

Obesity and Asthma



Majid Keivanfar M.D
Pediatric Pulmonologist
Isfahan University of Medical Sciences

Is the incidence of asthma higher in obese children?

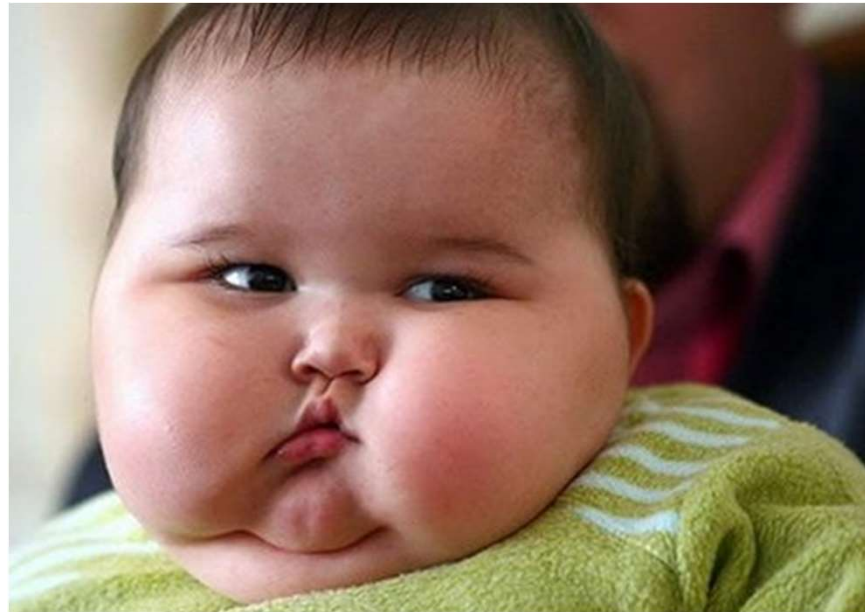
Is asthma more severe in obese children?

Is the response to asthma treatment lower in obese children?

Should different treatment methods be considered for asthma in obese children?



Numerous studies demonstrated that in children
overweight or obesity
are risk factors for asthma development.



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Childhood body mass index and subsequent physician-diagnosed asthma: a systematic review and meta-analysis of prospective cohort studies

[Kathryn B Egan](#) , [Adrienne S Ettinger](#) & [Michael B Bracken](#)

BMC Pediatrics **13**, Article number: 121 (2013) | [Cite this article](#)

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Egan et al. examined six prospective cohort studies and reported that compared to normal weight children, children with overweight or obesity have a **5.0% increased risk** of physician-diagnosed asthma.




OBESITY Reviews



Obesity Comorbidity

Gender difference of childhood overweight and obesity in predicting the risk of incident asthma: a systematic review and meta-analysis

Y. C. Chen, G. H. Dong, K. C. Lin, Y. L. Lee 

First published: 12 November 2012 | <https://doi.org/10.1111/j.1467-789X.2012.01055.x> | Citations: 140

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These results were supported by the meta-analysis by Chen et al. who evidenced that obese children have a **double risk** of developing asthma with a risk proportional to body mass index (BMI) values, particularly in boys.



Review Paper

A systematic review of the association between obesity and asthma in children

Pei-Ching Liu MSN RN, Gail M. Kieckhefer PhD RN ARNP-PNP, Bih-Shya Gau PhD RN 

First published: 08 April 2013 | <https://doi.org/10.1111/jan.12129> | Citations: 26

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Asthma and Obesity in Children

by  Francesco Sansone ¹ ,  Marina Attanasi ^{1,2} ,  Sabrina Di Pillo ¹  and  Francesco Chiarelli ^{1,2,*} 

¹ Department of Pediatrics, Pediatric Allergy and Pulmonology Unit, University of Chieti-Pescara, 66100 Chieti, Italy

² Pediatric Research Unit, University of Chieti-Pescara, 66100 Chieti, Italy

* Author to whom correspondence should be addressed.

