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Obesity and childhood asthma – mechanisms and manifestations

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Abstract

Obesity is a chronic condition affecting children worldwide. However, the prevalence is higher in asthmatic children. Obese children most likely become obese adults. Understanding the clinical presentation of this sub-group is essential to their clinical management, now and in the future. This review highlights the most recent findings over the past 18 months in understanding the presentation and potential mechanisms of obesity in childhood asthma.

Recent research suggests that inhaled corticosteroid efficacy is reduced in obese asthmatic children while ventilatory function and broncho-reactivity appear to be marginally affected. A paucity of studies describing airway inflammation and lung volume measurements in this sub-group limits their clinical characterisation. Recent studies indicate metabolic abnormalities that typically manifest with excess adiposity, may be associated with asthma providing an interesting factor in the asthma-obesity link. The inception, persistence and composition of obesity prove important considerations for future studies.

Highlighted is the need for more descriptive airway inflammation studies, lung volume assessments and longitudinal studies to better characterise the obese asthma phenotype in children and understand the pathogenesis from childhood through to adulthood. Understanding the manifestations and mechanisms of obese asthma in childhood will help direct clinical management and targeted therapeutic interventions.

Key words: asthma, child, obesity, overweight

Childhood Obesity: tipping the morbidity scales

Asthma, overweight and obesity are the most common chronic morbidities in children from economically developed regions, affecting up to one in six and one in five children respectively[1, 2]. Alarming, the prevalence of overweight and obesity increases further if asthma is present, with this trend being reported in children from America, Australia and Denmark[3-5]. A recent study in asthmatic children found more than one third were overweight or obese[6*]. Indeed, the prevalence of asthma has also been reported to be significantly greater in obese and morbidly obese children compared to those of a healthy weight[7**]. Although the obese phenotype in asthma has gained momentum in recent years and has been characterised in adults[8, 9], its clinical presentation in childhood has not been thoroughly investigated. The manifestations, mechanisms and management of both obesity and asthma differ through the life stages. Importantly, the pathogenesis and presentation of obese asthma in children is likely to differ from that of adults (Table 1).

In agreement with previous literature, an association between asthma and obesity in children and adolescents was reported in recent studies[7**, 10, 11*, 12, 13*]. Two recent analyses of large cohorts reported that increased body mass index (BMI) and/or adiposity in children was associated with increased asthma symptoms, asthma exacerbations and emergency department presentations[11*, 14**]. However, a contrasting report found no significant difference in baseline quality of life, asthma severity classification, or prospective health care usage between healthy weight, overweight, or obese children[6*].

The nature of the relationship between obesity and asthma in children remains to be elucidated. Multiple mechanisms, primarily surrounding obesity physiology, co-morbidities, and the hypersecretion of pro-inflammatory mediators as the causal factor, have been proposed[15, 16]. Given that a rise in prevalence of both conditions has paralleled Westernisation, it is also plausible that shared environmental factors are common to the rise of both obesity and asthma in childhood. Characteristic of Westernisation is the 'obesogenic environment', which encourages a chronic excess

intake of energy and an increased ratio of physical inactivity: activity. Given the perpetual rise in global childhood obesity rates, the presentation of the obese asthmatic child will likely become more common. Therefore, it is essential that we begin to understand the mechanisms and manifestations of asthma in this subgroup of children to appropriately inform clinical management. This review will summarise the most recent developments in exploring the link between asthma and obesity in childhood.

Manifestations of obese asthma

Evidence in adults suggests that obesity is associated specifically with non-atopic asthma[8]. Although the association between obesity and asthma exists in both atopic and non-atopic children, it is reportedly stronger in the absence of atopy[11*]. While Yao et al found no association between BMI and atopy[10], another study found overweight children were more likely to be atopic compared to their healthy weight peers[17].

