Decreased response to inhaled steroids in overweight and obese asthmatic children

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Background: The mechanisms and consequences of the observed association between obesity and childhood asthma are unclear.

Objectives: We sought to determine the effect of obesity on treatment responses to inhaled corticosteroids in asthmatic children.

Methods: We performed a post hoc analysis to evaluate the interaction between body mass index (BMI) and treatment with inhaled budesonide on lung function in the Childhood Asthma Management Program trial. Participants were then stratified into overweight/obese and nonoverweight groups, and their response to inhaled budesonide was analyzed longitudinally over the 4 years of the trial.

Results: There was a significant interaction between BMI and budesonide for prebronchodilator FEV1/forced vital capacity (FVC) ratio (P = .0007) and bronchodilator response (BDR; P = .049) and a nonsignificant trend for an interaction between BMI and budesonide on prebronchodilator FEV1 (P = .15). Nonoverweight children showed significant improvement with inhaled budesonide in lung function (FEV1, FEV1/FVC ratio, and BDR) during the early (years 1-2) and late (years 3-4) stages of the trial. Overweight/obese children had improved FEV1 and BDR during the early but not the late stage of the trial and showed no improvement in FEV1/FVC ratio. When comparing time points at which both groups showed a significant response, the degree of improvement among nonoverweight children was significantly greater than in overweight/obese children at most visits. Nonoverweight children had a 44% reduction in the risk of emergency department visits or hospitalizations throughout the trial (P = .001); there was no reduction in risk among overweight/obese children (P = .97).

Conclusions: Compared with children of normal weight, overweight/obese children in the Childhood Asthma Management Program showed a decreased response to inhaled budesonide on measures of lung function and emergency department visits/hospitalizations for asthma. (J Allergy Clin Immunol 2011;127:741-9.)

Key words: Asthma, obesity, pediatric asthma, childhood obesity, budesonide

Asthma and obesity are major public health concerns. Over the last few decades, the prevalence of both diseases has increased worldwide.1-4 In the United States the prevalence of overweight status increased from 6.5% to approximately 19% in school-aged children between 1976-1980 and 2003-2004.5,6 There is ample evidence of an association between obesity and asthma in children and adults.7-15 A recent meta-analysis of 12 longitudinal studies found that children with high birth weight, body mass index (BMI), or both had an increased risk of asthma.7 The mechanisms underlying the association between obesity and asthma are incompletely understood but might include genetic predisposition, abnormal immune modulation and/or a proinflammatory state in obese subjects, hormonal influences, and mechanical effects. For example, certain studies have reported decreased FEV1 and forced vital capacity (FVC) in morbidly obese adult asthmatic subjects, a restrictive deficit likely caused by the increased amount of adipose tissue in the chest wall and the abdominal cavity.9,16

Little is known about treatment responses in children with asthma who are overweight or obese. Because obesity might promote inflammation, we hypothesized that overweight/obese asthmatic subjects would have suboptimal responses to anti-inflammatory medications compared with those of nonoverweight/nonobese asthmatic subjects. In this report we demonstrate that the effect of inhaled budesonide on lung function and clinical outcomes is reduced in overweight or obese asthmatic children compared with that seen in nonoverweight asthmatic children.

METHODS

Study population

The Childhood Asthma Management Program (CAMP) study is a randomized clinical trial that enrolled 1,041 children with asthma between 1993 and 1995. A detailed description of the trial has been previously published.17 Inclusion criteria were age 5 to 12 years, a history of asthma for at least 6 months in the previous year, mild-to-moderate asthma severity, and airway responsiveness to 12.5 mg/mL or less of methacholine. Subjects were randomly assigned to one of 3 inhaled treatment arms (200 μg of budesonide twice daily, 8 mg of nedocromil twice daily, or placebo twice daily) and were followed.

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RESULTS

Baseline characteristics of the study population are presented in Table I. As expected from randomization, there were no differences in most subjects’ characteristics among treatment arms at baseline within each BMI group (overweight/obese vs nonoverweight). However, serum vitamin D levels were slightly higher in children receiving inhaled budesonide than in those receiving inhaled placebo or nedocromil regardless of BMI group. The mean age of the 1,041 participating children was 8.9 years, with a mean duration of asthma of approximately 6 years and a mean BMI of 63.2%. Of these, 1,041 children, approximately 60% were male and approximately 68% were white. As expected in a study of children with mild-to-moderate asthma, the mean prebronchodilator FEV₁ was normal (93.7% of predicted value), but the mean FEV₁/FVC ratio was slightly reduced (79.6%); the mean BDR was 10.8% of baseline FEV₁.

