ORIGINAL ARTICLE

Obesity and Airway Dysanapsis in Children with and without Asthma

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Abstract

Rationale: For unclear reasons, obese children with asthma have higher morbidity and reduced response to inhaled corticosteroids.

Objectives: To assess whether childhood obesity is associated with airway dysanapsis (an incongruence between the growth of the lungs and the airways) and whether dysanapsis is associated with asthma morbidity.

Methods: We examined the relationship between obesity and dysanapsis in six cohorts of children with and without asthma, as well as the relationship between dysanapsis and clinical outcomes in children with asthma. Adjusted odds ratios (ORs) were calculated for each cohort and in a combined analysis of all cohorts; longitudinal analyses were also performed for cohorts with available data. Hazard ratios (HRs) for clinical outcomes were calculated for children with asthma in the Childhood Asthma Management Program.

Measurements and Main Results: Being overweight or obese was associated with dysanapsis in both the cross-sectional (OR, 1.95; 95% confidence interval [CI], 1.62–2.35 [for overweight/obese compared with normal weight children]) and the longitudinal (OR, 4.31; 95% CI, 2.99–6.22 [for children who were overweight/obese at all visits compared with normal weight children]) analyses. Dysanapsis was associated with greater lung volumes (FVC, vital capacity, and total lung capacity) and lesser flows (FEV_1 and forced expiratory flow, midexpiratory phase), and with indicators of ventilation inhomogeneity and anisotropic lung and airway growth. Among overweight/obese children with asthma, dysanapsis was associated with severe disease exacerbations (HR, 1.95; 95% CI, 1.38–2.75) and use of systemic steroids (HR, 3.22; 95% CI, 2.02–5.14).

Conclusions: Obesity is associated with airway dysanapsis in children. Dysanapsis is associated with increased morbidity among obese children with asthma and may partly explain their reduced response to inhaled corticosteroids.

Keywords: childhood asthma; airway dysanapsis; pulmonary function; childhood obesity

At a Glance Commentary

Scientific Knowledge on the Topic: Obese children with asthma have higher morbidity and reduced response to inhaled corticosteroids, but the underlying mechanisms are not fully understood.

What This Study Adds to the Field: Being overweight or obese is associated with airway dysanapsis in children with or without asthma. Among obese children with asthma, dysanapsis had a significant clinical impact and may at least partly explain the reduced response to asthma medications in this group of patients.

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Obesity and asthma are major public health problems, particularly in industrialized nations. Among children and adults, obesity is a risk factor for asthma, asthma morbidity, reduced quality of life, and reduced response to inhaled corticosteroids (ICSs) (1–3). Obesity may impact asthma through multiple mechanisms, including changes in lung mechanics (4), comorbidities such as gastroesophageal reflux (5), dietary intake (6), alterations in insulin and/or glucose metabolism (7), and systemic inflammation (8).

Airway dysanapsis is a physiological incongruence between the growth of the lung parenchyma and the caliber of the airways (9), reflected by an abnormal FEV_1/FVC despite normal FEV_1 and FVC. Mead proposed that airway length depends on lung volume but airway caliber growth does not (10). Dysanapsis may occur in otherwise healthy subjects with expiratory flow limitation (11) and may be more pronounced in women than in men (12, 13).

Most studies have shown that obese adults (with and without asthma) have a reduced FVC but a normal FEV_1/FVC (suggestive of a restrictive ventilatory deficit). On the contrary, studies in children have shown that obesity is associated with reduced FEV_1/FVC (an obstructive deficit) (8, 14–17). However, rather than low FEV_1, researchers in several studies have reported a normal or high FEV_1 and a high FVC; thus, we hypothesized that the changes seen in obese children may be related to dysanapsis (normal flows in large lungs). We further hypothesized that obesity is associated with airway dysanapsis in children and that obesity-related dysanapsis leads to increased morbidity in obese children with asthma. We examined these hypotheses using data from pulmonary function test (PFT) clinical databases and from several research cohorts of children with and without asthma. Some of the results of this study were presented as a poster at the 2016 American Thoracic Society International Conference in San Francisco, California (18).

Methods

See online supplement for details.

Airway Dysanapsis

FVC and FEV_1 *z*-scores (zFVC and $zFEV_1$, respectively) were calculated using Global Lung Initiative equations (19). "Airway dysanapsis" was defined as normal to high zFVC ($\geq$0.674 or 75th percentile), normal $zFEV_1$ (greater than or equal to -1.645, the fifth percentile, or the lower limit of normal), and low FEV_1/FVC ($<$80%). Control subjects were defined by the same zFVC and $zFEV_1$ but normal FEV_1/FVC ($\geq$80%). Tests with FVC or FEV_1 below those cutoffs were excluded from analysis. The dysanapsis ratio (a lower ratio means more marked dysanapsis) was calculated as maximal expiratory flow at 50% of FVC ($MEF_{50\%}$)/(FVC $\times$ static recoil pressure at 50% of FVC [$Pst_{50\%}$]) when $MEF_{50\%}$ was available (Children's Hospital of Pittsburgh [CHP] and Dutch study [NL] cohorts) (11). $Pst_{50\%}$ was calculated as 6.3038–0.056 $\times$ age (20). In the Boston Children's Hospital (BCH) cohort, only forced expiratory flow, midexpiratory phase ($FEF_{25-75\%}$) was available, and thus the dysanapsis ratio was calculated as $FEF_{25-75\%}$/FVC (21, 22).

