

DIAGNOSTICS

Body mass index, asthma and exhaled nitric oxide in U.S. Adults, 2007–2010Michael D. Singleton, MS^{1,2}, Wayne T. Sanderson, PhD¹, and David M. Mannino, MD³¹Department of Epidemiology, University of Kentucky College of Public Health, Lexington, KY, USA, ²Kentucky Injury Prevention and Research Center, University of Kentucky, Lexington, KY, USA, and ³Department of Preventive Medicine and Environmental Health, University of Kentucky College of Public Health, Lexington, KY, USA**Abstract**

Objective: Increases in asthma and obesity over the past three decades have led to speculation about a causal link between the two diseases. However, investigations of the relationship between body mass index (BMI) and fractional exhaled nitric oxide (FeNO) – a marker of eosinophilic airway inflammation – have produced mixed results. The purpose of this study was to evaluate the relationship between body mass index (BMI), asthma and FeNO in a sample of U.S. adults using data from the National Health and Nutrition Examination Surveys (NHANES) for 2007–2010. **Methods:** We assessed the relationship between FeNO and BMI in subjects with and without asthma using categorical and continuous models for BMI. All models controlled for age, gender, ethnicity, household income-to-poverty ratio, atopy and current smoking. **Results:** Adjusted asthma prevalence was positively associated with BMI, and subjects with asthma had higher adjusted FeNO levels than subjects without asthma. However, no association between FeNO and BMI was observed in either those with ($\beta = 0.002$, $p = 0.74$) or without ($\beta = 0.0014$, $p = 0.51$) asthma after adjusting for covariates. **Conclusions:** Our results suggest that in the U.S. adult population, BMI is not associated with eosinophilic airway inflammation.

Keywords

BMI, FeNO, NHANES, Obesity, respiratory disease

History

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Introduction

Increases in asthma and obesity over the past three decades have led to speculation about a causal link between these two chronic diseases [1–4]. Several mechanisms have been proposed, including the hypothesis that biochemical changes resulting from increasing body fat contribute to airway inflammation, a defining characteristic of asthma [5]. A biological connection between obesity and systemic inflammation has been established [6,7], but it is not clear whether increasing adiposity leads to greater inflammation of the airways specifically.

Fractional exhaled nitric oxide (FeNO) is an established marker of eosinophilic airway inflammation [8,9]. Investigations of the relationship between body mass index (BMI) and FeNO in adults have produced conflicting results. In 2005, two small studies reported a positive correlation in healthy (non-asthmatic), non-smoking adults [10,11]. In 2006, Barros et al. reported a negative association in a sample of non-smoking, asthmatic adults who were obese, but no association in underweight and normal weight subjects [12].

Several subsequent studies of BMI and FeNO in adults have been published [13–17]. Three of them reported results for non-asthmatic adults, and all indicated no association [14–16]. Two of them reported results for persons with asthma, with one finding no association [14] and the other a negative association [15]. Several other more recent studies have issued similarly inconsistent findings [18–20].

Differences in study design factors likely contributed to the disparity in findings. These include small and/or highly selected samples and coverage of a limited range of the BMI spectrum. The population-based National Health and Nutrition Examination Surveys (NHANES) for 2007–2010 enabled us to investigate the relationship between BMI and FeNO while addressing several limitations of previous studies. The samples for the 2007–2008 and 2009–2010 NHANES cycles were large enough to include representation over a wide range of BMI and included observations on BMI, FeNO and several established covariates and confounders. This study was granted exempt status by the University of Kentucky's Medical Institutional Review Board.

Methods**Study population**

The NHANES is a nationally representative survey conducted periodically to assess the health and nutritional status of

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adults and children in the United States [21]. Details of the survey plan and operation can be found online at: <http://www.cdc.gov/nchs/nhanes.htm>. Survey personnel obtained written informed consent for all respondents.

The target population for NHANES is the civilian, non-institutionalized population of the U.S. The survey uses a stratified, multistage probability sampling design with oversampling of persons believed to be at increased health risk. There are four stages of sampling: the primary sampling unit (PSU), which is usually a county or a group of contiguous counties; segments (i.e. clusters of households) within PSU's; households within segments; and one or more participants within the household. The public use dataset includes weights that enable the calculation of estimates that reflect the U.S. population distribution and can be considered to be nationally representative. Eligible persons aged 16 years or older are interviewed directly. All persons who complete the household interview are invited to participate in the Medical Examination component of NHANES. Subjects aged 20 to 79 who complete both survey components were selected for inclusion in the present study.

