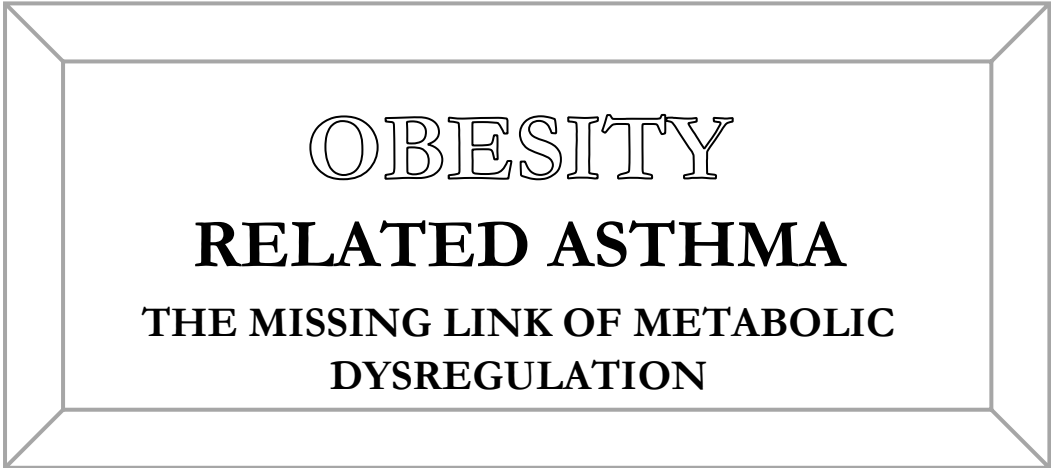


OBESITY

RELATED ASTHMA



**THE MISSING LINK OF METABOLIC
DYSREGULATION**

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OBESITY RELATED ASTHMA THE MISSING LINK OF METABOLIC DYSREGULATION

ANCC Accredited NCPD Hours: 2 hrs

Target Audience: RN/APRN

NEED ASSESSMENT

Obesity is a growing global epidemic, with nearly 40% of adults in the United States classified as obese, and it plays a significant role as both a risk factor and a disease modifier in asthma. Obese individuals are more likely to develop asthma and tend to experience more severe symptoms, frequent exacerbations, reduced responsiveness to standard asthma treatments, and a lower quality of life. The pathophysiology of asthma in obesity is complex and multifactorial, involving mechanical changes in lung function, systemic inflammation mediated by adipokines and cytokines, metabolic dysregulation, and altered dietary patterns, all of which can contribute to airway hyperresponsiveness and inflammation. Obese asthma is not a single disease but a

heterogeneous condition with distinct phenotypes, such as early-onset atopic asthma and late-onset non-atopic asthma, each with unique clinical and inflammatory profiles. Understanding these phenotypes and the underlying mechanisms is essential for developing personalized, effective treatment strategies. Through lifestyle interventions or bariatric surgery, weight loss has been shown to improve asthma control, reduce medication use, and enhance overall health outcomes. As such, addressing obesity through individual clinical care and broader public health strategies is critical to reducing the burden of asthma in affected populations.

OBJECTIVES

- **Understand how asthma and obesity are linked**, especially in children, and how this connection affects their diagnosis, treatment, and overall health.
- **Analyze the pathophysiological impact of obesity on asthma**, focusing on mechanical, metabolic, and immunological mechanisms that contribute to disease severity and treatment resistance.
- **Examine the epidemiological trends and associations between obesity and asthma**, including prevalence data, risk factors, and population-specific vulnerabilities.
- **Describe the distinct clinical manifestations of asthma in individuals with obesity**, with emphasis on symptom patterns, inflammatory profiles, and functional impairments.
- **Discuss the influence of a high-fat diet on asthma outcomes in obese individuals**, including its role in airway inflammation, immune modulation, and exacerbation risk.
- **Identify and evaluate evidence-based management strategies for obese asthma**, incorporating pharmacologic and non-pharmacologic interventions, including weight reduction approaches, and understand the comorbidities associated with it.

GOAL

The purpose of this article is to critically examine the epidemiology and clinical characteristics of obesity-associated asthma in both children and adults, with a focus on the underlying inflammatory and metabolic dysregulation. Additionally, the article aims to explore current and emerging strategies for the effective management of asthma in the context of obesity.

INTRODUCTION

Obesity is recognized as both a **major risk factor** and a **disease modifier** for asthma in both paediatric and adult populations. Traditionally, obesity is defined using **body mass index (BMI)** thresholds, specifically a BMI ≥ 30 kg/m² in adults. However, growing evidence indicates that **BMI may be an inadequate surrogate** for assessing metabolic health, particularly in **children and adolescents** with severe obesity, where body composition and fat distribution vary significantly. This discrepancy is clinically relevant for asthma, as BMI does not reliably capture the **metabolic and inflammatory profiles** that influence asthma pathophysiology.

Notably, **metabolic dysfunction** rather than absolute fat mass appears to play a **more critical role** in the link between obesity and asthma. For example, **serum interleukin-6**

(**IL-6**), an inflammatory cytokine produced by macrophages in adipose tissue, has been correlated with **asthma severity**, and elevated IL-6 levels have also been observed in some individuals with **normal-range BMIs**, suggesting that poor metabolic health can exist independent of obesity as traditionally defined. Further, studies have consistently demonstrated **increased adipose tissue inflammation** in obese individuals with asthma, highlighting the significance of adipocyte-driven cytokine release and immune dysregulation in worsening airway inflammation. Despite this, many asthma studies have historically used **BMI as a proxy** for obesity-related metabolic impairment, potentially oversimplifying the complex interplay between **obesity, inflammation, and asthma**.

A more nuanced approach, one that differentiates **metabolically healthy obesity** from **metabolically unhealthy phenotypes**, may improve the understanding and management of asthma in the context of obesity. This distinction is crucial for tailoring interventions, identifying at-risk populations more accurately, and developing **mechanism-targeted therapies**.

ASTHMA AS A HETEROGENEOUS DISEASE

Asthma is indeed a heterogeneous disease characterized by chronic airway inflammation and variable respiratory symptoms like wheezing, shortness of breath, chest tightness, and cough. Its heterogeneity stems from diverse underlying mechanisms, including allergic, inflammatory, and neuroendocrine pathways, which contribute to variable airway obstruction. Below, I'll address the key points raised, enhance the content with accurate details, and clarify the relationship between asthma and obesity, incorporating insights from recent research.

1. Asthma as a Heterogeneous Disease

Asthma's heterogeneity manifests in its varied phenotypes (e.g., allergic, non-allergic, eosinophilic, neutrophilic) and endotypes, driven by distinct immunological and molecular mechanisms. For instance:

- **Allergic asthma** is linked to IgE-mediated responses to allergens, often seen in early-onset cases.
- **Non-allergic asthma** may involve neutrophilic inflammation or irritant triggers, common in adult-onset cases.
- **Neuroendocrine mechanisms** can exacerbate symptoms through stress-related pathways affecting airway responsiveness.

This diversity complicates diagnosis and treatment, requiring personalized approaches

like biologics (e.g., anti-IgE or anti-IL-5 therapies) for severe cases.

2. Rising Incidence of Asthma

The global increase in asthma incidence is multifactorial:

- **Environmental factors:**
Urbanization, air pollution, and exposure to indoor allergens (e.g., dust mites) play significant roles.
- **Lifestyle changes:**
Shifts in diet (e.g., high processed food intake) and reduced physical activity contribute.
- **Obesity epidemic:**
The parallel rise in obesity rates is a key driver, as discussed below.

3. Asthma and Obesity: A Complex Relationship

Obesity is a major risk factor for asthma, exacerbating its severity, control, and diagnosis. The connection is driven by mechanical, inflammatory, and socioeconomic factors:

A. Mechanical Factors

- **Intrathoracic and neck fat deposition:**
Excess adipose tissue compresses the upper airways (throat, larynx, trachea), narrowing them and increasing airflow resistance. This exacerbates dyspnoea and mimics asthma symptoms.

- **Reduced lung capacity:**

Obesity restricts chest wall movement, decreasing vital capacity and functional residual capacity, which increases respiratory effort and resistance.

- **Airway hyperresponsiveness:**

Mechanical stress on airways may heighten their sensitivity to triggers.

B. Inflammatory Mechanisms

- **Systemic inflammation:**

Adipose tissue, particularly visceral fat, secretes pro-inflammatory cytokines (e.g., IL-6, TNF- α) and adipokines (e.g., leptin), which promote airway inflammation and hyperresponsiveness.

- **Leptin and adiponectin imbalance:**

Obese individuals have elevated leptin (pro-inflammatory) and reduced adiponectin (anti-inflammatory), contributing to asthma severity.

- **Comorbid conditions:**

Obesity-related conditions like gastroesophageal reflux disease (GERD) and sleep apnoea can worsen asthma symptoms.

C. Socioeconomic Factors

- **Access to care:**

Lower socioeconomic status is linked to poorer asthma management, higher exposure to pollutants, and obesity due to

limited access to healthy food or safe spaces for exercise.

- **Health disparities:**

These factors disproportionately affect marginalized communities, amplifying asthma-obesity comorbidity.

D. Diagnostic Challenges

- **Symptom overlap:**

Obesity-related dyspnoea and exercise intolerance can mimic asthma, leading to misdiagnosis or delayed diagnosis.

- **Increased dyspnoea perception:**

Obese individuals often perceive breathlessness more intensely, complicating symptom assessment.

- **Spirometry limitations:**

Obesity can alter lung function test results, making it harder to confirm airway obstruction.

E. Clinical Impact

- **Increased severity:** Obesity is associated with worse asthma control, more frequent exacerbations, and reduced response to standard treatments like inhaled corticosteroids.

- **Higher healthcare burden:** Asthma-obesity comorbidity leads to increased hospitalizations and healthcare costs.

4. Epidemiological Evidence

Numerous studies confirm the asthma-obesity link:

- A 2018 meta-analysis found that obesity increases asthma risk by 1.5–2-fold, with stronger associations in women.
- Longitudinal studies show that weight gain precedes asthma development, suggesting a causal relationship.
- Parallel rises in obesity and asthma rates globally, particularly in Westernized countries, support shared environmental and lifestyle drivers.

5. Mechanisms: Current Understanding and Gaps

While the asthma-obesity link is well-documented, the precise mechanisms remain incompletely understood:

- **Inflammation:**

The role of adipose tissue as an endocrine organ driving systemic and airway inflammation is clear, but specific pathways (e.g., leptin signalling) need further exploration.

- **Microbiome:**

Emerging research suggests that obesity-related gut dysbiosis may influence asthma via the gut-lung axis.

- **Genetics and epigenetics:**

Genetic predispositions and epigenetic changes (e.g., due to diet or pollutants) may mediate the interaction, but data are limited.

- **Sex differences:**

Women show a stronger asthma-obesity association, possibly due to hormonal influences or fat distribution patterns, warranting further study.

6. Management Implications

- **Weight loss:**

Studies show that weight loss (via diet, exercise, or bariatric surgery) improves asthma control, reduces exacerbations, and enhances lung function.

- **Personalized therapy:**

Obese asthmatics may benefit from targeted treatments addressing inflammation (e.g., biologics) or comorbidities (e.g., GERD management).

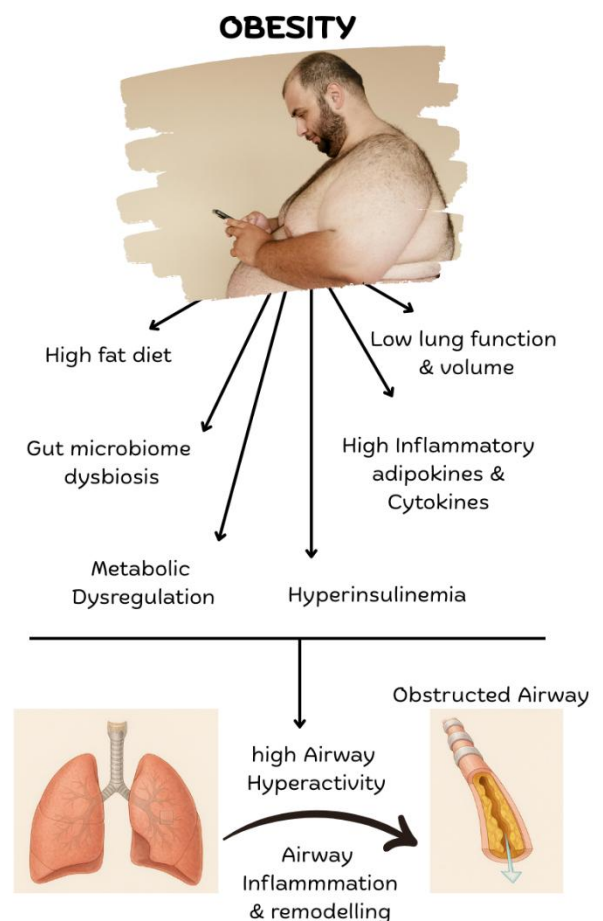
- **Multidisciplinary approach:**

Collaboration among pulmonologists, dietitians, and psychologists is key to addressing asthma-obesity comorbidity.

Asthma's heterogeneity and its interplay with obesity highlight the need for a nuanced understanding of its mechanisms and management. Obesity exacerbates asthma through mechanical compression, systemic inflammation, and diagnostic challenges, with socioeconomic factors amplifying the burden. While epidemiological evidence supports a strong link, ongoing research into inflammatory pathways, the microbiome, and personalized interventions will further clarify

this relationship. For clinical practice, addressing obesity is critical to improving asthma outcomes.

OBESITY AND ASTHMA: A CRITICAL PUBLIC HEALTH CONCERN



Obesity-associated factors that contribute to asthma development and severity. Obesity-associated characteristic features such as reduced lung volumes and function, increased proinflammatory cytokines and adipokines, hyperinsulinemia, dysregulation in metabolism, dysbiosis in gut microbiome, and consumption of high-fat diet promote asthma phenotype in individuals. These changes play an important role in increasing airway hyper-responsiveness and modulating immune response, resulting in inflammation and remodelling of the airway and poor response to standard asthma therapy. ↑—increase; ↓—decrease.

