

Review

Asthma interactions between obesity and other risk factors



Matthew Wong, DO; Erick Forno, MD, MPH; Juan C. Celedón, MD, DrPH

Division of Pulmonary Medicine, Department of Pediatrics, University of Pittsburgh, UPMC Children's Hospital of Pittsburgh, Pittsburgh, Pennsylvania

Key Messages

- Current evidence supports interactions between obesity and outdoor and indoor air pollutants (including second-hand smoke) on enhancing asthma risk, although there are sparse data on the specific pollutants underlying such interactions.
- Limited evidence suggests that obesity may modify the effects of depression or anxiety on asthma, whereas very few studies have examined interactions between obesity and sex-hormone levels or diet.
- Well-designed observational prospective studies and randomized clinical trials should help establish the impact of modifying coexisting exposures to reduce the harmful effects of obesity on asthma.
- Because obesity during childhood often persists into adulthood, clinicians should encourage behaviors known to prevent obesity in young children, including a healthy diet and physical activity. Such efforts must be complemented by policies that promote healthy dietary patterns at home and at school, and outdoor activities.

ARTICLE INFO

Article history:

Received for publication March 4, 2022.

Received in revised form April 7, 2022.

Accepted for publication April 21, 2022.

ABSTRACT

Objective: To review and critically discuss published evidence on interactions between obesity and selected risk factors on asthma in children and adults, and to discuss potential future directions in this field.

Data Sources: National Library of Medicine (via PubMed)

Study Selection: A literature search was conducted for human studies on obesity and selected interactions (with sex, race and ethnicity, socioeconomic status, indoor and outdoor pollutants, depression, anxiety, and diet) on asthma. Studies that were published in English and contained a full text were considered for inclusion in this review.

Results: Current evidence supports interactions between obesity and outdoor and indoor air pollutants (including second-hand smoke [SHS]) on enhancing asthma risk, although there are sparse data on the specific pollutants underlying such interactions. Limited evidence also suggests that obesity may modify the effects of depression or anxiety on asthma, whereas little is known about potential interactions between obesity and sex-hormone levels or dietary patterns.

Conclusion: Well-designed observational prospective studies (eg, for pollutants and sex hormones) and randomized clinical trials (eg, for the treatment of depression) should help establish the impact of modifying coexisting exposures to reduce the harmful effects of obesity on asthma. Such studies should be designed to have a sample size that is large enough to allow adequate testing of interactions between obesity and risk factors that are identified a priori and thus, well characterized, using objective measures and biomarkers (eg, urinary or serum cotinine for SHS, epigenetic marks of specific environmental exposures).

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Reprints: Juan C. Celedón, MD, DrPH, Division of Pediatric Pulmonary Medicine, Department of Pediatrics, UPMC Children's Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224. E-mail: juan.celedon@chp.edu.

Disclosures: Dr Celedón has received research materials from GSK and Merck (inhaled steroids) and Pharmavite (vitamin D and placebo capsules), to provide medications free of cost to participants in NIH-funded studies, unrelated to this work. The other authors have no conflicts of interest to report.

Funding: Dr Wong is supported by training grant T32 HL129949 from the US National Institutes of Health (NIH). Dr Celedón's contribution was supported by grants HL117191, MD011764, and HL152475 from the NIH. Dr Forno's contribution was supported by grant HL149693 from the NIH. The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

Introduction

Asthma is a complex disease, caused by the insufficiently characterized interplay between heredity and environmental risk factors. Multiple epidemiologic studies and a few clinical trials of weight loss have implicated obesity in the pathogenesis of asthma and worse asthma outcomes in children and adults.^{1–7}

The mechanisms underlying the link between obesity and asthma are insufficiently understood but may include changes in respiratory mechanics or lung structure (eg, airway dysplasia⁸), altered immune responses (eg, enhanced Th17-driven immunity⁹), systemic and airway inflammation,¹⁰ and reduced response to inhaled corticosteroids.¹¹ Such diverse potential pathways further suggest that “obesity-related asthma” is a syndrome encompassing several phenotypes and endotypes.

Coexposure to 2 or more risk factors for asthma is common and has synergistic effects. For example, a cross-sectional study of 2 independent cohorts of Puerto Rican and Swedish school-aged children showed that the presence of at least 4 risk factors (ie, parental asthma, male sex, allergic rhinitis, obesity, early-life second-hand smoke, and an unhealthy diet) was associated with 17.2 to 21.6 times increased odds of asthma.¹² Despite these findings, relatively little is known about the nature, mechanisms, and relative contributions of specific interactions between risk factors to asthma causation or severity.

A growing body of evidence suggests that the estimated effects of obesity on asthma are modified by other risk factors. Whether these risk factors are mutually independent or interact synergistically in either a detrimental or protective manner is not clear. In this review, we will first examine the published evidence of interactions between obesity and selected risk factors, including sex, race and ethnicity, socioeconomic status (SES), indoor and outdoor pollutants, depression and anxiety, and diet. We will then suggest future directions for research in this area.