Biomedicines **2020**, *8*(7), 231; <https://doi.org/10.3390/biomedicines8070231>

Received: 15 June 2020 / Revised: 17 July 2020 / Accepted: 18 July 2020 / Published: 21 July 2020

(This article belongs to the Section **Molecular and Translational Medicine**)

**Overall, obesity increases the risk of asthma
in all age groups across the paediatric age.**





ORIGINAL ARTICLE

Effects of age, sex, race/ethnicity, and allergy status in obesity-related pediatric asthma

Jason E. Lang MD, MPH , H. Timothy Bunnell PhD, John J. Lima PharmD, Md Jobayer Hossain PhD, Tim Wysocki PhD, Leonard Bacharier MD, Amanda Dempsey MD, PhD, MPH ... [See all authors](#) 

First published: 30 August 2019 | <https://doi.org/10.1002/ppul.24470> | Citations: 13

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Lang et al. demonstrated that the age group with the **highest risk** of developing obesity-related asthma was the **prepubertal** school-aged group (**7–11 years**).

Lang et al. suggested that the onset of asthma would be driven by both **duration and severity of overweight** and hypothesized that the years before the onset of puberty could represent a particularly high-risk moment for obesity-related asthma, particularly in girls.

This risk becomes higher in boys after 12 years old, suggesting a role of gender in obesity-related paediatric asthma.

In adults, obesity has been associated with severe asthma and exacerbations.

Barros et al. conducted a cross-sectional study in Brazil, including 5.8 adults, and demonstrated that obese asthmatics had the highest rate of hospitalization and emergency room accesses, suggesting a poor control of the disease.

Another Brazilian cross-sectional study showed that obese individuals with asthma had a poorer quality of life and more frequent asthma exacerbations requiring oral corticosteroids.

Barros, L.L.; Souza-Machado, A.; Corrêa, L.B.; Santos, J.S.; Cruz, C.; Leite, M.; Castro, L.; Coelho, A.C.; Almeida, P.; Cruz, A.A. Obesity and poor asthma control in patients with severe asthma. J. Asthma. 2011, 48, 171-176.



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Comorbidities

Association of obesity with severity outcomes in hospitalized pediatric asthma exacerbations

Raymond Parlar-Chun , MD, Grace Truong, BS, Tasia Isbell, BS MPH, Yesenia Delgado, BS & Makenna Arca, BS Med

Pages 54-58 | Received 16 Jun 2020, Accepted 20 Sep 2020, Accepted author version posted online: 22 Sep 2020, Published online: 29 Sep 2020

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Abstract

Introduction

While there seems to be an association between obesity and asthma, the exact nature of the

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> *Pediatr Allergy Immunol.* 2020 Jul;31(5):496-505. doi: 10.1111/pai.13237. Epub 2020 Mar 20.

Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study


Marjolein Engelkes ¹, Esme J Baan ¹, Maria A J de Ridder ¹, Elisabeth Svensson ², Daniel Prieto-Alhambra ^{3 4}, Francesco Lapi ⁵, Carlo Giaquinto ⁶, Gino Picelli ⁷, Nada Boudiaf ⁸, Frank Albers ⁹, Lee A Evitt ¹⁰, Sarah Cockle ¹⁰, Eric Bradford ¹⁰, Melissa K Van Dyke ¹¹, Robert Suruki ¹², Peter Rijnbeek ¹, Miriam C J M Sturkenboom ¹³, Hettie M Janssens ¹⁴, Katia M C Verhamme ^{1 15}

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PMID: 32115766 PMCID: PMC7496431 DOI: 10.1111/pai.13237

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In children, a recent study of 995 subjects (17% obese) **found no association between obesity and the severity of exacerbation**, which is expressed as length of hospitalization and admission to an intensive care unit.

Despite the high prevalence of obesity in some cohort of children with severe asthma, in a retrospective cohort including data from six European electronic healthcare databases obesity was **not considered as risk factor for exacerbation**.

Parlar-Chun, R.; Truong, G.; Isbell, T.; Delgado, Y.; Arca, M. Association of obesity with severity outcomes in hospitalized pediatric asthma exacerbations. *J. Asthma*. 2020, 3, 1-5.

