

Original Article

Comorbid Obesity and Depressive Symptoms in Childhood Asthma: A Harmful Synergy

Chiun Yu Hsu, PhD^{a,b}, Heather K. Lehman, MD^{b,c,d}, Beatrice L. Wood, PhD^{a,b,c,e}, Jaspreet Benipal, DO^c, Quratulain Humayun, MBBS, MS^b, and Bruce D. Miller, MD^{a,b,c,e} Buffalo, NY

What is already known about this topic? Depression and obesity are known to be associated with increased asthma severity and decreased asthma control in children. Various mechanisms to explain this morbidity have been proposed, but a systematic investigation of potential pathways is needed.

What does this article add to our knowledge? Among overweight/obese children with asthma, greater depressive symptoms are associated with compromised lung function. We present evidence that increased vagal/cholinergic reactivity (vagal bias) may be a mechanism underlying this association.

How does this study impact current management guidelines? Comorbid obesity and depression should be identified by clinicians for children with asthma. Treatment of these risk factors and/or anticholinergic inhaled medication as adjunct therapy may offer benefit in children with asthma, obesity, and depression.

BACKGROUND: Overweight/obesity (OV/OB) and depression have each been separately associated with worsened childhood asthma severity and control. Pathways by which these factors may jointly affect childhood asthma have not been elucidated. **OBJECTIVE:** To examine the interrelationship of OV/OB and depressive symptoms with childhood asthma and explore associated psychobiologic pathways. The present study investigated whether comorbid OV/OB and depressive symptoms are associated with impaired baseline lung function and increased airway resistance during emotional stress, and to assess whether such effects may be mediated by autonomic nervous system (ANS) dysregulation, specifically through predominance of vagal over sympathetic reactivity (vagal bias). **METHODS:** A total of 250 children with asthma, aged 7 to 17, were assessed for OV/OB using body mass index, depressive

symptoms using the Children's Depression Inventory (CDI), and asthma severity using National Asthma Education and Prevention Program Expert Panel Report 3 criteria. Baseline pulmonary function (forced expiratory volume in 1 second [FEV₁]) was assessed. The film "E.T. the Extra-Terrestrial" was used in a laboratory paradigm to evoke emotional stress/arousal. Airway resistance (R_{int}) was measured before and after the film to determine changes in airway function. ANS reactivity was assessed by measuring parasympathetic/vagal and sympathetic reactivity throughout the film.

RESULTS: In OV/OB children with asthma, depressive symptoms predicted lower baseline FEV₁ ($\beta = -0.67$, standard error [SE] = 0.24, $P = .008$), CDI predicted vagal bias under emotion stress/arousal ($\beta = 0.27$, SE = 0.09, $P = .009$), and vagal bias predicted increased R_{int} ($\beta = 3.55$, SE = 1.54, $P = .023$).

CONCLUSION: This study is the first to link OV/OB and depressive symptoms in their relationship to childhood asthma. In OV/OB children with asthma, depression may potentiate airway compromise, mediated by vagal bias. Use of antidepressant and anticholinergic therapies should be studied in this subgroup of patients. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: Asthma; depression; overweight; obesity; lung function; vagal bias

^aNeuroscience Program, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY

^bChild and Family Asthma Studies Center, Oishei Children's Hospital, Buffalo, NY

^cDepartment of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY

^dAllergy & Immunology, Oishei Children's Hospital, Buffalo, NY

^eDepartment of Psychiatry, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY

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Corresponding author: Bruce D. Miller, MD, Departments of Psychiatry and Pediatrics, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, New York; Child and Family Asthma Studies Center, 179 Bryant Street, Buffalo, NY 14222. E-mail: brumill@buffalo.edu.

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Asthma is a chronic inflammatory disease of the airways characterized by airflow obstruction, bronchial hyper-responsiveness, and airway inflammation.¹ Asthma impacts approximately 6.2 million children in the United States² and up to 10% of children in developing countries.³ Commonly identified triggers for childhood asthma exacerbations include infections, allergens, exercise, smoke exposure, stress, and emotions.