Biological Sex

Obesity and weight gain have been associated with asthma in both boys and girls, with multiple studies yielding conflicting results for sex differences in the link between obesity and asthma during childhood and adolescence.¹³ Some studies have reported a stronger or more marked association between weight gain and overweight or obesity in girls than in boys,^{14,15} whereas others have shown a male predominance.^{16,17}

Obesity and weight gain are associated with asthma and worse asthma outcomes in adults of both sexes, but these associations are consistently stronger in women than in men.¹³ Such sex differences in the obesity–asthma relationship in adults may be partly explained by diagnostic bias because obesity or weight gain has been associated with airway hyperresponsiveness (regardless of a physician’s diagnosis of asthma) in both women and men,^{18,19} and physicians could be more likely to diagnose asthma in female smokers than in male smokers (who may more often be diagnosed with chronic obstructive pulmonary disease [COPD]).¹⁸

Asthma prevalence and morbidity change according to life stages and sex, with a male predominance in childhood but a female predominance after adolescence. Sex- and age-related differences in asthma may be explained by changes in hormonal levels resulting from puberty or medication use²⁰ because recent cross-sectional studies showed that levels of sex steroid hormones are linked to asthma in adults,^{21,22} and that such association may be influenced by obesity.²² For example, our group recently demonstrated that high levels of serum-free testosterone and estradiol are associated with reduced odds of asthma in obese women, whereas a high serum estradiol is associated with reduced odds of asthma in nonobese men.²² Thus, prospective studies of the complex interactions between sex hormones, obesity, and asthma—including pre- and post-pubertal assessments—are warranted.

Race and Ethnicity

Although obesity and asthma disproportionately affect certain racial and ethnic minority groups such as African-Americans and Puerto Ricans,^{23–25} there has been conflicting or negative evidence for an interaction between race or ethnicity and obesity on asthma per se.^{2,24,26,27} For example, an analysis of data from children who participated in the National Health and Nutrition Examination Survey (NHANES) between 1988 and 1994 and between 2011 and 2014 found no significant ($P = 0.53$) 3-way effect modification between obesity, race or ethnicity, and asthma: neither overweight nor obesity explained the observed differences in asthma prevalence between non-Hispanic Blacks and non-Hispanic whites or Mexican Americans.²⁴ Similarly, there is conflicting or insufficient evidence of an interaction between race or ethnicity and obesity on asthma control or severity. A cross-sectional study of African American, Mexican American, and Puerto Rican youth found that obesity was associated with worse asthma control in all boys, but that obesity was only associated with worse asthma control in Mexican American girls.²⁸ In contrast, overweight or obesity has been associated with indicators of worse asthma control or asthma severity in Puerto Rican and African American youth of both sexes in other cross-sectional and longitudinal studies.^{25,29,30}

Socioeconomic Status (SES)

Both obesity and asthma are more common among economically disadvantaged individuals in the United States, but current evidence does not support an interaction between obesity and low SES on asthma. For example, a study of 6119 adults living in New York City showed that the percentage of asthma that was attributable to obesity in this population (assuming that obesity causes asthma) was similar between residents of low-income neighborhoods (7.3%) and residents of middle- and upper-income neighborhoods (7.7%).³¹ Moreover, the estimated effects of obesity on asthma did not differ significantly ($P = 0.36$) by neighborhood type. Similar results were obtained in a study of 849,659 Israeli adolescents, which reported that the estimated effect of obesity on asthma was similar across SES groups.³²

Cigarette Smoking

Cigarette smoking has been associated with the development of asthma, particularly in female smokers. Moreover, smoking has been linked to more severe symptoms and hospitalizations, accelerated decline in lung function, and reduced response to treatment in subjects with asthma.³³ To date, there is no convincing evidence of an interaction between obesity and cigarette smoking on asthma, as reviewed below.

A cross-sectional study of 112,830 Canadian adults examined whether the relationship between smoking and asthma differed in men and women across 3 body mass index categories: $< 25 \text{ kg/m}^2$ (underweight and normal weight), $25 \text{ to } 29.9 \text{ kg/m}^2$ (overweight), and $\geq 30 \text{ kg/m}^2$ (obese).³⁴ In a multivariable analysis stratified by sex, current smoking was associated with asthma in women who were underweight or of normal weight (adjusted odds ratio [aOR], 1.41; 95% confidence interval [CI], 1.23–1.62), overweight (aOR, 1.27; 95% CI, 1.05–1.54), and obese (aOR, 1.28; 95% CI, 1.03–1.59). In contrast, current smoking was associated with asthma in men who were underweight or had normal weight (aOR, 1.20; 95% CI, 1.01–1.43), but not in those who were overweight or obese (aOR, 1.02; 95% CI, 0.80–1.30). Although the authors of that study concluded that overweight and obesity may modify the effects of current smoking on asthma in adult men, diagnostic bias cannot be excluded as a potential explanation for their results in the absence of measurements of lung function or airway responsiveness. In a separate study, a meta-analysis was

conducted using individual-level data from 174,556 adults aged 18 to 44 years from 70 different countries. Although the estimated effect of obesity on asthma was higher in smokers (aOR, 2.27; 95% CI, 1.37–3.74) than in nonsmokers (aOR, 1.81; 95% CI, 1.28–2.55), there was no formal testing for an interaction between smoking and obesity on asthma.⁵

