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To cite this article: Faiza Khalid & Fernando Holguin (2018): A review of obesity and asthma across the life span, Journal of Asthma, DOI: [10.1080/02770903.2018.1424187](https://doi.org/10.1080/02770903.2018.1424187)

To link to this article: <https://doi.org/10.1080/02770903.2018.1424187>



Published online: 08 Feb 2018.



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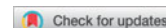
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A review of obesity and asthma across the life span

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ABSTRACT

Objective: This literature review aims to compare obese-asthmatic adults and children, and to characterize differences and similarities between the two subgroups from epidemiological, demographic, phenotypical, and physiological perspectives. **Methods:** Literature search was conducted using Pubmed database with "obesity," "asthma," "epidemiology," "cluster analysis," "demography," "mechanics," and "FeNO" as search terms. **Methods:** Articles investigating epidemiological, demographic, phenotypical variation, and mechanical aspects of breathing specifically in obese asthmatics were identified. The studies were then divided according to age: children (<18 years of age) and adults (>18 years of age). **Results:** Increase in asthma incidence and prevalence is observed in both obese-asthmatic children and adults. Asthma prevalence is greater in adult females regardless of ethnic background, and in men of African American and Hispanic ethnicities. Degree of weight gain and early onset of menarche appears to directly affect asthma severity in adolescent girls and females. Airway hyperresponsiveness and fractional exhaled nitric oxide do not have any positive correlation with high BMI in obese-asthmatic children and adults. Obesity also alters lung mechanics in asthmatics, but the impact is different for children and adults likely due to differential effect of obesity on central and peripheral airway. **Conclusion:** Existing literature suggests both similarities and differences in obese-asthmatic children and adults. The most pertinent differences are related to gender, ethnicity, and lung functions.

ARTICLE HISTORY

Received 6 September 2017

Revised 26 December 2017

Accepted 1 January 2018

KEYWORDS

Obese; asthmatics; demographics; phenotype; lung mechanics; FeNo

Introduction

It is established that obesity-asthma phenotype represents a unique set of observable characteristics (1–3). However, within this phenotype we believe that significant differences are present in the epidemiological, demographic, phenotypical, and physiological aspects when looked at from pediatric and adult perspectives. Tracing these differences from pediatric population into adulthood may provide better insight into the course of the disease for this phenotype. Most investigators define overweight and obesity as BMI >25 and >30 kg/m², respectively in adults. In children, overweight and obesity are typically defined as BMI of >85th and 95th percentile (adjusted for age and sex), respectively, unless mentioned otherwise. In this review, we aim to characterize differences in obesity-asthma phenotype in the pediatric and adult populations based on available literature.

Methodology

We conducted an initial Pubmed search using search terms "obesity," "asthma," "epidemiology," "cluster analysis," "demography," "mechanics," and "FeNO" for studies

published in English and including all ages from 1990 through the present. Bibliographies from the selected articles obtained through this search were screened for additional references which were also cross-checked for pertinent studies. Studies older than 1990, not published in English language, case reports or case series, review articles, and studies focusing on non-obese asthmatics or obesity without asthma were excluded.

Articles were then organized according to their content, i.e., discussing epidemiology, demographics, phenotypical variations, and physiological/mechanical aspects. For phenotypical comparison we selected studies deliberating airway hyper-responsiveness and fractional exhaled nitric oxide (FeNO).

After categorizing papers according to their content, research findings were further divided according to age groups involved: children (<18 years) and adults (>18 years) for comparison.

Results

In the sections below, we will compare obese-asthmatic children and adults from various aspects and summarize significant findings from literature.

Epidemiology of obese-asthma phenotype (Findings summarized in Table 1)

Asthma Incidence: Parallel increase in the incidence of both asthma and obesity has led to the speculation that there is a causal relationship between the two. This observation is supported by the data from retrospective studies (4), as well as longitudinal studies which are more indicative of a causal relationship. Among children, obesity seems to increase the risk of incident asthma (5). In fact, established obesity in early years of life (10 years or younger) is reported to be an independent risk factor for incident asthma, particularly in girls (6). A longitudinal cohort study noted that girls between 6 and 11 years of age who became overweight or obese had a higher odds ratio (OR) of developing new asthma symptoms (OR 3.2, CI: 1.1, 8.8) (7). A meta-analysis including 6 studies reported an overall higher risk of incident asthma (RR 2.02, CI: 1.16, 3.50) in obese-asthmatic children, with an even higher risk being reported in boys (RR 2.47; CI: 1.57, 3.87) (8). Another US based study conducted in Southern California concluded that new-onset asthma was more common among obese children (RR = 1.60, CI: 1.08, 2.36) with no gender predilection (9). In addition, it has been shown that the degree of weight gain has a positive correlation with new-onset asthma: the higher the annual weight gain, the greater the odds of developing incident asthma (6).

A positive association between asthma incidence and obesity has been reported predominantly in women (10,11). Relative risk of incident asthma can be as high as 2.7 times for a BMI ≥ 30 in women (12). In a prospective study including 4547 participants, increased incidence of asthma was reported among females with highest gain in BMI over a 10-year follow-up with a hazard ratio of 1.63 (CI: 1.17, 2.29) (13). However, a meta-analysis including 7 studies and 333,102 subjects identified a dose-response relationship between increased weight and annual odds of incident asthma with annual odds ratio (OR) of 1.38 and 1.92 in overweight and obese individuals, respectively (14).

Asthma prevalence: A noticeable surge has occurred in the prevalence of asthma and obesity among the children leading to more health-care utilization (15). Obesity-related mechanisms accounting for an increased prevalence of asthma are evident in multiple cross-sectional studies focusing on pediatric population (16,17). While presence of confounding factors such as family history, exposure to allergens/smoke, etc. can certainly skew the correlation between obesity and asthma, Mutius et al. has shown that the relationship between asthma prevalence and adiposity in children is persistent even after controlling for various confounding factors (18).

Recent data from Centers for Disease Control and Prevention (CDC) notes higher prevalence of asthma in adults with obesity (11.1%) as compared to adults with normal weight (7.1%) (19). In adult obese asthmatics, female gender has higher prevalence (10,20). Coronary Artery Risk Development in Young Adults (CARDIA) cohort showed sex-related differences in asthma prevalence. Longitudinal follow-up till 50 years of age revealed that adult-onset asthma was more prevalent among obese females than males (27.6 vs. 14.7%, $P = 0.001$) (21). The asthma-BMI association in females grows stronger with increasing weight (22). However a Colombian population-based study including 5539 subjects, reported significant association between asthma prevalence and obesity without any significant gender interaction (23). These studies are highly suggestive of significant asthma prevalence in obese adults, more so in females than males.

Reverse Causality: An often overlooked question is the role that asthma plays in weight gain, and how this in turn relates to disease severity (24). Theoretically, physical inactivity and increased systemic steroid use in severe asthma may cause weight gain. This observation may be more pronounced in asthmatic children as their mothers often impose restriction to physical activity due to the fear of worsening asthma symptoms (25). Children may limit activity to control exertional asthma symptoms, thereby reducing energy expenditure and promoting weight gain (26). Epstein and colleagues examined a nationally representative cross-sectional sample of 5154 children and adolescents aged 6–16 years from NHANES III, and found that asthma, television watching, and maternal BMI were independent predictors of youth obesity (27). A cross-sectional analysis of Severe Asthma Research Program (SARP) study found a linear relationship between duration of asthma and increasing BMI in early-onset asthmatics (<12 years) when compared to the late-onset group (>12 years) even after restricting the analysis to severe asthmatics (28).

CDC asthma statistics in 2010 show significantly higher rate of obesity in adult asthmatics (38.8%) as compared to non-asthmatics (26.8%) (29). To test the same hypothesis in adults, that obese asthmatics lower their physical activity resulting in weight gain, Beckett and co-workers conducted a longitudinal 10-year follow-up study. Physical inactivity alone, however, failed to explain weight gain in adult obese asthmatics (13).