Fractional exhaled nitric oxide measurement

FeNO measurements were made at 50 ml/s using a portable, hand-held nitric oxide analyzer (the Aerocrine NOX MINO[®], Solna, Sweden). In accordance with the manufacturer's recommendations and the guidelines of the American Thoracic Society/European Respiratory Society, the NHANES protocol required two valid and reproducible FeNO measurements. The test was deemed reproducible and complete if either of the first two valid FENO measurements was less than 30 ppb and the measurements were within 2 ppb of each other, or if both measurements were greater than 30 ppb and within 10% of each other. Examinees that had current chest pain or a physical problem with forceful expiration, or those who were using supplemental oxygen were medically excluded from participating [22].

BMI measurement

All survey participants were eligible for the body measurement component. There were no medical, safety, or other exclusions for the body measurements protocol. BMI was calculated as weight (kg)/standing height (m)².

Asthma assessment

Asthma history was based on the subject's responses to the following three questions. Q1: "Has a doctor or other health professional ever told you that you have asthma?" Q2: "Do you still have asthma?" Q3: "Including living and deceased, were any of your close biological – that is, blood relatives including father, mother, sisters, or brothers – ever told by a health professional that they had asthma?" Current asthma was defined by positive responses to Q1 and Q2. History of asthma was defined by a positive response to Q1 and a negative response to Q2. Family history of asthma was defined by negative responses to Q1 and Q2 and a positive response to Q3. No history of asthma was defined by a negative response to all three questions.

Other measurements

Subjects were classified as current smokers or non-smokers based on race-specific serum cotinine thresholds as described by Benowitz et al. [23]. We judged this to be the best, most straightforward measure of overall tobacco exposure available to us in NHANES. Because serum IgE testing was not conducted in the 2007–2008 and 2009–2010 survey cycles, we classified subjects as atopic if they reported experiencing an episode of hay fever in the past twelve months [24,25]. Household income-to-poverty ratio was used as an index of socioeconomic status. This variable is an index for the ratio of family income to poverty, as measured by the Department of Health and Human Services' (HHS) poverty guidelines. The variable was calculated by dividing family income by the poverty guidelines, specific to family size, as well as the appropriate year and state [26].

Statistical analysis

Differences in sample-weighted U.S. estimates of mean ln(FeNO) across three levels of asthma history were assessed by regressing ln(FeNO) on asthma history category and conducting pairwise Wald F-tests. A significance level of 0.05 was used for all hypothesis tests and confidence intervals were reported at 95%.

Our primary research question concerned the nature of the relationship between FeNO and BMI. For diseased and healthy subjects separately, two regression analyses were conducted. In the first, BMI was treated as a categorical variable with levels based upon the World Health Organization BMI classification: underweight or normal weight ($15 \leq \text{BMI} < 25$), overweight ($25 \leq \text{BMI} < 30$), obese ($30 \leq \text{BMI} < 40$) and very obese ($40 \leq \text{BMI} \leq 60$). Subjects with BMI less than 15 or greater than 60 were excluded. Underweight and normal weight were combined due the small number of underweight subjects with asthma in the sample. Adjusted differences between the estimated mean of ln(FeNO) in each BMI category and that of normal weight subjects without asthma were estimated using multiple linear regression. Within each group (asthma/no asthma), the estimated mean for the overweight, obese and very obese categories was subsequently tested for significant difference from the mean for the underweight/normal weight category within the same group using *t*-tests. In the second regression analysis, BMI was treated as a continuous variable and terms were included in the model to test for linear, quadratic and cubic effects of BMI. All models included age, gender, ethnicity, household income-to-poverty ratio, atopy, and current smoking status as covariates. The distribution of FeNO was skewed, so ln(FeNO) was used as the outcome variable in all regression models.

Finally, current asthma status was regressed on BMI to assess the relationship between asthma prevalence and BMI. Logistic regression was used to estimate asthma prevalence for U.S. adults for BMI values from 15 to 60 while adjusting for age, gender, race/ethnicity, income-to-poverty ratio, current smoking, atopy and family history of asthma.