Airway Inflammation

Obese asthma has been described in adults as a distinct clinical phenotype requiring alternate approaches to clinical management[9]. Studies examining airway differential cell counts have suggested that obese asthma in adults exhibits a non-eosinophilic pattern with significant neutrophilia, particularly predominant in females[8, 9]. However, there are minimal sputum studies in children, and to our knowledge none have investigated airway inflammation in obese children. Although exhaled nitric oxide (eNO) is increased in healthy weight asthmatic children and obese non-asthmatic children compared to healthy weight, healthy controls, no clinically significant difference in eNO has been found between obese and healthy weight asthmatic children[18*, 19*20*]. In fact, excess weight as determined by adjusted BMI or total percentage body fat is not associated with eNO in asthmatic children[14**]. However, differential cell count studies may demonstrate differences in airway inflammatory cells between obese and non-obese children and further investigation is required.

Lung function

Obesity adversely affects lung function in adults, both with and without asthma. The greatest reductions in adults are seen in expiratory reserve volume (ERV) and functional residual capacity (FRC)[21, 22]. However, in the obese child, ventilatory function appears to be largely unaffected, and lung volume measurements have not been reported. A recent large prospective trial which enrolled children and adults with asthma, reported significantly decreased baseline forced vital capacity (FVC) in obese adults which was not present in obese children[6*]. In fact, multiple studies have reported no difference in baseline forced expiratory volume in 1 second (FEV₁) or FVC between healthy weight, overweight and obese asthmatic children[6*, 17, 18*, 20*, 23**]. However, a recent post-hoc analysis of data from the Childhood Asthma Management Program (CAMP) found a significantly reduced FEV₁/FVC in children $\geq 85^{\text{th}}$ BMI percentile compared to healthy weight children[23**]. This was supported by similar findings in Korean adolescent males[17]. Likewise, in a large sample of predominantly non-Caucasian urban American youths, an inverse relationship between FEV₁/FVC and both percentage body fat and BMI was reported[14**]. Although, Peters et al reported the proportion of asthmatic children with FEV₁/FVC <70% to be similar between normal weight, overweight and obese children[6*].

Interestingly, smaller cross-sectional studies have noted significant deficits in lung function in obese children without asthma that did not exist in obese children with asthma[18*, 20*]. Reductions in baseline forced expiratory flow (FEF)₂₅₋₇₅ between obese and normal weight children, with and without asthma, have been reported by Baek et al[20*]. However, in addition, obese children without asthma had significant reductions in baseline FEV₁ and FEV₁/FVC compared to healthy controls[20*]. In another study, obesity was independently related to peak expiratory flow (PEF) and maximal expiratory flow at 75% of the FVC (MEF₇₅) with significantly lower baseline values in the obese children with and without asthma, compared to healthy controls[18*]. However, these differences were not evident between obese and normal weight asthmatic children[18*], suggesting

that the effect of obesity may be small compared to the effect of asthma. Given that the greatest deficits in lung function with adult obesity are seen in ERV, it would indicate that lung volume assessment is needed in future studies of childhood obesity.

Bronchoconstriction

Recent reports provide conflicting evidence as to whether the severity of bronchial reactivity is greater in obese children. Two recent studies did not find a significant difference in the prevalence of bronchial hyper-responsiveness (BHR) between overweight/obese and normal weight asthmatic children[18*, 20*]. Although, another study did find BHR to be significantly higher in overweight asthmatic females[17]. In a cross-sectional study, obese asthmatic children had the greatest FEV₁ reduction post-exercise and a greater AUC₂₀ (area under the FEV₁ time curve over a 20 mins post-exercise time period, expressed as a percentage change from baseline x minutes) compared to healthy weight asthmatic children, indicating that although bronchoconstriction in asthmatic children may not be more prevalent, it may be more severe, in those who are obese[20*]. Of interest, these differences were no longer evident after adjusting for serum leptin and adiponectin levels[20*], suggesting that the mechanism of action in bronchoconstriction may be via increased systemic inflammation created by excess adiposity, rather than the mechanical effects of excess weight. A similar study found obese children, both with and without asthma, had significantly lower post-exercise MEF₇₅ compared to healthy controls[18*]. However, there was no difference between obese and healthy weight asthmatics. Furthermore, the healthy weight asthmatics experienced a significant reduction in FEV₁, FVC and FEF₂₅₋₇₅ post-exercise, while the obese asthmatics had a significant reduction in only FEV₁/FVC post-exercise[18*].

