

Insulin resistance, metabolic syndrome, and lung function in US adolescents with and without asthma

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Background: Obesity increases both the risk of asthma and asthma severity and is a well-known risk factor for insulin resistance and the metabolic syndrome (MS) in children and adolescents.

Objective: We aimed to examine the association among obesity, insulin sensitivity, MS, and lung function in US adolescents with and without asthma.

Methods: We performed a cross-sectional study of 1429 adolescents aged 12 to 17 years in the 2007-2010 National Health and Nutrition Examination Survey. Adjusted regression was used to assess the relationships among obesity, insulin sensitivity/resistance, MS, and lung function in children with and without asthma.

Results: Insulin resistance was negatively associated with FEV₁ and forced vital capacity (FVC) in adolescents with and without asthma, whereas MS was associated with lower FEV₁/FVC ratios, with a more pronounced decrease found among asthmatic patients; these associations were driven by overweight/obese adolescents. Higher body mass index was associated with a decrease in FEV₁/FVC ratios among adolescents with insulin resistance. Compared with healthy participants, adolescents with MS had an approximately 2% decrease in FEV₁/FVC ratios, adolescents with asthma had an approximately 6% decrease, and those with MS and asthma had approximately 10% decreased FEV₁/FVC ratios ($P < .05$).

Conclusion: Insulin resistance and MS are associated with worsened lung function in overweight/obese adolescents. Asthma and MS synergistically decrease lung function, as do obesity and insulin resistance. These factors might contribute to the pathogenesis of asthma severity in obese patients and warrant further investigation. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Asthma, lung function, insulin resistance, adiposity, obesity, metabolic syndrome, National Health and Nutrition Examination Survey

Asthma and obesity are major public health issues in industrialized countries, such as the United States, with parallel increases in the prevalence of both diseases over the last few decades.¹⁻⁴ Epidemiologic studies have shown that childhood obesity is associated with increased risk of incident asthma, increased asthma severity and morbidity, and decreased response to long-term asthma medications.⁵⁻⁸

Childhood obesity is a known risk factor for insulin resistance, diabetes, and the metabolic syndrome (MS).^{9,10} There is growing evidence that metabolic derangements, such as hyperglycemia and hyperinsulinemia, can lead to airway dysfunction and increased airway responsiveness through several pathways, including epithelial damage and airway smooth muscle proliferation.¹¹ A recent population-based study reported higher rates of acanthosis nigricans (a marker of insulin resistance) in children with asthma than in those without asthma, regardless of body mass index (BMI).¹² Conversely, morbidly obese children and adolescents with asthma have a higher incidence of insulin resistance than morbidly obese children and adolescents without asthma.^{13,14} The MS has also been significantly associated with lung function impairment and asthma-like symptoms, with abdominal obesity being the key determinant of this association.^{15,16}

We hypothesized that measures of insulin sensitivity (fasting glucose/insulin [G/I] ratio and the quantitative insulin sensitivity check index [QUICKI]) and insulin resistance (homeostasis model assessment-estimated insulin resistance [HOMA-IR]) are associated with lung function in adolescents, particularly among those with obesity or increased adiposity. We further hypothesized that the MS is associated with worse lung function and that detrimental effects of insulin resistance and MS on lung function are more pronounced in adolescents with asthma. We examined these hypotheses in a cross-sectional study of adolescents living in the United States.

METHODS

Subject recruitment

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional nationwide survey designed to assess the health and nutritional status of the noninstitutionalized population of the United States.¹⁷ NHANES combines interviews and physical examinations of participants by highly trained personnel. Participants for the study are selected by using a stratified multistage probability design and are thus a representative sample of the US population. By design, ethnic minorities (African Americans and Mexican Americans) are oversampled to increase the statistical power for data analysis in these groups. Adolescents 12 to 17 years of age who participated in the 2007-2008 and 2009-2010 NHANESs were included in this analysis. Current

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Abbreviations used

BMI:	Body mass index
CRP:	C-reactive protein
FVC:	Forced vital capacity
G/I:	Glucose/insulin
HDL:	High-density lipoprotein
HOMA-IR:	Homeostasis model assessment-estimated insulin resistance
MS:	Metabolic syndrome
NHANES:	National Health and Nutrition Examination Survey
PBF:	Percentage body fat
QUICKI:	Quantitative insulin sensitivity check index
WC:	Waist circumference
WHtR:	Waist/height ratio

asthma was defined as both having had asthma diagnosed by a doctor or other health care professional and at least 1 asthma attack in the past year. Participants who had neither diagnosed asthma nor an asthma attack in the past year were selected as control subjects. Participants who reported a lifetime diagnosis of asthma but no asthma attacks in the past year were excluded from this analysis. NHANES was approved by the Institutional Review Board of the National Center for Health Statistics of the US Centers for Disease Control and Prevention. Informed consent was obtained from all participants.

Study procedures

Measures of obesity and adiposity were collected by trained health technicians, according to recommendations from the *Anthropometric standardization reference manual*.¹⁸ BMI was calculated as weight (in kilograms) divided by height (in meters squared). Percentage body fat (PBF) was calculated from tricipital and subscapular skin folds. For data analysis, all measures were transformed to *z* scores to obtain standardized and comparable coefficients: BMI *z* scores were calculated by using equations based on the 2000 US Centers for Disease Control and Prevention growth charts,¹⁹ PBF *z* scores were calculated by using reference equations for US children,²⁰ and waist circumference (WC) and waist/height ratio (WHtR) values were standardized by using the distribution of these measures in our study population. Overweight/obese was defined as a *z* score of greater than 1.0364 (85th percentile) for each adiposity indicator.

Fasting plasma glucose, serum insulin, high-density lipoprotein (HDL) cholesterol, triglyceride, and C-reactive protein (CRP) levels were measured at a morning examination session in all NHANES participants aged 12 years and older. Participants fasting for less than 9 hours, taking insulin or oral medications for diabetes, or refusing phlebotomy were excluded. Insulin sensitivity was measured by using 2 indicators: fasting glucose (in microunits per milliliter)/insulin (in milligrams per deciliter [G/I]) ratio and QUICKI value. The QUICKI value was defined as follows:

$$1/\log[\text{Fasting insulin}] + \log[\text{Fasting glucose}].^{21}$$

Conversely, the HOMA-IR value was used as a measure of insulin resistance and was defined as follows:

$$(\text{Fasting insulin} \times \text{Fasting glucose}[\text{mmol/L}])/22.5.^{22}$$

Systolic blood pressure was measured in all NHANES participants according to study protocols²³ and was standardized for this analysis by using its distribution in our study population. MS was defined as meeting at least 3 of the following 5 criteria: fasting glucose level of 110 mg/dL or greater, WC value of the 75th percentile or greater, fasting triglyceride level of 100 mg/dL or greater, HDL level of 50 mg/dL or less, and systolic blood pressure of the 90th percentile or greater.^{14,24}

Spirometry was performed according to American Thoracic Society recommendations.²⁵ The best FEV₁ and forced vital capacity (FVC) values were selected for data analysis. Participants were not eligible for spirometry

if they were receiving supplemental oxygen or had painful ear infections, current chest pain or a physical problem with forceful expiration, recent surgery (of the eye, chest, or abdomen), heart disease, or tuberculosis. Our main analyses were performed by using absolute values (in milliliters) adjusted for age, sex, height, and height squared; confirmatory analyses were performed with NHANES III predictive equations for lung function measures and are included in this article's Online Repository at www.jacionline.org.

