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Persistent overweight or obesity, lung function, and asthma exacerbations in Puerto Rican Youth

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Abstract

Background—Whether persistent overweight or obesity impacts lung function or asthma morbidity in youth is unclear.

Objective—To examine overweight or obesity that persists between school age and adolescence and change in lung function and total IgE, and severe asthma exacerbations in Puerto Rican youth.

Methods—Prospective study of 340 Puerto Rican youth assessed at two visits, the first at ages 6–14 years and the second at ages 9–20 years. Persistent overweight or obesity was defined as a BMI z-score ≥85th percentile at both visits. Outcomes of interest were change in %predicted lung function measures and total IgE between study visits, and severe asthma exacerbations in the year prior to visit 2. Logistic or linear regression was used for the multivariable analysis.

Results—In a multivariable analysis, persistently overweight or obese subjects had changes in %predicted FEV1 (β= −5.07%, 95% confidence interval [CI]= −1.51% to −8.62%, P<0.01) and %predicted FEV1/FVC (β=−2.85%, 95% CI= −0.18% to −5.51%, P=0.04) that were lower than those observed in subjects with normal weight at both study visits (control subjects). Compared with control subjects, those who were persistently overweight/obese and those who became overweight/obese at visit 2 had increased odds of ≥1 severe asthma exacerbation in the year prior to visit 2. There was no significant association between persistent overweight/obesity and change in %predicted FVC or total IgE.

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Conclusion—In a prospective study of Puerto Rican youth, persistently overweight or obese subjects had lower changes in FEV1 or FEV1/FVC and higher odds of severe asthma exacerbations than subjects of normal weight.

Keywords

overweight; obesity; lung function; asthma

INTRODUCTION

In the United States, there have been parallel epidemics of obesity and asthma over the last few decades. In this country, the current prevalence of childhood asthma is approximately 7%, while that of childhood obesity is approaching 20%[1 2].

Although multiple studies have identified an association between obesity and asthma or asthma-related outcomes such as lung function, some aspects of this relationship remain unclear. For instance, while a relationship between early-life weight trajectories and asthma has been reported, little is known about whether and how overweight or obesity that persists from school age to adolescence impacts lung function, asthma morbidity, or allergy markers.[3, 4]

Puerto Rican children are disproportionately affected with overweight, obesity, and asthma. The prevalence of childhood asthma (17%) is nearly three times higher in Puerto Ricans than in non-Hispanic whites (5.6%), and childhood obesity is more common in Puerto Ricans (~24.3%) than in the overall US population (~19.3%).[1, 2, 5, 6]

We previously showed that increased adiposity is associated with asthma, worse lung function, asthma morbidity, and atopy in a cross-sectional study of school-aged Puerto Rican children[7]. Based on those findings, we hypothesized that overweight or obesity persisting from school-age to adolescence would be associated with worse lung function, severe asthma exacerbations, and higher total IgE levels over time. We tested this hypothesis in a prospective cohort study of Puerto Rican children followed from ages 6–14 years to ages 9–20 years.

METHODS

Subject recruitment and study procedures

The PROspective study of Puerto Ricans and childhood Asthma (PROPRA) included Puerto Rican youth who completed an initial study visit at age 6 to 14 years and a follow-up study visit at age 9 to 20 years. Details of subject recruitment and the study protocol have been described elsewhere.[8] In brief, 678 children ages 6 to 14 years with (n=351) and without (n=327) asthma were recruited for the Puerto Rico Genetics of Asthma and Lifestyle (PR-GOAL) study from March 2009 through June 2010 from randomly selected households in San Juan and Caguas (Puerto Rico) using a multistage probabilistic sampling design.[9, 10] All participants had four Puerto Rican grandparents. Cases were children with asthma (defined as having physician-diagnosed asthma and ≥1 episode of wheeze in the previous year) and controls were children who had neither physician-diagnosed asthma nor wheeze

in the previous year. From February 2014 to May 2017, we conducted another study in 543 Puerto Rican youth aged 9 to 20 years, the Epigenetic Variation and Childhood Asthma in Puerto Ricans study (EVA-PR), using a similar approach to that used in PR-GOAL, as previously described.[11] Of the 543 participants in EVA-PR, 406 had previously participated in PR-GOAL. Of these 406 subjects, 340 (~84%, including 180 subjects with asthma) had data on body mass index (BMI) and lung function at both study visits (i.e., in PR-GOAL and EVA-PR) and were thus included in the current analysis. The study was approved by the IRBs of the University of Puerto Rico and the University of Pittsburgh. Written parental consent and child assent were obtained for participants under 18 years old, and written consent was obtained from participants 18 years and older.