In summary, obesity increases the risk of incident asthma in both boys and girls in general with female gender having slightly stronger association with incident asthma if obesity is established in early years of life. Female predilection is noted more consistently in obese adults with new-onset asthma. High asthma prevalence is

Table 1. Asthma incidence and prevalence in children and adults with obese-asthma phenotype.

Asthma Incidence				
Reference	Population Characteristics	Study Design	Results	Notes/Comments
Gennuso et al. (4)	171 children aged 4–16 years of age	Case-control retrospective study	One third of the children included in the study had concomitant asthma and BMI >95th percentile ($P = 0.02$).	Asthma diagnosed by a medical provider. Asthma was diagnosed by a combination of clinical symptoms and wheezing.
Chinn et al. (5)	9574 children aged 8–9 years	Prospective cohort study	Obese children had higher odds of developing asthma as compared to their peers with an OR 4.74 (CI: 2.23, 10.09) in boys and OR of 4.09 (CI: 1.40, 11.93) in girls.	The association between high BMI and new onset-asthma became significant after the year 1982.
Gold et al. (6)	9828 children aged 6–14 years	Prospective cohort study	Established obesity in girls is a risk factor for incident asthma with relative risk (RR) 1.41 (CI: 1.07, 1.86). Extreme annual weight gain increases the risk for incident asthma in both boys and girls with RR of 3.81 (CI: 1.88, 7.72) and 3.11 (CI: 1.55, 6.24), respectively.	Asthmatics included participants diagnosed with asthma by a physician within the past 12 months. Extreme annual weight gain defined as >75th percentile.
Chen et al. (8)	14,083 children aged 5–18 years	Meta-analysis	Obese boys had a significantly higher risk of incident asthma than obese girls (RR for boys: 2.47; CI: 1.57, 3.87; girls: 1.25; CI: 0.51, 3.03). Overall RR for incident asthma in obese children was 2.02.	
Castro-Rodriguez et al. (7)	1246 children aged 6–13 years	Prospective cohort study.	Overweight or obese girls at YR 11 had more asthma like symptoms at YR 13 (OR 3.2; CI: 1.1, 8.8). This was true for boys as well, however, not statistically significant.	Asthma like symptoms described as infrequent (<3 episodes per year) and frequent wheeze (>3 episodes per year). In results OR included for frequent wheeze only.
Gilliland et al. (9)	3792 children aged 7–18 years	Prospective cohort study	Incident asthma was significant among obese children (RR = 1.60, CI: 1.08, 2.36).	Cases include physician-diagnosed asthma
Chen et al. (10)	9149 adults aged 20–64 years	Prospective cohort study	The odds ratio for incident asthma among women whose baseline BMI was at least 30.0 kg/m ² was 1.9 (CI: 1.1, 3.4), whereas the corresponding odds ratio for men was 1.1 (CI: 0.3, 3.6).	
Guerra et al. (11)	1475 subjects at least ≥20 years	Nested case control study from a longitudinal cohort	BMI >28 kg/m ² significantly increased the risk of acquiring asthma among female subjects with an adjusted OR, 3.45 (CI: 2.10, 5.67), but not among male subjects (OR, 1.69; CI: 0.88, 3.27).	Asthma diagnosed by medical-care provider
Camargo et al. (12)	85,911 females aged 26–46 years	Prospective cohort study	The study used 3 different definitions of asthma with significant correlation between obesity and incident asthma for all 3 definitions.	The study population only included females. Def 1: physician-diagnosed asthma + use of controller medication. Def 2: Def 1 + use of long-term preventive medication within 1 year. Def 3: Def 1 + Def 2 + physician-diagnosed asthma within month
Beckett et al. (13)	4547 adults aged 18–30 years	Prospective cohort study	Overall incidence of asthma was reported among females with highest gain in BMI over a 10-year follow-up with a hazard ratio of 1.63 (CI: 1.17, 2.29).	Participants reported physician-diagnosed asthma
Buether et al. (14)	333,102 adults >18 years of age	Meta-analysis	Increase in the OR of incident asthma due to overweight/obesity was observed in men (OR, 1.46; CI: 1.05, 2.02) and women (OR, 1.68; CI: 1.4, 1.94).	

(Continued on next page)

Table 1. (Continued).

Asthma Prevalence				
Reference	Population Characteristics	Study Design	Results	Notes/Comments
Black et al. (15)	681,122 children aged 6–19 years	Cross-sectional study	Adjusted odds of prevalent asthma for overweight, moderately obese, and extremely obese children relative to those of normal weight were 1.22 (CI: 1.20, 1.24), 1.37 (CI: 1.34, 1.40), and 1.68 (CI: 1.64, 1.73), respectively.	Overweight defined as ≥ 85 th and < 95 th percentiles, moderately obese defined as > 95 th percentile, and extremely obese defined as $\geq 1.2 \times 95$ th percentile.
Von Kries et al. (16)	9357 children aged 5–6 years	Epidemiological cross-sectional study	The odds of being diagnosed with asthma by a doctor in girls was 2.12 (CI: 1.2, 3.68) for overweight, and 2.33 (CI: 1.13, 4.82) for obesity.	Overweight: BMI > 90 th percentile and < 97 th percentile. Obesity: BMI > 97 th percentile
Bibi et al. (17)	5984 children aged 5–7 years old	Epidemiological cross-sectional study	Asthma symptoms and inhaler use was more in obese children as compared to their normal weight peers ($P < 0.0001$).	Asthma defined as physician diagnosed asthma
Mutius et al. (18)	7505 children aged 4–17 years	Epidemiological cross-sectional study	Children in highest BMI quintile had greater prevalence of asthma ($P = 0.0001$).	Highest BMI quintile included children with BMI 20.5–37.2 kg/m ² .
Shaheen et al. (20)	8960 adults at 26 years of age	Population based cohort study	Women with BMI > 30 kg/m ² had higher odds of asthma (OR 2.00; CI: 1.36, 2.94) as compared to obese men (OR 1.39; CI: 0.89, 2.17).	Asthma defined as patient reported asthma.
Kim et al. (22)	45,973 individuals 18–34 years of age	Cross-sectional study	A strong association between BMI and asthma among women, but not among men.	
Sood et al. (21)	5115 adults with mean age of 25 years	Prospective cohort study. Date collected through standardized questionnaires at YR27, YR30, YR32, YR35, YR40, YR45, and YR50	Adult-onset disease was higher among women than men at age 25YR (27.6 vs. 14.7%, $P = 0.001$). Increase in asthma prevalence was noted among women with age for adult-onset asthma. By age 40YR adult-onset asthma was dominant among women (exceeded 50%).	Adult-onset asthma defined as development of asthma > 18 years of age. Asthma defined as self-reported provider diagnosis.

again noted in both boys and girls with concurrent obesity. In adults, asthma is more prevalent in obese females.

Available data also hints towards a possible reverse causal relationship (asthma leading to obesity) in children but not in adults.

Demographic comparison between obese asthmatic children and adults

1. Effect of Age and Age of Onset: (Findings summarized in Table 2)

Obesity has high comorbidity with asthma (5,13), but not all obese-asthmatic children are affected equally in terms of illness severity indicating that obesity–asthma association is complex and is affected by several factors such as age of onset of asthma. Cross-sectional analysis of SARP study revealed early-onset asthmatics (< 12 years of age) with concomitant obesity were more likely to be African Americans, with greater airway obstruction, higher bronchial hyper-responsiveness, higher response rate to bronchodilators, and greater health-care utilization. They were also likely to have a linear relationship between increase in BMI and duration of asthma. For

late-onset obese asthmatics, the median age for asthma development was 27 years. There was no association between asthma severity, serum IgE level, and airway obstruction in late-onset asthmatics. Just like early-onset asthmatics, higher health-care utilization was noted among late-onset asthmatics (28).