Abbreviations used

ANS- Autonomic nervous system
 BMI- Body mass index
 CDC- Centers for Disease Control and Prevention
 CDI- Children's Depression Inventory
 FEV₁- Forced expiratory volume in 1 second
 NW- Normal weight
 OV/OB- Overweight/obese
 PEP- Pre-ejection period
 R_{int}- Airway resistance by interrupter technique
 RSA- Respiratory sinus arrhythmia
 SD- Standard deviation
 SE- Standard error
 VB- Vagal bias

Childhood overweight/obesity is on the rise, with the reported obesity prevalence of up to 22%.⁴ Depression is also common in children and adolescents, and considerably higher in children with asthma.⁵ Obesity and depression co-occur with asthma, and each independently has been associated with severe or difficult-to-control asthma.¹ Despite the recognition that all 3 conditions are often found together in the same child, the interrelationship between obesity and depression and their impact on asthma has not yet been examined. Because of the high prevalence of comorbid asthma, obesity, and depression in children, it is important to explore the mechanisms by which these conditions impact child asthma to better target interventions to improve asthma control.

With comorbid asthma and obesity increasing in both adults and children in the United States, the association between these 2 conditions is the subject of substantial research.^{6,7} In the United States, the Centers for Disease Control and Prevention (CDC) reports that childhood obesity rates have more than tripled in the last 30 years, with 18.5% of US children now meeting the definition of obesity.⁴ Overweight children are at a significantly higher risk of developing asthma.⁸ The International Study of Asthma and Allergies in Childhood showed an increased prevalence of asthma in overweight children, but there was no association between asthma and atopy in this population; this is in contrast to typical atopic asthma phenotype most often identified in children.⁹ Patients with asthma who are obese have more severe and difficult-to-treat asthma,^{10,11} increased risk of hospitalization,¹² and reduced response to inhaled corticosteroids when compared with nonobese patients with asthma.¹³ Quinto et al¹⁴ reviewed records of 32,321 children aged 5 to 17 and found that β -agonist units dispensed annually and oral corticosteroids increased with body mass index (BMI). This was independent of age, race, sex, asthma controller use, parental education level, gastroesophageal reflux disease, and diabetes mellitus. Moreover, Lang et al¹⁵ conducted a secondary analysis involving preschoolers from 3 highly controlled trials (Individualized Therapy for Asthma in Toddlers [INFANT], Prevention of Early Asthma in Kids trial [PEAK], and Maintenance versus Intermittent Inhaled Steroids in Wheezing Toddlers trial [MIST]). Results suggested that being overweight was associated with an increased number of asthma exacerbations, and more days with asthmatic symptoms, compared with normal weight (NW) preschoolers.¹⁵ A study by Schatz et al¹⁶ demonstrated a significant relationship between obese status and poor asthma control in adults, even after adjusting for factors such as demographics, comorbidity, and prior utilizations.

The mechanisms by which obesity contributes to asthma severity and control remain unclear. The proposed underlying mechanisms of comorbidity of asthma and overweight/obesity in children include variations in physical inactivity, sleep duration, parental distress,¹⁷ gastroesophageal reflux,¹⁸ environmental tobacco smoke,¹⁹ increased weight on chest wall leading to reduced lung volumes,²⁰ and proinflammatory mediators released by adipocytes.²¹ Despite these various proposed mechanisms, the relationship between asthma and obesity is still poorly understood due to conflicting evidence and lack of a consistent theory, thus suggesting the need for additional research to clarify the mechanisms by which obesity affects asthma. It is important to identify modifiable factors that lead to worsened asthma control in overweight/obese (OV/OB) children, as this asthma phenotype is often difficult to treat, having poor response to conventional asthma medications.

Depression also co-occurs with asthma. Rates of current depressive disorders in outpatients with asthma were found to be between 14% and 25% in adult patients^{22,23} and 16% and 26% in pediatric populations,^{24,25} with 31% to 47% of asthmatics having had depression at some point in their lifetime.^{22,23,26} Depression is associated with unfavorable asthma outcomes including medication nonadherence, unscheduled visits for asthma, increased frequency of emergency department visits, hospitalizations,^{27,28} and even asthma-related death.²⁹ Furthermore, it has also been shown that depression is associated with worsened lung function on exposure to stress.³⁰