Study Populations

CHP. All PFTs conducted at CHP between August 1991 and April 2014 in children ages 7–19 years were reviewed using a PFT clinical database. We excluded the following diagnoses: cystic fibrosis, bronchopulmonary dysplasia, vocal cord dysfunction, chronic lung disease, obstructive sleep apnea, pneumonia or acute infection, "other," or missing. A total of 381 children with dysanapsis (783 tests) and 907 control subjects (1,523 tests) with complete data were included in the analysis. The electronic medical records of these children were also abstracted for relevant variables: race; asthma diagnosis; scheduled versus sick visit; and hospitalizations, emergency department visits, prednisone courses, use of inhaled steroids, and total number of medications for asthma.

Hartford–Puerto Rico cohort. As part of a case–control study of asthma in Puerto Rican subjects, we recruited 1,127 children (618 with asthma and 509 without asthma) living in San Juan, Puerto Rico, and Hartford, Connecticut (the HPR cohort). Details on subject recruitment and study procedures were reported previously (15, 23–25). A total of 147 children with dysanapsis (79 with and 69 without asthma) and 236 control subjects (120 with and 116 without asthma) and complete data were included in this analysis. Asthma-related outcomes and medication use were obtained by parental report.

BCH cohort. All PFTs conducted at BCH between January 1994 and December 2008 in children ages 6–18 years with a diagnosis of asthma or reactive airway disease were reviewed using a PFT clinical database. A total of 246 children with dysanapsis (730 PFTs) and 883 control subjects (1,700 PFTs) with complete data were included in this analysis.

National Health and Nutrition Examination Survey. Using 2007–2008 and 2009–2010 NHANES (National Health and Nutrition Examination Survey) spirometry data (26), we included results for 2,658 children (ages 6–19 yr) without asthma. A total of 1,213 children (189 with dysanapsis and 1,024 control subjects) were included in this analysis.

Childhood Asthma Management Program cohort. CAMP (Childhood Asthma Management Program) was a 4-year, multicenter, randomized clinical trial of long-term asthma medications (27). A total of 1,041 children were randomized to inhaled budesonide, inhaled nedocromil, or inhaled placebo, and followed for 48 months. A total of 195 children with dysanapsis (2,150 PFTs) and 200 control subjects (1,970 PFTs) were included in this analysis. Information on asthma exacerbations and medication use was recorded in diary cards each day during the trial (27).

Dutch study cohort. The Dutch study cohort (NL) consisted of data from a 7-year longitudinal study of 622 Caucasian children (ages 12–15 yr at enrollment) from The Hague, the Netherlands, enrolled in secondary school in 1978–1979 (28, 29). Anthropometric, spirometric, and lung function data were measured twice yearly. Nitrogen single-breath and multiple-breath techniques were used to calculate the residual volume (RV*sb* and RV*mb*) (30) and the washout phase III slope ($\%N_2$/L) (31). A total of 26 children with dysanapsis (142 PFTs) and 88 control subjects (642 PFTs) with complete data were included in this analysis.

Ethics statement. All studies were approved by the institutional review boards of the corresponding institutions and participating centers.

Statistical Analysis

In our primary analysis, we examined overweight or obesity and dysanapsis. Body

mass index (BMI) *z*-scores (zBMI) were calculated using formulas from the CDC (32), and overweight/obesity was assessed using both continuous (zBMI) and binary (overweight [BMI in the 85th–95th percentile] or obesity [BMI ⩾95th percentile]) measures. For each cohort, we performed a cross-sectional analysis including one test per subject; if more than one test was available, only the first test was selected. Multivariable logistic and linear regression models were adjusted for age, sex, race, and baseline FEV_1 in all cohorts; asthma status (in HPR); treatment arm (in CAMP); and study site (in HPR and CAMP).

We also performed a random-effects longitudinal analysis in cohorts with available data (CHP, BCH, CAMP, and NL) with three comparisons: "mostly obese" versus "mostly non obese" (children with BMI >85th percentile in >50% vs. <50% of visits), "mostly obese" versus "never obese" (>50% vs. 0% of visits), and "always obese" versus "never obese" (100% vs. 0% of visits). In addition, we performed cross-sectional and longitudinal combined analyses by pooling the PFTs from all cohorts at the individual level; these analyses were additionally adjusted for study cohort and study site.

Next, we examined dysanapsis and lung function measures in a combined examination of all cohorts for which measures were available, as well as dysanapsis and clinical outcomes in children with asthma. In the NL cohort, we also examined the difference between RV*sb* and RV*mb* and the phase III slope (31), both of which are greater when airway obstruction exists (30). Lung and airway growth were evaluated using the equation $MEF = c \times TLC^k$, where k values between approximately 0.7 and approximately 1.3 are consistent with isotropic (symmetric) growth (28, 33) and TLC is total lung capacity. We calculated k_{50} and k_{75} using $MEF_{50\%}$ and maximal expiratory flow at 75% of FVC [$MEF_{75\%}$], respectively. Finally, we assessed asthma-related outcomes using linear or logistic regression, as appropriate. In CAMP, survival analysis was performed in overweight/obese participants using log-rank tests of equality and Cox maximum-likelihood proportional hazards models, where each outcome (e.g., asthma exacerbation) was the "failure" event. Cumulative hazard was plotted, stratified by dysanapsis group. All analyses were performed using R v.3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and STATA v.13 software (StataCorp LP, College Station, TX).