SAS survey sampling procedures were used in all analyses to incorporate sample weights and the NHANES' complex sampling design in analyses (version 9.3; SAS Institute, Inc,

Cary, NC). Sample weights were adjusted to account for the combining of two survey cycles, in accordance with the NHANES Analytic Guidelines [27]. Domain analyses were conducted when results were calculated for subpopulations, such as within asthma history or current asthma categories. Plots were prepared using R version 2.15 [30].

Results

Between 2007 and 2010 a total of 20 015 persons (response rate 76%) completed both the interview and the medical examination components of the NHANES (CDC 2007–2010). From those respondents, all adults between the ages of 20 and 79 with BMI between 15 and 60 were included in the present analysis ($n = 10\,817$). Selected characteristics of those subjects are presented by BMI category in Table 1. Overall, the average weighted respondent age was just over 45 years. Fifty-one percent were female, 14% were Hispanic, 7.4% were asthmatic, 17% were atopic and 30% were smokers. Mean $\ln(\text{FeNO})$ was 2.51 parts per billion (ppb) and the mean household income-to-poverty ratio was 3.08.

There were some notable deviations from these overall means within certain BMI categories, particularly in the lowest and highest BMI categories. Underweight-to-normal weight subjects were younger (42 years) and more likely to be female (58%) and current smokers (34.2%). They also had lower mean $\ln(\text{FeNO})$ (2.43 ppb). Very obese subjects were much more likely to be female (66%) and to be asthmatic (14%), less likely to smoke (26.3%) and had a lower household income-to-poverty ratio (2.69). However, their mean $\ln(\text{FeNO})$ (2.53 ppb) did not differ significantly from the overall sample mean.

Figure 1 presents the estimated mean $\ln(\text{FeNO})$ by self-reported asthma status, adjusted for sample weights. Thus, these are estimates of the U.S. population means for the three groups. For subjects with current asthma, mean $\ln(\text{FeNO})$ was 2.63 ppb [95% CI (2.52, 2.73)]; for persons with a personal history of asthma, mean $\ln(\text{FeNO})$ was 2.62 ppb [95% CI (2.52, 2.71)]; and for those with no history of asthma, mean

$\ln(\text{FeNO})$ was 2.49 ppb [95% CI (2.44, 2.53)]. Pairwise mean comparisons indicated that subjects with current asthma ($F = 9.3$, $p = 0.005$) and those with a personal history of asthma ($F = 15.0$, $p < 0.001$) both had significantly higher mean $\ln(\text{FeNO})$ than persons with no history of asthma.

Figure 2 presents the results of regressing $\ln(\text{FeNO})$ on categorical BMI. Estimated means were adjusted for age, gender, ethnicity, atopy, household income-to-poverty ratio, and current smoking status. For healthy subjects, the adjusted mean $\ln(\text{FeNO})$ was not significantly different in any BMI category than it was in underweight-to-normal weight healthy subjects ($p_{\text{overweight}} = 0.48$; $p_{\text{obese}} = 0.86$; $p_{\text{very obese}} = 0.56$). Similarly, for those with asthma, the adjusted mean $\ln(\text{FeNO})$ was not significantly different in any BMI category than it

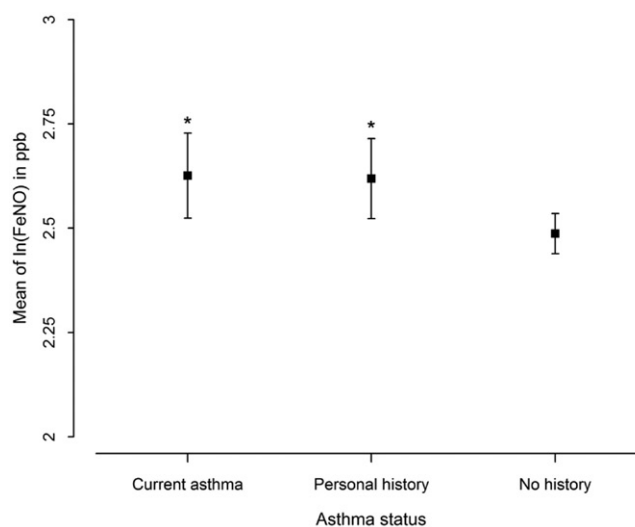


Figure 1. Estimated mean of $\ln(\text{FeNO})$ by asthma status for U.S. adults aged 20 to 79 years (NHANES 2007–2010). Means were adjusted for sample weights and therefore represent U.S. population estimates of $\ln(\text{FeNO})$. A “*” indicates means that differed from the mean for subjects with no history of asthma at significance level $p < 0.05$.