Engelkes, M.; Baan, E.J.; de Ridder, M.A.J.; Svensson, E.; Prieto-Alhambra, D.; Lapi, F.; Giaquinto, C.; Picelli, G.; Boudiaf, N.; Albers, F.; et al. Incidence, risk factors and re-exacerbation rate of severe asthma exacerbations in a multinational, multidatabase pediatric cohort study. *Pediatr. Allergy Immunol.* 2020, 31, 496-505.

Orriëns et al. hypothesized that overweight and obese children with asthma could have higher odds of **intentional non-adherence to ICS**, potentially resulting in a **greater asthmatic exacerbation rate**.
(75/8% vs. 65/0% in children with normal weight)

Orriëns, L.B.; Vijverberg, S.J.H.; Maitland van der Zee, A.H.; Longo, C. Nonadherence to inhaled corticosteroids: A characteristic of the pediatric obese-asthma phenotype? *Pediatr. Pulmonol.* 2021, 56, 948–956.

Among the factors that could contribute to the pathogenesis of asthma in obese children there are **mechanical**, **inflammatory**, **genetic**, **hormonal** and **immune factors**.



Mechanical Factors

Abdominal tissue deposition with subsequent increased abdominal pressure reduced chest expansion and consequent decrement in tidal volume and residual capacity contribute to **bronchial re-modelling** over time, increasing airway obstruction and hyper-responsiveness.

Dysanapsis is a condition characterized by **unequal growth of lung parenchyma and airway caliber** and it has been observed in overweight and obese children . This phenomenon would lead to higher FEV₁ but even higher FVC , with subsequent reduction of FEV₁/FVC ratio and airflow obstruction.

Recent evidence showed that obesity may increase susceptibility to air pollution in asthmatic children.



An obese child (at the 99th percentile for BMI) had almost a **30% higher rate of alveolar PM_{2.5} deposition** compared to a normal weight child.

Afshar-Mohajer, N.; Wu, T.D.; Shade, R.; Brigham, E.; Woo, H.; Wood, M.; Koehl, R.; Koehler, K.; Kirkness, J.; Hansel, N.N.; et al. Obesity, tidal volume, and pulmonary deposition of fine particulate matter in children with asthma. *Eur. Respir. J.* 2021.

Proinflammatory Factors

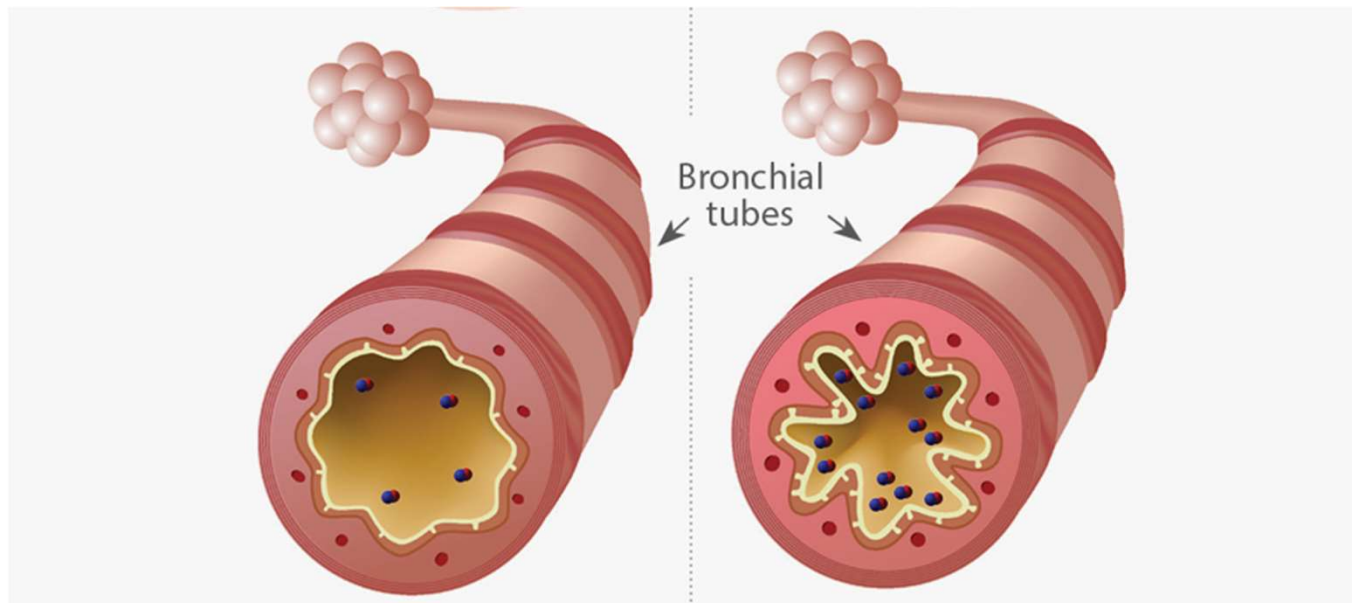
Adipose tissue is an important source of pro-inflammatory cytokines and adipokines, particularly **leptin**. Fat accumulation and excessive BMI have been associated with hypoxia, focal adipocyte necrosis, and subsequent **recruitment of macrophages** .