Statistical analysis

Primary sampling units and strata for the complex design of NHANES were taken into account for data analysis. Sampling weights, stratification, and clusters provided in the NHANES data set were incorporated into the analysis to obtain proper estimates and SEs; fasting sample weights were also used when analyzing fasting glucose and insulin levels. All multivariate analyses were performed with linear regression within the SURVEY procedure in SAS software (SAS Institute, Cary, NC). All models were adjusted for age, sex, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other), family history of asthma, health insurance coverage, environmental tobacco smoke exposure, CRP level, and number of fasting hours; models for FEV₁ and FVC were additionally adjusted for height and height squared. In a secondary multivariate analysis we examined the relation between FEV₁/FVC ratios and overweight/obesity (BMI ≥85th percentile for age and sex) after stratification by asthma and MS. All statistical analyses were conducted with SAS 9.3 software.

RESULTS

The main characteristics of the 1429 participating adolescents with and without current asthma are shown in Table I (see Fig E1 in this article's Online Repository at www.jacionline.org for derivation of the study sample from NHANES). Compared with adolescents without asthma, those with asthma were more likely to be black and to have a low annual household income, health insurance, a family history of asthma, lower FEV₁, and lower FEV₁/FVC ratios (*P* < .05 in all instances). Adolescents with asthma also had a nonsignificant trend toward higher adiposity *z* scores than their nonasthmatic counterparts (*P* < .10). There were no statistically significant differences in age, sex, environmental tobacco smoke exposure, CRP levels, or indicators of MS or insulin resistance between adolescents with and without asthma. Similar results were found when comparing adolescents with "ever asthma" with healthy control subjects (see Table E1 in this article's Online Repository at www.jacionline.org).

Table II shows the results of the multivariate analysis of the relation between indicators of insulin sensitivity or resistance and lung function measures among all subjects and after stratification by asthma status. In this analysis greater insulin sensitivity (defined by higher G/I ratios or QUICKI values) was significantly associated with higher FEV₁ and FVC values in all subjects. Among subjects without asthma, each unit increment in G/I ratio was significantly associated with approximately 11- to 13-mL increments in FEV₁ and FVC values, respectively, and each 0.01-point increment in QUICKI value was significantly associated with approximately 24- to 30-mL increments in FEV₁ and FVC values, respectively. Among adolescents with asthma, these findings were more pronounced: significant increments of approximately 20 mL in FEV₁ and approximately 45 mL in FVC per each unit increment in G/I ratio and significant increments of approximately 42 mL in FEV₁ and approximately 59 mL in FVC per each unit increment in QUICKI value. Conversely, insulin resistance (defined by higher HOMA-IR values) was associated with lower FEV₁ and FVC values: each unit increase in HOMA-IR

TABLE I. Characteristics of study participants by asthma status

Characteristics	No asthma (n = 1334)	Current asthma (n = 95)	P value
Age (y)	14.54 ± 0.05	14.53 ± 0.24	.97
Male sex	688 (50.03)	57 (56.77)	.34
Race/ethnicity			.007
Non-Hispanic white	439 (60.51)	25 (47.42)	
Non-Hispanic black	294 (13.34)	40 (29.64)	
Hispanic	530 (19.55)	24 (13.90)	
Other	71 (6.61)	6 (9.05)	
Household income <\$20,000/y	247 (13.81)	30 (24.95)	<.05
Health insurance coverage	1125 (88.45)	90 (97.18)	.002
Family history of asthma	314 (22.42)	64 (58.34)	<.001
ETS exposure	203 (15.04)	19 (20.47)	.37
Hay fever	115 (10.02)	32 (35.32)	.006
FEV ₁ (L)*	3.40 ± 0.03	3.27 ± 0.13	.02
FVC (L)*	3.93 ± 0.03	3.94 ± 0.15	.86
FEV ₁ /FVC ratio (%)	86.82 ± 0.22	83.08 ± 1.26	.008
CRP	0.14 ± 0.02	0.16 ± 0.03	.67
BMI z score	0.65 ± 0.04	0.92 ± 0.17	.09
PBF z score	0.24 ± 0.04	0.45 ± 0.11	.06
WC z score	−0.07 ± 0.04	0.16 ± 0.12	.09
WHtR z score	−0.11 ± 0.04	0.13 ± 0.13	.09
G/I ratio†	9.51 ± 0.38	8.31 ± 0.88	.21
QUICKI value†	0.33 ± 0.002	0.32 ± 0.005	.09
HOMA-IR value†	3.24 ± 0.11	3.90 ± 0.55	.24
MS†	58 (9.02)	7 (15.77)	.29

Results are shown as means (SEs) for continuous variables and numbers (percentages) for binary variables. Numbers might vary because of missingness.

ETS, Environmental tobacco smoke.

*Adjusted for age, sex, height, and height squared.

†Data were analyzed only for children who were examined after fasting (n = 701).

value was significantly associated with lower FEV₁ and FVC values among all subjects and in subjects with and without asthma. Insulin sensitivity or resistance was not significantly associated with the FEV₁/FVC ratio in all subjects or in those without asthma. Among subjects with asthma, both the G/I ratio and the QUICKI value were significantly and inversely associated with FEV₁/FVC ratios (range for the estimated effect, −0.63% to −0.86% per each unit increment in G/I ratio or QUICKI value). In these subjects the HOMA-IR value was significantly and positively associated with the FEV₁/FVC ratio (Table II).

Table III shows the results of the analysis of the relation between indicators of insulin sensitivity or resistance and lung function measures after stratification by obesity (defined by using BMI). In a multivariate analysis among adolescents of normal weight, there was no significant association between any indicator of insulin sensitivity or resistance and lung function. Among overweight or obese adolescents, insulin sensitivity (higher G/I ratio or QUICKI value) was significantly associated with higher FEV₁ (range of estimated effect, 28.6–46.1 mL per each unit increment) and FVC values, and insulin resistance (HOMA-IR value) was associated with lower FEV₁ (estimated effect, −36.3 mL per each unit increment) and FVC values. Similar results were obtained when defining obesity/adiposity on the basis of PBF, WC, or WHtR values (see Table E2 in this article's Online Repository at www.jacionline.org) or when analyzing overweight and obese subjects separately (data not shown).

On the basis of our results, we examined the relation between BMI z score and lung function after stratification by insulin resistance (Fig 1). Among adolescents without insulin resistance

(HOMA-IR value < 3.0), each 1.0-point z score increment in BMI was associated with approximately 200 mL higher FEV₁ values. Among adolescents with insulin resistance (HOMA-IR value > 3.0), the increment in FEV₁ per each 1.0-point z score increment in BMI was lower at approximately 70 mL (*P* for interaction = .0006). On the other hand, each z score unit increment in BMI was associated with a significant decrement in FEV₁/FVC values among adolescents with insulin resistance but with a nonsignificant decrement in FEV₁/FVC ratio among adolescents with normal sensitivity (*P* for interaction = .02).