Table 1. Characteristics of adult subjects aged 20 to 79 years ($n = 10\,817$) by BMI category (NHANES 2007–2010).

Variable ^a	Under/Normal 15 ≤ BMI < 25	Overweight 25 ≤ BMI < 30	Obese 30 ≤ BMI < 40	Very obese 40 ≤ BMI ≤ 60	All 15 ≤ BMI ≤ 60
Survey round					
2007–2008	1479 (50.2)	1782 (50.1)	1633 (48.3)	327 (45.9)	5221 (49.4)
2009–2010	1546 (49.7)	1874 (49.9)	1775 (51.7)	401 (54.1)	5596 (50.6)
Gender					
Female	1629 (58.0)	1635 (43.3)	1798 (50.2)	505 (66.1)	5772 (51.3)
Male	1396 (42.0)	2021 (56.7)	1610 (49.8)	253 (33.9)	5517 (48.7)
Ethnicity					
Hispanic	678 (10.2)	1261 (16.2)	1103 (15.5)	174 (12.2)	3216 (13.9)
Non-Hispanic	2347 (89.8)	2395 (83.8)	2305 (84.5)	554 (87.8)	7601 (86.1)
Current asthma	180 (5.7)	218 (6.1)	328 (9.4)	118 (14.3)	844 (7.4)
Personal history of asthma	361 (12.3)	419 (12.1)	529 (15.9)	170 (21.1)	1479 (13.8)
Family history of asthma	628 (21.6)	597 (16.5)	671 (19.9)	174 (22.7)	2170 (19.5)
Current smoker	1137 (34.2)	1065 (29.6)	893 (28.1)	200 (26.3)	3289 (30.4)
Atopic	437 (16.7)	495 (16.4)	517 (18.2)	116 (17.0)	1565 (17.0)
Age	42.1 (0.5)	46.4 (0.4)	47.3 (0.4)	46.1 (0.8)	45.3 (0.3)
Household income-to-poverty ratio	3.05 (0.06)	3.12 (0.07)	2.98 (0.06)	2.69 (0.10)	3.08 (0.05)
$\ln(\text{FeNO})$	2.43 (0.04)	2.54 (0.03)	2.54 (0.02)	2.53 (0.05)	2.51 (0.03)

^aSample count (weighted % of non-missing values within BMI category) for categorical variables, sample mean (standard error) for continuous variables.

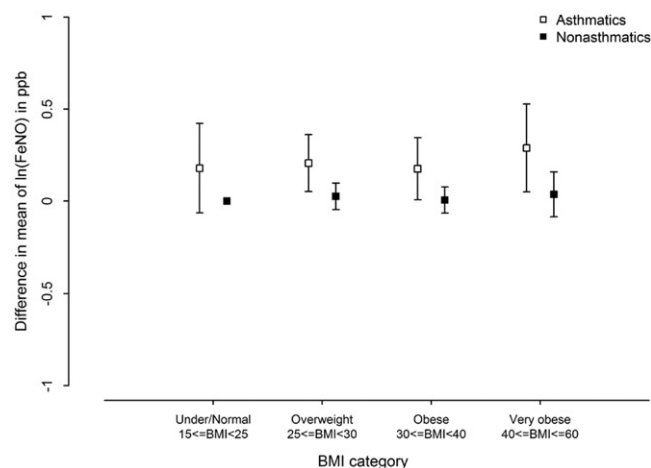


Figure 2. Difference in mean $\ln(\text{FeNO})$ relative to underweight-normal weight subjects without asthma by BMI category, U.S. adults aged 20 to 79 years (NHANES 2007–2010). Within each group considered separately, there were no significant differences in estimated means across BMI levels. For subjects without asthma, $p_{\text{overweight}} = 0.48$; $p_{\text{obese}} = 0.86$; $p_{\text{very obese}} = 0.56$. For those with asthma, $p_{\text{overweight}} = 0.86$; $p_{\text{obese}} = 0.99$; $p_{\text{very obese}} = 0.55$.

was in underweight-to-normal weight subjects with asthma ($p_{\text{overweight}} = 0.86$; $p_{\text{obese}} = 0.99$; $p_{\text{very obese}} = 0.55$).