Corticosteroid resistance

Obesity in asthmatic adults has been associated with resistance to inhaled corticosteroids (ICS)[24, 25]. A decrease in corticosteroid efficacy in obese asthmatic children has also been suggested by reports of more frequent and more severe exacerbations, and increased use of rescue short acting β_2 -agonists and steroid based medications[26, 27]. The effect of inhaled budesonide (400ug daily) in overweight and obese children enrolled in the 4 yr prospective CAMP trial, is reportedly reduced in magnitude and significance, suggesting steroid insensitivity may be present in children with a higher BMI[23**]. Compared to subjects receiving placebo/nedocromil, healthy weight asthmatics had initial and continued improvements in FEV₁, FEV₁/FVC and bronchodilator response with budesonide, whereas overweight and obese children had only minor initial improvements in FEV₁ and bronchodilator response with no further improvements in any lung function variables over time[23**]. Furthermore, although there was a significant reduction in the number of prednisone courses required by overweight/obese children receiving budesonide compared to those on placebo/nedocromil, the magnitude of effect was not as great as that reported for healthy weight asthmatics. Unlike the healthy weight asthmatics, there was no change in emergency department presentation/hospital admissions for obese children treated with the same ICS dose[23**]. These results may suggest that ICS efficacy in the obese asthmatic child is reduced. This is an important finding given the predominate use of ICS to control childhood asthma and may be relevant to the clinical management of the obese child and therefore requires further investigation.

Mechanisms of obese asthma

Given that the clinical presentation of obese asthma appears to differ in children compared to adults, it is plausible that the mechanisms may also differ. Research is indicating that the timing of both obesity and asthma onset influences the present and future clinical presentation of the obese individual with asthma, and therefore the mechanisms must differ[28**,29*,30*] (Fig. 1).

Growth & body composition

Hypothesised mechanisms for the deleterious effect of obesity upon respiratory status have focused on the effects of excess fat mass. However, most studies define obesity by measures of BMI, a crude translation of adiposity. Obesity defined by BMI measures describes excess collective mass, i.e. both lean and fat mass. This is an important consideration particularly in paediatrics, as the changes in body composition that occur with obesity have differential effects upon lung function. Indeed, unpublished data from our group have demonstrated positive effects of increased lean mass on lung function in obese and non-obese children, whereas fat mass was detrimental (*Jensen et al, unpublished data*).

Children follow a growth trajectory with periods of growth acceleration. Characteristic of growth is the favoured deposition of lean mass, in addition to fat mass. However, in adults the deposition of fat predominates with increasing weight. There are three critical periods of high adiposity risk that are thought to determine persistent childhood obesity: prenatal, adiposity rebound, and adolescence[31]. Periods of growth outside the critical periods for increased adiposity may not be linked to asthma outcomes. One study noted that the development of obesity at age 5 yrs, corresponding approximately to the period of adiposity rebound, was associated with increased risk of asthma diagnosis and poorer lung function at age 6 and 8 yrs[28**]. However, excess weight in

the period prior to this was not related to any future asthma outcomes. In fact, a higher BMI in infancy was associated with a reduced risk of asthma and greater lung function as a child[28**]. The first 12 months of life is a rapid growth stage and a higher BMI may reflect the optimal deposition of lean mass and/or a state of adequate nutrition which may influence lung development in early life.