We then focused on the MS (Table II). Among all subjects or subjects without asthma, the MS was significantly associated with a 2% to 2.3% decrement in FEV₁/FVC ratio but not significantly associated with FEV₁ or FVC values. Among asthmatic patients, the MS was significantly associated with a 12.6% decrement in FEV₁/FVC ratio and a 530-mL decrement in FEV₁. After stratifying this analysis by obesity status (Table III), there was no significant association between the MS and lung function measures among subjects of normal weight. Among subjects who were overweight or obese, the MS was significantly associated with (2.3%) lower FEV₁/FVC ratios but not FEV₁ or FVC values. In an analysis of the relation between each criterion used to define MS and lung function, there was no particular measure driving our results (see Table E3 in this article's Online Repository at www.jacionline.org).

Finally, we repeated the multivariate analysis of FEV₁/FVC ratios after stratification by asthma and MS status. Compared with healthy control subjects (subjects without asthma or MS), those with MS had an approximately 2% lower FEV₁/FVC ratio, those with asthma had an approximately 5% lower FEV₁/FVC ratio, and those with both asthma and MS had an approximately 10% lower FEV₁/FVC ratio (*P* for linear trend < .01). These findings remained significant after additional adjustment for any of the adiposity indicators (BMI, PBF, WC, or WHtR; Fig 2). We obtained similar but nonstatistically significant results for FEV₁ (see Fig E2 in this article's Online Repository at www.jacionline.org).

As a confirmatory analysis, we re-ran the models for Tables II–IV with FEV₁, FVC, and FEV₁/FVC ratio as percent predicted values using NHANES III predictive equations for lung function measures (see Tables E4–E6 in this article's Online Repository at www.jacionline.org). Although there was an approximately 16% to 19% decrement in sample size (because non-Mexican-American Hispanic participants were excluded given the lack of appropriate predictive equations) and coefficients are expressed in different units (percent predicted instead of milliliters), the results of this analysis are very similar to those of our main analyses. The direction and significance of all results for the whole sample and for nonasthmatic subjects remained the same, whereas among asthmatic patients (n = 25), only the association between MS and FEV₁/FVC ratio remained significant (Table II and see Table E4). As in the main analysis, all results continued to be driven by overweight/obese adolescents (Table III and see Table E5).

DISCUSSION

To the best of our knowledge, this is the first study of insulin resistance or the MS and lung function in a representative sample of US adolescents with and without asthma. Among adolescents with and without asthma, we found that insulin resistance is

TABLE II. Insulin sensitivity/resistance, MS, and lung function by asthma status

Outcome	G/I ratio (range, 0.98-37.86)	QUICKI value* (range, 0.24-0.44)	HOMA-IR value (range, 0.49-32.83)	MS
All participants† (n = 545)				
FEV ₁ (mL)	11.36 (2.50 to 20.21)‡	24.97 (7.72 to 42.22)§	-34.32 (-50.99 to -17.66)§	-37.42 (-221.57 to 146.729)
FVC (mL)	13.65 (4.26 to 23.04)§	32.74 (14.10 to 51.39)§	-42.28 (-63.22 to -21.35)§	68.65 (-144.50 to 281.81)
FEV ₁ /FVC ratio (%)	-0.01 (-0.17 to 0.14)	-0.09 (-0.37 to 0.19)	0.04 (-0.22 to 0.30)	-2.34 (-4.03 to -0.64)§
No asthma (n = 519)				
FEV ₁ (mL)	11.09 (2.15 to 20.04)‡	24.01 (6.24 to 41.79)§	-32.47 (-50.33 to -14.61)§	-37.55 (-226.67 to 151.57)
FVC (mL)	12.84 (3.53 to 22.16)§	30.73 (11.87 to 49.59)§	-39.16 (-61.39 to -16.92)§	58.74 (-158.55 to 276.02)
FEV ₁ /FVC ratio (%)	-0.01 (-0.16 to 0.15)	-0.08 (-0.35 to 0.19)	0.03 (-0.23 to 0.29)	-2.04 (-3.92 to -0.15)‡
Current asthma (n = 28)				
FEV ₁ (mL)	20.14 (7.82 to 32.47)§	41.84 (15.18 to 68.51)§	-37.04 (-59.52 to -14.57)§	-530.80 (-721.49 to -340.10)§
FVC (mL)	44.58 (29.18 to 59.99)§	59.17 (46.53 to 71.81)§	-39.13 (-54.44 to -23.81)§	58.18 (-99.95 to 216.31)
FEV ₁ /FVC ratio (%)	-0.63 (-0.83 to -0.42)§	-0.86 (-1.01 to -0.72)§	0.54 (0.50 to 0.59)§	-12.56 (-17.61 to -7.50)§

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and BMI z scores. FEV₁ and FVC values were additionally adjusted for height and height squared.

*Results are shown per 0.01 unit of QUICKI increment in each lung function measure.

†Additionally adjusted for asthma status.

‡ $P < .05$.

§ $P < .01$.

TABLE III. Insulin sensitivity/resistance, MS, and lung function by obesity status

Outcome	G/I ratio (range, 0.98-37.86)	QUICKI value* (range, 0.24-0.44)	HOMA-IR value (range, 0.49-32.83)	MS
BMI <85th percentile (n = 316)				
FEV ₁ (mL)	2.11 (-8.73 to 12.95)	-0.68 (-23.63 to 22.28)	-0.87 (-37.98 to 36.23)	-16.30 (-261.99 to 229.38)
FVC (mL)	1.14 (-8.13 to 10.42)	0.71 (-18.83 to 20.25)	-2.48 (-39.75 to 34.80)	80.95 (-129.61 to 291.50)
FEV ₁ /FVC ratio (%)	0.03 (-0.14 to 0.19)	-0.04 (-0.40 to 0.32)	0.01 (-0.65 to 0.66)	-3.07 (-6.50 to 0.35)
BMI ≥85th percentile (n = 229)				
FEV ₁ (mL)	28.55 (10.41 to 46.68)†	46.13 (21.87 to 70.40)†	-36.34 (-56.75 to -15.93)†	32.88 (-187.15 to 525.91)
FVC (mL)	33.75 (15.31 to 52.19)†	52.61 (30.09 to 75.13)†	-40.09 (-59.85 to -20.32)†	160.77 (-88.10 to 409.64)
FEV ₁ /FVC ratio (%)	0.01 (-0.21 to 0.23)	0.06 (-0.26 to 0.37)	-0.08 (-0.32 to 0.16)	-2.33 (-3.97 to -0.68)†

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and asthma status. FEV₁ and FVC values were additionally adjusted for height and height squared.

*Results are shown per 0.01 unit of QUICKI increment in each lung function measure.

† $P < .01$.

associated with decreased FEV₁ and FVC values and that the MS is associated with lower FEV₁/FVC ratios. Both findings were significant only in overweight or obese adolescents and were more pronounced for FEV₁ and FEV₁/FVC ratio among adolescents with asthma.