Age by itself also has important implications on obesity–asthma relationship. Lang et al. specifically investigated whether age has any impact on obese–asthma phenotype. The study comprised of mild persistent asthmatics and found that obese boys who developed asthma early (6–11 years) had significant reduction of lung functions as determined by forced expiratory volume (FEV₁)/forced vital capacity (FVC) ratio ($P < 0.01$) but fewer asthma symptoms. Within the age group of 12–17 years old adolescents, girls reported more symptoms even though the asthma severity did not change. Adult obese asthmatics aged 18–45 years reported worse asthma symptoms and reduction in FEV₁ until the age of 45, but after 45 years of age, no significant decline in lung function or gender interaction was observed (30).

In summary, age has significant impact on obese–asthma phenotype particularly in children. There are

Table 2. Effect of age and age of onset in children and adults with obesity and asthma.

Reference	Population Characteristics	Study Design	Results (Early-onset Asthmatics)	Results (Late-onset Asthmatics)	Notes/ Comments
Holguin et al. (28)	1049 adults, subjects divided into 2 groups depending on age of onset of asthma. <12 years of age (median age 4 years) and >12 years of age (median age 27 years)	Cross-sectional analysis of SARP study	Early-onset obese asthmatics had 1. Fewer females 2. More African Americans 3. Higher airway obstruction as determined by FEV ₁ /FVC ratio (mean ratio 0.69), 4. More bronchial hyper-responsiveness 5. Higher serum IgE level, 6. Greater health-care utilization. Also noted to have more weight gain.	Late-onset asthmatics had. 1. More females 2. More African Americans 3. Less atopy 4. Higher use of controller medications and health-care utilization. Non-linear relationship was noted between increase in BMI and asthma duration in late-onset asthmatics.	Response to bronchodilator measured as maximal reversal of FEV ₁ .
Reference	Population Characteristics	Study Design	Results (Age group 6–17 years)	Results (Age group 18–76 years)	Notes/Comments
Lang et al. (30)	490 participants. Age 6–76 years. Divided into 4 age groups: 6–11 years 12–17 years 18–44 years 45–76 years	Observational study	Subjects with age between 6–11 years had greater reduction in FEV ₁ /FVC ratio ($P < 0.01$) but reported fewer symptoms (boys only). Adolescent girls with age 12–17 years reported more symptoms even though no significant increase in asthma severity was noted.	Obese asthmatics >18 years of age reported worse asthma symptoms till 45 years of age. No significant decline in lung function was noted after 45 years of age.	Symptom reporting based on asthma control questionnaire (ACQ) and modified asthma control questionnaire which excluded FEV ₁ to create a score based solely on patient perception.

distinct differences between early and late-onset asthmatics but they both have greater health-care utilization. Lang and colleagues reported fewer asthma symptoms in boys 6–11 years of age and no significant decline in lung function after the age of 45 years but these findings should be interpreted with caution as the sample population had mild asthma severity.

2. Role of Puberty and Menarche: (Findings summarized in Table 3)

Factors associated with gender such as onset of puberty and menarche ramify the obese–asthma association. Literature review shows that for overweight children, early-onset puberty is a significant and independent risk factor for persistent asthma (31). Once menarche is reached, adolescent girls appear to be more consistently at risk of new obesity-related asthma and poor asthma control (7). Most girls reach menarche in the adolescent period and manifest stronger asthma–obesity association (32,33).

The obesity–asthma association is significant in women as discussed in the epidemiology section. Among adult females with obese–asthma phenotype, early menarche significantly increases the asthma severity score (34). The studies have not investigated increased asthma severity in obese males with early onset of puberty.

In summary, early onset of puberty is a risk factor for persistent asthma. Early menarche increases the asthma severity among obese girls and women.

3. Race and Ethnicity : (Findings summarized in Table 4)

Most of the literature cited previously has looked at Caucasian populations, with few investigations focusing on subjects of non-Caucasian ethnic and racial backgrounds.

A cross-sectional study comprising of Hispanic and Black inner city children with asthma and BMI >85th percentile noted significant asthma symptoms leading to missed school days, worsening lung function as measured by pulmonary expiratory flow rate, and greater use of controller medications (35). Using central obesity instead of BMI percentile in African American children seems to make the BMI–asthma association even more significant (36). However, this observation is not consistent; being African American seemed to have a protective effect on asthma–obesity association in a large cross-sectional study as noted by Borrell and colleagues. The study did mention worse odds of asthma among obese Mexican American girls (37). Kwon et al. reported that Hispanic children accounted for a larger portion of children who

Table 3. Impact of menarche and puberty on obesity-asthma phenotype in children and adults.

Reference	Population Characteristics	Study Design	Results	Notes/Comments
Guerra et al. (31)	1246 children (6–16 years)	Longitudinal cohort study. Data collected through questionnaires at YR6, YR8, YR11, YR13 and YR16	Obese children with continuous wheezing in pre-pubertal period were 2.34 times (CI 1.35, 4.07) more likely to experience unremitting asthma after puberty.	Asthma defined as >3 episodes of wheezing during the previous year or physician-confirmed asthma.
Castro-Rodriguez et al. (7)	1246 children (6–13 years)	Prospective cohort study. Data collected from questionnaires filled at age 6, 8, 11 and 13 years	Overweight/obese females at YR11 who started puberty before 11 years of age had a significantly higher prevalence of frequent wheezing at YR11 and YR13.	
Kattan et al. (32)	368 adolescents 12–20 years	Prospective cohort study	Higher BMI in females was associated with more asthma symptom days and exacerbations.	
Lu et al. (33)	4828 children aged 12–19 years	Cross-sectional population based study	Overweight/obese girls had higher odds of history of asthma (OR = 1.63, CI 1.16, 2.30), current asthma (OR = 1.73, CI 1.13, 2.64) as compared to obese boys.	Participants defined as asthmatics if physician or a health-care professional diagnosed them with asthma.
Varasso et al. (34)	366 adults, mean age 38.7 $\pm$ 14.1 in men and 35.5 $\pm$ 12.6 in women	Case-control study	Clinical asthma severity score increased in obese asthmatic females with early menarche ($P = 0.005$) and to a much lesser extent among those without early menarche ($P = 0.03$).	Patient reported asthma.

Table 4. Racial and ethnic variation in children and adults with obese-asthma phenotype.

Reference	Population Characteristics	Study Design	Results	Notes/Comments
Luder et al. (75)	209 children aged 2–18 years	Cross-sectional study.	The obese-asthmatic African American and Hispanic children had greater asthma severity as defined by >30 school day missed annually ($P = 0.03$), pulmonary expiratory flow rate (PEFR) value less than or equal to 60% of predicted value ($P = 0.001$), and three or more asthma medications prescribed ($P = 0.05$).	Asthma diagnosed by pediatrician or pediatric pulmonologist.
Musaad et al. (36)	1123 children (5–18 years)	Case-control study	Significantly more African American subjects with central obesity in the asthmatic group (43.13%) versus the control group (34.09%, $P < 0.05$).	Central obesity defined by coinicity index: waist circumference (m)/0.109 $\times$ square root (weight[kg]/height[m]). Asthma defined by ATS guidelines. (76)
Borrell et al. (37)	2174 children (8–19 years)	Cross-sectional study	African American girls were more likely to have better odds of controlled asthma (OR, 0.65; 95% CI, 0.41–1.05), whereas Mexican American girls had a 1.91 (95% CI, 1.12–3.28) greater odds of worse asthma control.	Asthma control defined as controlled, partially controlled, or poorly controlled based on NHBLI guidelines. (77)
Kown et al. (38)	853 children (2–11 years of age)	Cross-sectional study	Hispanic girls and boys in the age group 6–11 years accounted for a greater proportion of asthma cases as compared to African American and non-Hispanics.	Limited power due to small numbers.
Kim et al. (22)	45,973 adults (18–34 years)	Cross-sectional study	African American and Hispanic men with BMI > 30 have higher odds of current asthma (OR 2.9 and 2.7, respectively).	Study excluded race/ethnicity other than white, black, or Hispanic.
Celedon et al. (41)	7109 adults, mean age 37.7 $\pm$ 11.9 for men and 37.5 $\pm$ 12.0 for women	Prospective cohort study	Chinese women with a BMI of ≥ 30 had an OR of 2.1 (CI 1.0, 4.3) to have asthma. Results not significant in men.	Asthma defined as both physician-diagnosed asthma and positive result to methacholine challenge test.
Mishra et al. (42)	82,464 non-pregnant women aged 15–49 years	Cross-sectional study	Obese women in India have substantially higher risk of asthma than women with a normal BMI (OR 1.85; 95% CI: 1.30, 2.63), after adjusting for several confounding factors.	Self-reported asthma. The sample size included women <18 years as well.