Of the 1,027 participating children who had data for BMI at randomization, 322 (31.4%) were overweight/obese (176 were overweight and 146 were obese). Compared with nonoverweight children, overweight/obese children were more likely to be African American (P = .002), to be older (by approximately 0.4 years, P = .002) and taller (by approximately 6 cm, P < .0001), and to have a longer duration of asthma symptoms (by approximately 0.3 years, P = .02), a lower FEV₁/FVC ratio (approximately 1.1% lower, P = .046), and a lower vitamin D level. There were no differences in total IgE levels or eosinophil counts between the BMI groups or the treatment arms.

Table II summarizes the adjusted longitudinal analysis of the relations among BMI, treatment with inhaled budesonide, and lung function. Both BMI (as a continuous variable) and treatment arm (budesonide vs placebo/nedocromil) had significant effects on lung function. Beyond those effects, there was a significant interaction between BMI and budesonide (BMI*budesonide) on FEV₁/FVC ratio and BDR and a nonstatistically significant trend on percent predicted FEV₁ (P = .15). This means that, among children treated with budesonide, each 1% increase in BMI would diminish their response to budesonide treatment by approximately 0.04% in terms of FEV₁/FVC ratio (95% CI, 0.02-0.06) and by approximately 0.025% in terms of BDR (95% CI, 0.0001-.0.05).

Fig 1 depicts the mean responses to inhaled budesonide (assessed based on percent predicted FEV₁, FEV₁/FVC ratio, and BDR) from randomization to month 48 of the trial stratified by BMI group (overweight/obese vs nonoverweight). Nonoverweight children showed a significant improvement in all of the

every 4 months for 4 years. The institutional review board at each of the participating centers approved the study, and parents or guardians of the participating children provided informed consent. The present study is a post hoc analysis using data from CAMP.

**Pulmonary function tests**

Spirometric testing was performed according to American Thoracic Society criteria. The completion rate for lung function measures during the trial was approximately 94%.

**Serum 25-hydroxy vitamin D₃ (vitamin D)**

Measurement of serum 25-hydroxyvitamin D (vitamin D) was performed on all subjects by using sera banked at the start of the trial. Levels were log₁₀ transformed for analysis.

**Outcome measures**

Our main outcomes were prebronchodilator FEV₁ and FEV₁/FVC ratio and bronchodilator response (BDR). BDR was defined as the percentage change in FEV₁ from baseline ([post-FEV₁ − pre-FEV₁]/pre-FEV₁). Secondary asthma-related outcomes included the number of prednisone bursts and the number of emergency department (ED)/urgent care visits and hospitalizations reported for each visit interval during the trial.

**Overweight/obese status**

The Centers for Disease Control and Prevention defines “overweight” as having a BMI of the 85th percentile or greater for age and sex, and “obesity” is defined as a BMI of the 95th percentile or greater. To attain maximal power and because of clinical considerations, we grouped both categories into one: participants were classified as “overweight/obese” if their randomization BMI was the 85th percentile or greater and as “nonoverweight” if it was less than the 85th percentile. BMI data were available for 1,027 (98.7%) participants.

**Statistical analysis**

We analyzed data for each outcome from randomization through month 48 after randomization. As previously done, the placebo and nedocromil treatment arms were combined into one because of lack of effect of nedocromil on lung function and to maximize statistical power. All multivariate analyses were adjusted for age and height at randomization, sex, race/ethnicity, duration of asthma (Age at randomization − Self-reported age of onset of asthma symptoms), environmental tobacco smoke exposure in early life (parental report of environmental tobacco smoke exposure in the child’s household during the first approximately 5 years of life from birth to first grade), vitamin D level (at randomization), and study center.

To assess the longitudinal effect of inhaled budesonide on lung function over the 4-year course of the trial, we used mixed-effects regression models, incorporating all available measurements. Residual maximum likelihood estimation with a spatial-exponential covariance structure was used because measurements were obtained at different intervals. Fixed-effects test statistics were adjusted by using the “sandwich” error estimator. P values for the overall effect of treatment arm are from χ² tests with n-1 degrees of freedom, where n is the number of measurements for each outcome; the overall longitudinal effect was divided into an early stage (months 0-20) and a late stage (months 24-48) of the trial. When reported, P values at each time point are from t tests within the mixed-effects regression model. For count data (prednisone bursts) and binary outcomes (ED visits/hospitalizations), we used marginal logistic regression models with Poisson distribution and marginal log-linear regression models, respectively.