Insulin resistance, an immediate precursor of type 2 diabetes, has been associated with other illnesses, such as hepatic steatosis and cardiovascular disease. We found that insulin resistance (or decreased insulin sensitivity) is associated with lower lung function in adolescents, particularly those who are overweight or obese. For example, an increment in HOMA-IR values from 1.98 (the 25th percentile in our sample) to 4.47 (75th percentile) would be associated with approximately 90 mL lower FEV₁ and approximately 100 mL lower FVC values, whereas a similar decrease in QUICKI values would lead to approximately 171 mL lower FEV₁ and approximately 195 mL lower FVC values. These reductions were rather symmetrical, which is consistent with studies in adults that report a much higher prevalence of restrictive deficit among subjects with insulin resistance.^{26,27}

We also show significant modification of the estimated effect of BMI on lung function by insulin resistance, whereby a higher BMI in adolescents with insulin resistance is associated with a

smaller increment in FEV₁ (approximately 70 mL vs approximately 200 mL per 1.0-point BMI z score increase) but a greater decrement in FEV₁/FVC ratio than in their insulin-sensitive counterparts. Although prior studies have reported an association between a higher BMI and either higher FEV₁ or lower FEV₁/FVC ratio in children,^{6,28,29} this is the first study reporting that insulin resistance might modify or influence this association.

Insulin resistance and the resulting metabolic imbalances can affect lung function through several pathways. Insulin growth factor 1 is known to alter airway smooth muscle contractility^{30,31} and stimulate its proliferation.³² Several studies have reported links between adiponectin or leptin and asthma, asthma severity, or lung function.³³⁻³⁵ Selective leptin resistance might lead to loss of the anorexigenic and metabolic effects of leptin, whereas increasing levels of this hormone continue to affect other organs (eg, chronically activating the sympathetic system).^{36,37} Resistin, an adipokine implicated in insulin resistance, has proinflammatory properties in the lung through recruitment and activation of neutrophils.³⁸ Likewise, cytokines from the resistin-link molecule family have been shown to induce airway inflammation and fibroblast proliferation in murine models.³⁹ Prior studies in healthy adults have also found an association between insulin

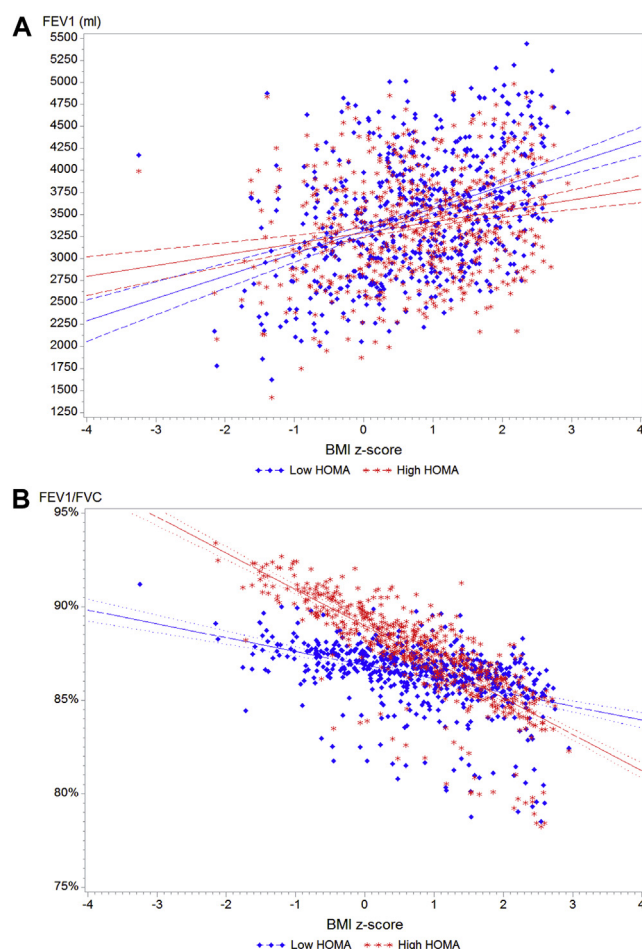


FIG 1. BMI z score and lung function by insulin resistance status (HOMA-IR value of <3.0 vs >3.0). **A**, Predicted values for FEV₁. **B**, FEV₁/FVC ratio. All models were adjusted for age, sex, race/ethnicity, asthma status, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, and CRP levels. Interaction P for FEV₁ = .0006; interaction P for FEV₁/FVC ratio = .02.

resistance and airway hyperresponsiveness.⁴⁰ On the other hand, murine models have shown that allergic airway inflammation might lead to reduced levels of insulin-degrading enzyme and decreased insulin receptor phosphorylation in the brain, producing changes that could induce insulin resistance and a proinflammatory response.⁴¹

The MS has been associated with asthma in large cross-sectional¹⁶ and longitudinal⁴² studies in adults (mean age, 55 and 43 years, respectively). Similarly, a large study of almost 122,000 adults (mean age, 46 years) reported an association between the MS and lower FEV₁ and FVC values after adjusting for potential confounders (including smoking status, alcohol consumption, BMI, and activity level).¹⁵ However, this and other studies in adults have shown that decrements in lung function associated with MS result in a restrictive ventilatory deficit (low FEV₁ and FVC values but normal FEV₁/FVC ratios).^{43,44} In contrast, we report a decreased FEV₁/FVC ratio in adolescents with MS, which is consistent with an obstructive deficit. This estimated effect of MS on FEV₁/FVC ratios was separate from and additive to the effect of asthma; thus adolescents with both asthma and MS had approximately 530 mL lower FEV₁ values and 10% lower FEV₁/FVC ratios than their healthy counterparts (both reductions

being clinically significant in adolescents). Based on these results, one might speculate that the mechanisms or effects of MS on lung function in children and adolescents might differ from those in adults.

One previous study has reported low FEV₁/FVC ratios in morbidly obese adults with MS. However, that study did not include patients with asthma, and the observed association was likely mediated by peripheral blood eosinophilia.⁴⁵ We did not find that one particular component of the MS explained our results; however, WC was most consistently associated with the outcomes of interest. Of note, a low HDL level was an additional independent risk factor for low FEV₁/FVC ratios in adolescents who were overweight or obese.

Several mechanisms might explain the decrements in lung function associated with the MS. In addition to insulin resistance, in patients with MS, increased protein turnover might lead to altered arginine metabolism and increased methyl-arginine molecules, such as asymmetric dimethylarginine; this in turn limits arginine availability for nitric oxide generation, which might result in epithelial damage and dysfunction.¹¹ In mouse models of allergy with diet-induced MS, electron microscopy has shown stressed and dysfunctional mitochondria in the bronchial epithelium, leading to airway hyperresponsiveness, even in the absence of allergen exposure.⁴⁶ Chemokine (C-X-C motif) receptor 3, which is involved in immune cell regulation and allergic airway inflammation,⁴⁷ has also been reported to modulate diet-induced insulin resistance and visceral adipose tissue macrophage infiltration and inflammation in mice.⁴⁸ As with insulin resistance, some studies have shown that the decrease in lung function in some cases precedes the development of MS⁴⁹; future studies should try to elucidate whether this is a cause-and-effect relationship or whether both are consequences of the same process (eg, obesity and inflammation), with the decrease in lung function merely being an earlier manifestation of disease.