Obesity, recognized as a leading public health challenge of the 21st century, affects over **1.9 billion adults and 41 million children under five worldwide**, as reported by the **World Health Organization in 2019**. Defined by a **body mass index (BMI) ≥ 30 kg/m²**, obesity arises from a combination of genetic predisposition and lifestyle factors, primarily over-nutrition (excessive intake of carbohydrates and fats coupled with low consumption of vegetables, fruits, and whole grains) and insufficient physical activity. This condition is characterized by **systemic low-grade inflammation, driven by adipose tissue-derived cytokines (e.g., IL-6, TNF- α) and adipokines (e.g., leptin)**, which contribute to metabolic dysregulation. Obesity significantly increases the risk of comorbidities, including type 2 diabetes, cardiovascular disease, and non-alcoholic fatty liver disease, amplifying its public health impact.

Asthma, a chronic inflammatory disorder of the airways, is marked by **airway hyper-responsiveness (AHR) and recurrent episodes of wheezing, breathlessness, chest tightness, and coughing**. These symptoms stem from variable airflow obstruction, which is often reversible spontaneously or with treatment. Predominantly originating in childhood, asthma is frequently associated with atopic conditions such as dermatitis and seasonal

rhinitis, reflecting a Th2-biased immune response. In the context of obesity, asthma presents a complex syndrome with distinct phenotypes, including early-onset atopic and late-onset non-atopic forms, the latter driven by obesity-related metabolic and inflammatory changes. Obese asthmatics, comprising nearly 40% of U.S. adults, experience heightened symptom severity, more frequent and severe exacerbations, reduced responsiveness to standard therapies (e.g., inhaled corticosteroids), and a lower quality of life.

Multiple mechanisms mediate the interplay between obesity and asthma. High-fat diets and low antioxidant intake exacerbate airway inflammation, while excess adipose tissue promotes systemic inflammation, altering immune responses and airway reactivity. Mechanical factors, such as reduced lung volume and increased airway resistance due to excess body weight, further aggravate asthma symptoms.

Comorbidities like gastroesophageal reflux disease (GERD) and obstructive sleep apnoea, prevalent in obesity, compound asthma control challenges. This nexus contributes to significant healthcare costs, health disparities, particularly among low-income and minority populations, and increased disease burden.

Addressing this public health crisis requires multifaceted strategies. Lifestyle interventions targeting weight loss through improved diet

(e.g., increased intake of fruits, vegetables, and whole grains) and physical activity can mitigate both obesity and asthma severity. Research into biomarkers for obese asthma phenotypes and novel therapeutics targeting metabolic pathways (e.g., leptin signalling) is essential for personalized treatment approaches. Public health initiatives must prioritize health equity, focusing on underserved communities disproportionately affected by both conditions. By tackling obesity as a modifiable risk factor, integrated clinical and preventive efforts can reduce the incidence and impact of asthma, improving outcomes and quality of life for millions worldwide.

THE RELATIONSHIP BETWEEN OBESITY AND ASTHMA

A growing body of evidence has established a strong association between **obesity and increased risk of asthma**, with both children and adults affected by this comorbid condition. Obesity-related asthma is frequently characterized by **more severe and persistent symptoms, poorer asthma control, increased frequency of exacerbations, diminished quality of life, and reduced responsiveness to standard controller medications, including corticosteroids**. Importantly, many obese individuals with asthma demonstrate **non-eosinophilic airway inflammation** and may develop **steroid resis-**

tance, complicating treatment efforts.

Currently, two distinct phenotypes of obesity-related asthma have been identified:

1. Early-onset allergic asthma:

typically beginning in childhood and associated with traditional atopic features.

2. Late-onset non-allergic asthma:

emerging in adulthood, is often more severe and is commonly linked to metabolic dysfunction and systemic inflammation.

Despite advances in understanding, the **pathophysiological mechanisms** underlying the obesity-asthma link remain **incompletely elucidated**. Contributing factors include **genetic predisposition, dietary habits, physical inactivity, and early-life microbial exposures**. Central to the relationship is **obesity-induced low-grade systemic inflammation**, primarily originating from **adipose tissue**, which functions as an active endocrine organ.

Adipose tissue secretes a wide range of biologically active molecules, including **interleukins (ILs)** and **adipokines**, such as **leptin** and **adiponectin**. These mediators play critical roles in **energy metabolism, immune regulation, and inflammatory pathways**. Leptin, typically elevated in obesity, has pro-inflammatory properties and has been implicated in **airway hyperresponsiveness**, whereas adiponectin, often reduced in obesity, has anti-inflammatory effects. Additionally,

immune cell infiltration within adipose tissue, including macrophages and T cells, contributes to the **chronic inflammatory state** observed in obese individuals.

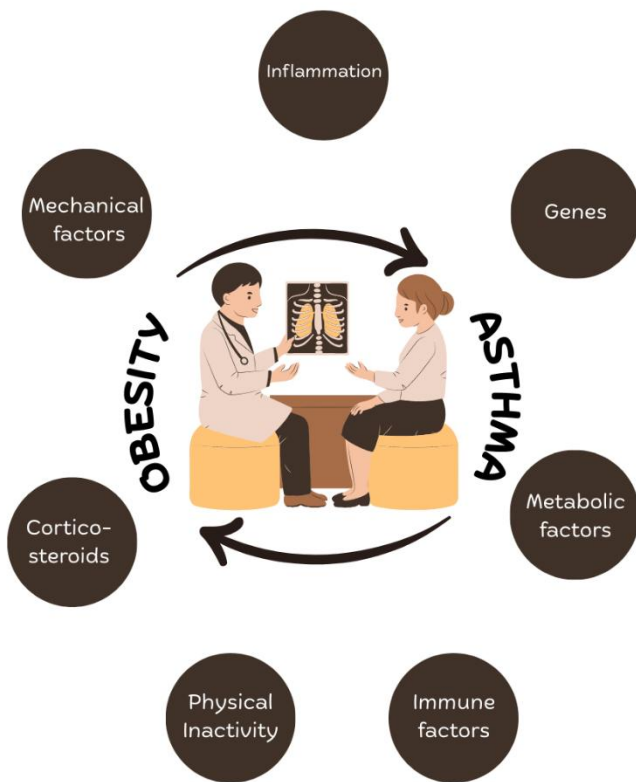
acid and **bile acid** metabolism, both of which influence immune and inflammatory responses. Taken together, these findings underscore the **complex, multifactorial interplay** between obesity and asthma. A deeper mechanistic understanding may open new avenues for **phenotype-specific interventions** and **personalized asthma management strategies** in individuals with obesity.

MECHANISMS LINKING OBESITY AND ASTHMA

Obesity and asthma frequently coexist, especially in children, and growing evidence suggests a complex, bidirectional relationship. Obesity can influence asthma development and severity through multiple mechanisms, including mechanical restriction of the lungs, systemic inflammation driven by adipose-derived cytokines, nutritional imbalances, sedentary behaviour, and metabolic dysregulation such as insulin resistance. Understanding these overlapping pathways is essential for identifying at-risk individuals and tailoring effective treatment strategies.

1. Mechanical Impact of Truncal Adiposity on Lung Function

Central or truncal obesity exerts significant mechanical effects on the respiratory system, contributing to the pathophysiology of asthma in affected individuals. Excess adipose tissue,



An emerging area of interest is the **gut-lung axis**, particularly the role of the **intestinal microbiota** in immune development and disease modulation. The **hygiene hypothesis** proposes that reduced exposure to environmental microorganisms during early life may impair immune system maturation, increasing susceptibility to **autoimmune and allergic diseases**, including asthma. **Dysbiosis**, or an imbalance in gut microbial composition, has been linked to **obesity and asthma**, potentially through the increased systemic absorption of **lipopolysaccharides (LPS)** and the disruption of **short-chain fatty**

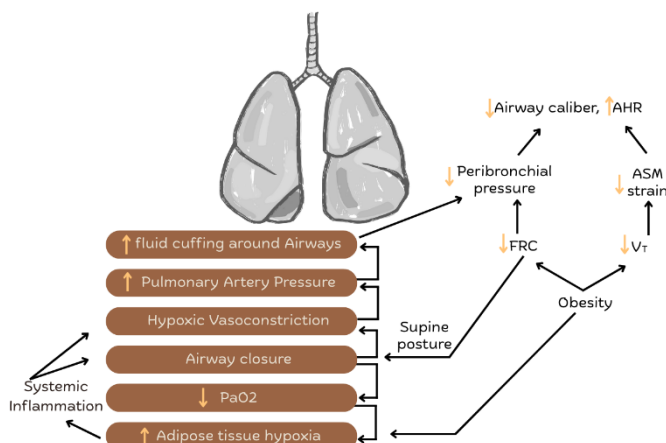
particularly around the thoracic and abdominal regions, imposes a restrictive load on the chest wall and diaphragm, impairing normal lung expansion and respiratory mechanics.

A. Diaphragmatic Restriction and Lung Volume Reduction

Truncal adiposity reduces the ability of the diaphragm to descend during inspiration, thereby limiting thoracic expansion. This mechanical restriction leads to a **decrease in functional residual capacity (FRC), residual volume (RV), and expiratory reserve volume (ERV)** parameters critical for maintaining airway patency and effective ventilation.

B. Bronchial Smooth Muscle Dynamics

Lower FRC in obese individuals reduces the stretch placed on bronchial smooth muscle, especially at the end of tidal exhalation. This decrease in tonic stretch can heighten airway responsiveness and increase the **perceived work of breathing**, contributing to symptoms of dyspnoea even in the absence of overt bronchoconstriction.

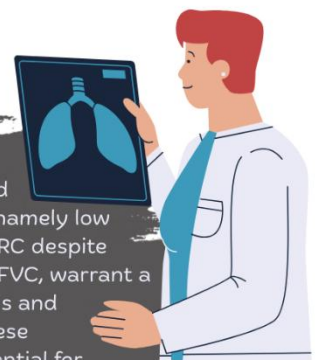


C. Altered Spirometry Patterns

Although obese children may exhibit **elevated forced expiratory volume in one second (FEV1)** and **forced vital capacity (FVC)**, likely due to increased thoracic effort, the **FEV1/FVC ratio** is commonly reduced. This pattern suggests a form of **obstructive ventilatory defect**, distinguishing the **obese asthma phenotype** from classical asthma seen in normal-weight individuals

CLINICAL IMPLICATIONS

The unique spirometry and mechanical features observed in obese asthmatic children, namely low lung volumes with reduced FRC despite normal or elevated FEV1 and FVC, warrant a tailored approach to diagnosis and treatment. Understanding these mechanical limitations is essential for optimizing respiratory therapies, exercise prescriptions, and weight management strategies in this population.



2. Immunomodulation via Adipocytokines

Obesity is increasingly recognized as a state of chronic low-grade systemic inflammation, largely mediated by bioactive molecules secreted by adipose tissue, known as **adipocytokines**. These substances, including **leptin, adiponectin, and resistin**, play key roles in immune regulation and inflammatory signalling, thereby linking obesity to asthma pathogenesis.

A. Leptin: A Pro-Inflammatory Mediator

Leptin, an adipocytokine whose levels rise with increasing adiposity, exerts **pro-inflammatory** effects by promoting the activation of **T-helper 1 (Th1) immune responses**, enhancing **cytokine production**, and increasing **airway hyperresponsiveness**. It also stimulates **macrophage** and **T-cell** activity, contributing to airway inflammation.

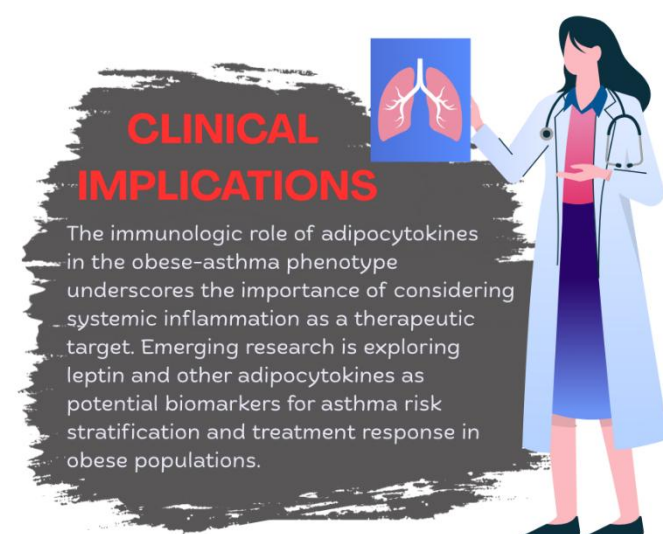
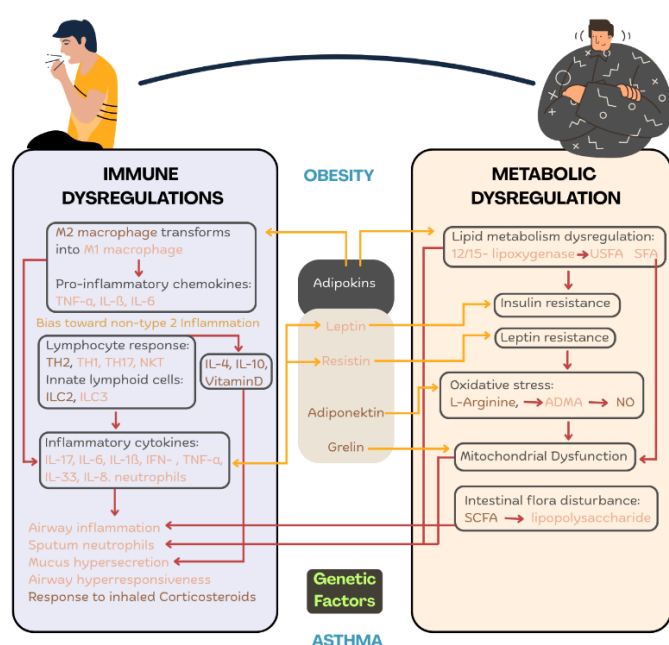
B. Adiponectin and Resistin: Modulatory Effects

In contrast, **adiponectin** generally has **anti-inflammatory** properties and is inversely related to body fat mass. Lower levels of adiponectin in obese individuals may fail to counterbalance the pro-inflammatory effects of leptin. **Resistin**, another adipocytokine, has been shown to upregulate pro-inflammatory cytokines and may further exacerbate airway inflammation.