The initial longitudinal analysis included the main effects for BMI (as a continuous variable) and treatment arm (budesonide vs placebo/nedocromil), as well as an interaction term (BMI*budesonide), to assess the interaction between BMI and budesonide beyond their main effects. Once the significance of the interaction was established, all subsequent analyses were performed by stratifying children according to their BMI, as above, to maximize power and to present data based on a clinically relevant definition. All analyses were performed with SAS version 9.1 software (SAS Institute, Inc, Cary, NC).
outcomes (FEV₁, FEV₁/FVC ratio, and BDR) during the early (months 0-20) and late (months 24-48) stages of the trial. Among overweight/obese children, there was significant improvement in FEV₁ and BDR during the early stage of the trial but not thereafter. Overweight/obese children had no improvement in FEV₁/FVC ratio at any point during follow-up.

We then analyzed the magnitude of improvement with budesonide at each time point (Table III). During the early stage of the trial (0-20 months), nonoverweight children had a significant improvement with inhaled budesonide: FEV₁ improved by 5.1% to 5.8% of predicted value, FEV₁/FVC ratio improved by 2.8% to 3.5%, and BDR decreased by 2.3% to 3.8%. Among overweight/obese children, inhaled budesonide produced a significant improvement in FEV₁ (approximately 3.5% to 3.9% of predicted value) but not in FEV₁/FVC ratio or BDR during the early stage of the trial. During the late stage of the trial (24-48 months), nonoverweight children continued to show a significant improvement: FEV₁ improved by 2.5% to 3.7% of predicted value, FEV₁/FVC ratio improved by 2.1% to 2.8%, and BDR decreased by 1.5% to 2.4%. In contrast, overweight/obese children showed no significant response to inhaled budesonide at any point in the late stage of the trial. At most time points, the improvement in the nonoverweight group was significantly greater than the improvement among the overweight/obese children.

The effect of inhaled budesonide on asthma-related outcomes after stratification by BMI group is shown in Fig 2. Nonoverweight children receiving inhaled budesonide had a significant overall reduction in the number of prednisone bursts reported at each visit (P < .0001). When evaluating individual visits by nonoverweight children during the trial, there was a significant decrease in the number of prednisone bursts in the budesonide arm at months 4, 8, 12, 16, 20, 28, and 32: nonoverweight children receiving inhaled budesonide received 32% to 55% fewer prednisone bursts than children receiving inhaled placebo/ nedocromil across these visits (95% CI, 0.5% to 74%). Among overweight/obese children, the overall effect of inhaled budesonide on reducing prednisone bursts was also significant (P = .001). When evaluating individual visits by overweight/obese children during the trial, children receiving inhaled budesonide reported a 58% (95% CI, 14% to 79%) reduction in prednisone bursts at month 24 compared with that seen in children receiving inhaled nedocromil or placebo; there was no significant difference in prednisone bursts between the treatment arms at the other time points.

For the interval incidence of ED visits/hospitalizations, the effect of inhaled budesonide among nonoverweight children was significant: the risk of requiring an ED visit or hospital admission between visits throughout the trial was reduced by approximately 44% (95% CI, 20.7% to 60.9%; P = .001). In contrast, among overweight/obese children, there was no significant difference in ED visits or hospital admissions between the treatment arms (P = .97).

**DISCUSSION**

To our knowledge, this is the first report of modification of the effect of inhaled corticosteroids on pediatric asthma control by overweight/obesity status. Among children in a large multicenter

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**TABLE I. Characteristics of study participants at randomization**