Our study has considerable strengths, including the use of a representative sample of US adolescents, performance of standardized procedures by uniformly trained personnel, and adjustment of data analysis for several potential confounders, including obesity/adiposity and CRP.

We also acknowledge several limitations of our findings. First, NHANES is a cross-sectional study, and therefore a temporal relationship between insulin resistance, MS, and lung function cannot be determined.

Second, we had limited statistical power for subgroup analyses because of the small number of adolescents with current asthma.

Third, the MS can be defined according to several sets of guidelines. The definition we used had less stringent criteria and thus allowed us to classify more subjects as having MS; using stricter criteria (International Diabetes Federation^{50,51}) yielded much fewer children classified as such ($n = 19$), but results for FEV₁/FVC ratios remained the same (data not shown).

Fourth, our definition of current asthma could have excluded a portion of participants with asthma who had low exacerbation risk but higher impairment in the year before the study.

Finally, we could not control for all factors related to obesity, insulin resistance, or MS, such as diet or family history of diabetes.

In summary, insulin resistance and MS are associated with significantly worsened lung function in overweight/obese adolescents. The effect of MS is worse among adolescents with asthma. Thus insulin resistance and MS might contribute to the

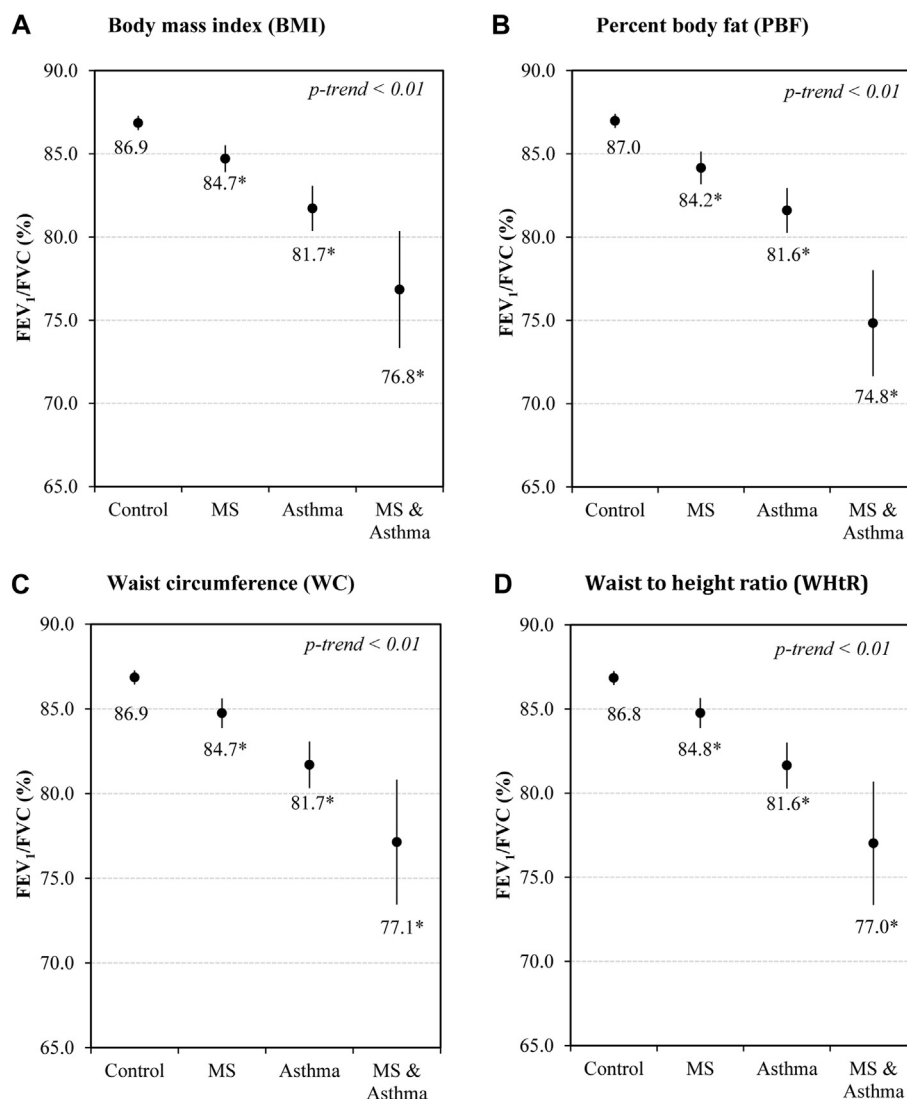


FIG 2. Predicted FEV₁/FVC ratio by asthma and MS status. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and z scores for each adiposity indicator (**A**, BMI; **B**, PBF; **C**, WC; **D**, WHtR). No asthma and no MS, n = 496; MS only, n = 58; asthma only, n = 23; and MS and asthma, n = 7. **P* < .05 compared with the control group (no asthma and no MS).

TABLE IV. MS criteria and FEV₁/FVC values by asthma and obesity status

	SBP ≥90th percentile	HDL <50 mg/dL	Triglyceride ≥100 mg/dL	WC ≥75th percentile	Fasting glucose ≥110 mg/dL
All participants*	-0.38 (-2.15 to 1.40)	-0.65 (-2.08 to 0.78)	-0.40 (-2.46 to 1.66)	-1.65 (-3.37 to 0.08)	-1.68 (-6.26 to 2.90)
Nonasthma	0.14 (-1.72 to 2.01)	-0.63 (-2.14 to 0.88)	-0.34 (-2.48 to 1.80)	-1.94 (-3.79 to -0.10)‡	-1.70 (-6.33 to 2.93)
Asthma	-12.73 (-16.97 to -8.50)§	1.61 (-1.25 to 4.47)	0.46 (-0.87 to 1.80)	2.82 (1.06 to 4.57)§	NA†
Normal weight*	-0.53 (-3.08 to 2.03)	0.33 (-1.73 to 2.39)	-0.51 (-3.45 to 2.44)	NA†	-2.85 (-8.79 to 3.08)
Overweight/obese*	-0.12 (-2.64 to 2.39)	-1.93 (-3.66 to -0.20)‡	-0.20 (-2.10 to 1.69)	-1.54 (-3.21 to 0.23)	2.07 (-1.32 to 5.45)

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, and CRP levels.

SBP, Systolic blood pressure.

*Defined on the basis of BMI z scores (additionally adjusted for current asthma).

†All asthmatic patients had fasting glucose levels of less than 110 mg/dL, and all children of normal weight had WC values of less than the 75th percentile.

‡*P* < .05.

§*P* < .01.

pathogenesis of asthma severity in obese patients and warrant further investigation.

Clinical implications: Insulin resistance and the MS might affect lung function in adolescents. Management of these conditions should be part of the treatment of obese asthmatic children and adolescents.