Results

A total of 4,521 children were included in this analysis. The main characteristics of the study populations are shown in Table 1. Studies included children ages 6–20 years old. The CHP and BCH cohorts include data from children referred to pulmonary clinics for management; the HPR cohort included a population-based and a school-based sample of children with and without asthma; the NHANES cohort included

Table 1. Characteristics of Study Participants by Cohort

		HPR					
	CHP	Cases	Controls	BCH	NHANES	CAMP	NL
Tests, n	2,306	198	184	2,430	1,213	4,120	784
Subjects, n*	1,288	198	184	1,129	1,213	395	114
Age, yr	10.7 (3.7)	9.9 (2.8)	9.8 (2.7)	10.0 (3.2)	12.3 (4.0)	10.4 (2.5)	15.3 (1.6)
Male sex, %	54.9	46.5	45.1	53.7	51.0	59.4	63.0
BMI *z*-score	1.09 (0.98)	1.23 (0.98)	0.93 (1.11)	1.13 (0.99)	0.88 (1.06)	0.76 (0.94)	0.21 (0.67)
FEV_1							
% predicted	120.7 (12.9)	108.6 (10.8)	110.4 (12.1)	112.0 (11.8)	114.4 (10.1)	105.0 (10.5)	112.4 (7.7)
z-score	1.74 (1.08)	0.73 (0.90)	0.88 (1.01)	1.01 (0.97)	1.21 (0.85)	0.42 (0.89)	1.07 (0.67)
FVC							
% predicted	129.6 (8.0)	119.9 (13.4)	121.8 (16.4)	118.6 (7.8)	118.1 (8.1)	117.1 (7.3)	114.5 (5.6)
z-score	2.40 (0.63)	1.71 (1.11)	1.86 (1.37)	1.51 (0.62)	1.53 (0.70)	1.43 (0.61)	1.23 (0.47)
FEV_1/FVC							
Ratio	81.9 (7.7)	80.9 (7.8)	81.5 (9.8)	83.2 (7.6)	85.5 (5.7)	78.8 (7.3)	85.0 (5.5)
z-score	−0.92 (1.01)	−1.28 (1.02)	−1.15 (1.27)	−0.76 (1.05)	−0.48 (0.87)	−1.38 (0.94)	−0.30 (0.83)
Race, %							
White	84.7	0	0	78.2	23.4	60.3	100
Black	14.3	0	0	14.8	19.5	14.1	0
Other(s)	1	100	100	7	57.1	25.6	0
Dysanapsis, %*							
Total study population	33.8	14.3	15.4	11.7	7.1	20.2	4.3
Sample included in the analysis	33.9	39.4	36.9	30.0	15.6	52.2	18.1
Cohort type	Clinical database	Case–control study of childhood asthma		Clinical database	U.S. population sample	Randomized clinical trial	Normative data

Definition of abbreviations: BCH = Boston Children's Hospital cohort; BMI = body mass index; CAMP = Childhood Asthma Management Program cohort; CHP = Children's Hospital of Pittsburgh cohort; HPR = Study of Asthma in Puerto Rican Children (Hartford and Puerto Rico) cohort; NHANES = National Health and Nutrition Examination Survey; NL = Dutch study cohort.
Numbers represent mean (SD) unless otherwise indicated.
*CHP data were specifically queried to include only dysanapsis and control subjects.

a population-based sample of children without asthma; the CAMP cohort included children with asthma who participated in a clinical trial; and the NL cohort included data from a normative longitudinal study of lung growth in adolescents.

Dysanapsis and Obesity

Table 2 summarizes the findings derived from the cross-sectional analysis of obesity and dysanapsis for each cohort. In the CHP cohort, each 1.0-point increase in zBMI was associated with 1.64 times higher odds of airway dysanapsis, and overweight or obese children had 2–2.35 times higher odds of dysanapsis than children of normal weight. Similarly, zBMI was associated with dysanapsis in all other cohorts of children (HPR, BCH, NHANES, CAMP, and NL), with odds ratios (ORs) ranging from 1.29 to 2.48 ($P < 0.01$ for each cohort). Overweight and obesity were also associated with dysanapsis, with ORs ranging from 1.36 to 2.48 (overweight OR, 7.95 in NL but only 14 children with dysanapsis and thus a very wide confidence interval [CI]). Moreover, zBMI and overweight/obesity were also associated with lower dysanapsis ratios by either definition (*see* Table E1 in the online supplement).