Outdoor Air Pollution

Exposure to outdoor air pollution leads to increased morbidity from asthma (eg, worse symptoms and severe exacerbations) in both children and adults.^{35,36} Current evidence strongly supports a causal role for long-term exposure to outdoor air pollution in childhood asthma, with suggestive but inconclusive evidence for such a role in new-onset asthma in adults. Children are most vulnerable to the detrimental effects of poor air quality on respiratory health, likely because of factors including a high minute ventilation rate, time spent outdoors, and still-developing lungs.^{36–38} An aggregate body of evidence from experimental and observational studies suggests that obesity enhances the detrimental effects of outdoor air pollution on asthma.

Murine models have shown that ozone exposure increases both airway responsiveness and airway inflammation to a greater degree in obese mice than in wild type mice,³⁹ and experimental studies in adults have reported that the negative effects of ozone exposure on FEV₁ and FVC are enhanced by obesity or an increased body mass index.⁴⁰ Consistent with those findings, results from observational studies largely suggest that outdoor air pollution or pollutants are more strongly associated with worse lung function or asthma in overweight or obese individuals than in those of normal weight. Indeed, a cross-sectional study of 30,056 Chinese children reported that both sulfur dioxide (SO₂) and nitrogen dioxide (NO₂) were more strongly associated with physician-diagnosed asthma in children who were overweight or obese than in those with normal weight.⁴¹ Moreover, a 10-year prospective study of 4664 adults showed that over time, better air quality led to decreased rates of age-related decline in FEF_{25–75}, FEF_{25–75}/FVC, and FEV₁/FVC in subjects of low or normal weight, but not in those who were overweight or obese.⁴² Although an analysis of data from adults in 2 European cohorts found no significant interaction between obesity and particulate matter (with either aerodynamic diameter < 2.5 μm [PM_{2.5}] or aerodynamic diameter 2.5–10 μm [PM_{coarse}]) on wheeze (*P* for interaction ≥ .07), this could be partly explained by clustering wheeze due to asthma with wheeze owing to other causes (eg, COPD, heart failure).⁴³

Indoor Air Pollution

Humans spend a substantial proportion of their time in indoor environments, with children spending up to 90% of their time indoors.⁴⁴ Indoor air pollution consists of a complex mixture of pollutants penetrating from outdoors and pollutants generated from indoor sources (eg, second-hand smoke [SHS], cooking, sweeping, and allergens). Indoor pollutants have been associated with reduced lung function, asthma symptoms, and worse asthma outcomes.⁴⁴ Current evidence suggests that obese subjects are more susceptible to the detrimental effects of some indoor pollutants on asthma.

Pre- and postnatal SHS exposure have been associated with childhood asthma.³ Findings from 2 prospective studies of 298 urban and predominantly African American school-aged children followed for 9 to 12 months suggest that obesity enhances the detrimental effects of SHS exposure (assessed by urinary cotinine measurements) on asthma symptoms.⁴⁵ Moreover, a cross-sectional survey of 28,807 US adolescents found that the prevalence of current asthma among subjects exposed to SHS at home was twice as high in obese subjects than in the nonobese.⁴⁶ In that study, obesity was associated with

increased odds of current asthma among adolescents exposed to SHS at home (OR, 2.01; 95% CI, 1.15–3.70) but not among adolescents unexposed to SHS (OR, 0.94; 95% CI, 0.71–1.23).⁴⁶

Exposure to polycyclic aromatic hydrocarbons (PAH) from traffic emissions and other combustion sources has been associated with childhood asthma. In a study of 311 inner-city children living in New York City and the Bronx, indoor residential levels of semivolatile PAH (methyl phenanthrenes) measured at age 5 or 6 years were associated with increased risk of current asthma at ages 5 and 7 years in obese children but not in nonobese children (*P* for interaction < .05).³⁷ Although not specifically assessed, indoor exposure to semivolatile PAH was likely owing to a combination of indoor (eg, SHS, cooking, space heating, and evaporation from petrochemicals such as hair sprays and deodorants) and outdoor (eg, traffic emissions) sources.³⁷

Children usually spend a considerable time at school. In a 1-year prospective study of 271 children aged between 4 to 13 years, NO₂ levels in the classroom were associated with asthma symptom days and change in the child's caregiver plans in obese children (eg, incidence rate ratio for asthma symptom days, 1.86; 95% CI, 1.15–3.02) but not in children with normal weight (*P* for interaction < .05 in both instances).⁴⁷ However, there was no association between NO₂ levels and lung function, and the overall results were not statistically significant after correction for multiple testing. In another study, exposure to indoor endocrine disrupting chemicals (EDCs) in the classroom was associated with obesity and asthma among children attending 20 schools in Porto (Portugal), but an interaction between obesity and EDCs was not adequately tested.⁴⁸

Few studies have examined whether obesity modifies the effect of indoor allergens on asthma. A cross-sectional study of 9668 adults showed that the prevalence of asthma attacks in the previous year was higher in obese subjects reporting mold at their homes than in nonobese subjects reporting mold at their homes (11.4% vs 5%), but an interaction between obesity and self-reported mold exposure on asthma (either on an additive or multiplicative scale) was not properly tested.⁴⁹ Moreover, those results were not adjusted for multiple testing for 3-way interactions and must thus be interpreted with caution, pending confirmation in other studies.