Immuno-inflammatory mechanisms of obesity-related asthma. Adipokines, including leptin, resistin, adiponectin, and ghrelin, may contribute to metabolic and immune dysregulation in patients with asthma via complex interactions and lead to inflammation, which is biased toward non-type 2, implying the important role of increased adipose tissue in asthma progression. TNF- α , tumor necrosis factor- α ; Th, T helper type; IL, innate lymphoid; ILC, innate lymphoid cell; NKT, natural killer T; IFN, interferon; USFA, unsaturated fatty acids; SFA, saturated fatty acids; ADMA, asymmetric dimethylarginine; NO, nitric oxide; SCFA, short chain fatty acid.

C. Modifier vs. Causative Role

Although these adipocytokines contribute to systemic and airway inflammation, their presence alone does not account for asthma development in all obese individuals. The observation that **not all obese children develop asthma** suggests that adipocytokines act more as **modifying factors**, interacting with other **genetic, environmental, and metabolic** influences to determine individual susceptibility.



3. Nutritional and Behavioural Factors

The interplay between poor dietary habits and sedentary behaviour in obesity may

significantly contribute to the development and exacerbation of asthma, particularly by influencing immune function and pulmonary health. These lifestyle factors serve as modifiable risk contributors to the obese asthma phenotype.

A. Sedentary Lifestyle and Obesogenic Behaviour

DIET & ASTHMA

May Trigger Asthma



Food Allergies: If you have a true food allergy, eating that food can cause a rapid and severe immune response that leads to a full-blown asthma attack. Common food allergens include peanuts, tree nuts, eggs, milk, wheat, soy, and shellfish.

Food Intolerances and Sensitivities: Some food components may not cause a full-blown allergic reaction but can still trigger asthma symptoms. This is often a dose-related effect.

- **Sulfites:** These are preservatives found in many processed foods, including dried fruits, wine, beer, bottled lemon juice, and some pickled foods. Sulfites are a known trigger for asthma in sensitive individuals.
- **Processed Foods and High-Fat Diets:** A "Western diet" high in processed foods, saturated fats, sugar, and red meat is associated with increased inflammation. This can worsen asthma symptoms and may even increase the risk of developing asthma.
- **Saturated Fats and Omega-6 Fatty Acids:** An imbalance of fatty acids in your diet, with too many pro-inflammatory omega-6s (found in many vegetable oils) and not enough anti-inflammatory omega-3s, can worsen inflammation in the airways.

May Manage Asthma



- **Fruits and Vegetables (The Foundation):** This is the most important dietary recommendation. They are rich in vitamins, minerals, and antioxidants like beta-carotene, Vitamin C, and Vitamin E. These nutrients protect your cells from damage and fight inflammation.
- **Good choices: Leafy greens** (spinach, kale), berries, apples, oranges, carrots, and bell peppers.
- **Omega-3 Fatty Acids:** These "healthy fats" have powerful anti-inflammatory effects.
- **Good choices: Fatty fish** like salmon, mackerel, and sardines, as well as flaxseeds, chia seeds, and walnuts.
- **Magnesium:** This mineral can help relax the smooth muscles in the airways, which can improve airflow.
- **Good choices: Nuts, seeds, leafy greens, and whole grains.**
- **Vitamin D:** Low levels of Vitamin D are linked to more severe asthma. Getting enough can support immune function and reduce airway inflammation.
- **Good choices: Fortified milk, eggs, and fatty fish.**
- **Turmeric and Ginger:** These spices contain powerful anti-inflammatory compounds like curcumin (in turmeric) and gingerols (in ginger) that may help reduce asthma symptoms.

Obese individuals, particularly children, often engage in **low levels of physical activity**, which independently correlates with **reduced cardiorespiratory fitness** and **suboptimal lung development**. Prolonged sedentary

behaviour may also lead to decreased airway clearance and reduced respiratory muscle tone, further impairing pulmonary function.

B. Macronutrient and Micronutrient Imbalances

Dietary patterns commonly observed in obesity, high in processed carbohydrates and saturated fats, and low in fruits, vegetables, and whole grains, can promote **systemic inflammation**. Imbalanced intake of **macronutrients** (e.g., excess refined sugars and fats) may enhance oxidative stress and inflammatory pathways contributing to asthma pathogenesis.

C. Micronutrient Deficiencies and Pulmonary Immunity

Several **micronutrients** essential for immune regulation and respiratory integrity are often deficient in obese individuals:

- **Vitamin D** deficiency, prevalent among obese children, has been associated with impaired lung function, increased airway reactivity, and reduced immune tolerance.
- **Antioxidants** such as vitamins C and E are crucial in neutralizing reactive oxygen species (ROS), and their deficiency can increase oxidative stress in the airway.
- **Omega-3 fatty acids**, with known anti-inflammatory properties, are typically under-consumed in Western diets, diminishing their potential protective effects against airway inflammation.



4. Metabolic Dysregulation and Asthma Risk

Beyond mechanical and inflammatory pathways, emerging evidence highlights a strong link between **metabolic abnormalities** and the risk of asthma in obese individuals. **Insulin resistance**, **dyslipidaemia**, and **metabolic syndrome** are increasingly recognized as independent contributors to altered lung function and airway inflammation in the obese asthma phenotype.

A. Insulin Resistance

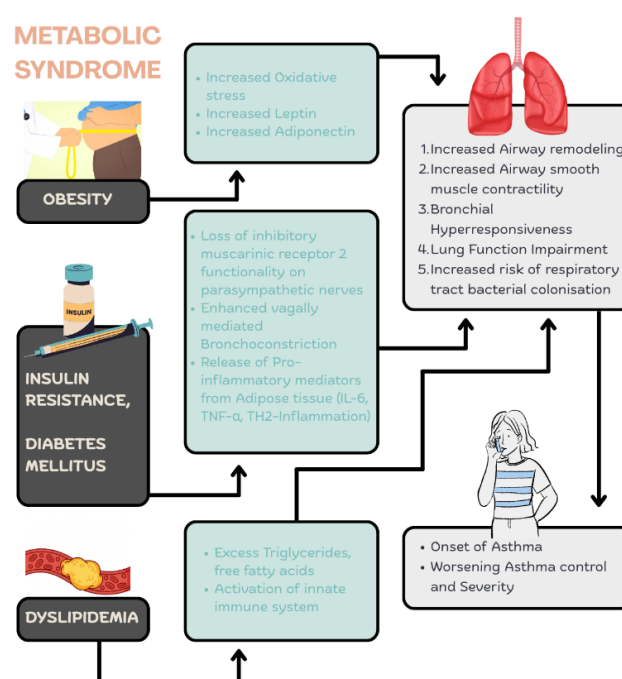
Insulin resistance, a hallmark of metabolic dysregulation, has been associated with **increased airway hyperreactivity** and **reduced lung function**, even after adjusting for body mass index (BMI). Hyperinsulinemia may exacerbate inflammation by promoting cytokine release, impairing smooth muscle function, and modulating immune cell responses within the airways

B. Dyslipidaemia

Abnormal lipid profiles, characterized by elevated triglycerides and low HDL cholesterol, are commonly observed in obese individuals and have been linked to **reduced expiratory reserve volume (ERV)** and **FEV1/FVC ratio**. Lipid peroxidation may also increase oxidative stress and damage pulmonary epithelium, contributing to airway remodelling and dysfunction.

C. Metabolic Syndrome

Metabolic syndrome, comprising central obesity, hypertension, hyperglycaemia, and dyslipidaemia, represents a **cluster of risk factors** that can synergistically worsen asthma outcomes. Studies suggest that obese children with metabolic syndrome have a higher prevalence of **airflow limitation**, **increased bronchial inflammation**, and **more frequent asthma exacerbations**.



D. Mediation of Pulmonary Dysfunction

Recent findings indicate that metabolic abnormalities mediate the relationship between **BMI, waist circumference, and key lung function indices** such as FEV1/FVC and ERV. This suggests that **biological mechanisms beyond mechanical load**, including systemic inflammation and endothelial dysfunction, may underlie the pulmonary deficits observed in obese asthmatic children.

CLINICAL IMPLICATIONS

Recognition of metabolic dysregulation as a contributor to asthma emphasizes the need for early screening and intervention in obese children. Management strategies that improve insulin sensitivity, optimize lipid profiles, and address cardiometabolic risk may improve both metabolic and respiratory outcomes in this vulnerable population.



5. Genetic and Epigenetic Influences in Obesity-Related Asthma

While environmental, behavioural, and metabolic factors contribute significantly to the obesity-asthma link, not all obese individuals develop asthma, suggesting a role for **genetic susceptibility** and **epigenetic modifications** in disease expression. These biological underpinnings may influence how obesity-driven inflammatory and metabolic signals

interact with the airways and immune system.

A. Genetic Predisposition

Certain **polymorphisms** in genes related to **immune regulation, airway responsiveness, and metabolic pathways** have been implicated in the co-occurrence of obesity and asthma. Variants in genes encoding **interleukins (e.g., IL-6, IL-13), TNF- α , leptin, and adiponectin receptors** may modify the inflammatory response and predispose individuals to airway hyperreactivity when exposed to obesogenic environments.

B. Epigenetic Modifications

Epigenetic mechanisms, such as **DNA methylation, histone modification, and microRNA expression**, can regulate gene expression without altering the DNA sequence. Obesity-induced metabolic and inflammatory stress may trigger epigenetic changes that influence the **development and severity of asthma**, particularly in early life. For example:

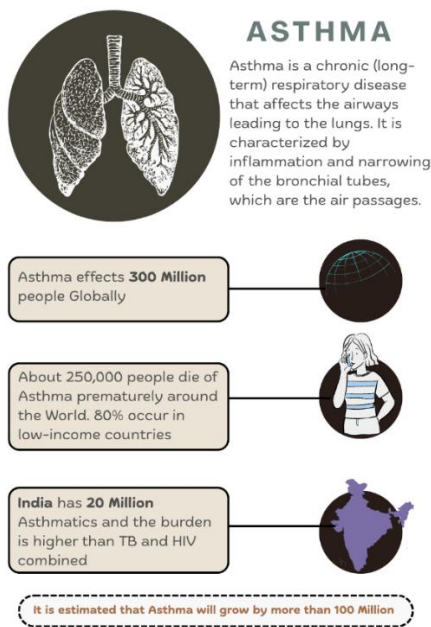
- DNA methylation patterns in genes related to **inflammation, glucose metabolism, and lung development** have been associated with asthma susceptibility in obese children.
- MicroRNAs (e.g., miR-155, miR-146a) involved in **immune modulation** may be dysregulated in obesity and contribute to chronic airway inflammation.

C. Gene-Environment Interactions

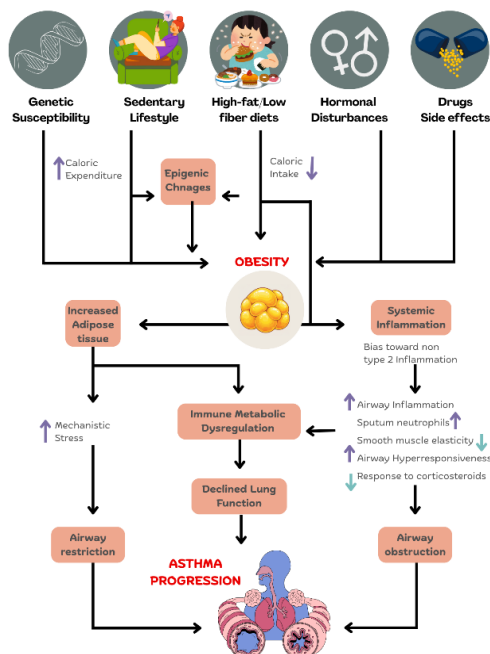
The interplay between **genetic predisposition**

and **environmental exposures** (e.g., diet, physical inactivity, pollutants) may determine the phenotypic expression of asthma in obese individuals. Children with specific gene variants may be more susceptible to asthma when exposed to obesogenic and inflammatory stimuli, supporting a **multi-hit model** of disease development.

Pathogenesis of obesity-related asthma. Obesity may be caused by several factors and is accompanied by increased adipose tissue and the appearance of chronic systemic inflammation. The increased adipose tissue increases the mechanical burden of bronchial physiological activities and causes airway restriction. Systemic inflammation with a bias towards non-type 2 causes airway inflammation, airway hyperresponsiveness, and low sensitivity to glucocorticoids, causing airway obstruction. These symptoms can lead to decreased lung function and demonstrate the immune-metabolic dysregulation present in obesity-related asthma. Airflow restriction and airway obstruction contribute to the progression of asthma.