Table 5. Airway hyper-responsiveness (AHR) in obese asthmatic children and adults.

Reference	Population Characteristics	Study Design	Results	Notes/Comments
Tantisira et al. (78)	1041 children aged 5–12 years	Cross-sectional analysis of a randomized controlled trial	No significant association was found between BMI, waist circumference, and waist to hip ratio and airway reactivity to methacholine in obese asthmatics.	Analysis included mild to moderate asthma severity. Methacholine sensitivity performed with a provocative concentration (PC ₂₀) of less than 12.5 mg/ml.
Hancox et al. (46)	1037 children aged 9–21 years	Prospective cohort study	BMI had an inverse relationship with airway hyperresponsiveness in females and no significant association in males.	Airway hyperresponsiveness was defined as provocative concentration of methacholine to induce a 20% fall in FEV ₁ of 8 mg/ml or less, or an increase in FEV ₁ of 10% or greater.
Celedon et al. (41)	7109 adults >18 years of age	Cross-sectional study	Among men and women with asthma BMI of 30 kg/m ² was associated with significant AHR with OR 2.3 (CI 1.2, 5.0) and OR 2.3 (CI 1.2, 4.5), respectively.	Symptomatic AHR defined as the presence of at least two respiratory symptoms (cough, wheezing, dyspnea or nocturnal cough/wheezing/dyspnea) or history of asthma attacks, as well as a ≥20% fall in FEV ₁ from baseline after administration of ≤8 mg of methacholine per ml.
Schachter et al. (49)	1971 adults aged 17–73 years	Epidemiological study	After adjusting for age, atopy, smoking, and family history, severe obesity (BMI >35 kg/m ² was a significant risk for recent wheeze without AHR (OR 3.33, <i>p</i> = 0.0001). No significant correlation between BMI and airway responsiveness was observed (<i>p</i> = 0.07).	Recent wheeze defined as presence of wheeze in the past 12 months. Asthma defined as presence of wheeze + physician-diagnosed asthma.

were both overweight/obese and had asthma than Black and non-Hispanic children (38). Strong asthma–obesity association is also seen in children from middle east (39) and Puerto Ricans (40).

In adults, significant association between asthma and high BMI is noted predominantly in men with African American and Hispanic background (22). It is possible that these population sub-groups are under-represented as most investigations focus on Caucasian population (13,20). Two other studies, one conducted in rural China and the other including Indian women reported significant obesity–asthma association in the studied population (41,42). But these two studies have significant limitations in terms of having only a small percentage of morbidly obese adults and therefore making it hard to extrapolate the findings to general population (41), and including asthmatics with self-reported asthma as opposed to physician-diagnosed asthma (42).

In summary, the obese–asthma association has also been reported in many non-Caucasian racial and ethnic backgrounds. The few inconsistencies between reports may be explained by differences in sample size and population characteristics.

Phenotypical variations

1. Airway Hyper-responsiveness (Findings summarized in Table 5)

Obesity has been regarded as a state of chronic inflammation and is linked to airway hyper-responsiveness (AHR) (43,44). One would expect greater airway reactivity in obese–asthmatic children but literature review suggests otherwise. Cross-sectional analysis of the Childhood Asthma Management Program (CAMP) cohort revealed no statistically significant relationship between high BMI and AHR to methacholine in obese asthmatic children after adjustment of baseline FEV₁ (45). Another US based prospective cohort study including old obese asthmatics revealed inverse relationship between increase in BMI and AHR (46). Positive correlation is reported between high BMI and AHR in obese non-asthmatics but not in obese-asthmatic children. BMI either does not affect or has an inverse relationship with AHR once the asthma phenotype has been established (21).

Investigators have explored the relationship between high BMI and AHR in adults, but most studies do not clarify whether the individuals included in the study had diagnosed asthma (47,48). However, in a cross-sectional study conducted in rural China, BMI of 30 kg/m² was associated with more symptomatic AHR (defined as asthma as it combined respiratory symptoms with spirometry) (41). One Australian study reported no association between BMI and AHR to histamine in a population of severely obese with wheezing, only a subset of which had physician-diagnosed asthma. The study did not report whether an association was present

Table 6a. Fractional exhaled Nitric Oxide in children with obese-asthma phenotype.

Pediatric Population						
Association Between Obesity and FeNO in Asthmatics	Author	Year of Publication	Age of Study Population (Years)	Positive Correlation	Negative Correlation	No Correlation
	Wong et al. (52)	2005	11–18			X
	Leung et al. (53)	2004	7–18			X
	Barros et al. (57)	2006	15–73		X	
	Santamaria et al. (54)	2007	6–18			X
	Han et al. (58)	2014	6–17		X	
	Erkocoglu et al. (55)	2013	6–17			X
	Cibella et al. (56)	2011	10–16			X
	Yao et al. (59)	2011	5–18		X	
	Kattan et al. (32)	2010	12–20			X

for the subset of subjects with physician-diagnosed asthma (49).

In summary, AHR appears to have either no association or inverse association with BMI in obese-asthmatic children. The relationship is unclear for adults as the available data is limited and inconsistent.

2. Fractional Exhaled NO in Obese Asthmatics (Findings summarized in Table 6a and 6b)

Obesity is known to activate inflammatory pathways causing high-exhaled NO (50). Surprisingly most investigations including obese children with asthma either did not find any correlation between FeNO and obesity (32,51–56) or negative correlation between the two (57–59). Findings are not limited to studies using BMI as a marker of obesity in children, in fact all markers of adiposity in asthmatic children including percent body fat (PBF) and waist circumference (WC) are associated with low FeNO (58).

Similar to children, in adult asthmatics FeNO and obesity either have a negative correlation with each other (57,60–62) or no correlation at all (32,51,63–65). In addition to BMI, other markers of adiposity such as waist to hip ratio and body fat also have a negative correlation with FeNO (61).

In summary, exhaled NO either has negative correlation or no correlation with obese-asthma phenotype, and this holds true for both pediatric and adult population.

Mechanical/physiological alterations (Findings summarized in Table 7)

In asthma there is disproportionate reduction in FEV₁ as compared to FVC, resulting in reduced FEV₁/FVC ratios. Children with severe asthma have lowest FEV₁ and FEV₁/FVC ratios that persist in the later decades of life (66,67). But reduction in FEV₁ and FVC in obese-asthmatics is not uniformly reported. Increase in BMI is associated with higher FEV₁ and FVC but overall reduction in FEV₁/FVC ratio as noted in a cross-sectional analysis of CAMP cohort (45). Chu and colleagues found similar association where obesity resulted in increased FEV₁ and FVC but a drop in FEV₁/FVC ratio (68). The aforementioned investigations have used BMI as a marker of obesity and one can argue that BMI in children is affected by growth and does not differentiate between lean body mass and adipose tissue which can potentially alter the results. However, when markers of obesity other than BMI, like PBF and WC were used, FEV₁/FVC ratio still declined as noted by Han and colleagues. The study did not note any significant change in FEV₁ and FVC (58).

In adult obese asthmatics, the consensus is that obesity does not cause airflow obstruction as measured by FEV₁/FVC ratio. The ratio may increase if significant air trapping occurs and reduces FVC in obese asthmatics (69). But pooled data from three large epidemiological

Table 6b. Fractional exhaled Nitric Oxide in adults with obese-asthma phenotype.

Adult Population						
Association Between Obesity and FeNO in Asthmatics	Author	Year Of Publication	Age of Study Population (Years)	Positive Correlation	Negative Correlation	No Correlation
	Van Veen et al. (60)	2008	18–75		X	
	Mclachlan et al. (63)	2007	32			X
	Barros et al. (57)	2006	15–73		X	
	Komakula et al. (61)	2007	18–70 years		X	
	Kazaks et al. (64)	2005	Not provided			X
	Kattan et al. (32)	2010	12–20			X
	Berg et al. (62)	2011	25–74		X	
	Sutherland et al. (65)	2008	19–50			X

Table 7. Lung function in children and adults with concomitant obesity and asthma.