Figure 3 parts A and B visualize the results of regressing $\ln(\text{FeNO})$ on continuous BMI for healthy and diseased subjects, respectively, with point-wise 95% confidence intervals. For healthy subjects (Part A), $\ln(\text{FeNO})$ for was regressed on continuous BMI using a linear regression model that adjusted for age, gender, ethnicity, atopy, household income-to-poverty ratio and current smoking. After adjustment for covariates, a one-unit increase in BMI was associated with an increase in $\ln(\text{FeNO})$ of 0.0014, but the association was not significant ($p = 0.51$). For those with asthma (Part B), $\ln(\text{FeNO})$ was regressed on continuous BMI using a linear regression model that adjusted for age, gender, ethnicity, atopy, household income-to-poverty ratio and current smoking. After adjustment for covariates, a one-unit increase in BMI was associated with an increase in $\ln(\text{FeNO})$ of 0.002, but the association was not significant ($p = 0.74$). Part C presents the estimated, adjusted prevalence of current asthma among U.S. adults for BMI values ranging from 15 to 60. Current asthma status was regressed on BMI using a logistic regression model that adjusted for age, gender, race/ethnicity, income-to-poverty ratio, current smoking, atopy and family history of asthma. The adjusted odds ratio estimate for BMI was 1.04 [95% CI = (1.03, 1.06), $p < 0.0001$], indicating that a unit increase in BMI was associated with a 4% increase in the odds of current asthma.

Estimates for all plots in Figure 3 were derived from the corresponding fitted regression model. In generating the estimates, continuous and categorical variables were held constant at their median and modal value, respectively.

Discussion

Both the categorical and continuous treatments of BMI suggested no association with FeNO in subjects with self-reported, physician-diagnosed asthma. Previous findings