KEY SUMMARY



PAEDIATRIC OBESITY AND ASTHMA: UNRAVELLING A BIDIRECTIONAL RELATIONSHIP

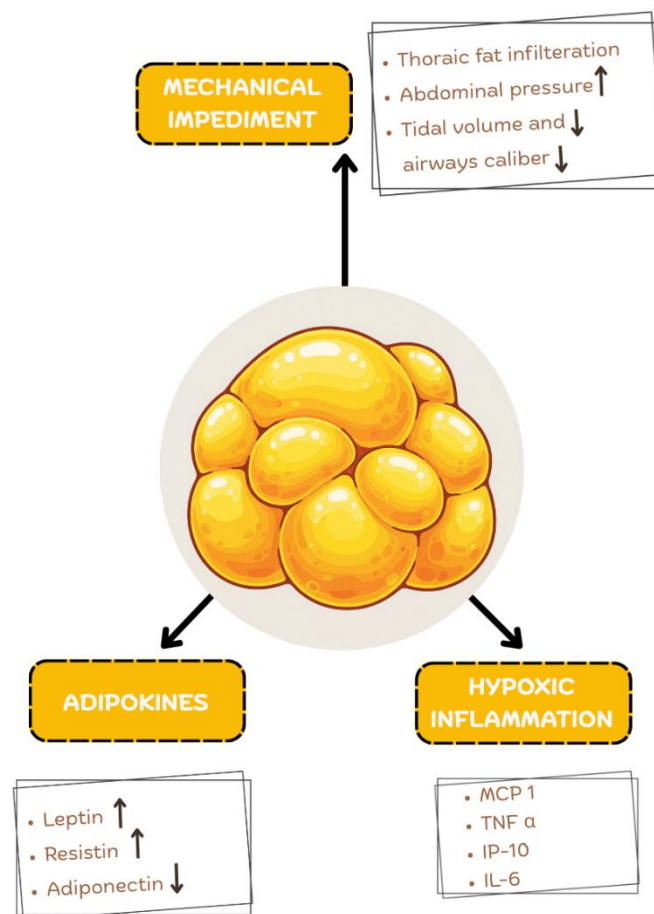
Paediatric obesity and asthma are prevalent chronic conditions, each affecting up to 25–30% of children in high-income countries like the United States, the United Kingdom, and Australia. High-quality epidemiological studies, including a 2018 meta-analysis, report a 1.5–2-fold increased asthma risk in obese children, highlighting a robust association. However, controversy persists regarding the underlying mechanisms, though it is undisputed that obesity complicates asthma diagnosis and management in children. Obesity-related dyspnoea and exercise intolerance often mimic asthma symptoms, reducing diagnostic accuracy, while obese asthmatics exhibit poorer response to inhaled corticosteroids and more frequent exacerbations.

Longitudinal data, such as a 2023 meta-analysis,

demonstrate that obesity often precedes and heightens the risk of incident asthma, with a 32% increased risk per 5 kg/m² BMI increase. In young children, rapid early weight gain may signal somatic growth dysregulation, potentially impairing airway epithelial development and leading to clinical wheezing. This aligns with findings linking maternal obesity and excessive gestational weight gain to a 20–30% increased incidence of childhood wheeze. These prenatal and early-life factors suggest a developmental origin, possibly mediated by epigenetic changes (e.g., DNA methylation) or inflammatory pathways (e.g., IL-6, leptin). Further research into maternal, prenatal, and postnatal growth, lung development, and respiratory outcomes is essential to elucidate this phenomenon.

Conversely, asthma may precede and contribute to obesity, supporting a bidirectional association. Children with asthma often face exercise limitations due to fear of symptom exacerbation, increased sedentary behaviour, and treatment with oral corticosteroids, which can increase body weight by 2–5 kg. A 2024 study noted greater weight gain in asthmatics compared to non-asthmatics, particularly in those with activity restrictions. However, reduced physical activity is not universal and depends on parental education about exercise's role in asthma control, as well as the child's emotional health. For instance, depression, prevalent in 10–15% of asthmatic children, may

exacerbate sedentary habits, further promoting weight gain.



Pathological mechanisms of obesity that might influence lung function in children. Abdominal tissue deposition increases (upwards green arrow) abdominal pressure, forcing superficial ventilation and a consequent decrease (downwards red arrow) in tidal volume and airway calibre. Fat accumulation determines higher serum concentration of leptin and resistin, together with a decrease in circulating adiponectin. Excessive abdominal fat results in hypoxia with the production of pro-inflammatory

cytokines such as monocyte chemoattractant protein 1 (MCP-1), tumour necrosis factor α (TNF α), IFN- γ

The causal mechanisms linking obesity and asthma are unlikely to be singular or uniform across all children, varying by age, sex, and environmental factors. Girls show a stronger

obesity-asthma association, possibly due to hormonal influences or visceral fat distribution, as noted in a 2024 study. Emerging research also highlights the gut-lung axis, where obesity-related gut microbiota dysbiosis produces metabolites (e.g., short-chain fatty acids) that modulate airway inflammation. Environmental exposures, such as air pollution, exacerbate both conditions, particularly in urban settings. Additionally, socioeconomic disparities, including limited access to healthy food or safe exercise spaces, amplify the burden in marginalized communities.

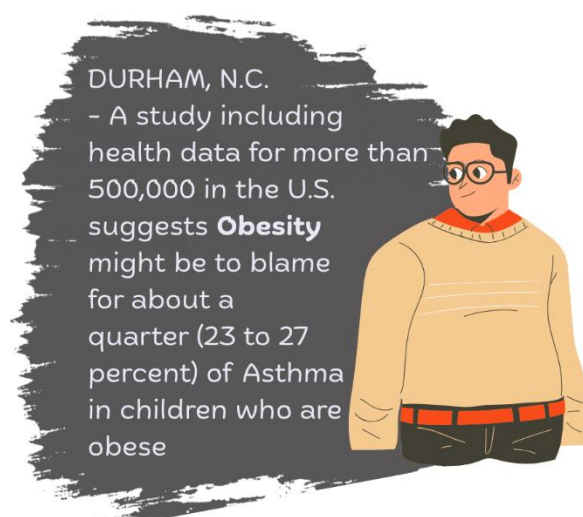
Obesity complicates asthma management by increasing airway hyperresponsiveness, reducing lung compliance, and altering spirometry results (e.g., lower FEV1). A 2024 review emphasized that weight loss, through diet or bariatric surgery, improves asthma control and reduces exacerbations, underscoring its therapeutic value. However, achieving sustained weight loss in children is challenging, necessitating multidisciplinary care involving pulmonologists, dietitians, and psychologists. Novel interventions, such as microbiota-targeted therapies (e.g., probiotics) or metabolic drugs (e.g., GLP-1 agonists), are under investigation but lack paediatric data.

Further studies are critical to untangle the asthma-obesity nexus, particularly exploring physical activity, dietary patterns, genetic/epigenetic factors, depression, and

environmental exposures. The role of visceral fat, as measured by waist circumference or lipid accumulation product index, is gaining attention as a stronger predictor of asthma risk than BMI alone. Addressing these complexities will inform personalized prevention and treatment strategies, reducing the burden of these intertwined conditions in children.

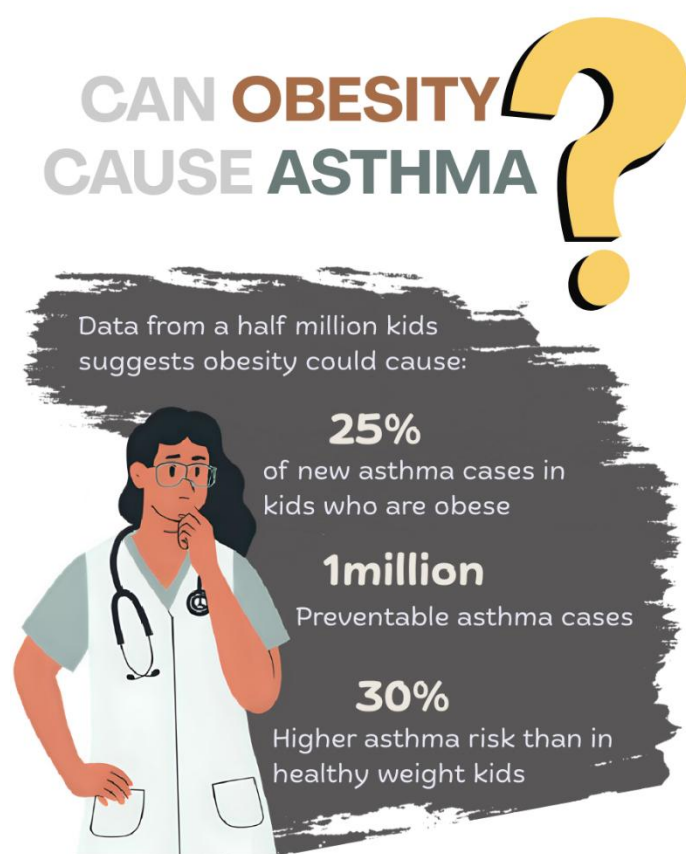
EPIDEMIOLOGY OF PAEDIATRIC OBESITY AND ASTHMA: PRENATAL AND LONGITUDINAL PERSPECTIVES

Asthma affects approximately 6.5 million children in the United States, representing about 8.7% of those aged 0–17 years, according to 2023 CDC data. Concurrently, 17% of U.S. children are obese (BMI $\geq$ 95th percentile), and an additional 15% are overweight (BMI 85th–94th percentile), contributing to a combined prevalence of 32% for excess adiposity. Obesity



is a well-established risk factor for asthma, with

longitudinal studies, such as a 2023 meta-analysis, demonstrating that increased adiposity precedes incident asthma. This analysis reported a 32% increased asthma risk per 5 kg/m² BMI increment (RR 1.32, 95% CI 1.21–1.44) and a 26% increased risk per 10 cm waist circumference increase (RR 1.26, 95% CI 1.09–1.46), underscoring visceral fat's role.



Sex differences in the obesity-asthma association are evident but inconsistent. A 2024 study noted a stronger association in girls, potentially due to hormonal influences or greater visceral fat deposition, while some studies report higher risks in boys, particularly pre-puberty. These discrepancies may stem from age, study design, or regional differences, necessitating further research. Obesity also

exacerbates asthma severity, increasing airway hyperresponsiveness, reducing lung compliance, and elevating exacerbation rates. A 2024 review found that obese asthmatics experience 1.5–2 times more hospitalizations and poorer response to inhaled corticosteroids, complicating management.

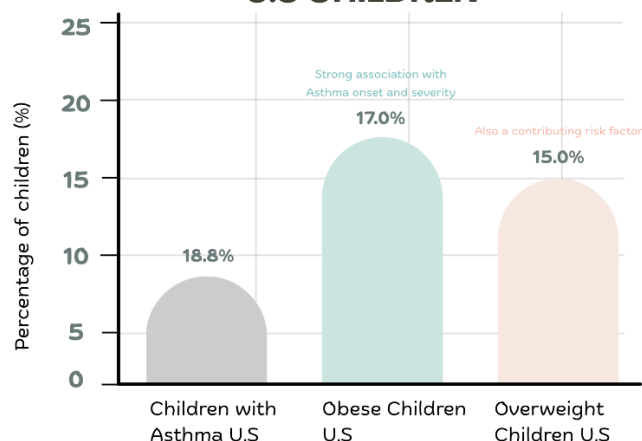
The obesity-asthma link may originate in utero. Maternal obesity (pre-pregnancy BMI ≥ 30) and excessive gestational weight gain are independently associated with a 15–30% increased risk of asthma in offspring, as confirmed by a 2024 study and consistent with prior findings. This risk persists after adjusting for the child's obesity, suggesting mechanisms beyond postnatal weight gain. Potential pathways include maternal inflammation (e.g., elevated IL-6, TNF- α), epigenetic modifications (e.g., DNA methylation of airway development genes), or altered foetal lung growth. Excessive weight gain in infancy, particularly in the first two years, is also linked to recurrent wheezing and asthma, with a 2024 study reporting a 20% increased risk per 1 kg rapid weight gain. These findings point to a critical early-life window where somatic growth dysregulation, possibly via gut microbiota dysbiosis or leptin-mediated inflammation, impairs airway development.

Emerging evidence highlights additional complexities. The gut-lung axis, where obesity-related microbiota changes produce pro-

inflammatory metabolites (e.g., short-chain fatty acids), may exacerbate airway inflammation. Environmental factors, such as air pollution, amplify risks, with a 2021 study linking urban exposures to both obesity and asthma in children. Socioeconomic disparities, including limited access to healthy food or safe exercise spaces, further exacerbate the burden in marginalized communities.

study showed improves asthma control. Visceral fat measures, such as waist circumference or lipid accumulation product index, are emerging as stronger predictors than BMI, guiding risk stratification. Addressing these epidemiological insights will inform targeted prevention and personalized treatment strategies for paediatric asthma and obesity.

PREVALENCE AND ASTHMA RISK ASSOCIATED WITH OBESITY AND OVERWEIGHT IN U.S CHILDREN



While the prenatal and longitudinal data establish obesity as a precursor to asthma, a bidirectional relationship is plausible, as asthma-related exercise avoidance and corticosteroid use (increasing weight by 2–5 kg) promote obesity.

Further research is needed to clarify sex-specific risks, elucidate prenatal mechanisms (e.g., epigenetics, microbiota), and explore interventions like weight loss, which a 2024

CLINICAL CHARACTERISTICS OF OBESITY AND ASTHMA IN CHILDHOOD

Asthma and obesity commonly coexist in the paediatric population. While asthma may sometimes lead to reduced physical activity and subsequent weight gain, or both conditions may develop independently, current evidence most strongly supports the presence of a distinct **“obese asthma” phenotype**. In this phenotype, **obesity actively influences the clinical course, severity, and treatment response of asthma** rather than being a passive comorbidity.

Children with obesity-related asthma often present with:

- **Increased asthma severity**
- **Reduced disease control**
- **Diminished overall quality of life**

Underlying biological mechanisms contributing to this phenotype include:

- **Chronic systemic inflammation** is associated with excess adipose tissue

- **Insulin resistance**, which may impair lung function and inflammatory regulation
- **Disruptions in lipid metabolism**, potentially exacerbating airway inflammation

These factors may enhance the body's inflammatory response, worsen respiratory symptoms, and contribute to a more difficult-to-control asthma profile.

Impact on Treatment Response

Overweight and obese children with asthma frequently exhibit a **reduced response to standard asthma therapies**, which complicates disease management and increases healthcare utilization.

- **Inhaled Corticosteroids (ICS):**
These children often show a **blunted response to ICS**, resulting in more frequent use of **systemic corticosteroids** (e.g., prednisone) and a **higher incidence of moderate-to-severe asthma exacerbations**.
- **Bronchodilators:**
Evidence suggests that **obese adolescents are 24% more likely to be unresponsive to bronchodilator therapy** than their non-obese counterparts, contributing to persistent symptoms and functional impairment.