There is also an association between obesity and depression. However, there are no data on the rate of co-occurrences of both depression and obesity with childhood asthma. Boudreau et al³¹ demonstrated a mediating effect of depressive symptoms in the association between BMI and asthma control in adult asthmatics. However, they did not demonstrate a mechanism by which depression impacted asthma. Poor treatment adherence is one mechanism by which depression may affect adult and childhood asthma.³² Psychobiologic pathways are also implicated. Miller's Autonomic Nervous System (ANS) Dysregulation Model of Emotions and Asthma proposes that depression impacts asthma by potentiating airway compromise via vagal/cholinergic ANS dysregulation.^{33,34} Findings demonstrate that depressive emotional states are accompanied by a predominance of vagal reactivity over sympathetic reactivity (vagal bias) in response to emotional stress.³⁰ OV/OB children also show ANS dysregulation, specifically reduction in resting vagal tone.³⁵ Low vagal tone impairs modulation of ANS reactivity, with dysregulation and unstable parasympathetic/vagal and sympathetic reactivity, and low vagal tone is generally related to poor health outcomes.^{36,37} The ANS dysregulation found in obesity, that is lower vagal tone, may be accompanied by increased vagal reactivity. If this is the case, obesity could synergistically add to the depression-related vagal reactivity and decrements in pulmonary function in children with asthma. However, there are no studies to date examining ANS reactivity in OV/OB children with asthma and depression.

The present study examines the joint effect of overweight/obesity and depressive symptoms on lung function in childhood asthma and explores whether this effect may be mediated by parasympathetic/vagal ANS dysregulation.

METHODS

This study was approved by the University at Buffalo's Child and Youth Institutional Review Board. Participants were 250 children with asthma from whom data were collected during 2 funded

TABLE I. Demographic characteristics of the study sample

	Normal weight (n = 110)		Overweight/obese (n = 140)		P
BMI	Mean	(SD)	Mean	(SD)	
	18.5	(2.5)	27.5	(6.2)	<.001
Age	11.5	(2.9)	11.2	(2.5)	.54
Gender	n	(%)	n	(%)	
Female	41	(37.3)	71	(50.7)	.04*
Male	69	(62.7)	69	(49.3)	
Race/ethnicity	n	(%)	n	(%)	.45
African American	63	(57.3)	91	(65.0)	
Caucasian	26	(23.6)	22	(15.7)	
Hispanic	11	(10.0)	14	(10.0)	
Other	9	(8.2)	12	(8.6)	
Insurance	n	(%)	n	(%)	.79
Medicaid	62	(56.4)	72	(51.4)	
Private	36	(32.7)	53	(37.9)	
Other	2	(1.8)	5	(3.6)	
Unknown	10	(9.1)	10	(7.1)	
Maternal education	n	(%)	n	(%)	.11
Less than high school	13	(11.8)	32	(22.9)	
High school graduate or equivalent	46	(41.8)	60	(42.9)	
Partial college (>1 y) and associate degree	31	(28.2)	34	(24.3)	
Standard college/university graduate	11	(10)	6	(4.3)	
Graduate professional training with degree	7	(6.5)	4	(2.9)	

BMI, Body mass index (kg/m²); SD, standard deviation.

*P < .05.

National Institutes of Health studies conducted between 2002 and 2011 at the Child and Family Asthma Study Center, University at Buffalo. Children, aged 7 to 17 years, were recruited from the pediatric hospital emergency department after treatment for an asthma exacerbation. Exclusion criteria included: (1) comorbid chronic medical conditions (other than allergy and obesity), (2) psychosis, and (3) pharmacotherapy treatment for depression. Participants were informed about the study and signed assent and consent forms.

Procedure

Two to six weeks after the asthma exacerbation for which the child initially presented to the emergency department, patients and caregivers came to the lab for 3 consecutive visits, each lasting 2 to 3 hours. At the first laboratory visit, evaluation by the study allergist along with pulmonary function testing was used to determine that subjects' asthma was stable. All asthma-modifying medications were withheld for 12 hours before each visit (with proper safety precautions) to assess the child's baseline lung function (forced expiratory volume in 1 second [FEV₁]); medication treatment was resumed after each visit. During visits 1 and 2, the children underwent assessment by the study allergist to affirm asthma diagnosis and profile asthma severity using National Asthma Education and Prevention Program Expert Panel Report 3 criteria.¹ Asthma control and medication adherence were monitored using a validated 24-hour recall telephone interview technique. Medication adherence scores reflected the consistency with which the children took their medications as prescribed.³⁸

To assess ANS activity associated with changes in lung function under stress, visit 3 involved a laboratory-based, emotional stress/arousal induction procedure using a film stimulus. The children watched the film "E.T. the Extra-Terrestrial," which was selected to provide ecologically valid emotional stress and arousal. Physiologic

indices (ANS measures) were monitored and recorded continuously throughout the movie, and airway resistance (R_{int}) was measured before and after the film. Eleven scenes with varying emotional content (sad, happy, scary, and mixed sad/happy) were preselected for analysis.