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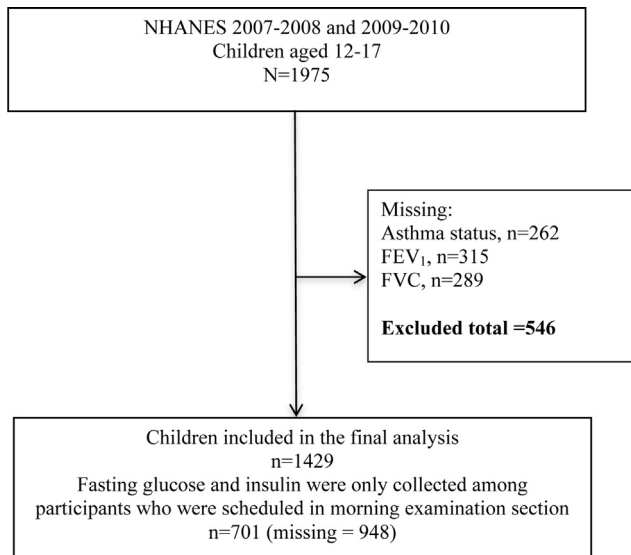


FIG E1. Derivation of the study sample from NHANES 2007-2008 and 2009-2010.

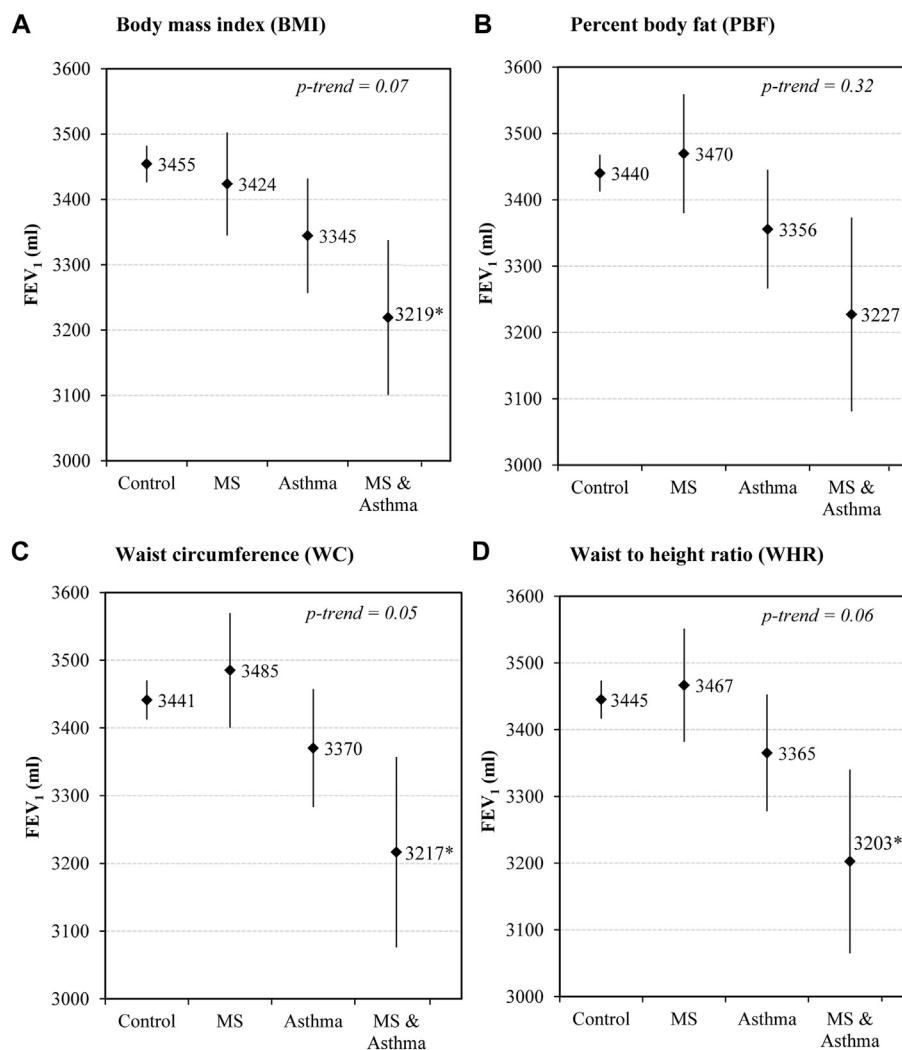


FIG E2. Predicted FEV₁ by asthma and MS status. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and z scores for each adiposity indicator (**A**, BMI; **B**, PBF; **C**, WC; **D**, WHtR). No asthma and no MS, n = 496; MS only, n = 58; asthma only, n = 23; and MS and asthma, n = 7. * $P < .05$ compared with the control group (no asthma and no MS).

TABLE E1. Characteristics of study participants by “ever asthma” status

Characteristics	No asthma (n = 1334)	Ever asthma (n = 315)	P value
Age (y)	14.54 ± 0.05	14.82 ± 0.12	.031
Male sex	688 (50.03)	177 (53.95)	.231
Race/ethnicity			
Non-Hispanic white	439 (60.51)	106 (61.68)	
Non-Hispanic black	294 (13.34)	90 (16.07)	.044
Hispanic	530 (19.55)	98 (14.79)	
Other	71 (6.61)	21 (7.47)	
Household income <\$20,000/y	247 (13.81)	62 (13.75)	.983
Health insurance coverage	1125 (88.45)	285 (94.01)	.013
Family history of asthma	314 (22.42)	176 (51.99)	<.001
ETS exposure	203 (15.04)	59 (20.48)	.058
Hay fever	115 (10.02)	65 (21.90)	.001
FEV ₁ (L)*	3.40 ± 0.03	3.43 ± 0.05	.003
FVC (L)*	3.93 ± 0.03	4.11 ± 0.05	.561
FEV ₁ /FVC ratio (%)	86.82 ± 0.22	83.52 ± 0.53	<.001
CRP	0.14 ± 0.02	0.11 ± 0.01	.225
BMI z score	0.65 ± 0.04	0.79 ± 0.08	.101
PBF z score	0.24 ± 0.04	0.39 ± 0.06	.046
WC z score	−0.07 ± 0.04	0.09 ± 0.07	.055
WHtR z score	−0.11 ± 0.04	0.01 ± 0.07	.145
G/I ratio†	9.51 ± 0.38	8.19 ± 0.39	.018
QUICKI†	0.33 ± 0.002	0.32 ± 0.002	.032
HOMA-IR value†	3.24 ± 0.11	3.49 ± 0.22	.276
MS†	58 (9.02)	14 (9.34)	.920

Values are presented as mean (SEs) for continuous variables and numbers (percentages) for binary variables. Numbers might vary because of missingness.

ETS, Environmental tobacco smoke.

*Adjusted for age, sex, height, and height squared.

†Data were analyzed only for children who were examined after fasting in morning sessions (n = 701).