Although body composition studies in adults have reported that fat mass is inversely associated with respiratory status, well designed studies are required in children, as use of BMI z-score can be misleading. Indeed, one study found no difference in weight or BMI z-score between asthmatic children and healthy controls[32*]. Despite this, the percentage of adiposity was significantly greater in the asthmatic children[32*]. Recent data have suggested that an increased childhood BMI is associated with increased adult FEV₁ and FVC[29*]. However, these seemingly positive effects disappeared after adjusting for indirect measures of lean body mass (handgrip strength and derivations from skin-fold tests).

Differential effects of obesity on lung function may also reflect the duration of obesity i.e. the longer the period of obesity, the more detrimental the effect upon respiratory status. Significantly reduced lung function in overweight and obese female adults was recently reported to be evident only in those who were overweight or obese as a child[29*]. In this group of women, an interaction effect between age and BMI was reported, indicating a worsening decline in lung function with persisting obesity as they aged[29*]. In another study, authors compared lung function of obese paediatric and adult subjects divided into groups according to the duration of obesity (≤ 5 yr, $>5-10$ yr, $>10-15$ yr, >15 yr)[30*]. After controlling for age and the presence of co-morbidities such as asthma, decrements in ventilatory lung function and lung volumes were significantly greater in those with the longest duration of obesity[30*]. This suggests that the onset and duration of obesity, as well as the composition of the excess weight, may be an important consideration when assessing effects upon lung function. Longitudinal studies, including direct measures of body composition, are

required to investigate the progression of obese asthma from childhood, through to adolescence and adulthood.

Inflammation

In obesity, the endocrine functions of adipose tissue lead to a chronic inflammatory state that contributes to the development of multiple chronic diseases, including cardiovascular disease and diabetes. Increased systemic inflammation has been hypothesised as a potential link between asthma and obesity in childhood, by augmenting airway inflammation[16]. However, this hypothesis has not been thoroughly investigated in children, largely due to a lack of descriptive airway inflammation studies.

Increased systemic inflammation is evident in obese adults compared to non-obese adults with asthma, particularly increased plasma leptin and IL-6 levels, and reduced adiponectin levels[8, 33]. Circulating levels of both IL-6 and CRP were recently reported to be weakly but significantly correlated with airway neutrophils[8]. In the same adult population, plasma IL-6 was associated with worsened clinical outcomes[8]. Increased leptin and reduced adiponectin levels are also evident in obese children as compared to non-obese children with asthma, while there are reportedly no differences in IL-6 or TNF- α levels[20*]. Recent studies have indicated that systemic inflammation may be related to asthma outcomes in children. Adiponectin is reportedly positively associated with asthma control, FEF_{25-75} and FEV_1/FVC ; and negatively correlated with asthma symptoms, exacerbations, and markers of exercise-induced bronchoconstriction (EIB) severity, even after controlling for BMI[14**, 20*]. The odds of an asthmatic child experiencing EIB and EIB of a greater severity is reportedly higher in the presence of raised serum leptin levels, independent of the child's BMI[20*]. These results may indicate that the mechanism is not the excess weight per se, but the associated increase in the leptin/adiponectin ratio. Whether this mechanism involves increased

airway inflammation is not known. Certainly, airway inflammation, as measured by eNO, has not been found to correlate with systemic inflammatory markers[20*]. This is not surprising given there are no reported differences in eNO between obese and normal weight asthmatic children[20*] and it is therefore unlikely that obese asthma operates via increased eosinophilic inflammation. Given the distinct differences in airway inflammation in obese asthmatic adults, and the implication for alternate asthma treatment, there is a need for more descriptive airway inflammation studies in paediatric obese asthma.

Metabolic abnormalities

The effects of obesity may only be seen when the hypersecretion of metabolic factors produced by excess adipose tissue reach a certain hypothetical threshold. These metabolic factors include adipokines which induce a proinflammatory environment and, more recently suggested, markers of insulin resistance and serum lipid levels[7**, 19*]. Hypertriglyceridemia, hypercholesterolemia and an increased HOMA-IR are metabolic abnormalities more common in obesity. While these abnormalities are typically associated with obesity, they can also occur in individuals with a healthy BMI and be absent in those with an increased BMI, introducing the concept of the metabolically healthy and metabolically unhealthy individual.