Overweight/obesity and depression measures

At visit 3 to the psychophysiology laboratory, participants were measured for weight and height between 8:00 am and 9:00 am by the study nurse using a Health O Meter scale with a built-in height rod. Overweight/obesity was indexed according to the World Health Organization criteria using BMI, defined as the weight in kilograms divided by the square of the height in meters (kg/m²).³⁹ The CDC established the threshold for overweight children as BMI >85 percentile, and for obesity as BMI >95 percentile.⁴ For this study, subjects were stratified into 2 groups: NW children (n = 110) and OV/OB children (n = 140). The Children's Depression Inventory (CDI)⁴⁰ measured the child's depressive symptoms with high reliability and validity.⁴¹ Scores ≥12 are considered indicative of clinical depression.

Pulmonary function measures

Lung function was assessed using 2 different but convergent measures: (1) air flow was measured by FEV₁, and (2) airway resistance was measured by the airflow interrupter technique (R_{int}).⁴² FEV₁ is the clinical gold standard for diagnosing airflow obstruction and was used to characterize the child's asthma severity and baseline lung function. However, FEV₁ is an effort-dependent measure and relatively less sensitive in detecting small changes in airway function. R_{int} is a noninvasive, effort-independent measure, used mostly for research, which has greater sensitivity in detection of an airflow change, and was used to measure airway resistance before and after

TABLE II. Medical, physiological, and emotional characteristics of the study sample

	Normal weight (n = 110)		Overweight/obese (n = 140)		P
Medication prescribed					.60
Controller, n (%)					
ICS monotherapy	27	(24.5)	35	(25)	
LTRA monotherapy	6	(5.5)	10	(7.1)	
ICS/LABA combination inhaler	9	(8.2)	13	(9.3)	
ICS and LTRA	6	(5.5)	7	(5)	
ICS/LABA combination and LTRA	6	(5.5)	9	(6.4)	
ICS/LABA combination, LTRA, and additional ICS	2	(1.8)	2	(1.4)	
Rescue, n (%)					.97
β-Agonist	102	(92.7)	129	(92.1)	
Anticholinergic and β-agonist	0		1	(0.7)	
Burst, n (%)					.44
Oral steroids	8	(7.3)	7	(5)	
Allergy, n (%)					.23
Nasal steroid monotherapy	14	(12.7)	21	(15)	
Oral antihistamine monotherapy	10	(9.1)	11	(7.9)	
Nasal steroid and oral antihistamine	3	(2.7)	12	(8.6)	
Others, n (%)					.35
Antibiotics, analgesics, nonsteroidals, etc	10	(9.1)	18	(12.9)	
Patient adherence based on patient/parent report, n (%)					.67
Very poor	22	(20)	25	(17.9)	
Fair	25	(22.7)	21	(15)	
Good	18	(16.4)	33	(23.6)	
Very good	45	(40.9)	57	(40.7)	
Asthma severity, n (%)					.40
Intermittent	15	(13.6)	15	(10.7)	
Mild persistent	14	(12.7)	22	(15.7)	
Moderate persistent	45	(40.9)	50	(35.7)	
Severe persistent	36	(32.7)	53	(37.9)	
Pulmonary function, mean (SD)					
FEV ₁ % baseline	85.4	(15.4)	87.3	(15.9)	.35
FEV ₁ % post-movie	88.2	(16.7)	88.6	(17.1)	.85
R _{int} baseline	0.35	(0.15)	0.38	(0.14)	.42
R _{int} post-movie	0.34	(0.16)	0.37	(0.15)	.38
Physiology, mean (SD)					
HR baseline	78.4	(12.30)	81.84	(11.19)	.02*
RSA baseline	7.37	(1.13)	7.04	(1.24)	.03*
PEP baseline	81.5	(9.94)	81.55	(9.24)	.97
Depression index (CDI), mean (SD)	8.23	(6.80)	7.46	(5.60)	.33
					.27
Nondepressed (<12), n (%)	79	(71.8)	109	(77.9)	
Depressed (≥12), n (%)	31	(28.2)	31	(22.1)	

CDI, Children's Depression Inventory; FEV₁%, percent of forced expiratory volume in 1 second of predicted value; HR, heart rate (beats/min); ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LTRA, leukotriene receptor antagonist; PEP, pre-ejection period (ms); R_{int}, airway resistance measured by interrupter technique (kPa/L/s); RSA, respiratory sinus arrhythmia; SD, standard deviation.

*P < .05.

the film stressor.⁴² The 2 lung function measures were used to capitalize on their relative strengths: FEV₁ for baseline clinical assessment and R_{int} to detect acute changes in airway function.