All participants completed a protocol that included administration of questionnaires to a child's caretaker (the mother in ~93% of subjects), collection of blood samples, and spirometry at both study visits. The first questionnaire was used to obtain information on demographics, general and respiratory health, and family history of asthma and allergies, and the second was a semiquantitative food frequency questionnaire (FFQ) developed for Hispanic populations.[12, 13] In a prior study of Puerto Rican youth, four food groups were found to be associated with increased (dairy products or sweets) or decreased (vegetables or grains) odds of asthma.[14] Based on the results of that analysis, cut-off points were chosen to assess high vs. low intake for each food group. A dietary score was then defined by the frequency of food group consumption, with study participants being assigned a score of +1 for high consumption of each "healthy" food group (associated with decreased odds of asthma) or −1 for the consumption of each "unhealthy" food group (associated with increased odds of asthma). Thus, the dietary score ranges from −2 ("least healthy diet") to +2 ("healthiest diet").

Spirometry was conducted using an EasyOne Spirometer (NDD Medical Technologies, Andover, MA), in accordance with American Thoracic Society and European Respiratory Society recommendations.[15, 16] All participants had to be free of respiratory illnesses for ≥4 weeks and were instructed to (when possible) avoid the use of inhaled short- and long-acting bronchodilators for ≥ 4 and ≥12 hours before testing, respectively. Percent predicted values were obtained utilizing the Global Lung Initiative (GLI) 2012 prediction equations, which account for age, sex, and height.[17] Body mass index (BMI) was calculated using weight in kilograms and height in meters, and then transformed to z-scores based on 2000 Growth Charts from the Centers for Disease Control.[18] Subjects were classified as overweight or obese if their BMI z-score was at or above the 85th percentile. Serum total IgE was measured using the UniCAP 100 system (Pharmacia & Upjohn, Kalamazoo, MI). Total IgE levels were transformed to a $\log_{10}$ scale for data analysis.

To measure residential distance from a major road, the home address of each participant was geocoded (linked) to a 15-digit 2000 US Census Federal Information Processing Standard + block code at the University of Puerto Rico. Using the program ArcMAP10.1 (ArcGIS 10.1, Esri, Redlands, CA), centroids were then created by obtaining X, Y coordinates for the center of individual census blocks based on a 2000 US Census map for Puerto Rico. The distance from the residential block centroid of a participant to the nearest major road (defined by Esri 2012 Data and Maps major road layer) was then calculated using the

geo-processing proximity tool “near,” which measures the nearest distance “as the crow flies” between two features. Because of the lack of a complete home address, one participant was excluded.[19] As in previous work, residential proximity to a major road at the baseline visit was classified as within 441 meters vs. greater than 441 meters (the first quartile vs. others) [19].

Statistical Analysis

Our control group included subjects who had a normal weight at both study visits (control subjects). We separately compared three groups of subjects to this control group, as follows: 1) those who had overweight or obesity at both study visits (persistent overweight or obesity, our main exposure of interest), 2) those who were overweight or obese at visit 1 but had a normal weight at visit 2, and 3) those who had a normal weight at visit 1 but were overweight or obese at visit 2.

Our outcomes of interest were change in percent predicted lung function measures (FEV_1, FVC, and FEV_1/FVC) and change in total IgE level between the first (baseline) and second study visits, and severe asthma exacerbations in the year prior to the second study visit. Severe asthma exacerbations were defined as at least 1 hospitalization for asthma or at least one visit to the emergency department or urgent care for asthma that required treatment with systemic corticosteroids, or one or more courses of systemic steroids for asthma in the year prior to the second study visit.

Bivariate analyses were conducted using chi-square or Fisher’s exact tests for categorical variables, and analysis of variance for continuous variables. Linear or logistic regression was used for the multivariable analyses of the outcomes of interest. A stepwise approach was used to build the multivariable models. All models were adjusted for parental education (at least one parent had completed high school at the first visit or not) and the time interval between study visits; models for severe asthma exacerbations and change in total IgE levels were additionally adjusted for age and sex; and models for percent predicted (%pred) lung function measures (which already account for age and sex) were additionally adjusted for asthma status. Other covariates considered for inclusion in the multivariable models were annual household income (< vs. ≥$15,000 per year at the first study visit, the median income in Puerto Rico); current exposure to second-hand smoke, prematurity, residential proximity to a major road, and a healthy diet (a dietary score of 1 or 2) at the first study visit; and use of inhaled corticosteroids (ICS) in the 6 months prior to the second study visit. Covariates that were associated at $P < 0.05$ or that changed the effect estimate (β or odds ratio) for persistent overweight or obesity by at least 10% were kept in the model. After the final models were built, we tested for interactions between persistent overweight or obesity and selected covariates (e.g., asthma status for the analysis of lung function and sex for the analysis of severe asthma exacerbations).