Hospitalization and Environmental

Triggers

Obesity further complicates the clinical course of asthma through its impact on **hospital outcomes and environmental susceptibility**:

- **Longer Hospital Stays:**
Obese children hospitalized for asthma often experience **prolonged admissions**, likely due to more severe disease and reduced treatment responsiveness.
- **Increased Need for Mechanical Ventilation:**
There is a **higher risk of requiring respiratory support** during acute exacerbations in this group.
- **Heightened Sensitivity to Environmental Triggers:**
Obese children may be **more vulnerable to indoor air pollutants** (e.g., dust mites, Mold, smoke), which can **exacerbate asthma symptoms** and reduce control.

CLINICAL CHARACTERISTICS OF OBESITY AND ASTHMA IN ADULTS: PHENOTYPES AND THERAPEUTIC CHALLENGES

Obesity significantly exacerbates asthma in adults, contributing to greater disease severity, poorer control, and reduced quality of life. In the United States, approximately 60% of adults with severe asthma are obese (BMI ≥ 30 kg/m²), compared to 38% of the general adult

population (CDC, 2023). Obese adults with asthma face a 4- to 6-fold higher risk of hospitalization compared to their lean counterparts, as reported in a 2024 study, reflecting increased exacerbation frequency and healthcare utilization. Asthma control questionnaire scores are 15–20% worse in obese asthmatics, driven by physical limitations, dyspnoea, and psychosocial stress, per the *Journal of Clinical Medicine* (2024).

Obese asthmatics exhibit impaired responses to standard controller medications, including inhaled corticosteroids (ICS) and ICS-long-acting beta-agonist (LABA) combinations, with 20–30% reduced efficacy compared to lean asthmatics. This is partly due to an altered pathogenesis distinct from conventional allergic asthma, characterized by non-eosinophilic inflammation, systemic meta-inflammation, and airway oxidative stress. Visceral adipose tissue secretes pro-inflammatory cytokines (e.g., IL-6, TNF- α) and adipokines (e.g., leptin), amplifying airway hyperresponsiveness, while reduced anti-inflammatory adiponectin exacerbates inflammation. A 2024 study also implicated gut microbiota dysbiosis, with altered short-chain fatty acid production contributing to airway inflammation via the gut-lung axis.

Several phenotypes within the obese asthma syndrome have been identified, reflecting its heterogeneity:

- **Early-onset obese asthma:**

Typically associated with higher Th2 inflammation (e.g., elevated IgE, eosinophils), this phenotype exhibits the most severe disease, with frequent exacerbations and poor ICS response. A 2024 study noted that early-onset obese asthmatics require 2–3 times more oral corticosteroid courses, promoting further weight gain (2–5 kg per course).

- **Late-onset obese asthma:**

Predominantly affecting women, this phenotype shows minimal airway inflammation but significant adipose tissue inflammation and airway oxidative stress. It is linked to insulin resistance (prevalent in 40–50% of obese adults) and hormonal factors, per *Frontiers in Allergy* (2024).

- **Neutrophilic obese asthma:**

Characterized by neutrophilic airway inflammation, this phenotype is more responsive to weight loss, particularly in women, with a 2024 trial showing 10–15% improvement in lung function post-weight reduction.

- **Pollutant-sensitive obese asthma:**

Obese asthmatics are 25–30% more susceptible to air pollutants (e.g., particulate matter, ozone), which exacerbate symptoms and may define a distinct phenotype or complicate existing ones, as noted in *StatPearls* (2024).

Environmental and socioeconomic factors worsen outcomes. Urban air pollution amplifies airway oxidative stress in obese asthmatics, increasing exacerbation risk by 20–30%. Socioeconomic disparities, such as limited access to healthcare or clean air, disproportionately affect marginalized communities, exacerbating disparities. Weight loss, through diet, exercise, or bariatric surgery, significantly improves asthma control, reducing exacerbations by 15–20% and enhancing ICS responsiveness, per *NPJ Primary Care Respiratory Medicine* (2024). Emerging therapies, including biologics targeting IL-6 or leptin pathways and microbiota-modulating probiotics, are under investigation but lack robust adult data.

Future research should refine phenotype classification, explore visceral fat metrics and investigate pollutant-asthma interactions. Personalized interventions, addressing metabolic, inflammatory, and environmental factors, are critical to mitigate the obese asthma syndrome's burden in adults.

OBESITY AS A RISK FACTOR FOR ASTHMA

Obesity has emerged as a critical global public health issue, impacting both children and adults. According to the **World Health Organization (WHO)**, the **global prevalence of obesity has nearly tripled since 1975**. By 2019:

- **41% of adults** were overweight
- **15% of adults** were obese
- Among **children and adolescents**, the prevalence of overweight and obesity increased from **4% to 18%**

In the **United States**, the statistics are particularly concerning:

- Approximately **17% of children and adolescents (ages 2–19)** are obese
- Around **35% of adults** are obese, with projections indicating this figure could rise to **51% by 2030**



Obesity is a well-established risk factor for numerous serious health conditions, including **atherosclerosis, hypertension, and type 2 diabetes**. Importantly, accumulating evidence indicates that **obesity significantly increases the risk of asthma**.

Epidemiological studies consistently

demonstrate a **higher prevalence of asthma among obese individuals** compared to those with normal weight. The relationship holds across different **age groups, ethnicities, and sexes**, making obesity a major modifiable risk factor for asthma.

Epidemiological Link Between Obesity and Asthma

In the United States, **asthma is nearly twice as prevalent in obese adults** compared to those with a healthy weight. This association remains consistent across **ethnicities, age groups, and both sexes**, although some studies suggest the association may be **stronger in females**.

Beyond body mass index (BMI), **central adiposity**, as measured by **waist circumference**, has also been independently linked to asthma even among individuals with BMI values in the normal range. This underscores the importance of **fat distribution**, not just total body weight, in asthma risk.

Role of Atopic Status in the Obesity–Asthma Relationship

Atopy, a genetic predisposition to allergic conditions, appears to influence how obesity affects asthma risk:

- Studies indicate that the **association between obesity and asthma is stronger**

in non-atopic individuals.

- This suggests that **non-allergic mechanisms**, such as systemic inflammation or metabolic dysregulation, may play a more prominent role in asthma development among the obese.
- In contrast, in **atopic individuals**, the already elevated baseline risk for asthma due to allergic sensitization may **mask the additional impact of obesity**, making it more difficult to detect statistically.

Obesity is a modifiable risk factor that increases the likelihood of developing asthma in people of all ages and backgrounds. The link between obesity and asthma tends to be stronger in individuals without allergies, suggesting that factors like inflammation, metabolism, or breathing mechanics may be involved. As obesity rates continue to rise, particularly in children and adolescents, we may see more cases of asthma and more severe symptoms over time.

THE IMPACT OF OBESITY ON ASTHMA

Numerous prospective studies have demonstrated that obesity significantly increases the risk of developing asthma. For instance, in a well-known longitudinal study involving women initially free of asthma, those who were obese had a **2.6-fold higher risk** of developing asthma over 4 years, even after

adjusting for confounding factors such as age, smoking status, and physical activity. A clear **dose-response relationship** was noted, with higher BMI correlating with increased asthma risk. Similar findings have been observed in men in larger-scale studies, supporting a consistent association between elevated BMI and incident asthma across sexes.

In paediatric populations, prospective data similarly indicate that **obese children have a 1.5 times higher risk** of developing asthma compared to their normal-weight peers. These effects are seen in both boys and girls, though some meta-analyses suggest a slightly stronger association in boys. Notably, studies tracking children from birth have found that **rapid weight gain in early life** also increases the risk of developing asthma later in childhood.

Importantly, the relationship between obesity and asthma appears to be **bidirectional**. Emerging research suggests that asthma itself may predispose children to obesity. One analysis revealed that children diagnosed with asthma were **50% more likely to become obese** than non-asthmatic peers. However, this risk was primarily seen in children who were already overweight at baseline. This raises the possibility that early overweight status may drive both the development of asthma and the progression to obesity, highlighting the complex **interplay between these two conditions**.

Additionally, **systemic corticosteroid therapy**, often used in managing severe asthma, can contribute to weight gain, further complicating this relationship. These findings underscore the importance of integrated management strategies that consider both asthma and obesity as interrelated conditions with shared pathophysiological and environmental contributors.

THE IMPACT OF ASTHMA ON OBESITY

While many studies have documented that obesity increases the risk of asthma, emerging evidence suggests a **bidirectional relationship**, where asthma may also contribute to the development of obesity, particularly in children and women. In a recent prospective study tracking individuals from age 20 to 40, **active asthma in women was associated with subsequent weight gain and the development of obesity**, whereas no such relationship was observed in men. This sex-specific finding suggests that hormonal, behavioural, or environmental factors may influence the link.

In paediatric populations, the connection appears even stronger. Children with asthma often engage in **lower levels of physical activity**, and some asthma medications, particularly systemic corticosteroids, can promote **lipid metabolism alterations and**

fat storage, especially in the trunk region. Although findings on medication-induced weight gain are mixed, **rescue medications** used in early childhood have shown a potential **protective effect against obesity**, independent of physical activity and other asthma treatments.

Notably, one study reported that children with early-life asthma or wheezing had a **significantly increased risk of developing obesity** in later childhood. These findings suggest that **early diagnosis and effective treatment** of asthma may help **break the cycle** wherein asthma contributes to weight gain, and excess weight subsequently worsens asthma symptoms and overall morbidity.

The biological mechanisms linking asthma to obesity remain under investigation, but may involve systemic inflammation, altered metabolic pathways due to medications, and behavioural changes like reduced physical activity. Importantly, early intervention in children with asthma may **prevent the onset of obesity** and associated metabolic diseases such as **type 2 diabetes and prediabetes** later in life.

THE IMPACT OF OBESITY AND ASTHMA AMONG CHILDREN AND ADULTS

Over recent decades, the prevalence of both obesity and asthma has risen significantly in

children and adults worldwide. A substantial body of research has documented the frequent co-occurrence of these two conditions, suggesting possible shared pathophysiological mechanisms. Proposed mechanisms linking obesity to asthma include altered lung physiology (such as reduced pulmonary compliance and airflow limitation), chronic low-grade systemic inflammation, sympathetic nervous system dysfunction, and potentially shared genetic factors.

Numerous studies have consistently demonstrated that overweight and obese individuals, both children and adults, are at increased risk for developing asthma and tend to experience more severe respiratory symptoms. While the role of obesity in asthma incidence is well established, evidence regarding whether asthma predisposes children to subsequent obesity remains mixed.

However, children with asthma often exhibit risk factors associated with obesity, including lower levels of physical activity and potential weight gain due to corticosteroid therapy.

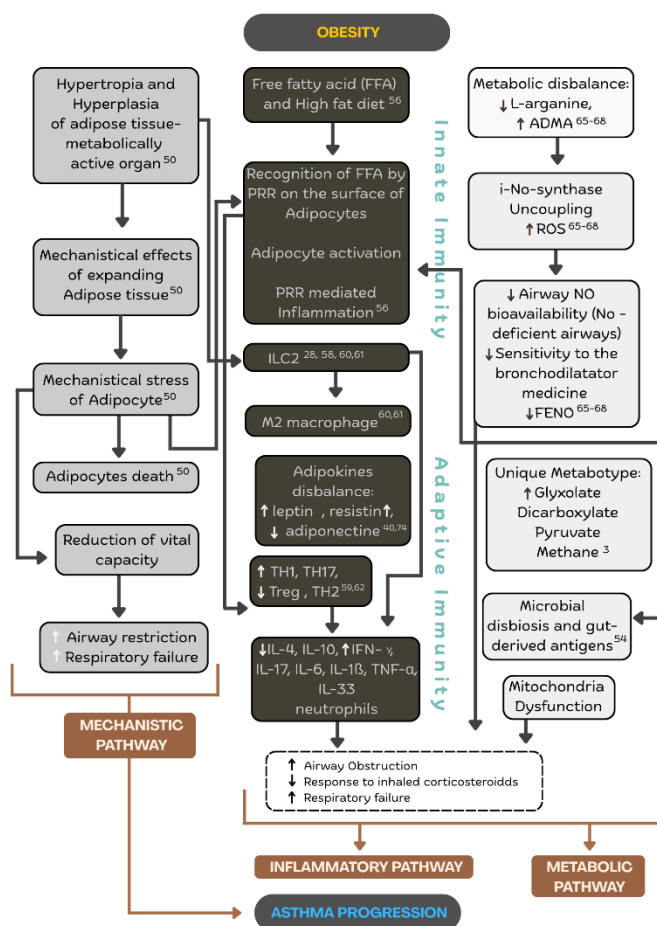
If asthma does indeed increase the risk of obesity, a portion of the current childhood obesity epidemic may be indirectly driven by rising asthma prevalence or by common etiological factors influencing both conditions. This possibility highlights the importance of **early identification and treatment of asthma**, not only for respiratory health but also

as a potential strategy for preventing obesity and related metabolic diseases. Early intervention is particularly crucial given that obese children are more likely to become obese adults and are at increased risk for metabolic disorders, including type 2 diabetes and cardiovascular disease.

OBESEITY AND SEVERITY OF ASTHMA

Obesity is highly prevalent among individuals with severe asthma, markedly exceeding the rates observed in the general population. Studies have shown that approximately **31% of children** and **57% of adults** with severe asthma are obese, compared to **20%** and **35%** obesity rates in the general U.S. child and adult populations, respectively. In another analysis, **48% of adults** with severe asthma were obese, compared to **25%** in the broader adult population. While the increased obesity burden among severe asthmatics may partly reflect the weight-promoting effects of systemic corticosteroids frequently used in this group, accumulating evidence suggests that **obesity itself contributes to increased asthma severity**.

Higher body mass index (BMI) has been consistently associated with greater asthma morbidity. In both children and adults with persistent asthma, elevated BMI correlates with **increased risk of exacerbations**, as evidenced by a greater frequency of oral corticosteroid prescriptions linked to asthma-related encounters. Obese adults with asthma are also at **higher risk for hospitalization**, and among those hospitalized for asthma exacerbations, obesity is linked to a **greater likelihood of mechanical ventilation and longer hospital stays**.