Depression and Anxiety

Depression and anxiety- or stress-related disorders have been associated with asthma, worse asthma outcomes, and reduced bronchodilator response in children and adults.^{50–55} Depression and anxiety have also been linked to obesity in subjects with and without asthma,^{56,57} and limited evidence suggests that obesity may interact with depression or anxiety on causing or worsening asthma.

In an 11-year prospective study of 23,599 Norwegian adults, subjects who were obese and reported anxiety or depression symptoms at baseline had a higher risk of incident asthma (adjusted [a]OR, 2.93; 95% CI, 2.20–3.91) than any other group (nonobese participants without anxiety or depression symptoms [reference group], nonobese participants with anxiety or depression symptoms [aOR, 1.20; 95% CI, 1.00–1.45], and obese participants without anxiety or depression symptoms [aOR, 1.47; 95% CI, 1.19–1.82]). In that study, the relative excess risk for incident asthma because of the interaction between anxiety or depression symptoms and obesity was 1.26 (95% CI, 0.39–2.12).⁵⁷ Of note, all analyses were adjusted for smoking, and similar results were obtained in sensitivity analyses including more stringent definitions of depression and asthma.

Two cross-sectional studies have yielded conflicting findings for an interaction between obesity and depression or depressive symptoms on lung function or disease control in subjects with asthma. In a study of 250 school-aged children with asthma, depressive symptoms were significantly associated with lower FEV₁ in overweight or obese subjects (*P* < .01) but not in subjects with normal weight. In

overweight or obese children, depressive symptoms were also associated with vagal bias (defined as vagal/cholinergic autonomic-nervous-system reactivity over sympathetic reactivity) under emotion and/or stress arousal. Moreover, such vagal bias was associated with increased airway resistance.⁵⁴ In contrast, a cross-sectional study of 601 adolescents and adults with asthma found that both obesity (aOR, 1.83; 95% CI, 1.23–3.52) and depressive symptoms (aOR, 2.08; 95% CI, 1.23–3.52) were independently associated with poorly controlled asthma, without evidence of a significant interaction ($P = .58$).⁵⁵

Diet

A recent review of published studies supports a role for a healthy diet—including high intake of fruits and vegetables, whole grains, fiber, and unsaturated fats but low intake of saturated fats and refined sugars—in preventing asthma and reducing asthma severity.⁵⁸ Moreover, such a diet reduces the risk of obesity, and thus, obesity may either mediate or modify the effects of dietary patterns on asthma or asthma severity. Although multiple studies have shown independent effects of diet and obesity on asthma or asthma outcomes,^{59,60} little is known about potential modification of the effects of obesity on asthma by diet or dietary patterns, or whether obesity interacts with or mediates the effects of diet on asthma.

Based on existing evidence, vitamin D supplementation should not be recommended for the prevention or treatment of asthma. However, low levels of vitamin D are more common in obese subjects than in subjects of normal weight, and children with vitamin D levels below 30 ng/mL and high exposure to traffic-related air pollution may be at increased risk of severe asthma exacerbations.⁶¹ Given this, Bose et al.⁶² tested for 3-way interactions between low vitamin D levels, obesity, and exposure to PM_{2.5} on asthma symptoms in a 9-month prospective study of 120 children with asthma living in Baltimore. Although the authors reported that indoor levels of PM_{2.5} were

associated with worse asthma symptoms only in children who were obese and had low vitamin D levels (defined as ≤ 15.5 ng/mL),⁶² their results were not corrected for multiple testing, and thus, no firm conclusions can be drawn pending confirmation in other studies.

Conclusions

Obesity negatively impacts respiratory and overall health. Because obesity during childhood often persists into adulthood, clinicians should encourage behaviors known to prevent obesity in young children, including healthy dietary patterns and physical activity. Such efforts must be complemented by policies that promote a healthy diet at home and at school (through education and access to fruits and vegetables), and outdoor activities (through physical-education classes at school, proximity to green spaces such as parks, and reduced outdoor air pollution). Once obesity is established, the treatment of this condition still remains challenging, and thus, identifying risk factors that can be modified to reduce the negative effects of obesity may help prevent or manage asthma in children and adults (Table 1 and Fig 1).

Current evidence supports interactions between obesity and outdoor and indoor air pollutants (including SHS) on enhancing asthma risk, although there are sparse data on the specific pollutants underlying such interactions. Moreover, no study has examined whether obesity interacts with active use or passive exposure to electronic vapor products (eg, e-cigarettes) to cause or worsen asthma in adolescents and young adults. Limited evidence also suggests that obesity may modify the effects of depression or anxiety on asthma, whereas little is known about potential interactions between obesity and sex-hormone levels or dietary patterns.