This can lead to higher blood levels of leptin and other pro-inflammatory hormones and **decreased levels of adiponectin, an anti-inflammatory adipokine**.

Leptin, whose production increases proportionally with adipose tissue, has **proinflammatory actions** and promotes neutrophil chemotaxis, reactive oxygen species production, natural killer cells and macrophage activation and phagocytosis.

Furthermore, leptin is responsible of Th₁ cytokines **(IL- α and IFN- γ)** release and suppression of Th₂ cytokines **(IL- β)** Production.

**Leptin receptors are expressed in human airway cells ,
and it has been hypothesized that leptin may be
related to airway reactivity.**



Instead, adiponectin would have a protective role against asthma. Adiponectin is an insulin sensitizing hormone with anti-inflammatory function; indeed, it inhibits effects of proinflammatory cytokines (i.e., TNF- α , IL- ϵ) and promotes expression of anti inflammatory cytokines (IL- δ and IL- γ receptor antagonist).



Genetic Factors

One of the most important studies that evidenced possible shared genetic causes in asthma and obesity was performed in 2007 by Hallstrand et al. The authors analyzed 1001 monozygotic and 383 dizygotic same-sex twin pairs registered in the University of Washington Twin Registry using a structural equation modelling.

They found that 16% of the genetic component of obesity was shared with asthma, suggesting a significant genetic pleiotropy between the two disorders.

Hallstrand, T.S.; Fischer, M.E.; Wurfel, M.M.; Afari, N.; Buchwald, D.; Goldberg, J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J. Allergy Clin. Immunol.* 2007, 116, 1235–1241.

Hormonal Factors

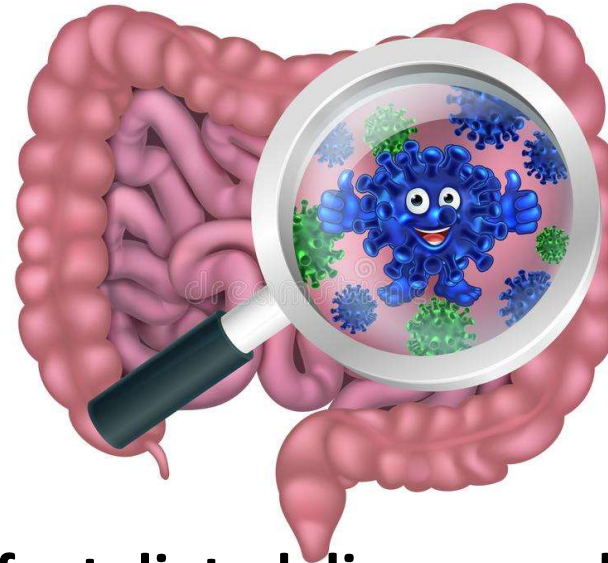
Obese asthmatic children with confirmed insulin resistance had higher bronchial hyperresponsiveness compared to obese children with normal glucose tolerance.