TABLE E2. Insulin sensitivity/resistance, MS, and lung function by adiposity status

	G/I ratio	QUICKI value*	HOMA-IR value	MS
PBF <85th percentile (n = 391)				
FEV ₁ (mL)	-2.10 (-13.37 to 9.17)	-7.38 (-31.51 to 16.73)	8.90 (-26.04 to 43.84)	-198.72 (-460.68 to 63.24)
FVC (mL)	-1.61 (-10.94 to 7.71)	-3.13 (-24.67 to 18.41)	0.67 (-37.94 to 39.28)	-71.52 (-371.52 to 228.49)
FEV ₁ /FVC ratio (%)	-0.01 (-0.17 to 0.15)	-0.13 (-0.45 to 0.20)	0.22 (-0.25 to 0.69)	-3.89 (-6.23 to -1.55)‡
PBF ≥85th percentile (n = 118)				
FEV ₁ (mL)	31.80 (1.16 to 62.43)†	35.73 (0.18 to 71.29)†	-25.41 (-51.95 to 1.13)	233.96 (56.41 to 411.51)†
FVC (mL)	36.47 (14.70 to 58.24)‡	44.40 (13.35 to 75.45)‡	-28.97 (-54.44 to -3.50)†	395.01 (178.97 to 611.06)‡
FEV ₁ /FVC ratio (%)	0.09 (-0.41 to 0.60)	0.06 (-0.46 to 0.58)	-0.09 (-0.42 to 0.24)	-2.09 (-4.00 to -0.18)†
WC <85th percentile (n = 457)				
FEV ₁ (mL)	-0.13 (-9.50 to 9.76)	-1.10 (-20.64 to 18.45)	-6.53 (-26.12 to 13.05)	-7.25 (-262.39 to 247.88)
FVC (mL)	-0.11 (-8.25 to 8.03)	1.58 (-15.87 to 19.03)	-9.47 (-29.57 to 10.62)	172.89 (-160.77 to 506.55)
FEV ₁ /FVC ratio (%)	0.01 (-0.14 to 0.16)	-0.06 (-0.35 to 0.24)	0.01 (-0.33 to 0.35)	-4.30 (-6.47 to -2.13)‡
WC ≥85th percentile (n = 84)				
FEV ₁ (mL)	40.66 (-6.77 to 88.09)	57.00 (2.66 to 111.33)†	-22.76 (-49.18 to 3.66)	298.01 (234.24 to 361.78)‡
FVC (mL)	68.26 (-1.29 to 137.80)	87.71 (6.80 to 162.63)†	-34.56 (-70.01 to 0.90)	394.86 (364.19 to 425.56)‡
FEV ₁ /FVC ratio (%)	-0.22 (-0.81 to 0.38)	-0.12 (-0.67 to 0.44)	0.06 (-0.23 to 0.34)	-0.30 (-0.95 to 0.34)
WHR <85th percentile (n = 453)				
FEV ₁ (mL)	0.73 (-9.34 to 10.80)	0.40 (-20.02 to 20.83)	-8.85 (-30.68 to 12.99)	-168.44 (-410.03 to 73.15)
FVC (mL)	0.23 (-8.37 to 8.83)	2.09 (-15.73 to 19.91)	-9.18 (-30.80 to 12.44)	-13.53 (-289.49 to 262.43)
FEV ₁ /FVC ratio (%)	0.02 (-0.13 to 0.16)	-0.04 (-0.32 to 0.24)	-0.04 (-0.37 to 0.29)	-4.28 (-6.28 to -2.29)‡
WHR ≥85th percentile (n = 88)				
FEV ₁ (mL)	59.56 (38.21 to 80.90)‡	79.56 (55.23 to 103.89)‡	-37.16 (-57.56 to -16.76)‡	229.16 (181.16 to 277.16)‡
FVC (mL)	65.33 (19.72 to 110.94)‡	92.08 (43.92 to 140.23)‡	-47.35 (-75.12 to -19.58)‡	383.34 (357.78 to 408.90)‡
FEV ₁ /FVC ratio (%)	0.15 (-0.56 to 0.83)	0.15 (-0.64 to 0.93)	0.01 (-0.37 to 0.38)	-2.01 (-2.49 to -1.53)‡

Data are presented as β coefficients (95% CIs). All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and current asthma. FEV₁ and FVC values were additionally adjusted for height and height squared.

*Results are shown per 0.01 unit of QUICKI increment in each lung function measure.

† $P < .05$.

‡ $P < .01$.

TABLE E3. MS criteria and lung function by asthma and obesity status

	SBP $\geq 90^{\text{th}}$ percentile	HDL < 50 mg/dL	Triglyceride ≥ 100 mg/dL	WC $\geq 75^{\text{th}}$ percentile	Fasting glucose ≥ 110 mg/dL
FEV ₁ /FVC ratio					
All participants*	−0.38 (−2.15 to 1.40)	−0.65 (−2.08 to 0.78)	−0.40 (−2.46 to 1.66)	−1.65 (−3.37 to 0.08)	−1.68 (−6.26 to 2.90)
Nonasthma	0.14 (−1.72 to 2.01)	−0.63 (−2.14 to 0.88)	−0.34 (−2.48 to 1.80)	−1.94 (−3.79 to −0.10)‡	−1.70 (−6.33 to 2.93)
Asthma	−12.73 (−16.97 to −8.50)§	1.61 (−1.25 to 4.47)	0.46 (−0.87 to 1.80)	2.82 (1.06 to 4.57)§	NA†
Normal weight*	−0.53 (−3.08 to 2.03)	0.33 (−1.73 to 2.39)	−0.51 (−3.45 to 2.44)	NA†	−2.85 (−8.79 to 3.08)
Overweight/obese*	−0.12 (−2.64 to 2.39)	−1.93 (−3.66 to −0.20)‡	−0.20 (−2.10 to 1.69)	−1.54 (−3.21 to 0.23)	2.07 (−1.32 to 5.45)
FEV ₁					
All participants*	−83.48 (−187.63 to 20.68)	92.85 (−1.31 to 187.00)	0.83 (−100.50 to 102.15)	71.40 (−38.99 to 181.78)	5.63 (−232.87 to 244.13)
Nonasthma	−101.58 (−215.95 to 12.78)	84.44 (−14.10 to 182.97)	22.96 (−74.20 to 120.12)	82.32 (−32.58 to 197.23)	10.55 (−229.17 to 250.27)
Asthma	−322.97 (−379.37 to −266.57)§	151.86 (−52.38 to 356.10)	−450.61 (−523.61 to −377.60)§	−71.00 (−206.91 to 64.91)	NA†
Normal weight*	−50.01 (−153.81 to 53.79)	150.53 (29.68 to 271.38)‡	−83.93 (−282.56 to 114.70)	NA†	160.96 (177.48 to 499.40)
Overweight/obese*	−77.84 (−205.30 to 49.62)	−75.34 (−213.64 to 62.96)	144.75 (−52.07 to 341.57)	−200.70 (−372.33 to −29.06)‡	−114.66 (−510.55 to 281.23)
FVC					
All participants*	−71.49 (−201.82 to 58.83)	121.29 (10.49 to 232.10)‡	17.19 (−125.09 to 159.47)	170.55 (40.73 to 300.37)‡	108.71 (−317.35 to 534.77)
Nonasthma	−125.14 (−247.89 to −2.39)‡	107.12 (−9.88 to 224.13)	43.34 (−93.04 to 179.71)	202.11 (70.56 to 333.65)§	114.76 (−323.20 to 552.71)
Asthma	282.05 (123.76 to 440.33)§	143.10 (47.3 to 238.87)§	−474.65 (−527.09 to −422.21)§	−101.12 (−163.14 to −39.10)§	NA†
Normal weight*	−25.97 (−156.59 to 104.65)	132.25 (1.80 to 262.70)	−84.30 (−292.06 to 123.45)	NA†	353.91 (−236.31 to 944.14)
Overweight/obese*	−62.04 (−291.97 to 167.89)	−10.92 (−131.2 to 109.35)	189.72 (−40.84 to 420.28)	−160.19 (−337.84 to 17.45)	−219.07 (−624.66 to 186.53)

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, race/ethnicity, health insurance coverage, family history of asthma, environmental tobacco smoke exposure, fasting hours, and CRP levels.