Bidirectional regulation between metabolic and inflammatory pathways promotes progression from obesity to asthma severity. Schematic overview input of the 3 pathways (inflammatory, metabolic, and mechanistic) to asthma progression in obese patients. Immunometabolism (inflammatory and metabolic) pathways impact lung dysfunction by increased airway obstruction (promotion of the airway obstruction and/or reduction of the response to inhaled corticosteroids), whereas the mechanistic pathway alters lung function by increased airway restriction. Both effects (obstruction and restriction) lead to respiratory failure and asthma progression in obese patients

In paediatric populations, similar findings have been reported. Obese children with asthma experience **longer durations of hospitalization** and an **increased risk of 30-day readmission** following inpatient care. Furthermore, among children presenting to emergency departments with severe asthma exacerbations, those who were obese were more likely to have used inhaled corticosteroids and theophylline in the week preceding the visit, indicating possible **reduced responsiveness to standard asthma therapies** in the context of obesity.

Collectively, these findings underscore that **obesity not only increases the risk of asthma but also exacerbates its severity**, complicating both disease control and treatment response.

CLINICAL CHARACTERISTICS OF OBESE SEVERE ASTHMATICS

Asthma is a heterogeneous disease encompassing a spectrum of phenotypes with distinct clinical, inflammatory, and treatment-response profiles. One such phenotype, known as **"obese asthma"**, has garnered increasing attention due to its unique characteristics and clinical implications. Recognizing and characterizing this phenotype is crucial for personalized treatment approaches, especially in the context of severe asthma.

Patients with obese asthma typically present

with a **late-onset form of the disease**, often beginning in adulthood, and are **predominantly female**. Despite reporting **high symptom burden**, these individuals tend to have **low sputum eosinophil counts**, **minimal atopy**, **moderate airway hyperresponsiveness**, and **only modest reversibility of airflow obstruction**. Importantly, they exhibit a **blunted response to inhaled corticosteroids (ICS)**, indicating a non-Th2 (non-eosinophilic) asthma phenotype.

Data from U.S.-based research cohorts applying cluster analysis techniques also identified a distinct subgroup of **obese patients with severe asthma**, sharing similar features: **low atopy**, **lower lung function**, and **later disease onset**. These findings were consistent across different populations and have informed the expansion of asthma phenotyping to better understand the interplay between obesity and asthma.

Further refinement of this phenotype led to the identification of at least **two subgroups of obese asthmatics**:

- **Early-onset allergic asthma**, often associated with **eosinophilia** and **elevated serum IgE**, which is worsened by obesity.
- **Late-onset, non-allergic asthma**, primarily affecting **adult women**, characterized by a lack of **Th2 inflammatory markers**. In this group,

airway hyperresponsiveness improves with weight loss, supporting a causal role of obesity in asthma pathogenesis.

These observations highlight that obese asthma is not a uniform entity but comprises **multiple phenotypes with differing pathophysiology's and treatment responses**. Understanding these distinctions is essential for developing targeted management strategies, particularly in those with corticosteroid-insensitive, obesity-driven asthma.

AIRWAY INFLAMMATION IN SEVERE ASTHMA

Airway inflammation in severe asthma is complex and heterogeneous, with mounting evidence suggesting that **obesity significantly alters the inflammatory landscape** of the disease. In particular, obesity appears to **shift the predominant airway inflammatory phenotype from eosinophilic to neutrophilic**, especially in individuals with severe or poorly controlled asthma.

Multiple clinical studies have investigated airway inflammatory patterns in obese versus non-obese individuals with asthma. These studies consistently report **elevated sputum neutrophils**, but not eosinophils, in obese asthmatic patients. Notably, one investigation using induced sputum samples found significantly higher neutrophil counts in obese

patients compared to non-obese asthmatics, with the association being more prominent in **female subjects**. This neutrophil predominance suggests a deviation from the classic **Th2-eosinophilic phenotype** towards a **non-Th2, neutrophilic-driven** asthma endotype in this population.

Further supporting this shift, studies have shown increased levels of **interleukin-17A (IL-17A)** in the sputum of obese patients. IL-17A is a pro-inflammatory cytokine involved in **neutrophil recruitment and activation**. Experimental data indicate that **airway hyperresponsiveness (AHR)**, a hallmark of asthma, is enhanced in obese patients, and this hyperresponsiveness is significantly attenuated in **IL-17A-deficient models**, emphasizing the cytokine's pivotal role. Moreover, obese individuals demonstrate **exaggerated responses to ozone exposure**, a known neutrophilic asthma trigger, which is again mitigated by IL-17A blockade.

While sputum eosinophil counts are generally reduced in obese asthmatics, **submucosal eosinophils are paradoxically elevated** in obese versus lean individuals with severe asthma. Additionally, **sputum IL-5 levels**, a critical eosinophil survival factor, are also increased in obese severe asthmatics. These findings suggest that **eosinophils are retained within tissue compartments** and fail to effectively migrate into the airway lumen, rather

than being absent or nonviable. As a result, some obese individuals may still harbour a **Th2-high asthma phenotype** at the tissue level, and could potentially **respond to eosinophil-targeted biologic therapies**, such as anti-IL-5 or anti-eosinophil agents.

In summary, obesity in severe asthma is associated with:

- **Predominantly neutrophilic airway inflammation**, especially in females.
- **Increased IL-17A expression**, contributing to neutrophil-mediated AHR.
- **Tissue-level eosinophilia with impaired luminal migration**, implying a hidden Th2 signature.

Understanding these immunologic shifts is essential for **personalizing treatment**, especially when considering **biologic therapies** in obese individuals with severe asthma.

THE IMPACT OF METABOLIC FUNCTIONS ON ASTHMA AND OBESITY

METABOLIC SYNDROME

Metabolic syndrome (MetS) is a cluster of interrelated metabolic abnormalities that includes **central (abdominal) obesity**, **impaired glycaemic control**, **dyslipidaemia** (elevated triglycerides and/or reduced high-density lipoprotein [HDL] cholesterol), and **hypertension**. This syndrome affects

approximately **two-thirds of the obese population**. Although not classified as a disease entity in itself, MetS significantly increases the risk for **type 2 diabetes**, **cardiovascular disease**, **non-alcoholic fatty liver disease (NAFLD)**, and **certain cancers**. Its multisystem impact raises concerns about potential pulmonary implications, particularly its association with asthma.

Given the systemic nature of MetS, it is plausible that its presence may contribute to the **increased incidence and severity of asthma in obese individuals**. Several epidemiological studies have investigated whether MetS independently influences **lung function impairment**, **asthma diagnosis**, and **asthma-related morbidity**.

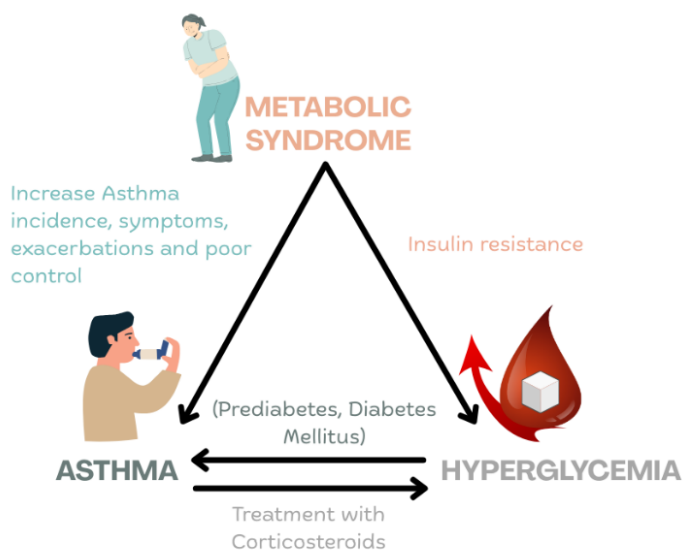
In both adult and paediatric populations, MetS has been associated with:

- **Reduced lung function**, notably lower **forced expiratory volume in 1 second (FEV₁)** and **forced vital capacity (FVC)**.
- **Increased respiratory symptoms**, even after adjusting for potential confounding variables.
- **Accelerated decline in lung function** over time.
- **Elevated risk of developing asthma**.

However, the extent to which these findings are directly attributable to MetS as opposed to being confounded by body mass index (BMI)

remains an area of active investigation. Nonetheless, individual components of MetS, particularly **abdominal adiposity**, **poor glycaemic control**, and **dyslipidaemia**, have consistently been linked to asthma in both adults and children.

Mechanistic Considerations



The interconnections between asthma, metabolic syndrome, and hyperglycaemia

The mechanisms by which MetS may influence asthma pathogenesis are **multifactorial** and involve complex **metabolic**, **immunologic**, and **inflammatory pathways**.

- **Insulin Resistance and Hyperinsulinemia:**

Poor glycaemic control, a hallmark of MetS, often leads to **insulin resistance** and **elevated circulating insulin levels**. Experimental studies suggest that insulin can enhance **airway smooth muscle**

(ASM) contractility, which may contribute to bronchial hyperreactivity. Epidemiological data reinforce this, showing an **inverse association between insulin sensitivity and lung function**. Moreover, clinical trials have observed that inhalation of exogenous insulin can provoke **respiratory symptoms**, including cough and dyspnoea, as well as reductions in FEV₁ and **diffusing capacity of the lung for carbon monoxide (DLCO)**.

These findings underscore the possibility that **insulin-mediated airway remodelling or hyperresponsiveness** may partly explain increased asthma burden in individuals with MetS.

A. Oxidative Stress

Obese individuals with asthma exhibit **elevated levels of both systemic and airway oxidative stress biomarkers** when compared to their lean counterparts. This heightened oxidative burden has been linked to **increased asthma severity**, **greater symptom burden**, and a **diminished therapeutic response to inhaled corticosteroids**.

Oxidative stress is a multifaceted pathophysiological process resulting from an imbalance between **pro-oxidant molecules** (such as reactive oxygen species [ROS]) and the body's **antioxidant defence systems**. When this balance is disrupted, excessive ROS can

contribute to **airway inflammation, epithelial damage, and bronchial hyperresponsiveness**, all of which are hallmarks of asthma pathogenesis.

In the context of **metabolic syndrome (MetS)**, a growing body of evidence supports its association with **systemic oxidative stress and chronic low-grade inflammation**. However, it remains **uncertain whether MetS exerts similar oxidative effects specifically within the airways of asthmatic individuals**. Additional research is needed to determine whether **MetS-related oxidative mechanisms** directly contribute to airway dysfunction and poor asthma control, or whether these effects are primarily mediated through overlapping factors such as **obesity and insulin resistance**.

B. Dyslipidaemias

Dyslipidaemias characterized by **elevated triglyceride levels and/or reduced high-density lipoprotein (HDL) cholesterol** are hallmark features of metabolic syndrome (MetS) and are independently associated with **increased asthma prevalence, heightened respiratory morbidity, and reduced lung function** in both paediatric and adult populations.

These lipid abnormalities reflect underlying **adipose tissue dysfunction** and are closely linked with **immune dysregulation**. In

individuals with obesity and asthma, dyslipidaemias are thought to contribute to systemic and airway inflammation via mechanisms involving **innate immune activation**, particularly of **monocytes and macrophages**. Emerging evidence suggests that these **lipid-induced immunological shifts** may enhance airway inflammation and hyperresponsiveness, thereby worsening asthma control and increasing symptom severity.

Specifically, **triglyceride-rich lipoproteins** have been implicated in promoting **pro-inflammatory monocyte phenotypes**, which may amplify airway inflammation in obese asthmatics. Conversely, reduced HDL levels may impair anti-inflammatory responses and **antioxidant capacity**, further exacerbating disease progression.

Taken together, these findings underscore the **pathophysiological relevance of dyslipidaemia** in the context of asthma among obese individuals, particularly those with MetS. Targeting lipid metabolism and restoring lipid homeostasis may represent **novel adjunctive strategies** in the management of asthma in this population.

THE RELATIONSHIP BETWEEN OBESITY, ASTHMA, AND GUT MICROBIOTA

The human colon harbours a dense and diverse

community of microorganisms collectively known as the **gut microbiota**, which plays a pivotal role in maintaining gastrointestinal and systemic health. This microbial ecosystem is integral to **intestinal development, metabolic regulation, immune modulation, and protection against pathogens.**

According to the "**hygiene hypothesis,**" reduced exposure to microbial agents in early life, often due to modern sanitation, reduced infections, and antibiotic use, contributes to the rise in allergic and autoimmune conditions, including asthma. Alterations in gut microbiota composition, or **dysbiosis**, have been increasingly implicated in the pathogenesis of **both obesity and asthma**, particularly when such alterations occur during **critical windows of immune development** in infancy.

The **initial colonization** and subsequent development of the infant gut microbiota are influenced by multiple factors, including:

- **Mode of delivery** (vaginal birth vs. caesarean section)
- **Infant feeding practices** (breastfeeding vs. formula feeding)
- **Antibiotic exposure**
- **Environmental microbial diversity**

Recent findings indicate that within the **first six weeks of life**, the infant gut microbiota undergoes **significant restructuring**, a process that appears to be **primarily influenced by body site rather than mode of**

delivery. Nonetheless, **breastfeeding has been consistently associated** with a gut microbiota composition that favors **immune tolerance and reduced allergy risk**, whereas formula feeding may predispose to a **microbiome profile associated with inflammation and metabolic dysfunction.**

In the context of obesity and asthma, **microbiota-mediated immune programming** may play a central role. Dysbiosis may promote a **pro-inflammatory state**, increase **gut permeability**, and contribute to **systemic immune dysregulation**, which may subsequently influence airway inflammation and metabolic outcomes. Thus, understanding the **gut–lung axis** and **microbial contributions to immune development** offers promising avenues for early-life interventions aimed at **preventing or mitigating obesity-related asthma.**

ANTIBIOTIC EXPOSURE AND ITS IMPACT ON BMI AND ASTHMA RISK

There is increasing evidence from various studies suggesting a significant relationship between **early antibiotic exposure** and an **increased body mass index (BMI)** in children, along with a potential link to asthma development. Antibiotics, particularly during early life, are known to disrupt the composition and diversity of the **gut microbiota**, a crucial factor for both metabolic and immune system

regulation.