Therefore, it was hypothesized that airway hyperreactivity in obese children is **caused by insulin resistance** and impaired glucose tolerance and not obesity alone.

Insulin resistance seems to promote the **development of Th1** inflammation through the production of pro-inflammatory molecules (i.e., IL-6, TNF- α).

Microbiome

Another interesting hypothesis identifies **gut microbiota** alterations as playing an important role in the development of many diseases, including asthma and obesity.



Some early life events, such as infant diet, delivery modality and early exposure to antibiotics may lead to microbiome alterations and longterm consequences, including an **increased risk of asthma, diabetes and obesity**.

**A bidirectional association
between asthma and obesity
in children**



some evidences supports the hypothesis that asthma may contribute to the increase in obesity onset.

In the period 2002–2003 more than 5000 children were enrolled in California(US) and followed-up for 10 years. This longitudinal study observed that **normal weight children with asthma had a higher risk of developing obesity compared to non asthmatic children.**

Chen et al. came to the same conclusion and found a further higher risk in children with asthma not controlled by rescue therapy.

Cottrell, L.; Neal, W.A.; Ice, C.; Perez, M.K.; Piedimonte, G. Metabolic abnormalities in children with asthma. *Am. J. Respir. Crit.Care Med.* 2011, 183, 441–448

Chen, Z.; Salam, M.T.; Alderete, T.L.; Habre, R.; Bastain, T.M.; Berhane, K.; Gilliland, F.D. Effects of childhood asthma on the development of obesity among school-aged children. *Am. J. Respir. Crit. Care Med.* 2017, 196, 1181–1188.

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SYSTEMATIC REVIEW article

Front. Pediatr., 29 October 2020

Sec. Pediatric Pulmonology

Volume 8 - 2020 | <https://doi.org/10.3389/fped.2020.576858>

Bidirectional Association Between Asthma and Obesity During Childhood and Adolescence: A Systematic Review and Meta-Analysis



Li-Shen Shan,



Qian-Lan Zhou and



Yun-Xiao Shang*

Department of Pediatrics, Shengjing Hospital of China Medical University, Shenyang, China



Does early onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts

Zuelma A. Contreras, Zhanghua Chen, Theano Roumeliotaki, Isabella Annesi-Maesano, Nour Baiz, Andrea von Berg, Anna Bergström, Sarah Crozier, Liesbeth Duijts, Sandra Ekström, Esben Eller, Maria P. Fantini, Henrik Fomsgaard Kjaer, Francesco Forastiere, Beatrix Gerhard, Davide Gori, Margreet W. Haskamp-van Ginkel, Joachim Heinrich, Carmen Iñiguez, Hazel Inskip, Thomas Keil, Manolis Kogevinas, Susanne Lau, Irina Lehmann, Dieter Maier, Evelien R. van Meel, Monique Mommers, Mario Murcia, Daniela Porta, Henriëtte A. Smit, Marie Standl, Nikos Stratakis, Jordi Sunyer, Carel Thijs, Maties Torrent, Tanja G.M. Vrijkotte, Alet H. Wijga, Kiros Berhane, Frank Gilliland, Leda Chatzi

European Respiratory Journal 2018 52: 1800504; DOI: 10.1183/13993003.00504-2018

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Contreras et al. performed an analysis of 16 European cohorts which had followed 21,130 children from the age of 3–4 years up to 8 years of age. They found that **persistent wheezing and early onset asthma were associated with a higher risk of developing obesity.**

A metaanalysis conducted in 2020 concluded that during childhood and adolescence there is a **bidirectional association between obesity and asthma.**

Contreras, Z.A.; Chen, Z.; Roumeliotaki, T.; Annesi-Maesano, I.; Baiz, N.; von Berg, A.; Bergström, A.; Crozier, S.; Duijts, L.; Ekström, S.; et al. Does early onset asthma increase childhood obesity risk? A pooled analysis of 16 European cohorts. *Eur. Respir. J.* 2018, 52, 3–11.

Shan, L.S.; Zhou, Q.L.; Shang, Y.X. Bidirectional association between asthma and obesity during childhood and adolescence: A systematic review and meta-analysis. *Front. Pediatr.* 2020, 8, 688.