Reference	Population Characteristics	Study Design	Results	Notes/Comments
Tantisira et al. (78)	1041 children aged 5–12 years	Cross-sectional analysis of a randomized controlled trial	Increase in BMI lead to increase in FEV ₁ ($P = 0.01$) and even greater increment in FVC ($P = 0.0001$). But FEV ₁ /FVC ratio declined in obese asthmatics ($P = 0.0001$)	Lung volumes noted post bronchodilator.
Chen et al. (68)	170,547 children, out of which 15,039 children (age 13–16 years)	Cross-sectional epidemiological study	Significant increase in FEV ₁ and FVC noted in obese-asthmatics with overall decline in FEV ₁ /FVC (boys > girls).	
Han et al. (58)	2681 children aged 6–17 years	Cross-sectional study	All markers of obesity including high BMI, percent body fat and waist circumference were associated with reduced FEV ₁ /FVC.	Small sample of children with obesity and concomitant asthma ($n = 86$)
Schachter et al. (49)	1971 adults aged 17–73 years	Cross-sectional epidemiological study	Severe obesity (BMI > 35) did not have any significant impact on FEV ₁ /FVC ratio.	

studies reported no significant impact of obesity on FEV₁/FVC ratio in individuals with asthma (49).

In summary, FEV₁/FVC ratio declines in obese-asthmatic children but no such impact is noted in obese-asthmatic adults.

Observations from cluster analysis

There are more obese adults with severe asthma than children (70). It would be interesting to see whether obesity has any affect on cluster analysis in both asthmatic children and adults.

Clusters derived from the analysis of SARP resulted in 4 novel asthma phenotypes in children (71). All clusters were characterized by some degree of atopy with variable magnitude of allergic sensitization. Surprisingly, BMI did not have any noticeable implications on cluster analysis ($p = 0.522$). The major determinants of asthma

phenotype were asthma duration, number of asthma controller medications, and baseline lung function. (Table 8a)

In adults, three cluster analysis (1,2,65) identified a unique obese-asthma phenotype. This specific asthma phenotype was female predominant, characterized by late-onset asthma, had low FeNO, non-eosinophilic by sputum characterization, non-atopic, and less likely to respond to conventional asthma treatment. (Table 8b)

High BMI does not play a substantial role in cluster analysis including asthmatic children but does form a separate phenotype in adult asthmatics.

Discussion

Comparing children and adults with obese-asthma phenotype has put forward both similarities and differences. Obesity increases both the incidence and prevalence of asthma in children and adults but there is significant

Table 8a. Cluster analysis findings in asthmatic children.

Author	Cluster	Mean Age (Years)	Gender Female/Male (%)	Onset of Asthma	Mean Duration of Asthma (Months)	Race	FeNO (ppb)	BMI > 90th Percentile (%)	Lung Functions	Controller Medications
Fitzpatrick et al. (3)	Cluster 1	9	54/46	Late onset	38	More non-Hispanic white subjects	7	27	Normal	Fewer controller medications with low daily use of ICS.
	Cluster 2	10	48/52	Early onset	95	Similar to Cluster 1	9	31	Normal	Increased use of controller medication and high daily dose of ICS
	Cluster 3	15	34/66	Early onset	170	Fewer non-Hispanic white subjects	12	38	Mild airflow limitation	Frequent use of oral steroids.
	Cluster 4	12	34/66	Early onset	129	Highest prevalence of African American subjects	14	21	Advanced airflow limitation	Highest daily dose of ICS.

Note. Table based on cluster analysis findings by Fitzpatrick et al.

Table 8b. Cluster analysis findings in asthmatic adults.

Author	Cluster	Mean Age of Onset (Years)	Gender Female/Male (%)	Mean Duration of Asthma (Months)	Race White/AA/Other (%)	FeNO (ppb)	Lung Function	Mean BMI (kg/m ²)	Misc.
Moore et al. (2)	Cluster 3	42	71/29	108	73/22/5	24.8	71% with FEV ₁ <80% of predicted. Reversible in 64% after bronchodilator use	>30 (58%)	Increased reliance on controller medication and High HCU.
Halдар et al. (1)	Primary care: Cluster 2	35.3	81.5/18.5	—	—	25.8	Post bronchodilator FEV ₁ 91.5% of predicted	36.2	Non-eosinophilic, high symptom expression.
	Secondary care: Cluster 2	15.4	87/13	—	—	<25	Post bronchodilator FEV ₁ 79.5% of predicted	40.9	Non-eosinophilic, increased symptoms.
	Longitudinal study: Cluster 1	—	—	—	—	—	—	—	Predominantly female population with high BMI, non-eosinophilic.
Sutherland et al. (79)	Cluster 3	10	311	83/17	37 (whites)	<25	FEV ₁ /FVC 71.5%, FEV ₁ 73.5% of the predicted	34.7	No significant improvement in asthma control with inhaled corticosteroids Highest airway hyper-responsiveness. Suboptimal asthma control with ICS. Reduced expression of glucocorticoid receptors.
	Cluster 4	16.1	295	76/24	26 (whites)	<25	FEV ₁ /FVC 69.7%, FEV ₁ 75.5% of predicted	38.5	Reduced expression of glucocorticoid receptors, less airway hyper-responsiveness, well controlled asthma.

Note. Table based on cluster analysis findings by Moore et al, Halдар et al, and Sutherland et al.

gender interaction. It appears that available longitudinal studies do suggest a causal relationship between obesity and new-onset asthma in children and women. Unlike children where obesity increases asthma incidence in both boys and girls, incident asthma is more common in obese adult females. Available data also point toward the possibility of children with asthma being at highest risk of weight gain. But this idea of reverse causality is unclear in adults as currently research findings are limited.

In general, asthma prevalence is seen in both obese boys and girls. But asthma is far more prevalent in obese females than men. This is consistent with findings reported by Sood et al.; subjects who developed asthma after 18 years of age consisted primarily of women by the time they were 40 (years) and the association was further strengthened by the presence of obesity (72). Obesity in females can be listed as an independent risk factor for asthma development.

Patient demographics like age and age of onset of asthma have significant repercussions on asthma–obesity relationship. Two observations are noteworthy: Firstly, early-onset asthma in obese children promotes likelihood of developing atopic sensitization and bronchospasm. Secondly, asthma symptoms in obese asthmatics correlate with disease severity in children less than 12 years of age, but the correlation between symptoms and disease severity does not hold for adolescents girls, who tend to report greater asthma symptoms even with mild asthma severity. Increased reporting of asthma symptoms despite mild disease severity suggests presence of additional mechanistic factors responsible for asthma symptoms. There is also the possibility of obese-asthmatic children limiting their physical activity to prevent asthma symptoms (26); however, this would not explain fewer symptoms in boys only. Early-onset asthma may be driven primarily by atopy and disease severity in children <12 years of age, and obesity contributing to asthma symptoms after age of 12 years. Independent of the age, all obese asthmatics have higher health-care utilization.

Early onset of puberty is an important determining factor for asthma severity in both girls and women. Obesity by itself is linked to higher serum level of sex hormones in females, early menarche, and asthma which can potentially explain the relationship. Obese males are also susceptible to greater asthma symptoms, but the association is not as significant as females. Gonzalez-Garcia et al. reported significant under-diagnosis of asthma in males >64 years of age. Additionally, increased asthma prevalence asthma is noted in men of non-caucasian ethnicities such as Hispanic and African Americans. This may lead to inflated asthma prevalence difference among male and female obese asthmatics as a significant number of investigations focus on young or middle-aged

Caucasians, leading to underrepresentation of elderly males and males from ethnic minorities.