Well-designed observational prospective studies (eg, for pollutants and sex hormones) and randomized clinical trials (eg, for the treatment of depression) should help establish the impact of modifying coexisting exposures to reduce the harmful effects of obesity on

Table 1
Evidence for Interactions Between Selected Risk Factors and Obesity on Asthma, and Possible Future Work

Interaction	Strength of available evidence	References	Suggestions for future work
1. Sex	Conflicting in children Moderate in adults, suggesting that obesity is more strongly associated with asthma in women than in men	Peters et al, ¹³ 2018; Castro-Rodríguez et al, ¹⁴ 2001; Lu et al, ¹⁵ 2016; Mannino et al, ¹⁶ 2006; Maltz et al, ¹⁷ 2016 Peters et al, ¹³ 2018; Celedón et al, ¹⁸ 2001; Litonjua et al, ¹⁸ 2002; Han et al, ²¹ 2020; Han et al, ²² 2020	Prospective studies of the interaction between sex hormones, obesity, and asthma, including pre- and postpubertal assessments.
2. Race/ethnicity	Weak and conflicting	Koebnick et al, ² 2016; Akinbami et al, ²⁴ 2017; Ramsey et al, ²⁵ 2005; Kim and Camargo, ²⁶ 2003; Lang et al, ²⁷ 2019; Borrell et al, ²⁸ 2013; Wong et al, ²⁹ 2022; Forno et al, ³⁰ 2014	Interactions between obesity and race or ethnicity and indicators of socioeconomic status can be further explored in prospective studies of multiracial/ethnic cohorts
3. Socioeconomic status	Weak and nonsupportive	Tonorezos et al, ³¹ 2008; Gordon et al, ³² 2016	Prospective studies of interactions between obesity, electronic cigarettes, and cigarette smoking on asthma
4. Cigarette smoking	Weak and nonsupportive	Patra et al, ⁵ 2016; Chen and Mai, ³⁴ 2011	Prospective studies assessing interactions between individual pollutants (eg, ozone, particulate matter), obesity, and asthma
5. Outdoor air pollution	Moderate to strong	Shore et al, ³⁹ 2003; Alexeeff et al, ⁴⁰ 2007; Dong et al, ⁴¹ 2013; Schikowski et al, ⁴² 2013; Doiron et al, ⁴³ 2019	Prospective studies of interactions between obesity and specific indoor pollutants such as allergens, NO ₂ , and polycyclic aromatic hydrocarbons, and second-hand smoke
6. Indoor air pollution	Moderate to strong, particularly for second-hand smoke exposure in youth	Jung et al, ³⁷ 2014; Wu et al, ⁴⁵ 2018; Kitsantas et al, ⁴⁶ 2016; Permaul et al, ⁴⁷ 2020; Paciencia et al, ⁴⁸ 2019; Wen et al, ⁴⁹ 2009	Prospective studies with concurrent and detailed assessment of depression- and anxiety-related disorders, including posttraumatic stress disorder
7. Depression or anxiety	Limited but generally supportive	Hsu et al, ⁵⁴ 2020; Kapadia et al, ⁵⁵ 2014; Brumpton et al, ⁵⁷ 2013	Prospective studies with detailed characterization of dietary profiles using validated questionnaires and biomarkers
8. Diet	Limited and insufficient	Bose et al, ⁶² 2019	

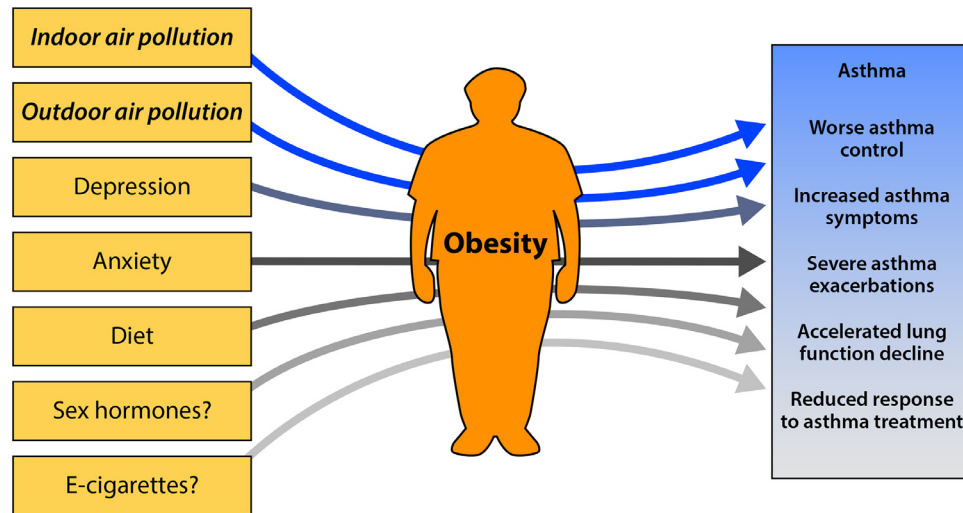


Figure 1. Potential interactions between modifiable risk factors and obesity could lead to asthma, poor asthma control, and worse asthma severity. Current evidence supports interactions between obesity and indoor and outdoor air pollution on asthma (blue arrows), whereas limited evidence suggests interactions between obesity and depression or anxiety on asthma (gray arrows). Little is known about interactions between obesity and diet, sex hormones, or use of electronic cigarettes on asthma (pale gray arrows).

