and laboratory endpoints in asthma by multiple statistical methodologies strengthens the conclusion that obesity is both a risk and exacerbating factor for asthma.

However, this study has potential limitations, including selection bias. Asthmatic patients who presented to this referral-based clinic were more likely to have severe disease. Thus, it is possible that obesity plays less of a role in mild asthmatics. As this study was retrospective, several important clinical factors were not consistently collected for all subjects, including age of asthma onset, stress and irritant exposures, and food and/or environmental histories; PF and spirometry were not available for non-asthmatic control subjects as they were not clinically indicated. Moreover, dosage of ICS was not consistently available for analysis. Thus, while class II/III obesity was associated with increased usage of ICS, it is unknown if higher doses of ICS were also required. Another limitation of this retrospective study

is the unbalanced follow-up between subjects and the need for additional techniques to address the problems of missing/uneven data. In addition, obesity was only assessed by BMI, which is a measure of total body fat. This was because only height and weight were collected as part of our routine clinical practice. However, previous studies found a strong association between inflammation, waist circumference and other parameters of body fat distribution, suggesting that both BMI and body fat distribution should be considered in studies of obesity [66]. Future studies are therefore necessary to distinguish between the effects of generalized vs. central obesity. Finally, the majority of subjects were African-American/Afro-Caribbean. Further, there were more smokers in the asthmatic than non-asthmatic group. These issues raise concern for making generalizations from the data for ethnically mixed non-smoking populations. Nevertheless, the study statistically controlled for smoking status and race/ethnicity in all models. Finally, all subjects included in the study were atopic from an allergy clinic setting and therefore generalizations for non-atopic general populations are limited.

In conclusion, obesity may be both a risk and exacerbating factor for asthma, independent of race, sex and smoking status. However, the retrospective nature of these studies limits any ability to make inferences about actual causality. Moreover, it is unknown what role aggressive weight reduction may play in the management of asthma in inner-city adults. Weight loss may be an important approach for prevention and treatment of asthma in adults. Future prospective studies are warranted to examine the role of aggressive weight loss on prevention and management of asthma in inner-city adults.

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