We then performed a combined analysis of PFTs for all cohorts (Table 2). In this analysis (which was additionally adjusted for cohort and study site), both zBMI (OR, 1.44; 95% CI, 1.31–1.58) and overweight or obesity (OR, 1.95; 95% CI, 1.62–2.35) were associated with dysanapsis. Figure 1 shows the behavior of FEV_1 and FVC by zBMI in children with and without dysanapsis: FEV_1 and FVC had similarly increasing slopes with zBMI regardless of dysanapsis, but in the dysanapsis group FVC was slightly higher ($\beta = +0.18$ *z*-score, or +2.1% of predicted; $P < 0.001$) and FEV_1 was markedly lower ($\beta = -1.24$ *z*-score, or −14.9% of predicted; $P < 0.001$). Figure E1 shows these results by individual cohort. Boys had slightly higher odds of dysanapsis than girls (Figure E2); there were no significant differences by race or ethnicity.

Longitudinal Analysis

The results of the longitudinal analysis of overweight or obesity measures and dysanapsis are shown in Table 3. In CHP, approximately 20% of children had at least two tests (maximum of 18 tests over a 9-yr span); each 1-point increase in zBMI was associated with a 2.25 times increased odds of dysanapsis, and children who were "always overweight or obese" had 4.34 higher odds of dysanapsis than those who were "never overweight or obese." In BCH, 50% of children had more than 2 tests, and 10% had more than 6 tests (maximum of 20 tests over an approximately

Table 2. Cross-Sectional Analysis of Obesity and Airway Dysanapsis

	Dysanapsis/Total, n	BMI *z*-Score	Overweight/Obese	Obese Only
CHP	381/1,288			
OR (95% CI)		1.64 (1.37–1.95)	2.35 (1.67–3.30)	2.00 (1.41–2.83)
P value		<0.001	<0.001	<0.001
n			721	436
HPR*	146/381			
OR (95% CI)		1.29 (1.01–1.67)	1.75 (1.05–2.92)	1.88 (1.11–3.19)
P value		0.048	0.033	0.018
n			207	136
BCH	246/1,128			
OR (95% CI)		1.36 (1.11–1.66)	2.02 (1.37–2.98)	1.36 (0.90–2.07)
P value		0.002	0.001	0.15
n			583	355
NHANES	189/1,213			
OR (95% CI)		1.35 (1.11–1.65)	1.58 (1.06–2.36)	1.67 (1.08–2.60)
P value		0.002	0.024	0.022
n			551	324
CAMP	195/392			
OR (95% CI)		1.32 (0.98–1.81)	1.42 (0.77–2.62)	2.48 (1.5–5.35)
P value		0.075	0.26	0.021
n			147	75
NL	26/114			
OR (95% CI)		2.48 (1.21–5.11)	7.95 (1.74–36.3)	0.94 (0.06–15.4)
P value		0.013	0.007	0.96
n			14	4
All†	1,183/4,516			
OR (95% CI)		1.44 (1.31–1.58)	1.95 (1.62–2.35)	1.75 (1.44–2.14)
P value		1.4×10^{-14}	1.3×10^{-12}	2.6×10^{-8}
n			2,223	1,330

Definition of abbreviations: BCH = Boston Children's Hospital cohort; BMI = body mass index; CAMP = Childhood Asthma Management Program cohort; CHP = Children's Hospital of Pittsburgh cohort; CI = confidence interval; HPR = Study of Asthma in Puerto Rican Children (Hartford and Puerto Rico) cohort; NHANES = National Health and Nutrition Examination Survey; NL = Dutch study cohort; OR = odds ratio.
*HPR combined data (cases and control subjects).
†Joined analysis of all cohorts.