asthma. Such studies should be designed to have a sample size that is large enough to allow adequate testing of interactions between obesity and risk factors that are identified a priori and thus well characterized using objective measures and biomarkers (eg, urinary or serum cotinine for SHS, epigenetic marks of exposure). Because such risk factors often co-occur (eg, SHS, outdoor pollution, and an unhealthy diet), testing for several interactions should be carefully considered, along with collection of DNA and RNA for studies of their underlying molecular and genetic mechanisms.

Identifying and understanding the mechanisms through which modifiable risk factors ameliorate or worsen the detrimental effects of obesity on asthma should lead to improved prevention and management of the “obese asthma phenotype” in children and adults.

References

- Jacobson JS, Mellins RB, Garfinkel R, Rundle AG, Perzanowski MS, Chew GL, et al. Asthma, body mass, gender, and Hispanic national origin among 517 preschool children in New York City. *Allergy*. 2008;63(1):87–94.
- Koebnick C, Fischer H, Daley MF, Ferrara A, Horberg MA, Waitzfelder B, et al. Interacting effects of obesity, race, ethnicity and sex on the incidence and control of adult-onset asthma. *Allergy Asthma Clin Immunol*. 2016;12:50.
- Castro-Rodríguez JA, Forno E, Rodríguez-Martínez CE, Celedón JC. Risk and protective factors for childhood asthma: what is the evidence? *J Allergy Clin Immunol Pract*. 2016;4(6):1111–1122.
- Forno E, Han YY, Mullen J, Celedón JC. Overweight, obesity, and lung function in children and adults—a meta-analysis. *J Allergy Clin Immunol Pract*. 2018;6(2):570–581. e10.
- Patra J, Maher YI, Mishra S, Bhatia M, Alam D, Malini DS, et al. Effects of body mass index, tobacco smoking, alcohol drinking and solid fuel use on the risk of asthma: Individual Participant Data (IPD) meta-analysis of 175 000 individuals from 51 nationally representative surveys. *BMJ Open Respir Res*. 2016;3(1):e000121.
- Miethe S, Karsonova A, Karaulov A, Renz H. Obesity and asthma. *J Allergy Clin Immunol*. 2020;146(4):685–693.
- Okoniewski W, Lu KD, Forno E. Weight loss for children and adults with obesity and asthma. A systematic review of randomized controlled trials. *Ann Am Thorac Soc*. 2019;16(5):613–625.
- Forno E, Weiner DJ, Mullen J, Sawicki G, Kurland G, Han YY, et al. Obesity and airway Dysanapsis in children with and without asthma. *Am J Respir Crit Care Med*. 2017;195(3):314–323.
- Kim HY, Lee HJ, Chang YJ, Pichavant M, Shore SA, Fitzgerald KA, et al. Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med*. 2014;20(1):54–61.
- Han YY, Forno E, Celedón JC. Adiposity, fractional exhaled nitric oxide, and asthma in U.S. children. *Am J Respir Crit Care Med*. 2014;190(1):32–39.
- Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedón JC, et al. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol*. 2011;127(3):741–749.
- Szentpetery SS, Gruzdeva O, Forno E, Han YY, Bergstrom A, Kull I, et al. Combined effects of multiple risk factors on asthma in school-aged children. *Respir Med*. 2017;133:16–21.
- Peters U, Dixon AE, Forno E. Obesity and asthma. *J Allergy Clin Immunol*. 2018;141(4):1169–1179.
- Castro-Rodríguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased incidence of asthmalike symptoms in girls who become overweight or obese during the school years. *Am J Respir Crit Care Med*. 2001;163(6):1344–1349.
- 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.
- Mannino DM, Mott J, Ferdinands JM, Camargo CA, Friedman M, Greves HM, et al. Boys with high body masses have an increased risk of developing asthma: findings from the National Longitudinal Survey of Youth (NLSY). *Int J Obes (Lond)*. 2006;30(1):6–13.
- Maltz L, Matz EL, Gordish-Dressman H, Pillai DK, Teach SJ, Camargo Jr. CA, et al. Sex differences in the association between neck circumference and asthma. *Pediatr Pulmonol*. 2016;51(9):893–900.
- Celedón 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):1835–1840.
- Litonjua AA, Sparrow D, Celedón 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):581–585.
- Han YY, Forno E, Witche SF, Manni ML, Acosta-Pérez E, Canino G, et al. Testosterone-to-estradiol ratio and lung function in a prospective study of Puerto Rican youth. *Ann Allergy Asthma Immunol*. 2021;127(2):236–242. e1.
- Han YY, Yan Q, Yang G, Chen W, Forno E, Celedón JC. Serum free testosterone and asthma, asthma hospitalisations and lung function in British adults. *Thorax*. 2020;75(10):849–854.
- Han YY, Forno E, Celedón JC. Sex steroid hormones and asthma in a nationwide study of U.S. Adults. *Am J Respir Crit Care Med*. 2020;201(2):158–166.
- Celedón JC, Sredl D, Weiss ST, Pisarski M, Wakefield D, Cloutier M. Ethnicity and skin test reactivity to aeroallergens among asthmatic children in Connecticut. *Chest*. 2004;125(1):85–92.
- Akinbami LJ, Rossen LM, Fakhouri THI, Simon AE, Kit BK. Contribution of weight status to asthma prevalence racial disparities, 2–19 year olds, 1988–2014. *Ann Epidemiol*. 2017;27(8):472–478. e3.
- Ramsey CD, Celedón JC, Sredl DL, Weiss ST, Cloutier MM. Predictors of disease severity in children with asthma in Hartford, Connecticut. *Pediatr Pulmonol*. 2005;39(3):268–275.
- Kim S, Camargo Jr. CA. Sex-race differences in the relationship between obesity and asthma: the behavioral risk factor surveillance system, 2000. *Ann Epidemiol*. 2003;13(10):666–673.
- Lang JE, Bunnell HT, Lima JJ, Jobayer Hossain M, Wysocki T, Bacharier L, et al. Effects of age, sex, race/ethnicity, and allergy status in obesity-related pediatric asthma. *Pediatr Pulmonol*. 2019;54(11):1684–1693.
- 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.
- Wong M, Han YY, Rosser F, Acosta-Pérez E, Canino G, Forno E, et al. Persistent overweight or obesity, lung function, and asthma exacerbations in Puerto Rican Youth. *Ann Allergy Asthma Immunol*. 2022;128(4):408–413. e2.
- Forno E, Acosta-Pérez E, Brehm JM, Han YY, Alvarez M, Colon-Semidey A, et al. Obesity and adiposity indicators, asthma, and atopy in Puerto Rican children. *J Allergy Clin Immunol*. 2014;133(5):1308–1314. e1.
- Tonorez ES, Karpatis AM, Wang Y, Barr RG. Does the relationship between asthma and obesity differ by neighborhood? *Respir Med*. 2008;102(12):1797–1804.