Most physicians consider presence of AHR as one of the criteria to define asthma. Unfortunately, most of the available studies comment on AHR in children and adults with high BMI but not necessarily with concomitant asthma. The few studies that have included obese-asthmatic children did not report any correlation or report a negative correlation between AHR and increasing BMI despite poor asthma control. In adults, the data is limited on whether AHR has any implication on obese–asthma association or not. It is worth mentioning here that inhaled corticosteroids do affect the AHR and since most of the obese asthmatics are on controller medications, it is plausible that absence of AHR may not be accurate (73).

Also, there is lack of association or negative correlation between exhaled NO and obesity in in asthmatic adults and children. Reduced fractional exhaled NO may be due to increase in oxidative stress leading to creation of more reactive oxygen species with subsequent conversion of airway NO into reactive nitrogen species (61) and use of inhaled corticosteroids (55). Thereby, altering the total amount of exhaled NO. Alternative methods should be explored to assess the severity of asthma in obese asthmatic children and adults.

Asthma is considered an obstructive lung disease with reduced FEV₁/FVC ratio in response to methacholine challenge test. In obese-asthmatic children, FEV₁/FVC ratio does represent an obstructive pattern but the changes in FEV₁ and FVC are less consistent. However, in adult obese asthmatics, the ratio either remains unchanged or increases; this does not necessarily mean absence of obstructive lung disease pattern, as peripheral airways have more elastance in obese asthmatics which is not reflected by traditional lung function tests. Impulse oscillometry (IOS) may be a more useful tool in obese individuals with asthma instead of established lung function tests. In majority of adults, BMI represents excess adiposity instead of lean mass which can lead to a restrictive effect on thoracic cavity. Another explanation for the lung functions to be largely unaffected in obese asthmatics can be differential influence of obesity on lung airways. Obesity impacts peripheral lung airways more as they are more prone to collapse than larger airways, which is not depicted accurately by traditional lung function tests (74). IOS measures lung impedance over a range of frequencies without involving large changes in lung volume and therefore can reflect subtle changes in distal airways of obese asthmatics. In asthmatic children, studies specifically designed to review impact of obesity on impulse oscillometry are not available to depict its usefulness.

Lastly, high BMI is not a pivotal factor in determining asthma clusters in children as the percentage of children with high BMI was almost similar across the clusters. However, it is important in identifying a unique phenotype in adults which is non-atopic, female predominant and associated with increased health care utilization.

Conclusion

There are significant differences and similarities present in obese-asthmatic children and adults. Weight gain increases the risk of asthma in both adults and children. In children, weight gain in early years of life and early onset of puberty are risk factors for new onset and severe asthma. The severity of asthma symptoms become more pronounced in girls after menarche and continues later in life. In children, asthma–obesity association is consistent across all ethnic backgrounds with no significant difference, but among adults, men from ethnic minorities appear to have higher prevalence of obese–asthma phenotype. Contrary to expectations, AHR and exhaled NO do not increase in obese-asthmatics children and adults, therefore, new markers for asthma severity should be sought out in this patient population. Lung function tests do reflect obstruction in obese-asthmatic children, but in adults they may not be accurate.

Declaration of interest

Both authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. Both authors have no conflicts of interests or disclosures to report.

References

1. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med*. 2008;178(3):218–24. doi:10.1164/rccm.200711-1754OC.
2. Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010;181(4):315–23. doi:10.1164/rccm.200906-0896OC.
3. Fitzpatrick AM, Teague WG, Meyers DA, Peters SP, Li X, Li H, et al. Heterogeneity of severe asthma in childhood: confirmation by cluster analysis of children in the National Institutes of Health/National Heart, Lung, and Blood Institute Severe Asthma Research Program. *J Allergy Clin Immunol*. 2011;127(2):382–9. e1–13. doi:10.1016/j.jaci.2010.11.015.
4. Gennuso J, Epstein LH, Paluch RA, Cerny F. The relationship between asthma and obesity in urban minority children and adolescents. *Arch Pediatr Adolesc Med*. 1998;152(12):1197–200. doi:10.1001/archpedi.152.12.1197.
5. Chinn S, Rona RJ. Can the increase in body mass index explain the rising trend in asthma in children? *Thorax*. 2001;56(11):845–50. doi:10.1136/thorax.56.11.845.
6. Gold DR, Damokosh AI, Dockery DW, Berkey CS. Body-mass index as a predictor of incident asthma in a prospective cohort of children. *Pediatr Pulmonol*. 2003;36(6):514–21. doi:10.1002/ppul.10376.
7. Castro-Rodriguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school sources. *Am J Respir Crit Care Med*. 2001;163(6):1344–9. doi:10.1164/ajrccm.163.6.2006140.
8. Chen YC, Dong GH, Lin KC, Lee YL. Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis. *Obes Rev*. 2013;14(3):222–31. doi:10.1111/j.1467-789X.2012.01055.x.
9. Gilliland FD, Berhane K, Islam T, McConnell R, Gauderman WJ, Gilliland SS, et al. Obesity and the risk of newly diagnosed asthma in school-age children. *Am J Epidemiol*. 2003;158(5):406–15. doi:10.1093/aje/kwg175.
10. Chen Y, Dales R, Tang M, Krewski D. Obesity may increase the incidence of asthma in women but not in men: longitudinal observations from the Canadian National Population Health Surveys. *Am J Epidemiol*. 2002;155(3):191–7. doi:10.1093/aje/155.3.191.
11. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest*. 2002;122(4):1256–63. doi:10.1378/chest.122.4.1256.
12. Camargo CA, Jr., Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult-onset asthma in women. *Arch Intern Med*. 1999;159(21):2582–8. doi:10.1001/archinte.159.21.2582.
13. Beckett WS, Jacobs DR, Jr., Yu X, Iribarren C, Williams OD. Asthma is associated with weight gain in females but not males, independent of physical activity. *Am J Respir Crit Care Med*. 2001;164(11):2045–50. doi:10.1164/ajrccm.164.11.2004235.
14. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. *Am J Respir Crit Care Med*. 2007;175(7):661–6. doi:10.1164/rccm.200611-1717OC.
15. Black MH, Smith N, Porter AH, Jacobsen SJ, Koebnick C. Higher prevalence of obesity among children with asthma. *Obesity (Silver Spring)*. 2012;20(5):1041–7. doi:10.1038/oby.2012.5.
16. von Kries R, Hermann M, Grunert VP, von Mutius E. Is obesity a risk factor for childhood asthma? *Allergy*. 2001;56(4):318–22. doi:10.1034/j.1398-9995.2001.00727.x.
17. Bibi H, Shoseyov D, Feigenbaum D, Genis M, Friger M, Peled R, et al. The relationship between asthma and obesity in children: is it real or a case of over diagnosis? *J Asthma*. 2004;41(4):403–10. doi:10.1081/JAS-120026097.