SBP, Systolic blood pressure.

*Defined on the basis of BMI z scores (additionally adjusted for current asthma).

†All asthmatic patients had fasting glucose levels of less than 110 mg/dL, and all children of normal weight had WC values of less than the 75th percentile.

‡ $P < .05$.

§ $P < .01$.

TABLE E4. Insulin sensitivity/resistance, MS, and percent predicted FEV₁, FVC, and FEV₁/FVC ratio by asthma status among white, black, and Mexican American participants

Outcome	G/I ratio	QUICKI value*	HOMA-IR value	MS
All Participants† (n = 446)				
FEV ₁ (% predicted)‡	3.11 (0.90 to 5.33)¶	7.56 (2.67 to 12.45)¶	−9.45 (−14.59 to −4.31)¶	−27.38 (−77.86 to 23.10)
FVC (% predicted)‡	2.75 (0.73 to 4.76)¶	7.84 (3.80 to 11.87)¶	−9.16 (−13.36 to −4.96)¶	7.66 (−41.41 to 56.74)
FEV ₁ /FVC ratio (% predicted)‡	<0.001 (−0.002 to 0.002)	−0.03 (−0.36 to 0.30)	<−0.001 (−0.003 to 0.003)	−0.02 (−0.05 to −0.002)§
No asthma (n = 421)				
FEV ₁ (% predicted)‡	3.06 (0.78 to 5.34)§	7.37 (2.25 to 12.48)¶	−9.18 (−14.66 to −3.70)¶	−26.50 (−75.79 to 22.79)
FVC (% predicted)‡	2.64 (0.58 to 4.69)§	7.54 (3.35 to 11.74)¶	−8.83 (−13.35 to −4.32)¶	3.73 (43.85 to 51.32)
FEV ₁ /FVC ratio (% predicted)‡	<0.001 (−0.002 to 0.002)	−0.02 (−0.35 to 0.31)	<−0.001 (−0.003 to 0.003)	−0.02 (−0.04 to 0.005)
Current asthma (n = 25)				
FEV ₁ (% predicted)‡	−5.33 (−12.78 to 2.12)	−8.54 (−36.29 to 19.20)	8.12 (−21.61 to 37.86)	7.14 (−664.54 to 678.82)
FVC (% predicted)‡	1.06 (−26.19 to 28.31)	4.17 (−56.56 to 64.89)	0.48 (−50.10 to 58.07)	106.24 (−372.10 to 584.59)
FEV ₁ /FVC ratio (% predicted)‡	−0.01 (−0.04 to 0.03)	−1.16 (−4.40 to 2.08)	0.008 (−0.01 to 0.03)	−0.09 (−0.18 to −0.03)§

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and BMI z scores.

*Results are shown per 0.01 unit of QUICKI increment in each lung function measure.

†Additionally adjusted for asthma status.

‡Percent predicted based on NHANES III equations.

§ $P < .05$.

¶ $P < .01$.

TABLE E5. Insulin sensitivity/resistance, MS, and percent predicted FEV₁, FVC, and FEV₁/FVC ratio by obesity status among white, black, and Mexican American participants

Outcome	G/I ratio	QUICKI value*	HOMA-IR value	MS
BMI <85th percentile (n = 257)				
FEV ₁ (% predicted)†	0.33 (−1.90 to 2.55)	0.34 (−5.05 to 5.73)	−1.40 (−12.36 to 9.56)	12.21 (−51.87 to 76.29)
FVC (% predicted)†	−0.40 (−1.82 to 1.02)	−0.30 (−3.95 to 3.55)	−1.39 (−8.37 to 5.59)	28.23 (−13.44 to 73.91)
FEV ₁ /FVC ratio (% predicted)†	0.001 (−0.001 to 0.003)	<0.001 (−0.004 to 0.004)	−0.001 (−0.007 to 0.006)	−0.01 (−0.07 to 0.04)
BMI ≥85th percentile (n = 191)				
FEV ₁ (% predicted)†	6.73 (2.23 to 11.24)§	10.95 (4.85 to 17.05)§	−7.84 (−11.69 to 3.99)§	0.78 (−55.43 to 56.99)
FVC (% predicted)†	5.71 (3.18 to 8.25)§	9.08 (6.02 to 12.14)§	−5.79 (−7.44 to −4.13)§	37.19 (−15.87 to 90.25)
FEV ₁ /FVC ratio (% predicted)†	<0.001 (−0.002 to 0.004)	0.002 (−0.002 to 0.006)	−0.002 (−0.005 to 0.001)	−0.03 (−0.05 to −0.004)‡

Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, family history of asthma, environmental tobacco smoke exposure, fasting hours, CRP levels, and asthma status.

*Results are shown per 0.01 unit of QUICKI increment in each lung function measure.

†Percent predicted based on NHANES III equations.

‡ $P < .05$.

§ $P < .01$.

TABLE E6. MS criteria and percent predicted FEV₁/FVC ratios by asthma and obesity status among white, black, and Mexican-American participants

	SBP ≥90th percentile	HDL <50 mg/dL	Triglyceride ≥100 mg/dL	WC ≥75th percentile	Fasting glucose ≥110 mg/dL
All participants*	0.001 (−0.02 to 0.02)	−0.002 (−0.02 to 0.01)	−0.01 (−0.02 to 0.01)	−0.02 (−0.03 to −0.01)§	−0.02 (−0.07 to 0.03)
Nonasthma	0.01 (−0.01 to 0.03)	−0.002 (−0.02 to 0.01)	−0.004 (−0.02 to 0.01)	−0.02 (−0.04 to −0.01)§	−0.02 (−0.07 to 0.03)
Asthma	−0.16 (−0.28 to −0.05)§	0.06 (−0.05 to 0.17)	0.03 (−0.28 to 0.33)	0.01 (0.001 to 0.03)‡	NA†
Normal weight*	−0.002 (−0.02 to 0.02)	0.01 (−0.01 to 0.04)	−0.01 (−0.03 to 0.01)	NA†	−0.03 (−0.10 to 0.03)
Overweight/obese*	0.001 (−0.02 to 0.04)	−0.02 (−0.04 to 0.002)	0.003 (−0.01 to 0.02)	−0.02 (−0.04 to −0.01)§	0.01 (−0.02 to 0.04)

FEV₁/FVC ratios are shown as percent predicted values based on NHANES III equations. Data are presented as β coefficients (95% CIs). Values in boldface indicate statistical significance. All models were adjusted for age, sex, family history of asthma, environmental tobacco smoke exposure, fasting hours, and CRP levels.

SBP, Systolic blood pressure.

*Defined on the basis of BMI z scores (additionally adjusted for current asthma).

†All asthmatic patients had fasting glucose levels of less than 110 mg/dL, and all children of normal weight had WC values of less than the 75th percentile.

‡ $P < .05$.

§ $P < .01$.