<table>
<thead>
<tr>
<th></th>
<th>Nonoverweight</th>
<th>Overweight/obese</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Budesonide</td>
<td>Placebo/nedocromil</td>
<td>All</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
<td>Placebo/nedocromil</td>
<td>All</td>
</tr>
<tr>
<td>No.</td>
<td>205</td>
<td>500</td>
<td>705</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9.0 (2.04)</td>
<td>8.7 (2.12)</td>
<td>8.8 (2.10)*</td>
</tr>
<tr>
<td>Duration of asthma (y)</td>
<td>5.9 (2.5)</td>
<td>5.7 (2.6)</td>
<td>5.8 (2.6)*</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>59</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>Race (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>70</td>
<td>73</td>
<td>72*</td>
</tr>
<tr>
<td>African American</td>
<td>11</td>
<td>11</td>
<td>11*</td>
</tr>
<tr>
<td>Hispanic/other</td>
<td>19</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Tobacco exposure (%)</td>
<td>38</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>BMI (percentile)</td>
<td>50.4 (22.8)</td>
<td>48.8 (23.7)</td>
<td>49.3 (23.5)*</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>16.5 (1.5)</td>
<td>16.3 (1.6)</td>
<td>16.4 (1.6)*</td>
</tr>
<tr>
<td>BMI (absolute)</td>
<td>132.5 (12.8)</td>
<td>131.2 (13.5)</td>
<td>131.5 (13.3)*</td>
</tr>
<tr>
<td>Pre-FEV₁ (% predicted)</td>
<td>93.2 (14.7)</td>
<td>93.7 (13.9)</td>
<td>93.6 (14.1)</td>
</tr>
<tr>
<td>Pre-FEV₁/FVC ratio (%)</td>
<td>79.9 (8.8)</td>
<td>80.0 (8.3)</td>
<td>80.0 (8.4)*</td>
</tr>
<tr>
<td>BDR (FEV₁ % change)</td>
<td>11.9 (11.4)</td>
<td>10.8 (10.0)</td>
<td>11.1 (10.4)</td>
</tr>
<tr>
<td>Vitamin D (log₁₀)</td>
<td>1.58 (0.17)†</td>
<td>1.54 (0.19)</td>
<td>1.55 (0.18)*</td>
</tr>
<tr>
<td>Total IgE (IU/mL)</td>
<td>398 (145-1,072)</td>
<td>452 (186-1,259)</td>
<td>427 (178-1,175)</td>
</tr>
<tr>
<td>Eosinophils (cells/mm³)</td>
<td>398 (200-653)</td>
<td>407 (200-646)</td>
<td>398 (200-647)</td>
</tr>
<tr>
<td>Compliance§</td>
<td>1.05 (0.26)</td>
<td>1.08 (0.33)</td>
<td>1.07 (0.32)</td>
</tr>
<tr>
<td>Household income</td>
<td>3.1 (0.98)</td>
<td>3.1 (0.90)</td>
<td>3.1 (0.92)</td>
</tr>
<tr>
<td>Parental education level¶</td>
<td>5.2 (0.80)</td>
<td>5.2 (0.86)</td>
<td>5.2 (0.84)</td>
</tr>
</tbody>
</table>

Numbers shown are means (SDs) for continuous variables and percentages of subjects in groups for categorical variables. Categorical variables: §Subjective report of compliance by the treating physician (most of the time, some of the time, or rarely). ||Yearly combined household income (<$15,000, $15,000-$30,000, $30,000-$50,000, or >$40,000). ¶Highest parental education level (<8th grade, completed 8th grade, some high school, completed high school, some college or post-high school training, or completed college).

*P < .05 for the comparison by BMI group (all subjects).

†P < .05 for the comparison by treatment arm (budesonide vs placebo/nedocromil) within each BMI group.

||Presented as medians (interquartile ranges) and analyzed as log₁₀.
Many mechanisms have been suggested to explain the relationship between asthma and obesity. Studies in morbidly obese adult asthmatic subjects have reported symmetrically reduced FEV$_1$ and FVC values with a normal FEV$_1$/FVC ratio, pointing toward a restrictive pattern that could explain increased dyspnea and other symptoms based on mechanical effects. However, some pediatric studies have found that overweight asthmatic children have low FEV$_1$/FVC ratios compatible with an obstructive deficit. We found a similar pattern, with overweight/obese children in CAMP showing low FEV$_1$/FVC ratios. More importantly, inhaled budesonide failed to improve the obstructive deficit observed in these children.

There is increasing evidence of shared genetic determinants of asthma and obesity. The genes for the β$_2$-adrenergic (ADRB2) and glucocorticoid (NR3C1) receptors are located on chromosome 5q and have been implicated in pathways related to both asthma and obesity. Recentely, the gene for protein kinase Cα (PRKCA) was reported to be associated with both asthma and BMI. Similarly, different genetic polymorphisms could reduce the efficacy of inhaled steroids by conferring obese asthmatic subjects higher resistance, lower receptor binding, and/or lower retention of medication in the lung.