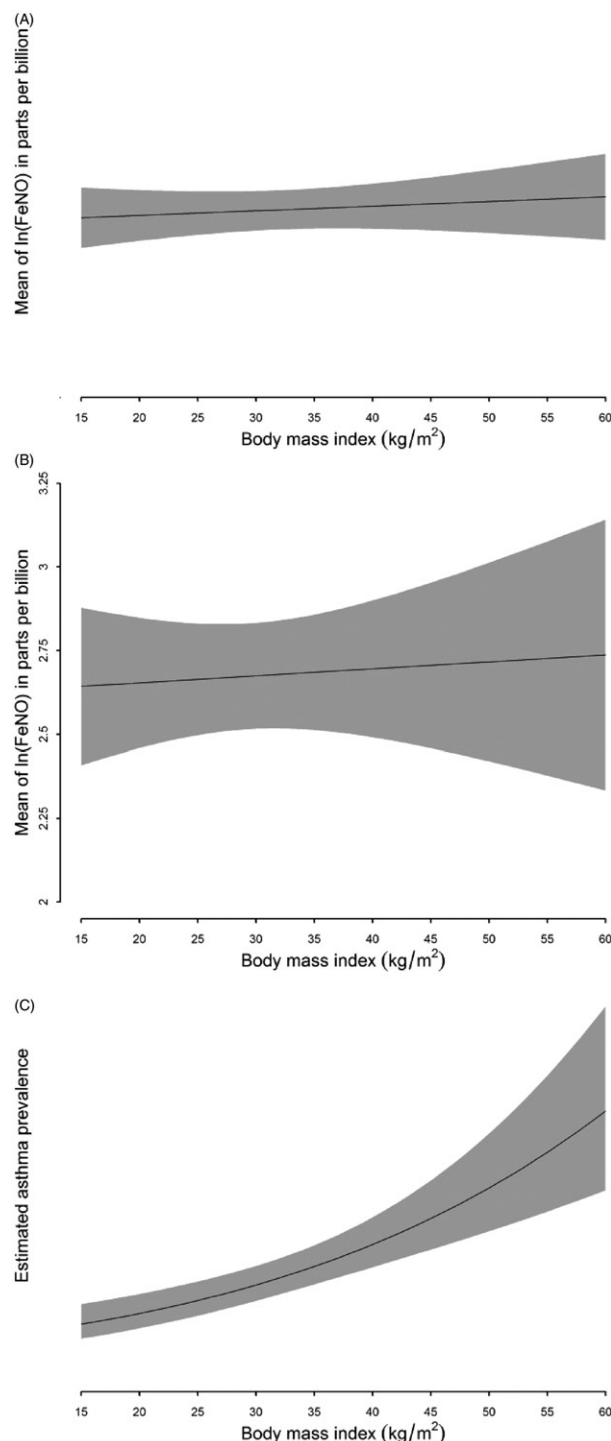


Figure 3. Estimated asthma prevalence and mean $\ln(\text{FeNO})$ levels by BMI, U.S. adults aged 20 to 79 years (NHANES 2007–2010). (A) For healthy subjects, $\ln(\text{FeNO})$ for was regressed on continuous BMI using a linear regression model that adjusted for age, gender, ethnicity, atopy, household income-to-poverty ratio and current smoking. After adjustment for covariates, a one-unit increase in BMI was associated with an increase in $\ln(\text{FeNO})$ of 0.0014, but the association was not significant ($p = 0.51$). (B) For subjects with asthma, $\ln(\text{FeNO})$ was regressed on continuous BMI using a linear regression model that adjusted for age, gender, ethnicity, atopy, household income-to-poverty ratio and current smoking. After adjustment for covariates, a one-unit increase in BMI was associated with an increase in $\ln(\text{FeNO})$ of 0.002, but the association was not significant ($p = 0.74$). (C) For all subjects, current asthma status was regressed on BMI using a logistic regression model that adjusted for age, gender, race/ethnicity, income-to-poverty ratio, current smoking, atopy and family history of asthma. The adjusted odds ratio estimate for BMI was 1.04 [95% CI = (1.03, 1.06), $p < 0.0001$], indicating that a unit increase in BMI was associated with a 4% increase in the odds of current asthma.

on this topic have varied. Todd et al. (2007) found no association between continuous BMI and any of several indicators of airway inflammation based on sputum cell counts (neutrophils, eosinophils, lymphocytes and macrophages) in 163 subjects with asthma recruited from a University-based clinic in Canada [14]. However, they did not assess the relationship with FeNO. Barros et al. had (2005) previously reported a negative association between continuous BMI and FeNO in 297 non-smoking subjects with asthma recruited from an outpatient clinic in Portugal [12]. They also conducted separate regression analyses in underweight and normal weight patients versus overweight and obese patients, and found a negative association in the latter but no association in the former. Komakula et al. reported a negative association between continuous BMI and FeNO in a U.S. hospital clinic-based sample of 67 currently non-smoking subjects with asthma that was strongly skewed (86%) toward overweight and obese persons [15]. Subjects in that study were also predominantly female (83%) and black (81%). It is possible that different relationships between FeNO and BMI exist in highly specific subgroups with asthma.

For those without asthma, both of our analyses found no association between BMI and ln(FeNO). De Winter-De Groot and Kazake independently reported a significant positive linear association between BMI and FeNO among subjects without asthma in 2005 [10,11]. Both studies were based on small samples ($n=24$ and $n=25$, respectively) and apparently the maximum BMI in either study was 36 m/kg². The BMI range for the subjects without asthma in our sample was 15 to 60. Several subsequent studies with considerably larger samples of subjects without asthma failed to detect an association [14–16]. The later studies also apparently included relatively few subjects with extremely high BMI.

Conclusions/key findings

We investigated the relationship between BMI and FENO in a large, unselected sample of U.S. adults. The major advantage of our approach over previous investigations is the use of NHANES survey data for 2007 to 2010, which comprise a nationally representative sample of the civilian, non-institutionalized population of the United States.

We acknowledge certain limitations in our approach. Cross-sectional studies can indicate the presence or absence statistical associations, but they cannot establish causality. Furthermore, FeNO measurements could not be obtained for 19% of adults in NHANES 2007–2010. Missing values for FeNO, BMI and covariates resulted in 24% of eligible adult subjects without, and 30% of those without, asthma being excluded from the multiple regression analyses. BMI is an imperfect indicator of obesity [28], and asthma may be differentially misdiagnosed across BMI levels [29]. Finally, complete and reliable data on corticosteroid use and recent asthma exacerbations was lacking in NHANES, and serum IgE testing was not performed in the 2007–2008 and 2009–2010 survey cycles.

In summary, our findings suggest that in the U.S. adult population, BMI is not associated with eosinophilic airway inflammation.

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Declaration of interest

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

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