A. Effects of Early Antibiotic Use on BMI

Research has demonstrated that **early-life antibiotic exposure** may independently contribute to an increase in BMI, particularly in **boys**. The impact of antibiotics on the microbiota seems to play a pivotal role in this association, as disruptions in the gut microbiome may affect energy balance, fat storage, and metabolism, which are factors influencing body weight. For example, the use of **perinatal vancomycin** has been shown to alter the gut microbiota and subsequently affect disease severity, though it did not influence the severity of **hypersensitivity pneumonitis**, suggesting specific microbiota-mediated effects.

B. Long-Term Effects on Gut Microbiota and Metabolic Health

The **intestinal microbiota** is essential for maintaining metabolic and immune homeostasis. **Antibiotic use** has been shown to cause lasting changes in the microbiota, with some alterations persisting for **up to 6 months**. These shifts in microbial composition may contribute to long-term metabolic effects, such as altered BMI trajectories. Among the different classes of antibiotics, **macrolides** have been particularly implicated in modifying the gut microbiota and its associated functions.

Studies have reported a **positive correlation** between **lifetime antibiotic use** and BMI in children, alongside an **increased risk of asthma**. This suggests that antibiotics, particularly macrolides, may induce microbial shifts that influence both **weight gain** and **respiratory health** later in childhood.

C. Impact on Mucosal Barrier Function and Allergic Risk

An important function of the gut microbiota is to support **intestinal integrity** and maintain a healthy **mucosal barrier**, which helps prevent the development of systemic inflammation and immune dysregulation. **Children with allergic manifestations**, such as asthma, often exhibit a **lower proportion of IgA at 12 months of age**, which may indicate **impaired mucosal barrier function**. This dysfunction could lead to increased susceptibility to infections and inflammatory conditions, including **asthma**. Moreover, research has shown that **elevated faecal calprotectin levels**, an indicator of intestinal inflammation, at **2 months of age** can **predict the development of asthma and atopic dermatitis** by **6 years of age**, further linking early microbial disruptions to long-term allergic disease risk.

The association between early antibiotic exposure and **increased BMI** or **asthma risk** underscores the need for **prudent antibiotic use** in paediatric populations. **Targeted**

interventions to restore a healthy gut microbiota, such as **probiotics**, could potentially mitigate some of the adverse effects OF antibiotics on metabolic and immune health. Additionally, identifying **biomarkers** like faecal calprotectin may provide early diagnostic tools for predicting the development of **allergic diseases** in children exposed to antibiotics.

OBESITY-RELATED CHANGES IN MICROBIOME AND VITAMIN D DEFICIENCY

Obesity and overweight are complex conditions that impact multiple systems in the body, including the **gut microbiome** and **vitamin D metabolism**. Both of these factors contribute to metabolic and immune dysregulation, which may increase susceptibility to diseases such as **asthma**.

A. Vitamin D Deficiency in Obesity

Obesity is commonly associated with **vitamin D deficiency**, likely due to the **sequestration of vitamin D** in **adipose tissue**, which reduces its bioavailability. Several studies consistently show that **obese and overweight individuals** have **lower serum levels of vitamin D** compared to those of normal weight. Vitamin D, a fat-soluble vitamin, plays a crucial role in **bone health**, but its functions extend beyond the skeletal system. There is growing evidence

suggesting that vitamin D is also involved in **immune regulation**, **blood pressure control**, and the **inflammatory response**, making it relevant in the context of asthma and other immune-related conditions.

B. Vitamin D Deficiency and Asthma

The association between **vitamin D deficiency** and **asthma** exacerbations has been increasingly recognized, particularly in paediatric populations. Several studies have found that **children with vitamin D insufficiency** experience more **severe asthma exacerbations** compared to their counterparts with adequate vitamin D levels. Interestingly, this association is stronger in **non-atopic children** than in **atopic children**, suggesting that the effects of vitamin D may not solely be related to immune system modulation, but potentially to other factors, such as **airway smooth muscle function** or **inflammatory pathways**.

Moreover, the relationship between **vitamin D levels** and **asthma severity** remains significant even after controlling for **time spent outdoors** (which could provide additional exposure to ultraviolet radiation). This suggests that the effects of vitamin D on asthma exacerbations are independent of direct sun exposure and may be linked to dietary intake or **obesity-related changes** in the **bioavailability** of vitamin D.

C. Obesity, Gender Differences, and Vitamin D

The impact of obesity on **vitamin D deficiency** may also differ by **sex**. One report indicates that **central obesity** (fat accumulation around the abdomen) has a more pronounced effect on **vitamin D deficiency** in **women** than in men. This finding may suggest that **central obesity** plays a role in the **pathophysiology of asthma**, particularly in women, and could explain why **late-onset obese asthma** is more common among women. The reasons behind these sex differences could involve **hormonal differences** and **differences in fat distribution**, which may affect **vitamin D metabolism** and its systemic effects.

While observational studies suggest a link between vitamin D deficiency and asthma severity, **intervention studies** have yielded mixed results. For example, a study of **intermittent bolus-dose vitamin D supplementation** in **adult asthma patients** showed **modest improvements in serum vitamin D levels** but no significant impact on **asthma exacerbations**. This highlights the need for further research into **vitamin D supplementation** as a potential therapeutic approach for asthma, particularly in obese individuals.

The relationship between **obesity, vitamin D deficiency**, and **asthma** points to the impor-

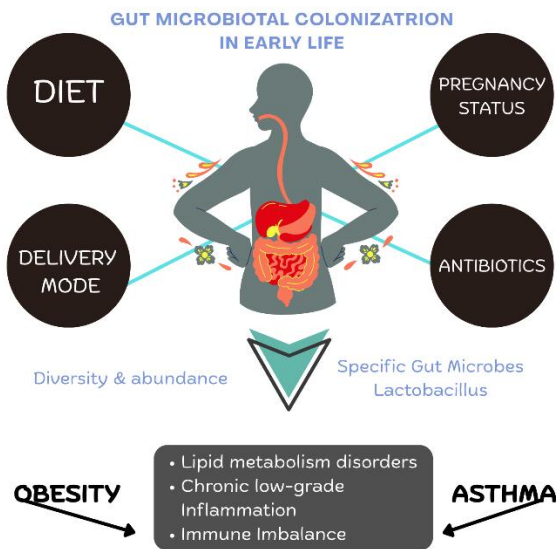
tance of **integrating dietary management, weight control, and nutrient supplementation** into clinical strategies aimed at managing asthma in obese children and adults.

GUT MICROBIOME AND OBESITY-RELATED ASTHMA

The human gastrointestinal (GI) tract is home to over 100 trillion bacteria from more than 1000 species. These microorganisms outnumber human genes and play a significant role in health. Increasing evidence suggests that the **gut microbiome** is involved in the development and progression of **obese asthma**, with changes in the gut microbiome contributing to both **allergic** and **non-allergic asthma**.

A. Impact of Obesity on the Gut Microbiome

Obesity alters the balance of bacteria in the gut, and poor dietary habits associated with obesity, such as high-fat diets, further influence this microbial community. Additionally, **metabolic issues** such as **hyperglycaemia, insulin resistance**, and **systemic inflammation** are regulated by gut microbiota. These changes are not confined to the gut alone but can also affect the **lung microbiome**, where differences between **obese** and **non-obese asthmatic** individuals have been observed.



Early-life gut microbiota colonization is disturbed by a variety of factors, including pregnancy status, delivery mode, diet, and antibiotic treatment, leading to alterations in microbial diversity, abundance, and specific microbes, which ultimately contribute to dysfunction and disease in the host.

B. The Role of Early Life Events

Early life factors, such as **antibiotic exposure**, **type of delivery** (caesarean vs. vaginal), **breastfeeding vs. formula feeding**, and **early exposure to pets or farm animals**, can significantly influence the development of the gut microbiome. These early microbial exposures have been linked to the **risk of developing allergic asthma**. Studies show that changes in the microbiome early in life can predict later asthma development, and interventions like **faecal microbiota transfer** may help attenuate allergic responses if performed during this critical early life window.

C. Microbiome and Immune System Regulation

The microbiome generates **short-chain fatty acids (SCFAs)** by fermenting dietary fibre, which enter the bloodstream and can influence immune responses in both the gut and lungs. SCFAs play a crucial role in regulating **immune cells**, particularly **dendritic cells** involved in allergic reactions in the lungs. This process underscores the **gut-lung axis**, where the microbiome of the gut can impact lung health and asthma severity.

D. Sex Differences in Microbiome and Pulmonary Response

There are significant **sex differences** in the structure of the gut microbiome, and these differences may influence how the body responds to environmental triggers like **ozone**. The microbiome may also contribute to these sex differences in immune responses, further influencing asthma outcomes.

E. Potential Treatments: Prebiotics and Probiotics

Manipulating the gut microbiome could offer a promising avenue for managing asthma in obese individuals. **Prebiotics** like **inulin**, a fermentable fibre, have been shown to improve **glucose tolerance** and **insulin resistance** in high-fat diets and may also protect from asthma symptoms. Additionally,

probiotics like **Lactobacillus gasseri** have demonstrated benefits in reducing **allergic airway inflammation** and improving **lung function** in children with asthma. While these treatments show promise, their effectiveness in obese asthmatics, particularly those with severe asthma, still requires further investigation.

Research into the **gut microbiome** offers exciting potential for new treatments for **obese asthma**, especially with the use of **prebiotics** and **probiotics** to regulate inflammation and immune responses. However, more studies are needed to determine the precise role of the microbiome and the efficacy of these treatments in **obese asthmatic** patients.

SYSTEMIC INFLAMMATION AND OBESITY-RELATED ASTHMA

Obesity causes **low-grade systemic inflammation**, which is linked to various health issues, including **asthma**. This inflammation is mainly caused by **cytokines** (inflammatory proteins) produced by fat tissue, especially **IL-6**.

A. IL-6 and Asthma

IL-6 is an important cytokine that contributes to **increased inflammation** in obese individuals, worsening asthma symptoms. Studies show that **reducing IL-6** in animal models leads to less **airway inflammation** and

bronchial hyperresponsiveness (which causes wheezing and shortness of breath) in allergic asthma. However, **IL-6** may just be a **marker** of the inflammation caused by obesity, rather than the direct cause of asthma.

B. Treatment Implications

Targeting the **inflammation** caused by obesity, including **IL-6**, may help reduce asthma symptoms. Improving metabolic health in obese patients may not only reduce **inflammation** but also help **control asthma**.

C. Sex Differences

Women with obesity tend to have **higher levels of CRP**, a marker of inflammation, than men. This could explain why **females** are more likely to have **severe asthma** related to obesity. More research is needed to better understand how **IL-6** and other **inflammatory markers** contribute to asthma in obese individuals, especially considering **gender differences**. Finding ways to **reduce inflammation** through **weight loss** and **other treatments** could be key in managing **obese asthma**.

EFFECT OF HIGH-FAT DIET ON ASTHMA

A growing body of research has highlighted the impact of a **high-fat diet** (HFD) on the development and exacerbation of **airway diseases**, including **asthma**. While the precise

mechanisms linking dietary fat to airway dysfunction are not fully understood, several key findings have emerged, shedding light on how a high-fat diet might affect asthma, both directly and indirectly.

A. High Fat Diet and Airway Reactivity

Studies suggest that a **high-fat diet** can lead to **airway reactivity**, even in the absence of allergen exposure or other external challenges. This means that the body's airways become more responsive and possibly over-reactive to normal stimuli, contributing to **asthma-like symptoms**. Additionally, exposure to **environmental pollutants**, such as **ozone**, results in **enhanced airway responses** in individuals consuming a high-fat diet.

Interestingly, **airway inflammatory responses** in response to allergens may not always be consistently affected by a high-fat diet. Some studies report increased airway inflammation, while others show a more variable response. These differences may be attributed to factors like **genetic strain differences** or variations in the **specific composition** of the high-fat diets used in these studies.

B. Free Fatty Acids and Immune Responses

One of the mechanisms by which a high-fat diet might contribute to asthma is through the

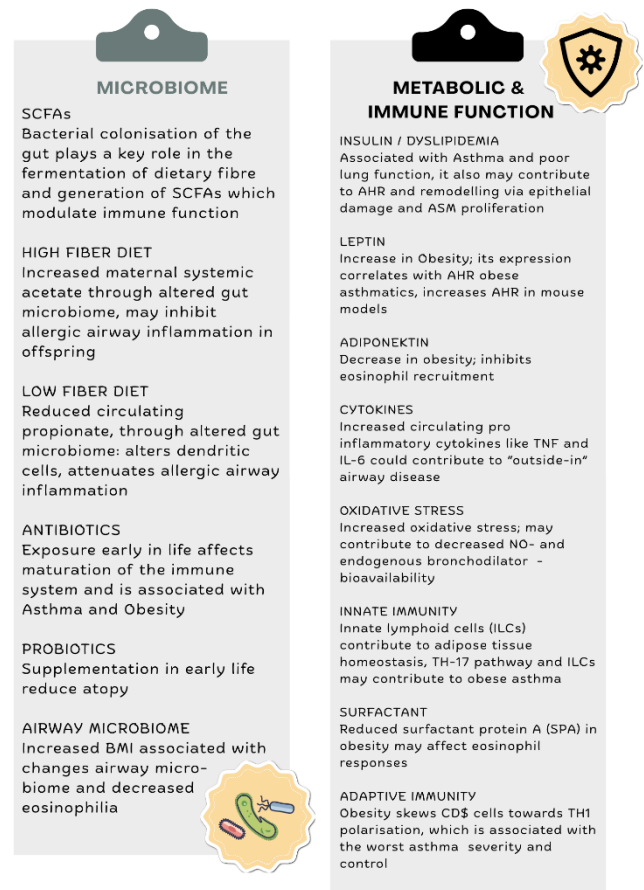
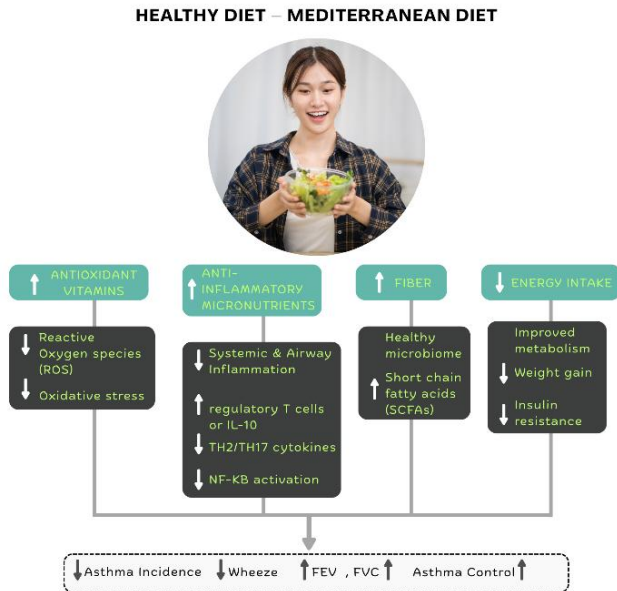
circulating levels of free fatty acids. As the body consumes a high-fat diet, **free fatty acids** increase in the bloodstream. These fatty acids can activate the **innate immune system**, potentially leading to heightened inflammation in the airways. This immune activation could worsen airway disease, even in the absence of obesity.