Physical Activity

It has been proposed that asthmatic children are at a greater risk of becoming overweight and obese than non-asthmatic children, because they tend to be less physically active, for fear of asthma exacerbation



Steroid Therapy

Another factor that may contribute to the **development of obesity** in asthmatic children is the potential adverse effects of systemic glucocorticosteroid therapy.

A longterm systemic treatment with glucocorticosteroids could promote **lipid deposition** in tissues, especially in the shoulders and in the trunk.

The “Obese-Asthma” Phenotype



Traditionally, classic childhood asthma has a **Th γ phenotype** with **eosinophilic inflammation** and history of **atopy**.

Asthma symptoms can increase in terms of prevalence and severity when children living with asthma also have obesity.



	“Classic” Asthma Phenotype	“Obese Asthma” Phenotype
Prick tests for inhaled allergens	Positive	Negative
Biomarkers:		
- FeNO	High	Low
- Blood eosinophils	High	Low
- IgE levels	High	Low
Inflammation pattern	Th2 polarization	No Th2 polarization (Th1 or Th17 polarization)
Cells involved	Th2 lymphocytes, type 2 innate lymphoid cells, eosinophils, mast cells	Neutrophils, type 3 innate lymphoid cells, macrophages
Inflammatory cytokines	IL-4, IL-5, IL-13	IL-6, IL-17, IL-21, IL-22, IFN-gamma
Airway inflammation	Mainly eosinofilic	Mainly neutrofilic
Disease control/Response to steroid therapy	Generally good	Generally poor

FeNO: Fractional exhaled Nitric Oxid. IL: interleukin; IFN: interferon; Th: T helper.

Treatment of the Obese-Asthma Phenotype

Obese children with asthma may be poorly reactive or non-reactive to currently available drugs for asthma control.

Steroids are less effective in obese than in lean individuals with asthma compared to subjects with normal BMI.

Steroids target the immune processes that mediate allergic responses, but many obese subjects with severe asthma are non-atopic.

Orries et al. analyzed data from 566 children aged 4–13 years with asthma under ICS as maintenance therapy and showed that obese children with moderate to severe asthma had less adherence to therapy than those with mild asthma.

Their findings suggested that a more careful monitoring of children with excess weight and asthma is necessary.

Orriëns, L.B.; Vijverberg, S.J.H.; Maitland van der Zee, A.H.; Longo, C. Nonadherence to inhaled corticosteroids: A characteristic of the pediatric obese-asthma phenotype? *Pediatr. Pulmonol.* 2021, 56, 948–956.

Exercise, Weight Loss, Diet

Non-atopic systemic inflammatory patterns of the “obese asthma” phenotype are connected with lower airway obstruction and exercise-induced bronchoconstriction.

Weight reduction in asthmatic children can lead to a **better prognosis** of asthma through a **better quality of life** related to asthma, **increased asthma pulmonary control** and **better lung function**.

It has been reported that even a $\Delta -1.0\%$ reduction in weight can lead to improved asthma outcomes.



Epidemiologic studies suggested that specific dietary features provide both a **decreased risk of asthma** and the **enhanced management** of existing asthma.

Several studies have demonstrated that **fish, omega- ω fatty acids, fresh fruits, vegetables** and **low saturated fat** content food, might be associated with **reduced risk of asthma** development and **better control** of existing asthma.



There is evidence that **Mediterranean diet** rich in fruit, vegetable and n- ω polyunsaturated fatty acids is **protective for asthma development**, exacerbations and asthma symptoms due to the positive impacts on inflammation, oxidation and microbial composition.

Conversely, the **Western diet**—rich in saturated fatty acids and low in antioxidants—**stimulates inflammation** and may increase the risk of preschool wheezing and asthma with a effect on lung function.

Calcaterra, V.; Verduci, E.; Ghezzi, M.; Cena, H.; Pascuzzi, M.C.; Regalbuto, C.; Lamberti, R.; Rossi, V.; Manuelli, M.; Bosetti, A.; et al. Pediatric obesity-related asthma: The role of nutrition and nutrients in prevention and treatment. *Nutrients* 2021, 13, 3708.