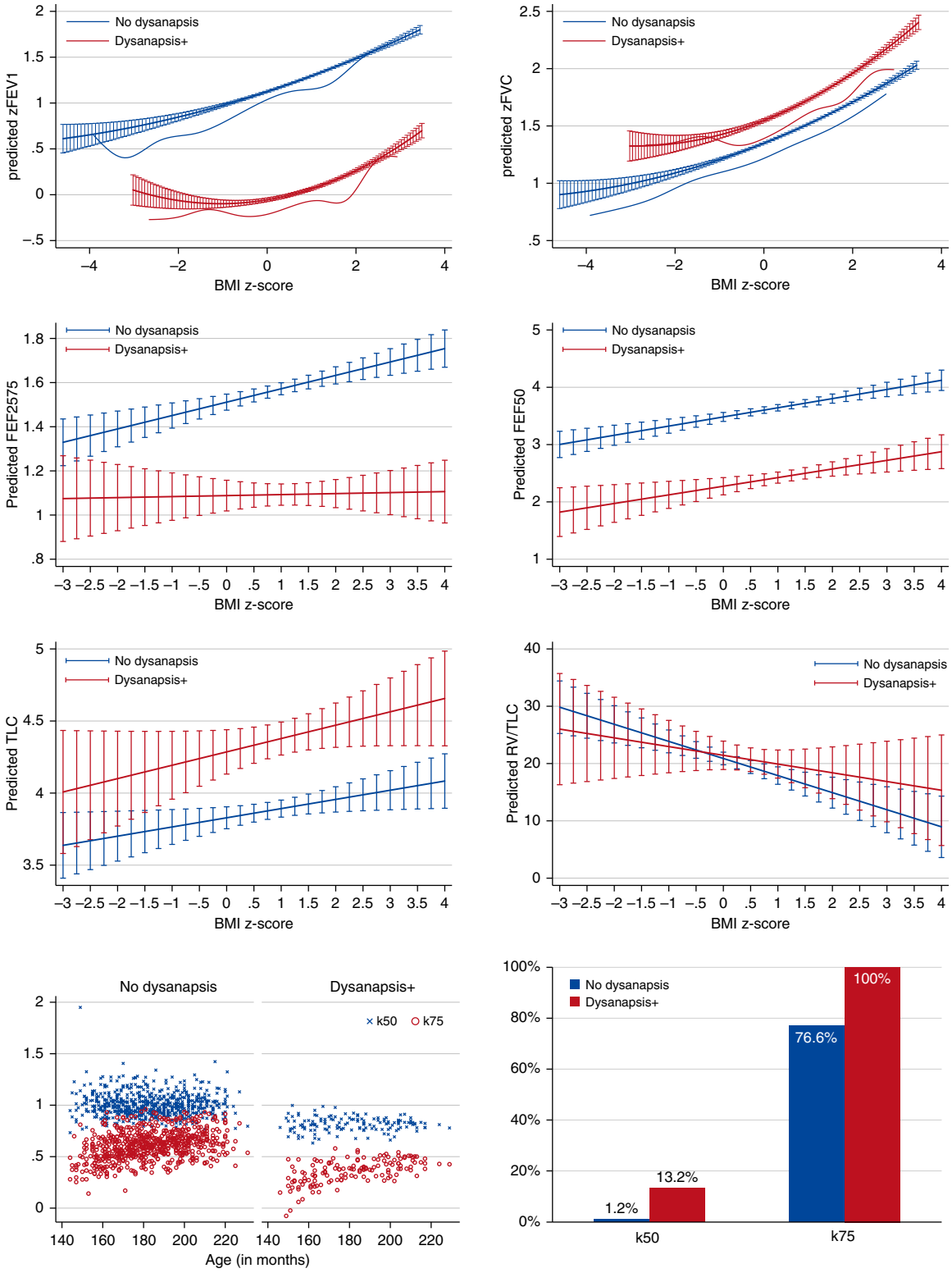

Figure 1. Body mass index (BMI) *z*-score, airway dysanapsis, and lung function. The *top six panels* show predicted lung function (FEV_1; FVC; forced expiratory flow, midexpiratory phase [$FEF_{25-75\%}$]; expiratory rate at 50% of FVC [FEF_{50}]; total lung capacity [TLC]; and residual volume [RV]/TLC) and 95% confidence intervals, by BMI *z*-score and airway dysanapsis status (with dysanapsis in *red*; no dysanapsis in *blue*). Children with dysanapsis had lower FEV_1, $FEF_{25-75\%}$, and FEF_{50} but higher FVC and TLC. *Bottom left panel* shows values for k_{50} and k_{75}. *Bottom right panel* shows the percentage of children with k_{50} or k_{75} values consistent with anisotropic (asymmetric) growth of the lungs and airways. Children with dysanapsis had lower k_{50} and k_{75} values, which was more consistent with anisotropic lung and/or airway growth.

Table 3. Longitudinal Analysis of Obesity and Airway Dysanapsis

	BMI *z*-Score	"Mostly" vs. "Mostly Not" Obese*	"Mostly" vs. "Never" Obese†	"Always" vs. "Never" Obese‡
CHP				
OR (95% CI)	2.25 (1.49–3.42)	3.49 (1.55–7.86)	4.76 (1.81–12.6)	4.34 (1.71–11.0)
P value	0.001	0.003	0.002	0.002
n	915	915	869	781
BCH				
OR (95% CI)	1.82 (1.32–2.44)	2.78 (1.54–5.02)	2.86 (1.54–5.31)	3.48 (1.72–7.02)
P value	0.001	0.001	0.001	0.001
n	2,429	2,429	2,308	2,014
CAMP				
OR (95% CI)	1.62 (1.23–2.13)	2.94 (1.61–5.41)	4.77 (2.31–9.85)	4.95 (2.25–10.9)
P value	0.001	0.001	0.001	0.001
n	4,412	4,120	3,105	2,370
NL				
OR (95% CI)	3.24 (1.33–7.90)	3.03 (0.33–28.3)	3.42 (0.38–31.0)	6.18 (0.35–108)
P value	0.01	0.33	0.27	0.21
n	783	783	735	715
All				
OR (95% CI)	1.93 (1.67–2.23)	3.41 (2.45–4.73)	4.18 (2.94–5.98)	4.31 (2.99–6.22)
P value	3.1×10^{-19}	3.0×10^{-13}	3.0×10^{-15}	5.0×10^{-15}
n	10,060	8,856	7,594	6,336

Definition of abbreviations: BCH = Boston Children's Hospital cohort; BMI = body mass index; CAMP = Childhood Asthma Management Program cohort; CHP = Children's Hospital of Pittsburgh cohort; CI = confidence interval; NL = Dutch study cohort; OR = odds ratio.
*Overweight or obese at more than 50% of visits versus less than 50% of visits.
†Overweight or obese at more than 50% of visits versus 0% of visits.
‡Overweight or obese at 100% of visits versus 0% of visits.