18. von Mutius E, Schwartz J, Neas LM, Dockery D, Weiss ST. Relation of body mass index to asthma and atopy in children: the National Health and Nutrition Examination Study III. *Thorax*. 2001;56(11):835–8. doi:10.1136/thorax.56.11.835.
19. Akinbami LJ, Fryar CD. Current asthma prevalence by weight status among adults: United States, 2001–2014. *NCHS Data Brief*. 2016(239):1–8.
20. Shaheen SO, Sterne JA, Montgomery SM, Azima H. Birth weight, body mass index and asthma in young adults. *Thorax*. 1999;54(5):396–402. doi:10.1136/thx.54.5.396.
21. Sood A, Verhulst SJ, Varma A, Eagleton LE, Henkle JQ, Hopkins-Price P. Association of excess weight and degree of airway responsiveness in asthmatics and non-asthmatics. *J Asthma*. 2006;43(6):447–52. doi:10.1080/02770900600758309.
22. Kim S, Camargo CA, Jr. Sex-race differences in the relationship between obesity and asthma: the behavioral risk factor surveillance system, 2000. *Ann Epidemiol*. 2003;13(10):666–73. doi:10.1016/S1047-2797(03)00054-1.
23. Gonzalez-Garcia M, Caballero A, Jaramillo C, Maldonado D, Torres-Duque CA. Prevalence, risk factors and underdiagnosis of asthma and wheezing in adults 40 sources and older: a population-based study. *J Asthma*. 2015;52(8):823–30. doi:10.3109/02770903.2015.1010733.
24. Baffi CW, Winnica DE, Holguin F. Asthma and obesity: mechanisms and clinical implications. *Asthma Res Pract*. 2015;1(1):1–7. doi:10.1186/s40733-015-0001-7.
25. Dantas FM, Correia MA, Jr., Silva AR, Peixoto DM, Sarinho ES, Rizzo JA. Mothers impose physical activity restrictions on their asthmatic children and adolescents: an analytical cross-sectional study. *BMC Public Health*. 2014;14:287. doi:10.1186/1471-2458-14-287.
26. Unger R, Kreeger L, Christoffel KK. Childhood obesity. Medical and familial correlates and age of onset. *Clin Pediatr (Phila)*. 1990;29(7):368–73. doi:10.1177/000992289002900701.
27. Epstein LH, Wu YW, Paluch RA, Cerny FJ, Dorn JP. Asthma and maternal body mass index are related to pediatric body mass index and obesity: results from the Third National Health and Nutrition Examination Survey. *Obes Res*. 2000;8(8):575–81. doi:10.1038/oby.2000.74.
28. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, et al. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol*. 2011;127(6):1486–93. e2. doi:10.1016/j.jaci.2011.03.036.
29. Center for Disease Control and Prevention. Asthma and obesity. 2011. Available from: https://www.cdc.gov/asthma/asthma_stats/asthma_obesity.htm [accessed 27 June 2017].
30. Lang JE, Hossain J, Dixon AE, Shade D, Wise RA, Peters SP, et al. Does age impact the obese asthma phenotype? Longitudinal asthma control, airway function, and airflow perception among mild persistent asthmatics. *Chest*. 2011;140(6):1524–33. doi:10.1378/chest.11-0675.
31. Guerra S, Wright AL, Morgan WJ, Sherrill DL, Holberg CJ, Martinez FD. Persistence of asthma symptoms during adolescence: role of obesity and age at the onset of puberty. *Am J Respir Crit Care Med*. 2004;170(1):78–85. doi:10.1164/rccm.200309-1224OC.
32. Kattan M, Kumar R, Bloomberg GR, Mitchell HE, Calatroni A, Gergen PJ, et al. Asthma control, adiposity, and adipokines among inner-city adolescents. *J Allergy Clin Immunol*. 2010;125(3):584–92. doi:10.1016/j.jaci.2010.01.053.
33. Lu KD, Billimek J, Bar-Yoseph R, Radom-Aizik S, Cooper DM, Anton-Culver H. Sex differences in the relationship between fitness and obesity on risk for asthma in adolescents. *J Pediatr*. 2016;176:36–42. doi:10.1016/j.jpeds.2016.05.050.
34. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Epidemiological Study on the G, et al. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med*. 2005;171(4):334–9. doi:10.1164/rccm.200405-674OC.
35. Luder E, Ehrlich RI, Lou WY, Melnik TA, Kattan M. Body mass index and the risk of asthma in adults. *Respir Med*. 2004;98(1):29–37. doi:10.1016/j.rmed.2003.08.004.
36. Musaad SM, Patterson T, Ericksen M, Lindsey M, Dietrich K, Succop P, et al. Comparison of anthropometric measures of obesity in childhood allergic asthma: central obesity is most relevant. *J Allergy Clin Immunol*. 2009;123(6):1321–7. e12. doi:10.1016/j.jaci.2009.03.023.
37. Borrell LN, Nguyen EA, Roth LA, Oh SS, Tcheurekdjian H, Sen S, et al. Childhood obesity and asthma control in the GALA II and SAGE II studies. *Am J Respir Crit Care Med*. 2013;187(7):697–702. doi:10.1164/rccm.201211-2116OC.
38. Kwon HL, Ortiz B, Swaner R, Shoemaker K, Jean-Louis B, Northridge ME, et al. Childhood asthma and extreme values of body mass index: the Harlem Children's Zone Asthma Initiative. *J Urban Health*. 2006;83(3):421–33. doi:10.1007/s11524-006-9050-9.
39. Nahhas M, Bhopal R, Anandan C, Elton R, Sheikh A. Investigating the association between obesity and asthma in 6- to 8-source-old Saudi children: a matched case-control study. *NPJ Prim Care Respir Med*. 2014;24:14004. doi:10.1038/nppcr.2014.4.
40. Vangeepuram N, Teitelbaum SL, Galvez MP, Brenner B, Doucette J, Wolff MS. Measures of obesity associated with asthma diagnosis in ethnic minority children. *J Obes*. 2011;2011:517417. doi:10.1155/2011/517417.
41. Celedon JC, Palmer LJ, Litonjua AA, Weiss ST, Wang B, Fang Z, et al. Body mass index and asthma in adults in families of subjects with asthma in Anqing, China. *Am J Respir Crit Care Med*. 2001;164(10 Pt 1):1835–40. doi:10.1164/ajrccm.164.10.2105033.
42. Mishra V. Effect of obesity on asthma among adult Indian women. *Int J Obes Relat Metab Disord*. 2004;28(8):1048–58. doi:10.1038/sj.ijo.0802700.
43. Kaplan TA, Montana E. Exercise-induced bronchospasm in nonasthmatic obese children. *Clin Pediatr (Phila)*. 1993;32(4):220–5. doi:10.1177/000992289303200407.
44. del Rio-Navarro B, Cisneros-Rivero M, Berber-Eslava A, Espinola-Reyna G, Sienra-Monge J. Exercise induced bronchospasm in asthmatic and non-asthmatic obese children. *Allergol Immunopathol (Madr)*. 2000;28(1):5–11.
45. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003;58(12):1036–41. doi:10.1136/thorax.58.12.1036.
46. Hancox RJ, Milne BJ, Poulton R, Taylor DR, Greene JM, McLachlan CR, et al. Sex differences in the relation between body mass index and asthma and atopy in a birth