32. Gordon B, Hassid A, Bar-Shai A, Derazne E, Tzur D, Hershkovich O, et al. Association between asthma and body mass index and socioeconomic status: a cross-sectional study on 849,659 adolescents. *Respirology*. 2016;21(1):95–101.
33. Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2013;41(3):716–726.
34. Chen Y, Mai XM. Smoking and asthma in men and women with normal weight, overweight, and obesity. *J Asthma*. 2011;48(5):490–494.
35. Stevens EL, Rosser F, Forno E, Peden D, Celedón JC. Can the effects of outdoor air pollution on asthma be mitigated? *J Allergy Clin Immunol*. 2019;143(6):2016–2018.e1.
36. Thurston GD, Balmes JR, Garcia E, Gilliland FD, Rice MB, Schikowski T, et al. Outdoor air pollution and new-onset airway disease. An official American Thoracic Society workshop report. *Ann Am Thorac Soc*. 2020;17(4):387–398.
37. Jung KH, Perzanowski M, Rundle A, Moors K, Yan B, Chillrud SN, et al. Polycyclic aromatic hydrocarbon exposure, obesity and childhood asthma in an urban cohort. *Environ Res*. 2014;128:35–41.
38. Limaye S, Salvi S. Obesity and asthma: the role of environmental pollutants. *Immunol Allergy Clin North Am*. 2014;34(4):839–855.
39. Shore SA, Rivera-Sanchez YM, Schwartzman IN, Johnston RA. Responses to ozone are increased in obese mice. *J Appl Physiol* (1985). 2003;95(3):938–945.
40. Alexeeff SE, Litonjua AA, Suh H, Sparrow D, Vokonas PS, Schwartz J. Ozone exposure and lung function: effect modified by obesity and airways hyperresponsiveness in the VA normative aging study. *Chest*. 2007;132(6):1890–1897.
41. Dong GH, Qian Z, Liu MM, Wang D, Ren WH, Fu Q, et al. Obesity enhanced respiratory health effects of ambient air pollution in Chinese children: the seven North-eastern Cities study. *Int J Obes (Lond)*. 2013;37(1):94–100.
42. Schikowski T, Schaffner E, Meier F, Phuleria HC, Vierkötter A, Schindler C, et al. Improved air quality and attenuated lung function decline: modification by obesity in the SAPALDIA cohort. *Environ Health Perspect*. 2013;121(9):1034–1039.
43. Doiron D, de Hoogh K, Probst-Hensch N, Fortier I, Cai Y, Matteis SD, et al. Air pollution, lung function and COPD: results from the population-based UK Biobank study. *Eur Respir J*. 2019;54(1):1802140.
44. Breyse PN, Diette GB, Matsui EC, Butz AM, Hansel NN, McCormack MC. Indoor air pollution and asthma in children. *Proc Am Thorac Soc*. 2010;7(2):102–106.
45. Wu TD, Brigham EP, Peng R, Koehler K, Rand C, Matsui EC, et al. Overweight/obesity enhances associations between secondhand smoke exposure and asthma morbidity in children. *J Allergy Clin Immunol Pract*. 2018;6(6):2157–2159.e5.
46. Kitsantas P, Aguisanda F. Association of asthma with obesity among adolescents exposed to environmental tobacco smoke. *J Asthma*. 2016;53(1):25–29.
47. Permaul P, Gaffin JM, Petty CR, Baxi SN, Lai PS, Sheehan WJ, et al. Obesity may enhance the adverse effects of NO₂ exposure in urban schools on asthma symptoms in children. *J Allergy Clin Immunol*. 2020;146(4):813–820.e2.
48. Paciência I, Cavaleiro Rufo J, Silva D, Martins C, Mendes F, Farraia M, et al. Exposure to indoor endocrine-disrupting chemicals and childhood asthma and obesity. *Allergy*. 2019;74(7):1277–1291.