11-yr span); each 1-point increase in zBMI was associated with a 1.82 higher odds of dysanapsis, and children who were "always overweight/obese" had 3.48 times higher odds of dysanapsis than those who were "never overweight/obese." In CAMP, children had an average of 9.5 tests over approximately 48 months; each 1-point increment in zBMI was significantly associated with a 1.62 times increased odds of dysanapsis, and children who were "always overweight/obese" had 4.95 times higher odds of dysanapsis than those who always had normal weight. In NL, children had an average of 6.5 tests (range, 1–13 over 7 yrs of follow-up); each 1-point increment in zBMI was associated with a 3.24 times increased odds of dysanapsis, while the dichotomous analyses were not statistically significant. The combined analysis that each 1-point increment in zBMI was associated with a 1.93 times increased odds of dysanapsis, a 3.41 times increased odds of dysanapsis for the comparison of "mostly" obese versus "mostly not" obese, and a 4.18–4.31 times increased odds of dysanapsis for the comparison of "mostly" or "always" obese versus "never" obese.

Dysanapsis and Other Lung Function Measures

We analyzed other lung function measures jointly for the cohorts for which each measure was available. Children with dysanapsis had lower $FEF_{25-75\%}$ ($\beta = -1.89$ *z*-score or -43% of predicted; $P < 0.001$ [combined analysis of CHP, BCH, and NL]) and $MEF_{50\%}$ percent predicted ($\beta = -41.4\%$ of predicted; $P < 0.001$ [CHP]), and higher TLC ($\beta = +457$ ml; $P < 0.001$ [CHP, BCH, and NL combined analysis]) than those without dysanapsis (Figure 1), with no significant differences in residual volume (RV)/TLC. In NL, dysanapsis was associated with higher VC ($\beta = +322$ ml; $P = 0.034$), lower $MEF_{75\%}$ ($\beta = -0.281$ L/s; $P = 0.018$), and no changes in closing volume or closing capacity.

We also evaluated markers of ventilation inhomogeneity and found that dysanapsis was not associated with the phase III nitrogen slope, but the RV*sb* − RV*mb* difference was more pronounced in the dysanapsis group ($\beta = 26.9$ ml; $P = 0.002$). Children with dysanapsis had lower mean values of k_{50} (0.79 vs. 1.01) and k_{75} (0.35 vs. 0.61) (Figure 1). After adjustment for age, sex, and FEV_1, children with dysanapsis had 4.6 times increased odds (95% CI, 1.9–7.3; $P = 0.001$) of having k_{50} values consistent with anisotropic lung and/or airway growth.

Clinical Outcomes

We assessed airway dysanapsis and clinical outcomes in children with asthma. In CHP, children with dysanapsis were more likely to use at least three medications for asthma (OR, 1.72; 95% CI, 1.02–2.90; $P = 0.04$). In HPR, children with dysanapsis were more likely to use daily albuterol (OR, 8.3; 95% CI, 1.1–64.0; $P = 0.04$) and miss school due to asthma (OR, 10.5; 95% CI, 1.9–58.5; $P = 0.007$).

At the randomization visit in CAMP, children with dysanapsis (n = 197) had higher odds of reporting at least one hospitalization for asthma in the year prior to the trial (OR, 3.03; 95% CI, 1.10–8.37; $P = 0.033$) than those without dysanapsis. Figure 2 shows the proportion of children with dysanapsis by treatment arm during the trial; there was no significant differences in the proportion of children with dysanapsis between budesonide and nedocromil/placebo at either the beginning or the end of the trial. After adjustment for treatment arm and other covariates, dysanapsis was associated with shorter time to a severe asthma exacerbation requiring emergency department visit, hospitalization, or systemic corticosteroids ($\beta = -3.29$ mo; 95% CI, -5.70 to -0.89; $P = 0.007$). Compared with overweight/obese children without dysanapsis, those with dysanapsis had an increased risk of at least one severe exacerbation (hazard ratio, 1.40; 95% CI, 1.07–1.75; $P = 0.014$) and of having at least two prednisone bursts between study visits (hazard ratio, 2.53; 95% CI, 1.71–3.73; $P < 0.001$) (Figure 2). The effects were all more pronounced in overweight/obese children than in children of normal weight (Table E2). We found no significant modification of the effect of dysanapsis (or the association between obesity and dysanapsis) by treatment arm.