SAS version 9.4 (SAS institute, Cary, NC) was used for all analyses.

RESULTS

A comparison of the main characteristics of study participants who were (n=340) and were not (n=66) included in the current analysis is shown in eTable 1 in the e-Supplement. There were no significant differences in overweight or obesity status, percent predicted lung function measures, or any other covariate at the baseline study visit between subjects who were and were not included in this analysis. Among the 223 participants with asthma, those included in this analysis (n=180) were more likely to report a severe asthma exacerbation in the year prior to the initial (baseline) visit than those excluded (56.7% vs. 37.2%, P <0.05), but there was no significant difference in use of ICS prior to the baseline visit (18% vs. 24.2%, P >0.05).

The main baseline characteristics of the 340 study participants are shown in Table 1. Compared to subjects with normal weight at both study visits (control subjects, n=163), those with persistent overweight or obesity (n=108) were more likely to have a higher total IgE level at the baseline visit. There were no significant differences in %pred FEV_1, FVC, FEV_1/FVC, or any other covariate between subjects with persistent overweight or obesity and control subjects at the baseline visit. There were no significant differences between subjects with non-persistent overweight or obesity (i.e., those who were overweight or obese at visit 1 but not at visit 2, and those who were overweight or obese at visit 2 but not at visit 1) and control subjects.

eTable2 shows a comparison of outcomes at the second study visit by overweight or obesity status. Compared to control subjects, those with persistent overweight or obesity were more likely to have a higher total IgE but a lower %pred FEV_1/FVC, and to have had at least one severe asthma exacerbation in the previous year. Non-persistent overweight or obesity was not significantly associated with any outcome at the second study visit.

The results of the unadjusted and adjusted analyses of overweight or obesity and change in percent predicted lung function measures between study visits are shown in Figure 1 and eTable 3. In a multivariable analysis adjusted for parental education, asthma status, and the time interval between study visits, subjects who were persistently overweight or obese had a change in %pred FEV_1 that was 5.07% lower than that observed in control subjects (95% confidence interval [CI] for β: −8.62 to −1.51, P<0.01). Similarly, subjects who were persistently overweight or obese had a change in %pred FEV_1/FVC that was 2.85% lower than that observed in control subjects (95% CI for β = −5.51 to −0.18, P=0.04). There was no significant difference in change in any lung function measure between subjects with non-persistent overweight or obesity and control subjects. We found no significant modification of the estimated effect of persistent overweight or obesity on change in lung function by asthma status (P for interaction >0.10 in all instances).

eTable 4 shows the results of a sensitivity analysis of overweight or obesity and change in lung function after additional adjustment for the corresponding lung function measure at the baseline study visit. Subjects who were persistently overweight/obese had changes in %pred FEV_1 (β= −3.81%, 95% CI= −6.94 to −0.69, P=0.02) and %pred FEV_1/FVC (β= −4.09%, 95% CI: −6.05 to −2.13, P<0.01) that were significantly lower than those observed in control

subjects. There was no significant difference in change in %pred FVC between persistently overweight/obese subjects and control subjects.

Table 2 shows the results of the unadjusted and adjusted analyses of overweight or obesity status and severe disease exacerbations in subjects with asthma. In a multivariable analysis adjusting for age, sex, parental education, residential proximity to a major road, ICS use in the 6 months prior to the second visit, and the time interval between study visits, youth with persistent overweight or obesity had 3.3 times higher odds of ≥1 severe asthma exacerbation in the year prior to the second study visit than control subjects. Moreover, subjects who had normal weight at visit 1 but were overweight or obese at visit 2 had 11.3 times higher odds of ≥1 severe asthma exacerbation in the year prior to the second study visit than control subjects. In this analysis, being overweight or obese at visit 1 but not at visit 2 was not significantly associated with ≥1 severe asthma exacerbation in the year prior to the second study visit.