Physiologic measures

ANS reactivity was measured by monitoring electrocardiography and impedance cardiography at baseline and throughout the

film. Parasympathetic/vagal activation was indexed by the respiratory sinus arrhythmia (RSA) method.⁴³ Sympathetic activation was indexed by computing the pre-ejection period (PEP) of the cardiac cycle, which was measured using both electro- and impedance cardiography.⁴⁴ To assess the relative balance of parasympathetic/vagal versus sympathetic reactivity in response to the emotional stress/arousing movie scenes, we constructed a variable

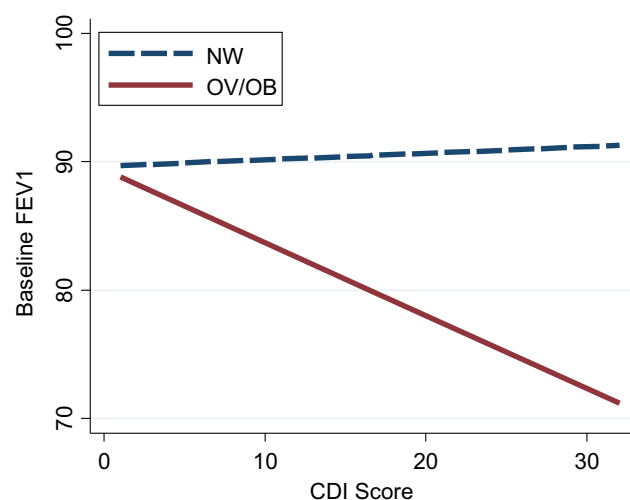


FIGURE 1. Representation of baseline FEV_1 (pulmonary function) as a function of the CDI score: OV/OB group coefficient ($\beta = -0.67$, $SE = 0.24$, $P = .01$); NW ($\beta = 0.29$, $SE = 0.20$, $P = .16$). *CDI*, Children's Depression Inventory; *FEV₁*, forced expiratory volume in 1 second; *NW*, normal weight; *OV/OB*, overweight/obese; *SE*, standard error.

called "vagal bias" (VB). To make this comparison, a mathematical computation was conducted using Z scores for RSA and PEP ($Z_{RSA} - Z_{PEP}$). A positive VB score indicates greater parasympathetic relative to sympathetic reactivity, whereas a negative score indicates greater sympathetic relative to parasympathetic reactivity. This mathematical approach provides a reliable method to compare the relative effects of RSA and PEP on the airways and lungs.³⁰

Data analysis

Descriptive statistics summarized demographic, physiologic, and asthma characteristics. The sample was stratified into NW and OV/OB groups. NW children were classified between the 5th and 85th percentile, and OV/OB children were above the 85th percentile. This stratification allowed the examination of within-group pathways and mechanisms by which depression and OV/OB impact lung function in children with asthma. Demographics and disease characteristics for the OV/OB and NW groups were compared using Independent Samples t -test, and Independent Samples Tests of Proportions.

Standard Linear Regression Modeling was used to test the effects of depressive symptoms and overweight/obesity on lung function. Possible demographic confounds including age, gender, ethnicity, maternal education, and medication adherence were included in the models. Analyses were performed with STATA 12.0.⁴⁵ We ran 2 independent Standard Linear Regression models to test whether CDI predicted baseline FEV_1 for the OV/OB and the NW groups. To further refine our results, we ran an established analysis designed for comparing beta coefficients between models to test whether the associations between CDI and FEV_1 were significantly different between the OV/OB and the NW groups.⁴⁶ We also used Standard Linear Regression Modeling to test the effects of depressive symptoms on VB and the effect of VB on changes in lung function (R_{int}) under emotional stress.

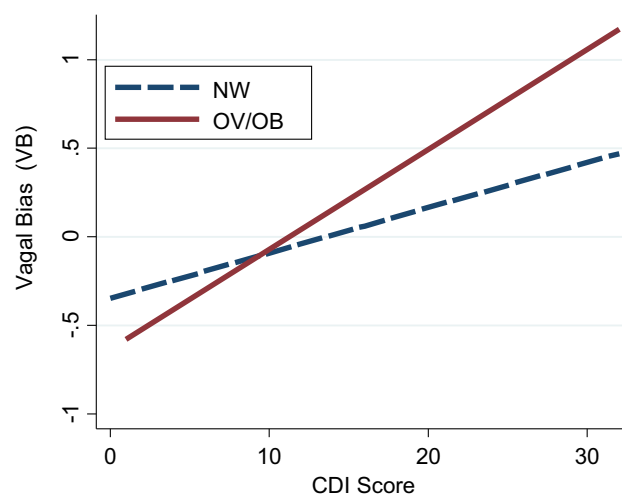


FIGURE 2. Representation of vagal bias (parasympathetic/vagal ANS dysregulation) as a function of the CDI score: OV/OB ($\beta = 0.27$, $SE = 0.09$, $P = .01$); NW ($\beta = 0.17$, $SE = 0.12$, $P = .15$). *ANS*, Autonomic nervous system; *CDI*, Children's Depression Inventory; *NW*, normal weight; *OV/OB*, overweight/obese; *SE*, standard error.