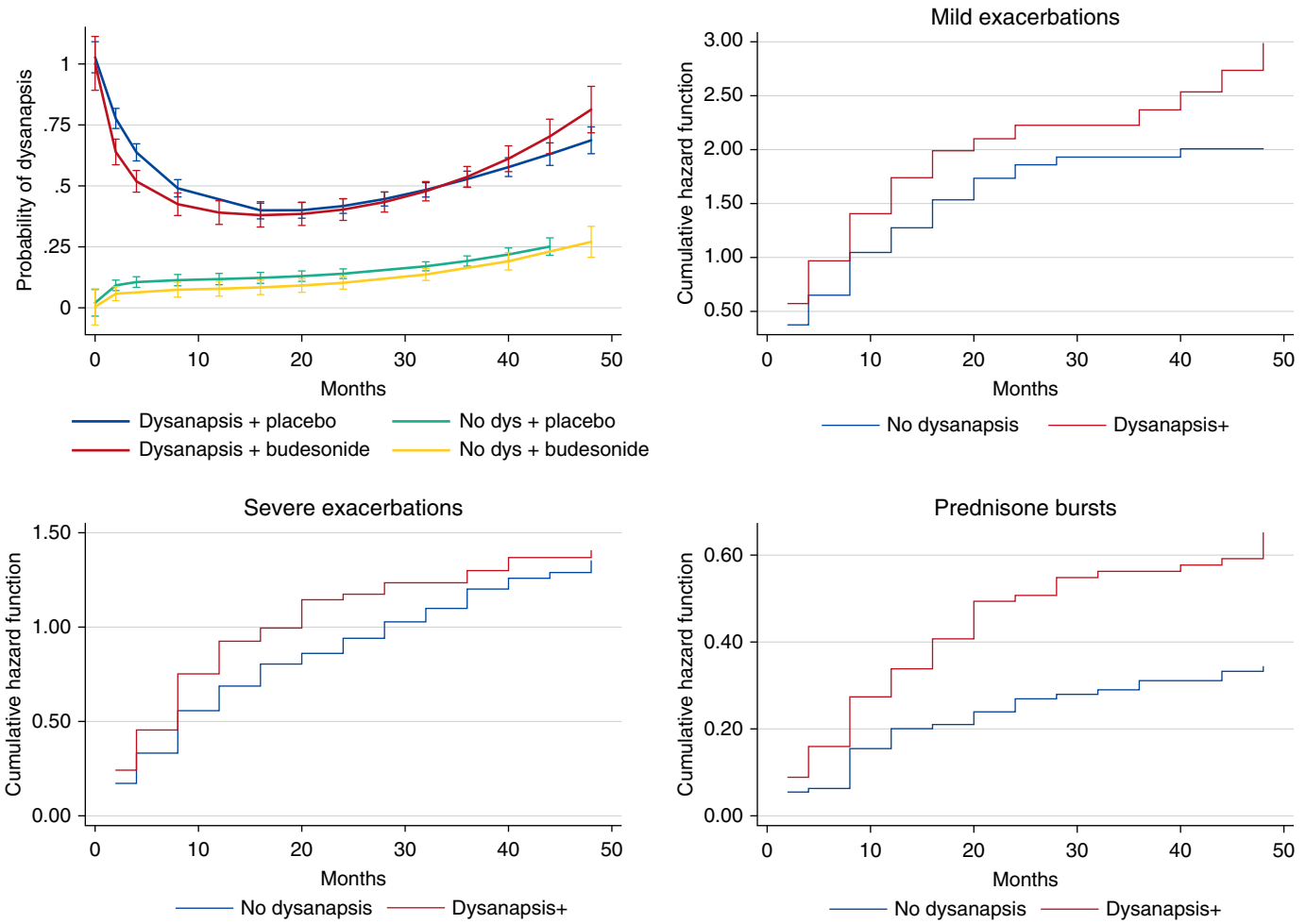

Figure 2. Dysanapsis (dys) and clinical outcomes in children with asthma in CAMP (Childhood Asthma Management Program). *Top left panel* shows the probability of dysanapsis during 48 months in CAMP by treatment arm in children with dysanapsis at randomization. There were no significant differences between the budesonide or nedocromil and/or placebo arms. Error bars represent 95% confidence intervals. The other three panels show cumulative hazard function of dysanapsis for mild exacerbations (*top right*), severe exacerbations (*bottom left*), and requiring more than two prednisone bursts between study visits (*bottom right*). Children with dysanapsis had a higher risk of exacerbations and prednisone courses during the trial.

Sensitivity Analyses

We repeated the analysis using different FEV_1, FVC, and FEV_1/FVC cutoffs to define dysanapsis, with essentially unchanged results (Table 4). In addition, we performed sensitivity analyses with other FEV_1/FVC or FVC cutoffs (Tables E3 and E4), indicating that the associations did not depend solely on our cutoff selection. Finally, we repeated the analysis after excluding subjects with significant bronchodilator response (>12%) or using only post-bronchodilator spirometry (in cohorts with available data), with similar results (data not shown), suggesting that the associations were likely not due to unrecognized bronchoconstriction.

Discussion

In this report, we show that overweight or obesity are associated with airway dysanapsis in children with and without asthma. Moreover, we demonstrate that airway dysanapsis is associated with symptoms, medication use, and severe disease exacerbations in children with asthma. To our knowledge, this is the first report of an association between obesity and airway dysanapsis in childhood, as well as the first report linking dysanapsis to worse disease severity or control in children with asthma.

Obesity measures were consistently associated with airway dysanapsis in all cohorts of children, in both cross-sectional and longitudinal analyses. Furthermore, lower FEV_1, $FEF_{25-75\%}$, $MEF_{50\%}$, and/or $MEF_{75\%}$ in the dysanaptic groups strongly suggests that the relative airflow obstruction is likely present throughout airways of all sizes; however, a normal RV/TLC suggests the absence of significant air trapping. These children had larger vital capacity, RV, and TLC, indicating they have larger lungs; this is in sharp contrast to studies in adults that have described a restrictive deficit in obesity, with lower lung volumes and a preserved FEV_1/FVC (4). Our analysis of the NL data (19) evaluating the exponential relationship between flows and volumes (28, 33) further