The result of the analysis of overweight or obesity status and change in total IgE are shown in Table 3. There was no significant association between overweight or obesity status and change in total IgE between study visits.

In a final sensitivity analysis, we excluded 23 subjects who reported a change in asthma status between study visits (including 11 subjects who reported asthma at visit 1 but not at visit 2, and 12 subjects who reported asthma at visit 2 but not at visit 1), obtaining similar results (data not shown).

DISCUSSION

To our knowledge, this is the first study to examine the relation between persistent overweight or obesity and change in lung function measures or severe asthma exacerbations from school age into adolescence. In a cohort of Puerto Rican youth followed from ages 6–14 years to ages 9–20 years, subjects with persistent overweight or obesity (overweight or obesity at both study visits) had changes in FEV_1 and FEV_1/FVC that were lower than those observed in subjects who had normal weight at both study visits (control subjects). Compared with control subjects, those who were persistently overweight or obese had increased odds of severe asthma exacerbations in the year prior to the second study visit.

We also show that subjects with normal weight at the first visit but overweight or obesity at the second visit had increased odds of severe asthma exacerbations at the second study visit. Although this finding suggests that new onset of overweight or obesity is linked to worse asthma morbidity in youth, it must be cautiously interpreted due to small sample size.

Epidemiological studies support a link between obesity and asthma[20 21], but the nature and mechanisms underlying this association over time are less well understood, particularly in children.[22, 23] In a recent meta-analysis, overweight or obesity was associated with lower FEV_1 in cross-sectional studies or in studies examining baseline overweight or obesity against subsequent changes in FEV_1 in adults.[24, 25] In that analysis, overweight or obesity was associated with reduced FEV_1/FVC in children but not in adults. Our findings expand on prior results by showing that overweight or obesity that persists between school age and

adolescence is associated with changes in FEV_1 and FEV_1/FVC that are lower than those observed in control subjects. Although this finding did not differ between youth with and without asthma, we had limited statistical power to detect a modest interaction between persistent overweight/obesity and asthma on FEV_1 or FEV_1/FVC.

Our findings for severe asthma exacerbations are consistent with and expand those of prior cross-sectional studies that showed that overweight or obesity was associated with increased asthma morbidity[7], unscheduled emergency department visits for asthma,[26] and worse asthma control and asthma exacerbations (measured by beta-agonist units dispensed and oral steroid courses prescribed per year) in children.[27] In contrast, Lang et al. found no association between obesity and asthma exacerbations or high treatment burden in a cross-sectional study of ~10,000 children with asthma.[21]

There is conflicting evidence of an association between overweight/obesity and total IgE. Our negative findings are contrary to results from a cross-sectional study of US children aged 2–19 years that reported higher total IgE in overweight and obese youth, but consistent with those of an international multicenter study showing no significant associations between BMI and total IgE in youth[31,32]. Our results suggest that persistent overweight/obesity may negatively impact FEV_1 and FEV_1/FVC through non-allergic mechanisms, including systemic inflammation from pro-inflammatory cytokines in adipose tissue,[22, 23, 28–31] increased Th17 immunity leading to steroid resistance, structural changes in the airways, or metabolic dysregulation.[29, 32–34] For example, we previously showed that metabolic syndrome was associated with lower FEV_1/FVC in a cross-sectional study of over 1,400 US adolescents with and without asthma, though the effect estimates were stronger in subjects with asthma.[30]

We recognize additional study limitations. First, selection bias is possible in any observational study. However, selection bias is an unlikely explanation for our findings, as there was no difference in persistent overweight/obesity or lung function measures between children who were and were not included in this analysis. Second, we had a limited assessment of the dietary profiles of study participants. Third, we had no data on some potential confounders or modifiers of the relation between persistent overweight/obesity and asthma, including adherence with controller medications and indoor pollutants. Although we lacked data on asthma severity, our findings were unchanged in analyses adjusted for use of ICS (a marker of disease severity among children with asthma in Puerto Rico).

In a cohort of Puerto Rican youth followed for ~5 years, persistent overweight or obesity was associated with changes in FEV_1 and FEV_1/FVC than were lower than those observed in subjects with consistently normal weight. Moreover, persistent overweight or obesity and overweight or obesity at the second study visit were associated with severe asthma exacerbations in this cohort. Our results support health policies aiming to promote a healthy diet and physical activity to prevent overweight or encourage weight loss to reduce the impact of “obese asthma” in Puerto Rican children and other underserved minority children.[28]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of interest: Dr. Celedón has received research materials from GSK and Merck (inhaled steroids) and Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in NIH-funded studies, unrelated to this work. The other authors have no conflicts of interest to declare.