- cohort. *Am J Respir Crit Care Med*. 2005;171(5):440–5. doi:[10.1164/rccm.200405-623OC](https://doi.org/10.1164/rccm.200405-623OC).
47. Chinn S, Jarvis D, Burney P, European Community Respiratory Health S. Relation of bronchial responsiveness to body mass index in the ECRHS. *Eur Community Respir Health Surv. Thorax*. 2002;57(12):1028–33.
48. Litonjua AA, Sparrow D, Celedon JC, DeMolles D, Weiss ST. Association of body mass index with the development of methacholine airway hyperresponsiveness in men: the Normative Aging Study. *Thorax*. 2002;57(7):581–5. doi:[10.1136/thorax.57.7.581](https://doi.org/10.1136/thorax.57.7.581).
49. Schachter LM, Salome CM, Peat JK, Woolcock AJ. Obesity is a risk for asthma and wheeze but not airway hyperresponsiveness. *Thorax*. 2001;56(1):4–8. doi:[10.1136/thorax.56.1.4](https://doi.org/10.1136/thorax.56.1.4).
50. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. *Mediat Inflamm*. 2010;2010:1–10. doi:[10.1155/2010/289645](https://doi.org/10.1155/2010/289645).
51. Todd DC, Armstrong S, D'Silva L, Allen CJ, Hargreave FE, Parameswaran K. Effect of obesity on airway inflammation: a cross-sectional analysis of body mass index and sputum cell counts. *Clin Exp Allergy*. 2007;37(7):1049–54. doi:[10.1111/j.1365-2222.2007.02748.x](https://doi.org/10.1111/j.1365-2222.2007.02748.x).
52. Wong GW, Liu EK, Leung TF, Yung E, Ko FW, Hui DS, et al. High levels and gender difference of exhaled nitric oxide in Chinese schoolchildren. *Clin Exp Allergy*. 2005;35(7):889–93. doi:[10.1111/j.1365-2222.2005.02263.x](https://doi.org/10.1111/j.1365-2222.2005.02263.x).
53. Leung TF, Li CY, Lam CW, Au CS, Yung E, Chan IH, et al. The relation between obesity and asthmatic airway inflammation. *Pediatr Allergy Immunol*. 2004;15(4):344–50. doi:[10.1111/j.1399-3038.2004.00164.x](https://doi.org/10.1111/j.1399-3038.2004.00164.x).
54. Santamaria F, Montella S, De Stefano S, Sperli F, Barbarano F, Valerio G. Relationship between exhaled nitric oxide and body mass index in children and adolescents. *J Allergy Clin Immunol*. 2005;116(5):1163–4; author reply 1164–5. doi:[10.1016/j.jaci.2005.07.018](https://doi.org/10.1016/j.jaci.2005.07.018).
55. Erkocoglu M, Kaya A, Ozcan C, Akan A, Vezir E, Azkur D, et al. The effect of obesity on the level of fractional exhaled nitric oxide in children with asthma. *Int Arch Allergy Immunol*. 2013;162(2):156–62. doi:[10.1159/000351454](https://doi.org/10.1159/000351454).
56. Cibella F, Cuttitta G, La Grutta S, Melis MR, Bucchieri S, Viegi G. A cross-sectional study assessing the relationship between BMI, asthma, atopy, and eNO among schoolchildren. *Ann Allergy Asthma Immunol*. 2011;107(4):330–6. doi:[10.1016/j.anai.2011.08.001](https://doi.org/10.1016/j.anai.2011.08.001).
57. Barros R, Moreira A, Fonseca J, Moreira P, Fernandes L, de Oliveira JF, et al. Obesity and airway inflammation in asthma. *J Allergy Clin Immunol*. 2006;117(6):1501–2. doi:[10.1016/j.jaci.2006.02.027](https://doi.org/10.1016/j.jaci.2006.02.027).
58. Han YY, Forno E, Celedon JC. Adiposity, fractional exhaled nitric oxide, and asthma in U.S. children. *Am J Respir Crit Care Med*. 2014;190(1):32–9. doi:[10.1164/rccm.201403-0565OC](https://doi.org/10.1164/rccm.201403-0565OC).
59. Yao TC, Ou LS, Lee WI, Yeh KW, Chen LC, Huang JL, et al. Exhaled nitric oxide discriminates children with and without allergic sensitization in a population-based study. *Clin Exp Allergy*. 2011;41(4):556–64. doi:[10.1111/j.1365-2222.2010.03687.x](https://doi.org/10.1111/j.1365-2222.2010.03687.x).
60. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy*. 2008;63(5):570–4. doi:[10.1111/j.1398-9995.2007.01597.x](https://doi.org/10.1111/j.1398-9995.2007.01597.x).
61. Komakula S, Khatri S, Mermis J, Savill S, Haque S, Rojas M, et al. Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostanes in asthmatics. *Respir Res*. 2007;8:32. doi:[10.1186/1465-9921-8-32](https://doi.org/10.1186/1465-9921-8-32).
62. Berg CM, Thelle DS, Rosengren A, Lissner L, Torén K, Olin A-C. Decreased fraction of exhaled nitric oxide in obese subjects with asthma symptoms: data from the population study intergene/adonix. *Chest*. 2011;139(5):1109–16. doi:[10.1378/chest.10-1299](https://doi.org/10.1378/chest.10-1299).
63. McLachlan CR, Poulton R, Car G, Cowan J, Filsell S, Greene JM, et al. Adiposity, asthma, and airway inflammation. *J Allergy Clin Immunol*. 2007;119(3):634–9. doi:[10.1016/j.jaci.2006.10.029](https://doi.org/10.1016/j.jaci.2006.10.029).
64. Kazaks A, Uriu-Adams JY, Stern JS, Albertson TE. No significant relationship between exhaled nitric oxide and body mass index in people with asthma. *J Allergy Clin Immunol*. 2005;116(4):929–30; author reply 930. doi:[10.1016/j.jaci.2005.06.005](https://doi.org/10.1016/j.jaci.2005.06.005).
65. Sutherland TJ, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, et al. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med*. 2008;178(5):469–75. doi:[10.1164/rccm.200802-301OC](https://doi.org/10.1164/rccm.200802-301OC).
66. Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964–1999. *J Allergy Clin Immunol*. 2002;109(2):189–94. doi:[10.1067/mai.2002.120951](https://doi.org/10.1067/mai.2002.120951).
67. Spathopoulos D, Paraskakis E, Trypsianis G, Tsalkidis A, Arvanitidou V, Emporiadou M, et al. The effect of obesity on pulmonary lung function of school aged children in Greece. *Pediatr Pulmonol*. 2009;44(3):273–80. doi:[10.1002/ppul.20995](https://doi.org/10.1002/ppul.20995).
68. Chu YT, Chen WY, Wang TN, Tseng HI, Wu JR, Ko YC. Extreme BMI predicts higher asthma prevalence and is associated with lung function impairment in school-aged children. *Pediatr Pulmonol*. 2009;44(5):472–9. doi:[10.1002/ppul.21023](https://doi.org/10.1002/ppul.21023).
69. Dixon AE, Holguin F, Sood A, Salome CM, Pratley RE, Beuther DA, et al. An official American Thoracic Society Workshop report: obesity and asthma. *Proc Am Thorac Soc*. 2010;7(5):325–35. doi:[10.1513/pats.200903-013ST](https://doi.org/10.1513/pats.200903-013ST).
70. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, et al. Baseline features of the severe asthma research program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract*. 2017. doi:[10.1016/j.jaip.2017.05.032](https://doi.org/10.1016/j.jaip.2017.05.032).
71. Wener RR, Bel EH. Severe refractory asthma: an update. *Eur Respir Rev*. 2013;22(129):227–35. doi:[10.1183/09059180.00001913](https://doi.org/10.1183/09059180.00001913).
72. Sood A, Qualls C, Schuyler M, Arynchyn A, Alvarado JH, Smith LJ, et al. Adult-onset asthma becomes the dominant phenotype among women by age 40 sources. the longitudinal CARDIA study. *Ann Am Thorac Soc*. 2013;10(3):188–97. doi:[10.1513/AnnalsATS.201212-115OC](https://doi.org/10.1513/AnnalsATS.201212-115OC).
73. Currie GP, Fowler SJ, Lipworth BJ. Dose response of inhaled corticosteroids on bronchial hyperresponsiveness: a meta-analysis. *Ann Allergy Asthma Immunol*. 2003;90(2):194–8. doi:[10.1016/S1081-1206\(10\)62140-0](https://doi.org/10.1016/S1081-1206(10)62140-0).
74. Mahadev S, Salome CM, Berend N, King GG. The effect of low lung volume on airway function in obesity. *Respir Physiol Neurobiol*. 2013;188(2):192–9. doi:[10.1016/j.resp.2013.05.021](https://doi.org/10.1016/j.resp.2013.05.021).

75. Luder E, Melnik TA, DiMaio M. Association of being overweight with greater asthma symptoms in inner city black and Hispanic children. *J Pediatr*. 1998;132(4):699–703. doi:[10.1016/S0022-3476\(98\)70363-4](https://doi.org/10.1016/S0022-3476(98)70363-4).
76. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319–38. doi:[10.1183/09031936.05.00034805](https://doi.org/10.1183/09031936.05.00034805).
77. National Asthma E, Prevention P. Expert panel report 3 (EPR-3): guidelines for the diagnosis and management of asthma-summary report 2007. *J Allergy Clin Immunol*. 2007;120(5 Suppl):S94–138.
78. Tantisira KG, Litonjua AA, Weiss ST, Fuhlbrigge AL, Childhood Asthma Management Program Research Group. Association of body mass with pulmonary function in the Childhood Asthma Management Program (CAMP). *Thorax*. 2003;58(12):1036–41. doi:[10.1136/thorax.58.12.1036](https://doi.org/10.1136/thorax.58.12.1036).
79. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, et al. Cluster analysis of obesity and asthma phenotypes. *PLoS One*. 2012;7(5):e36631. doi:[10.1371/journal.pone.0036631](https://doi.org/10.1371/journal.pone.0036631).