Table 4. Sensitivity Analysis Using Different Cutoffs to Define Dysanapsis

Cutoff Values			BMI *z*-Score	
FVC	FEV_1	FEV_1/FVC*	OR (95% CI)	*P* Value
>75th percentile	>LLN	<80% vs. >80%	1.44 (1.31–1.58)	1.4×10^{-14}
>75th percentile	>100% predicted	<80% vs. >80%	1.48 (1.34–1.63)	4.9×10^{-15}
>100% predicted	>100% predicted	<80% vs. >80%	1.54 (1.41–1.69)	8.8×10^{-21}
>100% predicted	>100% predicted	<LLN vs. >LLN	1.54 (1.38–1.72)	3.4×10^{-14}
>LLN	>LLN	<LLN vs. >LLN	1.44 (1.34–1.53)	7.3×10^{-26}

Definition of abbreviations: BMI = body mass index; CI = confidence interval; LLN = lower limit of normal; OR = odds ratio.
Odds ratios (and confidence intervals) for the association between BMI *z*-score and dysanapsis.
*The same FEV_1 and FVC criteria were used for both groups, but the dysanapsis group was defined as low FEV_1/FVC (e.g., <80% or <LLN) and the control subjects as normal FEV_1/FVC (e.g., >80% or >LLN). The first line represents the definition used in the main analysis (see Table 2).

supports that children with dysanapsis have anisotropic (asymmetric) growth of the lungs and airways.

Dysanapsis is merely a reflection of the incongruence between a (faster) growth in lung volume and airway length, and the (slower) increase in airway caliber. Such incongruence may happen physiologically and may be accentuated by several mechanisms, including *in utero* exposures such as tobacco smoke or vitamin D deficiency (34, 35), although it is unclear whether these effects would persist later in childhood. Chronic hypoxemia has been associated with a higher risk of dysanaptic lung growth (36); dysanapsis may also be present in breathhold divers, who use glossopharyngeal insufflation to force their lung volumes above TLC (providing extra oxygen and preventing compression when diving) (37). Compensatory lung growth after pneumonectomy may also be dysanaptic (38).

There is evidence that lung function may "track" from birth throughout life, and this may be influenced by weight from early on. As early as 1990, Barker and coworkers described that low birth weight was associated with low lung function in adults approximately 59–70 years old and with death caused by chronic obstructive pulmonary disease (39). More recently, den Dekker and colleagues (40) performed a metaanalysis of 25,000 children from 24 birth cohorts and found that greater birth weight and infant weight gain were associated with higher FEV_1 and FVC at school age (independent of gestational age); the increases were greater for FVC than for FEV_1. Moreover, infant weight gain was associated with lower FEV_1/FVC and $FEF_{25-75\%}$. Therefore, the changes we observed may be established very early in life. Further studies are needed to discern whether these changes are fixed or vary, particularly in the transition from childhood to adulthood.

Obesity-related airway dysanapsis was associated with worse clinical outcomes in children with asthma. In CAMP, ICSs had no effect on the association between BMI and dysanapsis, and, despite ICS treatment, children with dysanapsis remained at higher risk of severe asthma exacerbations. Our findings thus suggest that airway dysanapsis partly explains previous reports of a strong link between obesity and increased morbidity (8, 15, 41) or reduced response to treatment (2, 42) in children with asthma. We speculate that obese children with dysanapsis may have airflow obstruction that is anatomical and/or developmental and thus at least partly not related to bronchospasm or airway inflammation.

We found evidence of sex differences, with higher odds of dysanapsis among boys. This could partly explain prior reports that obesity is more consistently associated with worse asthma control in boys than in girls (41). Some of the initial studies on airway dysanapsis (not related to obesity) described that women have smaller airways than men relative to their lung volumes (10, 43). Later studies have reported that boys have smaller airways than girls (44, 45) and described changes in dysanapsis ratios before and after puberty (46). Moreover, a longitudinal population-based study of children with asthma reported that dysanapsis was more pronounced in boys, but this became less significant with age (47).

Our study has several limitations. None of the study cohorts was specifically designed to assess obesity and airway dysanapsis; however, we show consistent replication in independent and diverse populations. We cannot completely exclude reversible airflow obstruction, but this is unlikely because we included cohorts of children without asthma, and our results did not change when we used post-bronchodilator measurements (when available) or excluded children with a bronchodilator response. Moreover, budesonide treatment had no effect on the association between obesity and dysanapsis. There is evidence that using an arbitrary cutoff may not be the best way to identify "abnormal" lung function; however, we used cutoffs (e.g., FEV_1/FVC <0.80) that are widely accepted and used in research and clinical practice. Furthermore, we performed sensitivity analyses using different cutoffs for FVC, FEV_1, and/or FEV_1/FVC to define dysanapsis, and the results remained essentially unchanged. We cannot assess whether children with high BMI are able to exhale more forcibly, resulting in higher intrathoracic pressure, more airway compression, and relatively reduced FEV_1. We lack imaging of the airways or other measurements of airway diameter to confirm findings derived from lung function testing. Finally, we cannot determine whether dysanapsis was solely responsible for the observed differences in asthma outcomes among obese children.

In summary, obesity is associated with airway dysanapsis in children with or without asthma. Among obese children with asthma, dysanapsis has significant clinical impact and may at least partly explain the decreased response to asthma medications in this group of patients. ■

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