There also is evidence of a generalized proinflammatory state in obesity, with levels of several cytokines and chemokines increased in obese subjects. TFN-α and IL-6 are produced by adipocytes and correlate with total body fat, and TNF-α increases production of IL-6 and IL-1β, levels of which are increased in both obesity and asthma. Adipose tissue can express other proinflammatory molecules, such as TGF-β1, which has also been linked to asthma and asthma exacerbations. Similarly, polymorphisms of the fractalkine CX3CR1 receptor have been linked with asthma, atopy, and obesity.

Inhaled steroids might be less effective in overweight and obese asthmatic subjects, in whom the inflammatory state might have a systemic component rather than being confined to the airways. Peters-Golden et al reported a decreased effect of inhaled beclomethasone on asthma control days and nighttime awakenings for asthma with increasing BMI, whereas the response to oral montelukast was not affected. The β$_2$-isofrom of the glucocorticoid receptor (GRβ) has been associated with steroid resistance in subjects with asthma. GRβ does not activate glucocorticoid-responsive genes, but it strongly inhibits the activation of such genes by GRα, which is the active isoform. Cytokines associated with obesity, such as TFN-α and IL-6, regulate GR expression with accumulation of GRβ. Sutherland et al demonstrated that increasing BMI in asthmatic subjects produced a decreased in vitro response to glucocorticoids (eg, blunted inhibition of mitogen-activated protein kinase phosphatase 1 and a consequent increase in TNF-α levels) both in blood mononuclear cells and in bronchoalveolar lavage cells, with no such effect in nonasthmatic control subjects.

Clinical trial, nonoverweight children had more consistent and significant effects of inhaled budesonide on measures of lung function and asthma morbidity than overweight/obese children.

FEV$_1$ and FEV$_1$/FVC ratio are widely used in clinical practice and constitute one of the components of the “Guidelines for the diagnosis and management of asthma” from the National Heart, Lung, and Blood Institute to assess asthma severity and asthma control and to adjust management.

TABLE II. Longitudinal analysis of the relation among BMI, use of inhaled budesonide, and measures of lung function

<p>| P values from adjusted longitudinal analysis | |</p>
<table>
<thead>
<tr>
<th>FEV$_1$ (% predicted)</th>
<th>FEV$_1$/FVC ratio</th>
<th>BDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time†</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Budesonide‡</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI (percentile)</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BMI*budesonide</td>
<td>.15</td>
<td>.0007</td>
</tr>
<tr>
<td>Sex</td>
<td>&lt;.0001</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>.02</td>
<td>.29</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>.002</td>
<td>.003</td>
</tr>
<tr>
<td>Duration of asthma</td>
<td>.07</td>
<td>.004</td>
</tr>
<tr>
<td>Tobacco exposure</td>
<td>.02</td>
<td>.91</td>
</tr>
<tr>
<td>Race§</td>
<td>.56</td>
<td>.19</td>
</tr>
<tr>
<td>Hispanic/Other</td>
<td>.009</td>
<td>.96</td>
</tr>
<tr>
<td>Vitamin D (log10)</td>
<td>.03</td>
<td>.92</td>
</tr>
</tbody>
</table>

| P values from adjusted longitudinal analysis | |
|---|---|---|
| Age | .02 | .91 | .6 |
| Duration of asthma | .07 | .004 | .005 |
| Tobacco exposure | .02 | .91 | .6 |

| Shown are the P values for each variable from the adjusted longitudinal analysis. The interaction between BMI (as a continuous variable) and treatment with budesonide is shown in boldface. Both budesonide and BMI had significant effects on all 3 lung function measures (P < .05), as do some of the covariates. There was a significant interaction between budesonide treatment and BMI (budesonide*BMI) for FEV$_1$/FVC and BDR.

*Prebronchodilator FEV$_1$ and FEV$_1$/FVC ratio.
†As months of follow-up during CAMP.
‡Effect of budesonide compared with placebo/nelcromil.
§Compared with non-Hispanic white subjects.
All models were adjusted for all of the variables listed in the first column.

Moreover, we performed an exploratory analysis including only children who belonged to the same BMI category at all time points and excluding all children whose BMI crossed the 85th percentile at any time during the trial: the effects seen on FEV$_1$ in the overweight/obese group at months 2, 4, 12, and 16 became nonsignificant, whereas all time points remained significant and of the same magnitude for the nonoverweight group (data not shown). Although this exploratory analysis needs to be interpreted with caution, it suggests that the initial response seen for FEV$_1$ in overweight/obese asthmatic subjects might have been driven by a subgroup of children who were “incorrectly” classified as overweight/obese but who had normal BMI after randomization.