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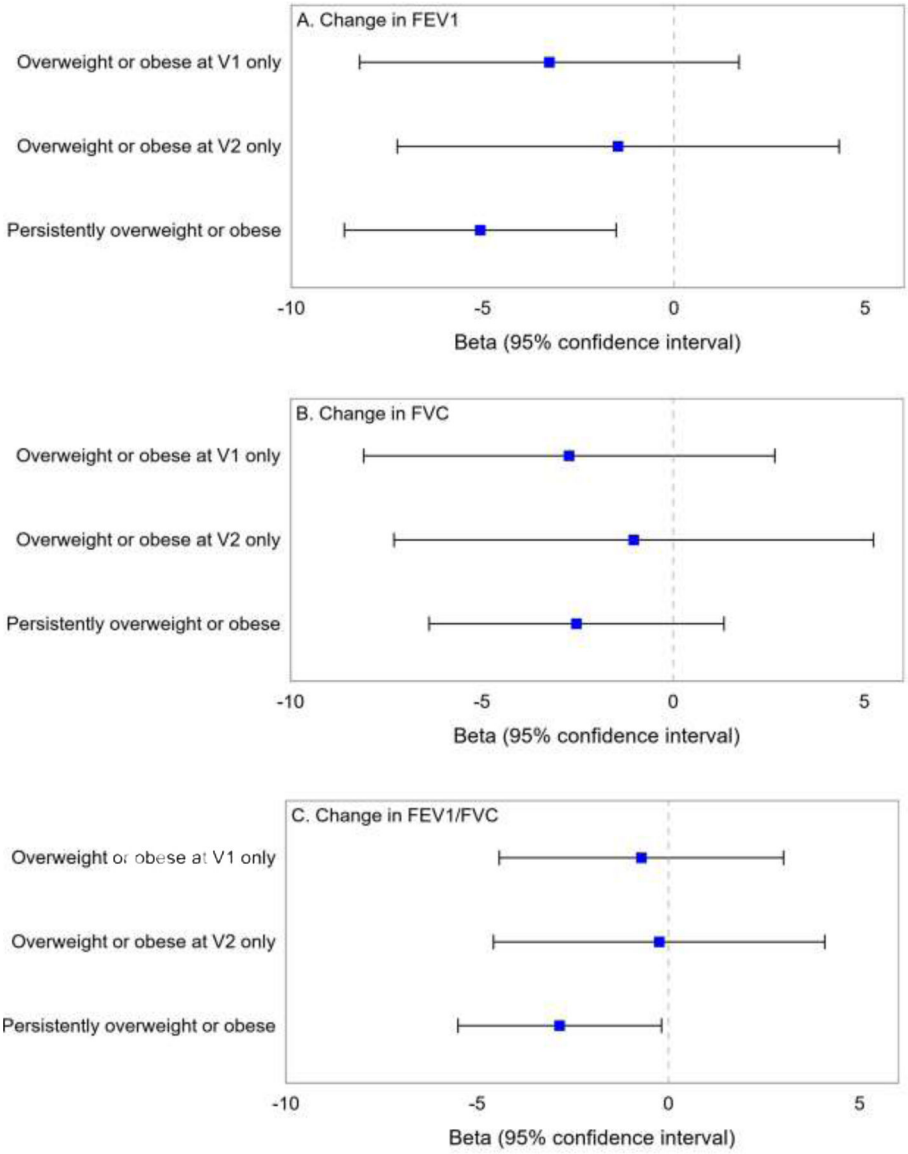

Figure 1. Multivariable Linear Regression Analysis of Overweight or Obesity and Change in Lung Function Measures.

Footnote: %pred=percent predicted; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity. Beta represents the difference in change in lung function between each weight group compared with the control group (subjects who had a normal weight at both visits). Models were adjusted for asthma status, parental education, and the time interval between study visits.

Table 1.