49. Wen XJ, Balluz L, Mokdad A. Do obese adults have a higher risk of asthma attack when exposed to indoor mold? A study based on the 2005 Behavioral Risk Factor Surveillance System. *Public Health Rep*. 2009;124(3):436–441.
50. Brehm JM, Ramratnam SK, Tse SM, Croteau-Chonka DC, Pino-Yanes M, Rosas-Salazar C, et al. Stress and bronchodilator response in children with asthma. *Am J Respir Crit Care Med*. 2015;192(1):47–56.
51. Han YY, Forno E, Celedón JC. Health risk behaviors, violence exposure, and current asthma among adolescents in the United States. *Pediatr Pulmonol*. 2019;54(3):237–244.
52. Han YY, Forno E, Marsland AL, Miller GE, Celedón JC. Depression, asthma, and bronchodilator response in a nationwide study of US adults. *J Allergy Clin Immunol Pract*. 2016;4(1):68–73.e1.
53. de la Hoz RE, Jeon Y, Miller GE, Wisnivesky JP, Celedón JC. Post-traumatic stress disorder, bronchodilator response, and incident asthma in World Trade Center rescue and recovery workers. *Am J Respir Crit Care Med*. 2016;194(11):1383–1391.
54. Hsu CY, Lehman HK, Wood BL, Benipal J, Humayun Q, Miller BD. Comorbid obesity and depressive symptoms in childhood asthma: a harmful synergy. *J Allergy Clin Immunol Pract*. 2020;8(8):2689–2697.
55. Kapadia SG, Wei C, Bartlett SJ, Lang J, Wise RA, Dixon AE, et al. Obesity and symptoms of depression contribute independently to the poor asthma control of obesity. *Respir Med*. 2014;108(8):1100–1107.
56. Bedolla-Barajas M, Morales-Romero J, Fonseca-López JC, Pulido-Guillén NA, Larenas-Linnemann D, Hernández-Colín DD. Anxiety and depression in adult patients with asthma: the role of asthma control, obesity and allergic sensitization. *J Asthma*. 2021;58(8):1058–1066.
57. Brumpton BM, Leivseth L, Romundstad PR, Langhammer A, Chen Y, Camargo Jr CA, et al. The joint association of anxiety, depression and obesity with incident asthma in adults: the HUNT study. *Int J Epidemiol*. 2013;42(5):1455–1463.
58. Reyes-Angel J, Han YY, Litonjua AA, Celedón JC. Diet and asthma: is the sum more important than the parts? *J Allergy Clin Immunol*. 2021;148(3):706–707.
59. Han YY, Jerschow E, Forno E, Hua S, Mossavar-Rahmani Y, Perreira KM, et al. Dietary patterns, asthma, and lung function in the Hispanic community health study/study of latinos. *Ann Am Thorac Soc*. 2020;17(3):293–301.
60. Reyes-Angel J, Han YY, Rosser F, Forno E, Acosta-Perez E, Canino G, et al. Diet, asthma, and severe asthma exacerbations in a prospective study of Puerto Rican youth. *J Allergy Clin Immunol Pract*. 2022;10(4):1013–1019.e1.
61. Rosser F, Brehm JM, Forno E, Acosta-Perez E, Kurland K, Canino G, et al. Proximity to a major road, vitamin D insufficiency, and severe asthma exacerbations in Puerto Rican children. *Am J Respir Crit Care Med*. 2014;190(10):1190–1193.
62. Bose S, Diette GB, Woo H, Koehler K, Romero K, Rule AM, et al. Vitamin D status modifies the response to indoor particulate matter in obese urban children with asthma. *J Allergy Clin Immunol Pract*. 2019;7(6):1815–1822.e2.