Clinical trial, nonoverweight children had more consistent and significant effects of inhaled budesonide on measures of lung function and asthma morbidity than overweight/obese children.

FEV$_1$ and FEV$_1$/FVC ratio are widely used in clinical practice and constitute one of the components of the “Guidelines for the diagnosis and management of asthma” from the National Heart, Lung, and Blood Institute to assess asthma severity and asthma control and to adjust management.

Decreased inhaled corticosteroid response in terms of FEV$_1$ and FEV$_1$/FVC ratio has been reported in adults followed for 6 to 12 months. In our study children of normal weight receiving inhaled budesonide showed a significant improvement in FEV$_1$, FEV$_1$/FVC ratio, and BDR throughout the 4 years of the trial. Overweight/obese children had an improvement in FEV$_1$ that was of lesser magnitude, and it was limited to the first half of the trial; they also showed no improvement in their FEV$_1$/FVC ratio. By the latter half of the trial, overweight/obese children showed no improvement in any of the measures of lung function. A secondary analysis with BMI values for each variable from the adjusted longitudinal analysis. The interaction between BMI (as a continuous variable) and treatment with budesonide is shown in boldface. Both budesonide and BMI had significant effects on all 3 lung function measures (P < .05), as do some of the covariates. There was a significant interaction between budesonide treatment and BMI (budesonide*BMI) for FEV$_1$/FVC and BDR.

*Prebronchodilator FEV$_1$ and FEV$_1$/FVC ratio.
†As months of follow-up during CAMP.
‡Effect of budesonide compared with placebo/nelcromil.
§Compared with non-Hispanic white subjects.
||All models were adjusted for all of the variables listed in the first column.
in mice exposed to inhaled allergens.\textsuperscript{43} Recently, Kattan et al\textsuperscript{44} reported that adiponectin was associated with increasing FEV1/FVC ratios and decreasing asthma symptoms and exacerbations in asthmatic teenage male subjects. Our group has reported that reduced vitamin D levels are associated with asthma severity\textsuperscript{45} and that vitamin D levels differ between lean and obese subjects.

Accordingly, we showed decreased serum levels of vitamin D among overweight/obese participants, and these levels were significantly associated with some of our outcomes. However, the interaction between BMI and budesonide remained significant after adjustment for vitamin D levels.

Medication compliance plays an important role in asthma control.\textsuperscript{46} Gamble et al\textsuperscript{47} reported that up to 35% of patients with

![FIG 1. Effect of budesonide on measures of lung function and BDR by BMI group. A, Pre-FEV1 (percent predicted). B, Pre-FEV1/FVC ratio. C, BDR. Budesonide is shown as blue diamonds, and placebo and nedocromil are shown as red squares. Solid lines indicate time points where the difference between treatment arms was significant. Nonsignificant visits are shown as dotted lines. Stars show points where there was a significant difference between arms and from baseline values. Arrows and \textit{P} values are for overall longitudinal effect of budesonide over months 0 to 20 or 24 to 48 compared with baseline values.](image)
severe asthma filled less than 50% of their inhaled medication prescriptions. Although they did not find a difference in compliance between obese and nonobese asthmatic subjects, obesity is associated with depression and other factors\(^48,49\) that could decrease compliance with asthma medications. However, our results were unchanged by further adjustment for medication compliance (as reported by the child or the CAMP physician) or indicators of socioeconomic status.

Despite our incomplete understanding of the mechanisms involved, overweight and obese asthmatic subjects report a higher prevalence and severity of symptoms than nonoverweight asthmatic subjects.\(^7,50\) In our analysis nonoverweight children receiving budesonide had a significant decrease in the number of prednisone courses between visits when looking at either the overall effect over time or at individual visits. Overweight/obese children had an overall accumulated improvement over time, but only 1 visit (at 24 months) showed significant interval improvement. Finally, children of normal weight had a significant reduction in the incidence of ED visits and hospitalizations during the trial, whereas there was no improvement in the overweight/obese group.