Main characteristics of study participants at the baseline study visit (n=340)

Variables	Normal weight at both visits (control group, n=163)	Overweight or obesity at visit 1 only (n=41)	Overweight or obesity at visit 2 only (n=28)	Persistent overweight or obesity (n=108)
Age in years	10.1 ± 2.7	9.7 ± 2.2	9.7 ± 2.8	9.9 ± 2.5
Male sex	95 (58.3)	21 (51.2)	11 (39.3)	56 (51.9)
Asthma	75 (46.0)	25 (61.0)	15 (53.6)	65 (60.2)
Household income < $15,000 per year	107 (69.0)	23 (60.5)	18 (66.7)	61 (57.0)
At least one parent completed High School	121 (74.2)	33 (80.5)	23 (82.1)	93 (86.1)
Current exposure to second-hand smoke	58 (35.6)	18 (43.9)	16 (57.1)	37 (34.3)
Prematurity	6 (3.7)	2 (4.9)	1 (3.6)	12 (11.3)
Residential proximity to (within 441 meters of) a major road	125 (77.2)	34 (82.9)	23 (82.1)	82 (75.9)
Healthy diet	96 (58.9)	25 (61.0)	17 (60.7)	71 (65.7)
%predicted FEV_1	93.6 ± 16.7	96.0 ± 15.2	90.0 ± 16.8	96.1 ± 13.5
%predicted FVC	100.9 ± 17.5	104.3 ± 15.7	98.2 ± 16.3	105.3 ± 15.2
%predicted FEV_1/FVC	92.8 ± 10.7	92.1 ± 10.2	91.2 ± 11.1	91.0 ± 7.7
Log10 total IgE	2.3 ± 0.7	2.3 ± 0.6	2.1 ± 0.6	2.5 ± 0.6 *
≥1 severe asthma exacerbation in the prior year †	38 (50.7)	15 (60.0)	10 (66.7)	39 (60.0)
Time interval between study visits (years)	5.4 ± 0.8	5.2 ± 0.8	5.3 ± 1.1	5.3 ± 0.9

Results reported as n (%) for binary variables or mean ± standard deviation for continuous variables

* $p < 0.05$ for the comparison with the control group.

† Among subjects with asthma (n=180).

Table 2.

Analysis of overweight or obesity and at least one severe asthma exacerbation in the year prior to the second study visit

	Unadjusted	Adjusted**
Variables	**Odds ratio (95% confidence interval), P-value**	
Overweight or obese *		
Overweight or obese at Visit 1	1.5 (0.3 to 6.4), 0.60	1.6 (0.3 to 8.1), 0.60
Overweight or obese at Visit 2	**9.0 (2.4 to 33.7), <0.01**	**11.3 (2.4 to 53.1), <0.01**
Persistently overweight or obese	**3.3 (1.2 to 9.1), 0.02**	**3.3 (1.0 to 10.6), 0.04**
At least one parent completed High School	-	1.2 (0.3 to 5.1), 0.82
Residential proximity to (within 441 meters of) a major road	-	4.6 (0.9 to 24.5), 0.07
Use of inhaled corticosteroids in the 6 months prior to the second visit	-	3.1 (1.1 to 8.6), 0.03

* Compared to a control group including subjects who had normal weight at both visits

** The multivariable model was adjusted for age, sex, and the time interval between study visits, in addition to all covariates listed in the column.

Table 3:

Analysis of Overweight or Obesity and Change in Log_{10} Total IgE Between Study Visits

Variables	Unadjusted	Model 1	Model 2
	β (95% confidence interval): *P* value		
Overweight or obesity[a]			
Overweight or obese at visit 1 only	0.03 (−0.09 to 0.15): .61	0.03 (−0.10 to 0.15); .67	0.03 (−0.08 to 0.15): .58
Overweight or obese at visit 2 only	0.01 (−0.14 to 0.15); .92	0.001 (−0.14 to 0.15); .99	−0.03(−0.17 to 0.11): .65
Persistently overweight or obese	0.01 (−0.08 to 0.10): .80	0.01 (−0.08 to 0.10); .87	0.04 (−0.04 to 0.13): .32
At least 1 parent completed high school	–	−0.03 (−0.13 to 0.07): 57	−0.04 (−0.13 to 0.05); .38
Asthma	–	−0.02 (−0.10 to 0.06): .63	0.01 (−0.06 to 0.09): .72
Healthy diet	–	**0.09 (0.01–0.17); .03**	**0.09 (0.010–0.16); .03**
Log_{10} total IgE level at baseline study visit	–	–	**−0.17 (−0.23 to−0.12); < .01**

Abbreviation: IgE. immunoglobulin E.

NOTE. Model 1 was adjusted for age. sex. and the time interval between study visits, in addition to all covariates listed in the column. Model 2 was also adjusted for the log_{10} total IgE level at baseline.

[a]Compared with a control group including subjects who had normal weight at both visits.