In a large cross-sectional analysis of American children enrolled in the CARDIAC study, hypertriglyceridemia and insulin resistance were positively associated with asthma, independent of BMI[7**]. Another study of interest in an Australian sample of children reported significantly higher levels of HOMA-IR in asthmatics compared to matched controls, regardless of BMI z-score[19*]. In fact insulin resistance, determined as HOMA-IR ≥ 1.77 , was prevalent only in the asthmatic children (42.9%)[19*]. These studies did not include a measure of body composition which may have provided more insight, given that adiposity levels are reportedly higher in asthmatic children compared to age, gender and BMI matched healthy controls[32*]. However, these studies introduce

an interesting concept that the presence of obesity may be reflecting underlying metabolic abnormalities that usually accompany excess adiposity, such as insulin resistance and altered serum lipid levels. The potential role of such abnormalities in asthma pathophysiology is an interesting consideration for future studies.

Future implications:

Given that asthma and obesity are the most common chronic morbidities in children from Western societies, the co-presentation of these conditions in childhood demands thorough investigation, including more descriptive studies of airway inflammation, respiratory function, and body composition. Importantly, there is a call for longitudinal studies to track changes in clinical asthma markers and body composition in this subgroup of children as they transition into adulthood. Although it appears that the efficacy of inhaled steroid medication in asthmatic children may be attenuated in the presence of obesity, the effects of excess weight upon childhood asthma treatment requires more in depth investigation. The obese child most likely becomes an obese adult, and the girth of the 'asthma-obeso-genic' environment is only expanding. Therefore, paediatric obese asthma is an important area of research for the clinical management of the obese child now and for the health of the future adult.

Key points:

- Overweight and obesity is higher in children with asthma compared to general population.
- The timing of onset and persistence of obesity, and the composition of excess mass are important considerations for future studies.
- Manifestations typical of excess adiposity e.g. insulin resistance, may be important in the asthma-obesity link.
- Obese asthma remains to be adequately characterised in children and descriptive airway inflammation studies and lung volume measurements are required.

Table 1: Clinical manifestations of obese asthma

Manifestations	Child	Adult
Airway Inflammation ^[8, 9, 18-20]	— ^a	↑ (neutrophilic)
Systemic Inflammation ^[8, 14, 20]	↑	↑
Steroid response ^[23-25, 34]	↓	↓
Bronchial hyperreactivity: ^[15, 18, 20, 22, 27, 35]		
- Prevalence	— / ↑	— / ↑
- Severity	↑	—
Severity: ^[6, 11, 14, 15, 26, 36, 37]		
- Symptoms	↑	↑
- HCU	— / ↑	↑
- Medication use	↑	↑
Lung function: ^[6, 21, 22, 38]		
- Obstruction	— / ↑	↑
- Restriction	?	↑
Quality of life ^[6, 27]	— / ↓	↓

— No difference, ↑ increased in obese asthma, ↓ decreased in obese asthma; ^a data based on eNO only

Figure Legend

Figure 1. Multiple factors influence body composition, which may be an important factor when considering the effects of excess mass upon respiratory status. Lean mass may attenuate detriments in lung function caused by excess adiposity and may have neutral effects on other clinical asthma markers.