RESULTS

The demographics of the NW and OV/OB groups did not differ substantially, although the OV/OB group had a small, but statistically significant larger proportion of females (Table I). The NW and OV/OB groups did not differ in asthma characteristics, including severity, medications prescribed, adherence, or baseline lung function (Table II). The NW and OV/OB groups did not differ with respect to depressive symptoms (CDI). The CDI score in the NW group was $M = 8.23$, 6.80 standard deviation (SD), with 28% of participants above the clinical cutoff for depression ($CDI \geq 12$). In the OV/OB group, the CDI was $M = 7.46$, 5.60 SD, with 22% of participants above the clinical cutoff (Table II). In our sample, 12.4% of the children were both OV/OB and depressed, but we found no correlation between degree of overweight/obesity and level of depressive symptoms. As typically found in the literature, the OV/OB group's baseline heart rate was significantly higher ($t = -2.44$, $P = .02$) and baseline RSA (vagal tone) was significantly lower ($t = 2.21$, $P = .03$) than the NW group (Table II). Also, as expected, in the OV/OB group, low vagal tone was associated with greater vagal reactivity, indexed by VB ($\beta = -0.21$, $P = .005$).

Results of the multiple regression examining the joint impact of depressive symptoms and overweight/obesity on lung function were elucidating. In the OV/OB group, higher CDI predicted significantly lower baseline FEV_1 ($\beta = -0.67$, standard error [SE] = 0.24, $P = .01$). In contrast, CDI in the NW group did not predict levels of FEV_1 at baseline ($\beta = 0.29$, $SE = 0.20$, $P = .16$) (Figure 1). The difference between the slopes of these 2 groups was significant ($t = -2.0$, $P = .04$), indicating that increased depressive symptoms in the OV/OB group predicted decrement in (FEV_1) lung function, whereas they did not in the NW group. Results of the multiple regression examining the joint effect of depressive symptoms and BMI on parasympathetic/vagal ANS dysregulation showed that in the OV/OB group, higher CDI scores did predict greater VB averaged

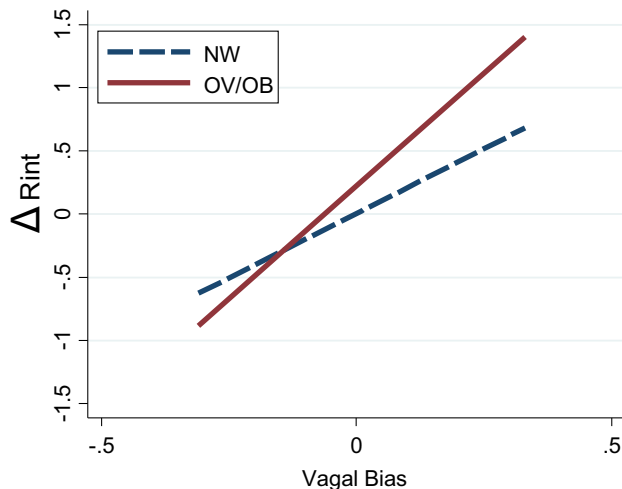


FIGURE 3. Representation of ΔR_{int} (change in airway resistance) as a function of vagal bias in reaction to film-induced emotional stress/arousal: OV/OB ($\beta = 3.55$, $SE = 1.54$, $P = .02$); NW ($\beta = 2.52$, $SE = 2.11$, $P = .24$). NW, Normal weight; OV/OB, overweight/obese; SE, standard error.

across the 11 scenes ($\beta = 0.27$, $SE = 0.09$, $P = .01$) (Figure 2). In contrast, in the NW group, CDI did not predict VB averaged across the 11 scenes ($\beta = 0.17$, $SE = 0.12$, $P = .15$). This indicates that increased depressive symptoms in conjunction with OV/OB contribute to the parasympathetic/vagal ANS dysregulation, which can potentiate worse lung function.