Of interest, overweight/obese children receiving placebo had a steady increase in percent predicted FEV\(_1\) during the 4 years of the trial (ie, FEV\(_1\) increased approximately 0.5%/y from approximately 94% to approximately 96%, whereas children of normal weight had stable levels at approximately 93% to 94%). Rather than an improvement in overweight/obese asthmatic subjects, this might represent residual confounding by BMI in the equations used to calculate predicted values. Current pediatric reference values might thus underestimate the effect of high BMI on lung function.

There are several limitations to this study. First, this is a post hoc analysis of a randomized clinical trial. Bias could thus be present of which we are not aware. For example, children were not randomized based on their BMI status; there might be other

### TABLE III. Improvement in lung function in the budesonide arm at each visit

<table>
<thead>
<tr>
<th>Month of follow-up</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>12</th>
<th>16</th>
<th>24</th>
<th>28</th>
<th>36</th>
<th>40</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV(_1) (% predicted)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonoverweight</td>
<td>NS</td>
<td>5.4*</td>
<td>5.3*</td>
<td>5.8</td>
<td>5.1</td>
<td>3.3*</td>
<td>2.5*</td>
<td>3.7</td>
<td>2.5*</td>
<td>3.3*</td>
</tr>
<tr>
<td>Overweight</td>
<td>NS</td>
<td>3.6</td>
<td>3.9</td>
<td>3.7</td>
<td>3.5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>FEV(_1)/FVC ratio (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonoverweight</td>
<td>NS</td>
<td>2.9*</td>
<td>2.8*</td>
<td>3.5*</td>
<td>3.1*</td>
<td>2.5*</td>
<td>2.1*</td>
<td>2.8*</td>
<td>2.1*</td>
<td>2.1*</td>
</tr>
<tr>
<td>Overweight</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td><strong>BDR (% FEV(_1))</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonoverweight</td>
<td>NS</td>
<td>−2.3</td>
<td>−2.4</td>
<td>−3.8*</td>
<td>−3.5*</td>
<td>−2.4*</td>
<td>−1.5*</td>
<td>−2.3*</td>
<td>−1.8*</td>
<td>−1.9*</td>
</tr>
<tr>
<td>Overweight</td>
<td>NS</td>
<td>−2.4</td>
<td>−2.9</td>
<td>−2.9</td>
<td>−3.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Predicted improvement in lung function with budesonide (compared with placebo nedocromil) at each individual visit based on means from multivariate mixed effects regression models is shown. NS, No statistically significant improvement with budesonide at that time point. \(\*P < .05\) for comparison between the improvement in the overweight versus nonoverweight groups (\(t\) test for the difference of the means from the longitudinal models assuming all other covariates are equal).

![FIG 2. Effect of budesonide on asthma-related outcomes by overweight status. Lines represent the difference between treatment arms (Budesonide – Placebo/nedocromil; negative numbers indicate an improvement in the budesonide arm compared with the nonbudesonide arm). The overweight/obese group is shown as orange circles, and the nonoverweight group is shown as green triangles. A, Average number of prednisone courses per patient since the previous visit. B, Percentage of children reporting any urgent care visits or hospital admissions. Note: Solid lines/symbols represent visits where the difference was significant, and nonsignificant time points are shown as dotted lines.](image-url)
unmeasured characteristics that account for our findings. The probability of a type I error in subgroup analysis increases significantly with the number of subgroups tested.51

Second, CAMP excluded children with severe asthma, and thus we had limited ability to evaluate modification of the effect of inhaled budesonide by BMI in these children. Similarly, given that the budesonide doses were predetermined in the trial, we could not assess whether higher doses would have been effective in overweight children. Although frequent systemic steroid use in subjects with poorly controlled asthma can lead to being overweight, this is an unlikely explanation for our findings because there was no difference in the number of days receiving oral corticosteroids in the 6 months before the study between overweight and nonoverweight children (2.6 ± 4.9 vs 2.9 ± 5.1, P = .43).

Finally, our power to assess small differences in the overweight/obese subgroup might have been suboptimal, particularly for binary and count data, such as hospitalizations or number of prednisone courses.

In summary, we found that the effect of budesonide on measures of lung function and clinical outcomes among overweight/obese asthmatic children was of lesser significance, magnitude, or both than in nonoverweight children with asthma. The treatment of asthma in overweight/obese children might require new approaches, such as simultaneous management of obesity, treatment of systemic inflammation, or both.

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CAMP CREDIT ROSTER
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Clinical implications: Overweight/obese asthmatic children have a decreased response to inhaled steroids. Management of these children might require other treatment approaches, such as weight management.

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