Figure 1. Mechanisms of Paediatric Obese Asthma

References

1. Lobstein T, Baur L, Uauy R. Obesity in children and young people: a crisis in public health. *Obesity Reviews*. 2004;5:4-85.
 2. Masoli M, Fabian D, Holt S, Beasley R. Global Burden of Asthma: Global Initiative for Asthma 2004.
 3. Welsh L. Physical Activity, Aerobic Fitness, Body Composition and Asthma Severity in Children and Adolescents. Fitzroy: Australian Catholic University; 2006.
 4. Vahlkvist S, Pedersen S. Fitness, daily activity and body composition in children with newly diagnosed, untreated asthma. *Allergy*. 2009;64:1649-55.
 5. Bender B, Fuhlbrigge A, Walders N, Zhang L. Overweight, Race, and Psychological Distress in Children in the Childhood Asthma Management Program. *Pediatrics*. 2007;120:805-13.
 6. Peters JI, McKinney JM, Smith B, et al. Impact of obesity in asthma: evidence from a large prospective disease management study. *Annals of Allergy, Asthma & Immunology*. 2011;106(1):30-5.
- *This study provides an assessment of clinical outcomes in obese and non-obese asthmatic children and adults.
7. Cottrell L, Neal WA, Ice C, et al. Metabolic Abnormalities in Children with Asthma. *Am J Respir Crit Care Med*. 2011 February 15, 2011;183(4):441-8.
- **This study was conducted in a very large sample of children and suggests that metabolic abnormalities may be the link between asthma and obesity.
8. Scott HA, Gibson PG, Garg ML, Wood LG. Airway Inflammation is Augmented by Obesity and Fatty Acids in Asthma. *European Respiratory Journal*. 2011 February 10.
 9. Halder P, Pavord ID, Shaw DE, et al. Cluster Analysis and Clinical Asthma Phenotypes. *Am J Respir Crit Care Med*. 2008;178:218-24.
 10. Yao T-C, Ou L-S, Yeh K-W, et al. Associations of Age, Gender, and BMI with Prevalence of Allergic Diseases in Children: PATCH Study. *Journal of Asthma*. 2011;48(5):503-10.
 11. Visness CM, London SJ, Daniels JL, et al. Association of Childhood Obesity With Atopic and Nonatopic Asthma: Results From the National Health and Nutrition Examination Survey 1999-2006. *Journal of Asthma*. 2010;47(7):822-9.
- *Large data set with asthmatic children divided by atopy status and relationship to weight and inflammation levels.
12. Suglia SF, Chambers EC, Rosario A, Duarte CS. Asthma and Obesity in Three-Year-Old Urban Children: Role of Sex and Home Environment. *The Journal of Pediatrics*. 2011;159(1):14-20.e1.
- *Demonstrated that the relationship between obesity and asthma in girls and boys exists despite accounting for shared social and environmental factors.
13. Okabe Y, Itazawa T, Adachi Y, et al. Association of overweight with asthma symptoms in Japanese school children. *Pediatrics International*. 2011;53(2):192-8.
- *Provides needed nation-wide data on body weight and asthma in children of different age groups and regions of Japan.
14. Kattan M, Kumar R, Bloomberg G, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol*. 2010;125:584-92.
- **This study collected important clinical outcome data at multiple time-points in a large sample of pre-dominantly ethnic children over a 12 month period. Measurements included body composition analysis and systemic inflammatory markers.
15. Farah CS, Salome CM. Asthma and obesity - a known association but unknown mechanism. *Respirology*. 2011.
 16. Jensen ME, Collins CE, Gibson PG, Wood LG. The Obesity Phenotype in Children with Asthma. *Paediatric Respiratory Reviews*. 2011 Sep;12(3):152-9.

17. Yoo S, Kim H-B, Kim B-S, et al. Association between obesity and the prevalence of allergic diseases, atopy, and bronchial hyperresponsiveness in Korean adolescents. *Int Arch Allergy Immunol*. 2011;154:42-8.

18. Consilvio NP, Di Pillo S, Verini M, et al. The reciprocal influences of asthma and obesity on lung function testing, ahr, and airway inflammation in prepubertal children. *Pediatric Pulmonology*. 2010;45(11):1103-10.

*This study reports the individual and combined effect of obesity and asthma upon exercise induced bronchoconstriction in children.

19. Arshi M, Cardinal J, Hill RJ, et al. Asthma and insulin resistance in children. *Respirology*. 2010;15(5):779-84

*This small study suggests that metabolic abnormalities and insulin resistance are a potential link between overweight and asthma in children.