We examined the possible effect of scene types. For the OV/OB group, the association between CDI and VB appeared to be stronger in the 5 sad scenes ($\beta = 0.23$, $P = .012$) than in the 2 happy scenes ($\beta = 0.19$, $P = .045$) and the 4 mixed scenes ($\beta = 0.18$, $P = .035$). However, possibly due to power constraints, we were unable to establish statistically significant differences among the scene types. In contrast, in the NW group, CDI did not predict VB regardless of scene type.

To test whether VB/ANS dysregulation in response to the film stress predicted a change in lung function (before and after the film), VB scores were used in multiple regression as predictors of a change in airway resistance (ΔR_{int}). In the OV/OB group, greater VB predicted increased airway resistance after emotional stress/arousal (ΔR_{int}) ($\beta = 3.55$, $SE = 1.54$, $P = .02$), whereas VB did not predict ΔR_{int} in the NW group ($\beta = 2.52$, $SE = 2.11$, $P = .24$) (Figure 3).

DISCUSSION

The results of our study show that, for children with asthma, overweight/obesity in conjunction with increased levels of depressive symptoms predicted worse lung function and that vagal/cholinergic ANS dysregulation may be a mediating mechanism.

Although both obesity and depression independently are associated with poor asthma control in children and adults, an aspect of these comorbidities that has been less fully explored is the joint effect of depression and obesity in children with asthma. A longitudinal community-based study suggested that childhood depressive symptoms were associated with comorbid asthma and obesity in adulthood.⁴⁷ However, this study did not assess

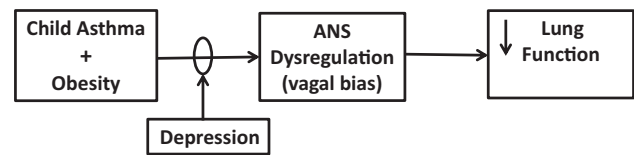


FIGURE 4. Summary interpretation of results. In children with asthma who are obese, depression contributes to decreased lung function mediated by autonomic nervous system (ANS) dysregulation, ie, vagal bias.

mechanisms underlying the inter-relations among depressive symptoms, obesity, and asthma severity or control. Kapadia et al⁴⁸ found that obesity and depression were both associated with higher risk of poor asthma control, but found no interaction between the effects of obesity and depression on asthma control. Boudreau et al³¹ demonstrated that depressive symptoms act as a mediator between obesity and asthma control in adults, but also did not explore the possible underlying mechanism.

Several mechanisms have previously been proposed to explain the association between asthma and obesity, including alterations in lung mechanics, inflammation, and hormonal/metabolic influences. When considering these potential mechanisms of the effect of obesity on asthma, several prospective pathways to link depression to these comorbidities emerge. Both obesity and depression have been associated with systemic states of chronic low-grade inflammation,⁴⁹ with the presence of increased proinflammatory cytokines such as TNF- α and IL-6.^{21,50,51} However, although inflammation is clearly present in obesity, studies show that OV/OB asthmatic patients have a poor response to anti-inflammatory inhaled corticosteroids, when compared with nonobese asthmatics.^{13,52,53}

Vitamin D deficiency has been associated with obesity, increased viral infections, and asthma exacerbations in both children and adults.^{54,55} Schatz et al⁵⁶ propose that the observed relationship between BMI and seasonal asthma exacerbations indirectly supports the hypothesis that vitamin D supplementation in obese/overweight patients may decrease asthma exacerbations, specifically those in the winter and fall seasons. As referenced above, vitamin D deficiency is associated with obesity and asthma. However, vitamin D deficiency is also associated with depression,^{57,58} and therefore depression may be implicated as a possible mechanism by which vitamin D deficiency is associated with worse asthma in the context of obesity.

In the current study, we found that an increase in depressive symptoms predicted a decrement in baseline lung function (FEV₁) in OV/OB children with asthma (Figure 1). Furthermore, these elevated levels of depressive symptoms were accompanied by ANS dysregulation, specifically VB, under conditions of emotional stress (Figure 2). This suggests that it is, in part, the presence of depression in OV/OB children with asthma that affects lung function and disease control, and that the effect of depressive symptoms on asthma control may be mediated by ANS dysregulation, specifically VB. Although depressive symptoms were not seen at a higher rate in OV/OB children than in NW children in our study population, it was in this OV/OB group that the presence of depressive symptoms was associated with impaired lung function measurements. It will be important to focus future research on determining whether

depression is a modifiable risk factor for uncontrolled asthma in the OV/OB population, who demonstrate a disproportionate impact of depressive symptoms on lung function. Our findings are consistent with Boudreau's findings in adults, which show depression as mediating the effect of obesity on asthma.³¹ In addition, our findings extend these results to children and demonstrate ANS dysregulation, ie, vagal bias, as a possible mechanism of effect.