In addition, childhood asthma may be influenced by **maternal diet during pregnancy**, particularly by the intake of certain foods such as fish or fruits and vegetables, and nutrients such as vitamin E, vitamin D, zinc or polyunsaturated fatty acids.



However, **the most effective intervention** for producing significant weight loss is **bariatric surgery**. Bariatric surgery has been reported to promote highly significant developments in asthma control, airway reactivity and lung function in all studies.

Hasegawa et al. demonstrated that bariatric surgery led to a nearly **6.0% reduction in the risk of having an asthma exacerbation**.

Hasegawa, K.; Tsugawa, Y.; Chang, Y. Risk of an asthma exacerbation after bariatric surgery in adults. J. Allergy Clin. Immunol. 2015, 136, 288-294.e8

Pharmacotherapy

No specific medications are recommended for obesity in paediatric patients with asthma.

Weight loss drugs are recommended only for children with severe obesity-related complications.

Orlistat is the only widely available and authorized medication for weight loss in children and **little is known about its effects on asthma.**



Metformin is another drug that requests additional investigation in the perspective of obese children with asthma. The fact that metformin supports weight loss and **may have an appropriate action to lung health**, makes it an attractive target for further investigation.

Vitamin D

There is growing literature on the potential relationship between vitamin D deficiency, defined as $25\text{-OH vitamin D} < 20 \text{ ng/mL}$, and the development of obesity and asthma besides a higher risk of respiratory infections and decreased corticosteroid responsiveness Asthma.



Lautenbacher and colleagues found that obese asthmatic children, affected by vitamin D deficiency, had lower FEV₁, TLC and FRC compared to obese children with normal vitamin D levels.

Lautenbacher, L.A.; Jariwala, S.P.; Markowitz, M.E.; Rastogi, D. Vitamin D and pulmonary function in obese asthmatic children. *Pediatr. Pulmonol.* 2016, 51, 1276–1283.

Vitamin D supplementation has been proposed to **improve asthma severity and control.**



There is not enough evidence to recommend its use in all asthmatic children.

Management of “Obese-Asthma” Comorbidities and Potential Triggers

Gastroesophageal reflux disease (GERD) is very common in severe asthma , especially in obese patients.

In obese patients with severe asthma, there is also a high prevalence of obstructive sleep apnea (OSA) with rates as high as 80%.

Davies, S.E.; Bishopp, A.; Wharton, S.; Turner, A.M.; Adel, H.M. The association between asthma and obstructive sleep apnea(OSA): A systematic review. *J. Asthma.* 2018, 56, 118–129.

Wu et al. compared two observational studies in cohorts of urban children with asthma and they showed that exposure to secondhand smoke was associated with the worsening of symptoms in overweight /obese children compared to normal weight children, suggesting that a high body mass index may increase susceptibility to secondhand smoke.

Wu, T.D.; Brigham, E.P.; Peng, R.; Koehler, K.; Rand, C.; Matsui, E.C.; Diette, G.B.; Hansel, N.N.; McCormack, M.C. Overweight/obesity enhances associations between secondhand smoke exposure and asthma morbidity in children. *J. Allergy Clin. Immunol. Pract.* 2018, 6, 2157–2159.e5.

Therefore, smoke exposure should be identified and eliminated **immediately after a diagnosis of asthma, before starting pharmacological treatment**; the family should be assisted in finding supportive strategies, along with pharmacotherapy, to quit smoking and limit exposure to this risk factor.



The use of controller and steroid medications was not associated with the risk of developing obesity independently from physical activity and other asthma medication use.

Asthma rescue medication in early childhood might protect against weight gain in later life.

Chen, Z.; Salam, M.T.; Alderete, T.L.; Habre, R.; Bastain, T.M.; Berhane, K. Effects of Childhood Asthma on the Development of Obesity among School-aged Children. *Am. J. Respir. Crit. Care Med.* 2017, 195, 1181–1188.

Thank you for your attention.