20. Baek H-S, Kim Y-D, Shin J-H, et al. Serum leptin and adiponectin levels correlate with exercise-induced bronchoconstriction in children with asthma. *Ann Allergy, Asthma Immunol*. 2011;107(1):14-21.

*This study suggests that exercise induced bronchoconstriction is related to increased systemic inflammation, rather than the actual weight.

21. Sin D, Sutherland E. Obesity and the lung: 4 Obesity and asthma. *Thorax*. 2008;63:1018-23.

22. Sutherland TJ, Cowan JO, Young S, et al. The Association between Obesity and Asthma. Interactions between Systemic and Airway Inflammation. *Am J Respir Crit Care Med*. 2008;178:469-75.

23. Forno E, Lescher R, Strunk R, et al. Decreased response to inhaled steroids in overweight and obese asthmatic children. *Journal of Allergy and Clinical Immunology*. 2011;127(3):741-9.

**This study reports for the first time the reduced efficacy of inhaled corticosteroids in obese children over a 4 year period. This addresses an important issue in the clinical management of the obese child with asthma.

24. Boulet L-P, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med*. 2007;101(11):2240-7.

25. Sutherland ER, Goleva E, Strand M, et al. Body Mass and Glucocorticoid Response in Asthma. *Am J Respir Crit Care Med*. 2008;178:682-7.

26. Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr*. April 1998;132(4):699-703.

27. van Gent R, van der Ent C, Rovers M, et al. Excessive body weight is associated with additional loss of quality of life in children with asthma *J Allergy Clin Immunol*. 2007;119:591-6.

28. Zhang Z, Lai HJ, Roberg KA, et al. Early childhood weight status in relation to asthma development in high-risk children. *Journal of Allergy and Clinical Immunology*. 2010;126(6):1157-62.

**This study is privy regularly collected data on children of an atopic parent(s). Measurements taken from birth to age 8 years provides an interesting look at the effects of weight status on future asthma risk and lung function.

29. Curry BA, Blizzard CL, Schmidt MD, et al. Longitudinal Associations of Adiposity With Adult Lung Function in the Childhood Determinants of Adult Health (CDAH) Study. *Obesity*. 2011;19(10):2069-75.

*This longitudinal study provides an indication that the duration and composition of obesity is an important consideration when assessing respiratory status.

30. Santamaria F, Montella S, Greco L, et al. Obesity Duration Is Associated to Pulmonary Function Impairment in Obese Subjects. *Obesity*. 19(8):1623-8.

*This study reports for the first time the effects of persistent obesity upon lung function in a group of paediatric and adult subjects.

31. Adair LS. Child and adolescent obesity: Epidemiology and developmental perspectives. *Physiology & Behavior*. 2008;94(1):8-16.
32. Vahlkvist S, Inman MD, Pedersen S. Effect of asthma treatment on fitness, daily activity and body composition in children with asthma. *Allergy*. 2010;65(11):1464-71.

*This study demonstrates that asthma may be associated with higher adiposity and increased risk for weight gain via reduced physical activity levels unless properly controlled.

33. Lessard Aa, St-Laurent J, Turcotte Hln, Boulet L-P. Leptin and adiponectin in obese and non-obese subjects with asthma. *Biomarkers*. 2011;16(3):271-3.
34. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index on the response to asthma controller agents. *Eur Respir J*. 2006;27:495-503.
35. Ulger Z, Demir E, Tanac R, et al. The effect of childhood obesity on respiratory function tests and airway hyperresponsiveness. *Turk J Pediatr*. 2006;48:43-50.
36. Taylor B, Mannino D, Brown C, et al. Body mass index and asthma severity in the National Asthma Survey. *Thorax*. 2008;63:14-20.
37. Carroll C, Bhandari A, Zucker A, Schramm C. Childhood obesity increases duration of therapy during severe asthma exacerbations. *Pediatr Crit Care Med*. 2006;7:527-31.
38. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003 December 1, 2003;58(12):1036-41.