More specifically, we found that depressive symptoms in the OV/OB group were associated with greater VB in response to the emotional stress/arousal film, and that this ANS dysregulation was accompanied by increased airway resistance (ΔR_{int}) from pre-to post-film measurement (Figure 3). Although OV/OB children in our study had lower vagal tone at baseline, regardless of their depressive symptoms, only those with both overweight/obesity and increased depressive symptoms showed greater vagal reactivity under conditions of emotional stress/arousal. These findings suggest that the airway compromise demonstrated in OV/OB children with asthma is mediated, at least in part, by depression. They further point to ANS dysregulation, specifically VB, as one mechanism by which emotional stress leads to airway constriction.

In conclusion, our findings suggest that depression potentiates the negative effect of overweight/obesity on airway function in children with asthma, and that this effect may be mediated by vagal bias (Figure 4). We posit that it is the stress-induced, vagal/cholinergic influence on bronchial smooth muscle that leads to consequent airway constriction. We have found in another study that increased depressive symptoms are associated with increased bronchodilatory response to short-acting inhaled anticholinergics in child asthmatics (H.K. Lehman, MD, unpublished communication, 2019). The findings from this study may explain in part why children with asthma who are depressed and overweight/obese have more difficult-to-control asthma and do not respond well to conventional asthma therapies, because these treatments target the sympathomimetic and allergic-immune pathways, and not the vagal/cholinergic pathways implicated herein.

Clinical implications

Findings from our study indicate a potentially harmful synergy when childhood asthma is complicated by comorbid overweight/obesity and depression. In particular, children with asthma who are OV/OB and depressed may have increased susceptibility to the effect of stress on their lung function, by way of vagal/cholinergic pathways. In real-life situations, where emotional stress is an everyday occurrence and at times extreme, this may explain in part the increased difficulty in managing some OV/OB children with asthma, where depression may be implicated but not recognized. This points to the importance of assessing depressive symptoms in children with asthma, especially if they are overweight or obese, and in arranging for referrals for therapeutic intervention to treat both the depression and the overweight/obesity. Pharmacotherapy may be effective in treating depression, along with psychosocial and psychotherapeutic interventions to reduce child stress. Diet and exercise programs may be beneficial in treating overweight/obesity as well as depression.⁵⁹ When resources are scarce, our findings suggest that screening and treatment for depression in children with asthma should be especially prioritized in those with comorbid overweight/obesity.

In light of our findings that the effects of depressive symptoms on airway function in OV/OB children with asthma may be mediated in part by vagal/cholinergic pathways, anticholinergic asthma medications that target the cholinergic system, for example, ipratropium, may be of greater benefit in treating children with asthma with comorbid overweight/obesity and depression. This approach to treatment may address the clinical observation that conventional treatment targeting immune-inflammatory pathways and sympathomimetics are less effective in some obese asthmatic patients.

Limitations and future research

This study included a predominance of subjects from minority backgrounds, and therefore the findings may not apply generally. Future investigations that include a diverse ethnic and socioeconomic population would allow for greater specification or generalization of the findings reported herein.

Furthermore, we did not examine alternative pathways by which depression may impact disease activity and lung function in OV/OB children with asthma, for example, hypothalamic pituitary adrenal axis and immune/inflammatory pathways. There is a possibility of additional mediators involved in the interplay of asthma, depression, and overweight/obesity. One such candidate could be leukotrienes. Cysteinyl leukotrienes are potent bronchoconstrictors⁶⁰ and induce eosinophilic inflammation.⁶¹ Leukotriene modifiers benefit some asthmatics, although the subset of antileukotriene-responsive asthmatics is relatively ill-defined. It is recognized that adipocytes secrete leukotrienes⁶² and that abdominal obesity is associated with increased urinary leukotriene E4.⁶³

Studies examining the interplay of ANS dysregulation with hypothalamic pituitary adrenal axis and immune/inflammatory pathways, including those exploring leukotriene-mediated inflammation and airway constriction, may allow for a more comprehensive understanding of mechanisms underlying the problematic relationships of overweight/obesity and depression in childhood asthma. Such studies could lead to the development of more targeted pharmacologic and psychosocial interventions.

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