C. Effect on Bronchodilator Response

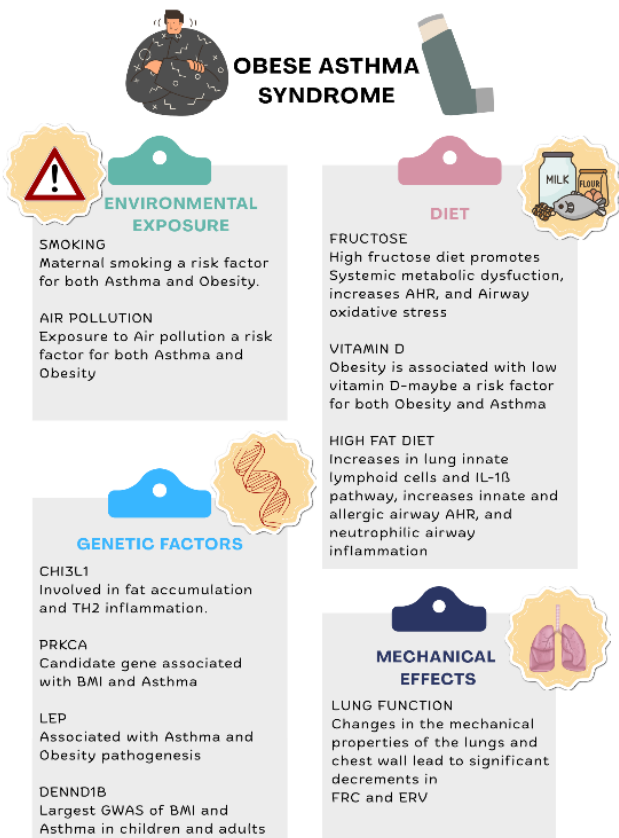
In humans, a **single high-fat meal** has been shown to have immediate effects on airway function. This challenge increases **neutrophilic inflammation** in the airways (a type of inflammation associated with asthma) while also **decreasing the effectiveness of bronchodilators**. Bronchodilators are medications used to open the airways, and their reduced effectiveness could contribute to a **reduced capacity to manage asthma symptoms**, making it harder to control the disease.

While the link between a high-fat diet and asthma is complex, existing research points to a potential mechanism through which dietary fat, independent of obesity, can **alter immune responses, increase airway inflammation, and decrease bronchodilator efficacy**. These findings suggest that dietary modification, particularly in terms of fat intake, could play a role in **managing asthma** and preventing

exacerbations, although further research is needed to fully understand the impact and identify the specific dietary components most responsible.



KEY SUMMARY



MANAGEMENT OF OBESE ASTHMA

Pharmacological Management of Obese Asthma

Currently, no pharmacologic agents are specifically approved for the treatment of asthma in obese individuals, and weight loss medications are not routinely recommended, particularly in children, unless severe obesity-related comorbidities are present. Evidence regarding the impact of these drugs on asthma outcomes is limited and largely speculative.

1. Orlistat

- **Indication:**

Approved for weight loss; may be prescribed to adolescents under strict medical supervision.

- **Mechanism of Action:**

Reversible inhibition of **gastric and pancreatic lipases**, leading to reduced triglyceride hydrolysis and up to **30% reduction in dietary fat absorption**.

- **Potential Benefits:**

- May lower **LDL cholesterol** and **total cholesterol**.
- Can improve **glycaemic control** in obese individuals with insulin resistance.

- **Limitations and Risks:**

- Common **gastrointestinal side effects** (e.g., steatorrhea, flatulence, faecal urgency) may reduce adherence.
- **Limited long-term safety data** beyond 2 years.
- May induce **iron deficiency** in adolescents.
- **No established benefit** for asthma control.
- Not recommended for **unsupervised use** in individuals under 18 years.

mellitus.

- **Mechanism of Action:**

- Reduces **hepatic glucose production**.
- Enhances **peripheral glucose uptake**.
- Induces **modest weight loss** by increasing satiety and decreasing nutrient absorption.

- **Potential Role:**

- Has shown metabolic benefits in obesity.
- Requires **further investigation** for potential efficacy in **asthma control among obese patients**.

- **Limitations:**

- Not FDA-approved for simple weight loss in children.
- Unknown direct effects on airway inflammation or asthma outcomes.



2. Metformin

- **Indication:**

Commonly prescribed for **obese adolescents with type 2 diabetes**

The Role of Micronutrients in Obesity and Asthma

Emerging evidence suggests that specific

micronutrients and **dietary patterns** may significantly contribute to the **development** and **progression** of asthma in individuals with **obesity**, through both **direct airway effects** and **indirect systemic influences** (metabolic, immune, and gut microbiome-mediated).

1. Vitamin D

Association with Obesity and Asthma

- **Low circulating vitamin D levels** are commonly observed in individuals with obesity.
- **Prenatal vitamin D deficiency** has been associated with:
 - Increased risk of **childhood obesity**.
 - Higher incidence of **early-life wheezing** and **respiratory morbidity**.

Respiratory Implications

- Vitamin D deficiency may:
 - **Increase susceptibility** to respiratory tract infections.
 - **Exacerbate asthma severity** by promoting airway inflammation.
 - **Contribute to corticosteroid resistance**, complicating pharmacologic asthma management.

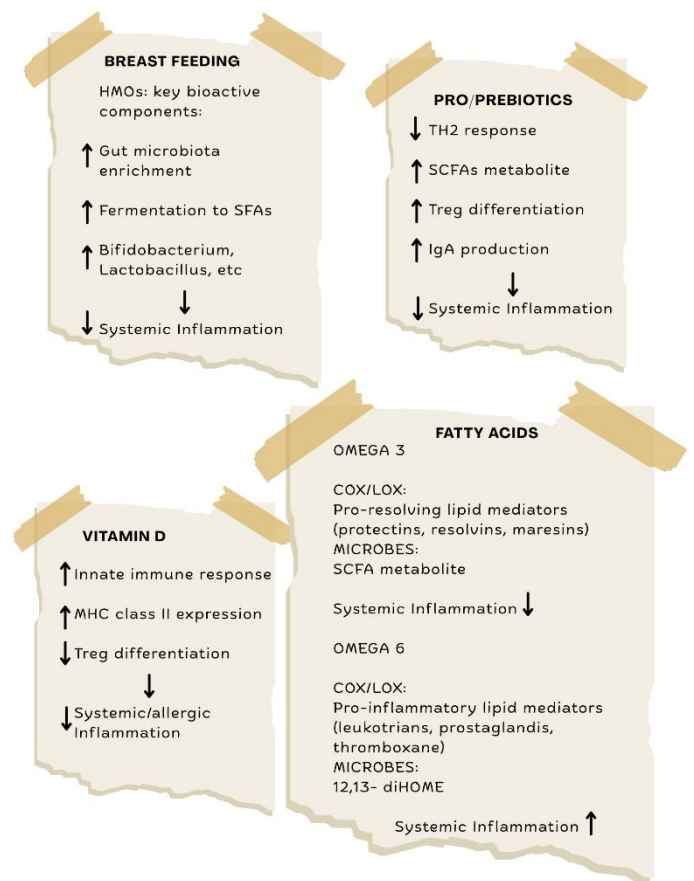
Clinical Relevance

- While observational data link vitamin D deficiency with worse asthma outcomes, the **efficacy of vitamin D supplementation** in improving **asthma control in obese patients** remains **unclear** and under inve-

stigation.

- Routine supplementation should be **individualized** and guided by **serum vitamin D levels** and clinical context.

Mechanisms of dietary interventions on asthma.



2. Western Diet and Pro-Inflammatory Effects

Diet Characteristics

- Typically **high in saturated fatty acids**, **refined sugars** (e.g., fructose), and **low in dietary fibre and antioxidants**.
- Commonly associated with **weight gain**, **systemic inflammation**, and **metabolic**

- dysregulation.

Airway Inflammatory Response

- Consumption of a **single high-fat meal** has been shown to:
 - **Increase neutrophilic inflammation** in the airways.
 - **Reduce responsiveness to bronchodilators**, potentially worsening asthma control.

Micronutrient Imbalances and Indirect Effects

- Western dietary patterns may lead to:
 - **Deficiencies in essential micronutrients** such as **vitamin D** and **antioxidants**.
 - **Disruption of the gut microbiome**, which can indirectly promote **airway inflammation** via immune modulation.

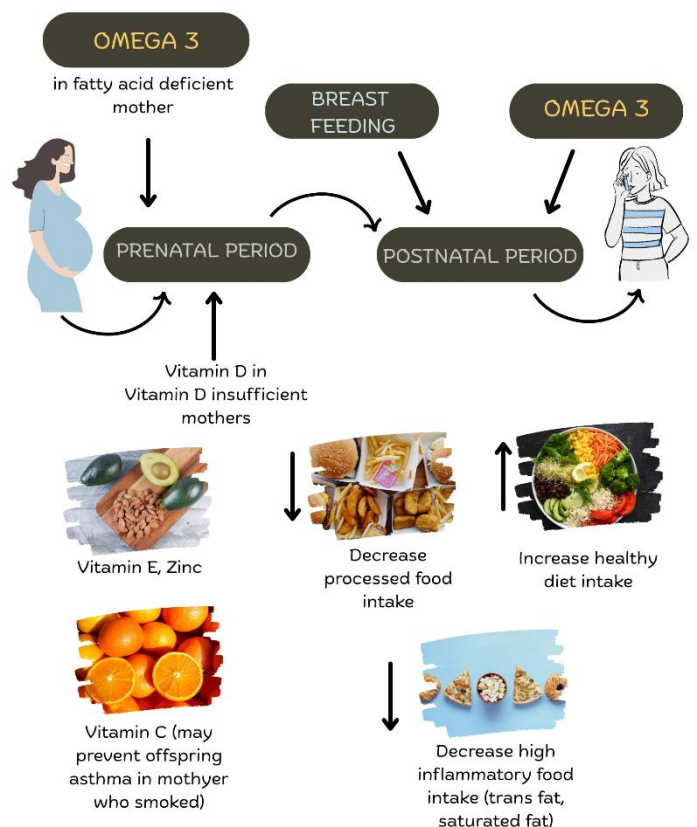
3. Paediatric Nutritional Risk and Protection

Protective Dietary Factors

- **Breastfeeding:**
 - Associated with a **reduced risk** of both **childhood obesity** and **asthma**.
- **Omega-3 fatty acids** (e.g., from fish oil or fatty fish):
 - Linked to a **lower incidence** of asthma
 - in children due to their **anti-inflammatory properties**.

Dietary Risk Factors

- **Omega-6 fatty acids:**
 - Associated with a **higher risk of asthma**, potentially due to their **pro-inflammatory effects**.
- **Unhealthy dietary patterns**, including:
 - **High intake of sugar-sweetened beverages**.
 - **Diets rich in sweets and dairy products**.
 - **Low consumption of vegetables and whole grains**.
 - These patterns are linked to **increased risk of asthma** and **metabolic dysfunction** in children.



4. Dietary Interventions and the Gut Microbiome

Beyond Weight Loss: Nutrient-Focused Interventions

- Emerging **pilot studies** indicate that **nutrient-rich, anti-inflammatory diets** (e.g., Mediterranean-style) may **improve asthma outcomes** in obese individuals **independent of weight loss**.
- These diets emphasize **whole grains, fruits, vegetables, lean proteins, and healthy fats**, promoting **immune balance** and **reduced systemic inflammation**.

Gut Microbiome and Airway Health

- Diet-induced alterations in the gut microbiota** may influence **airway inflammation** through immune-modulating pathways.
- Although the **gut–lung axis** is still under investigation, **dysbiosis** associated with high-fat, low-fibre diets may contribute to asthma severity.

Impact of Weight Loss Interventions on Asthma Outcomes

A. Lifestyle Weight Loss Interventions

- Overview:**
Weight loss interventions, such as liquid diet replacements and graduated dietary education, significantly improve asthma control and spirometry lung function in obese individuals.
- Weight Loss Threshold for Impact:**
A minimum of 5% body weight loss is

required for significant improvement in asthma control.

- Key Improvements:**

- Peak expiratory flow (PEF): 10–15% improvement.
- Forced expiratory volume in 1 second (FEV1): 5–10% improvement.
- Expiratory reserve volume (ERV): 15–20% improvement.

- Exacerbation Reduction:**

A 20–30% reduction in exacerbation frequency after intensive interventions (10–15% weight loss).

- Variability in Airway Reactivity:**

Some studies show 10–20% improvement in methacholine challenge tests, but others report no change.

B. Factors Influencing Variability in Asthma Response

- Obese Asthma Phenotypes:**

- Th2-high Asthmatics:**
Show less improvement in airway hyperreactivity (AHR) after weight loss.
- Late-onset/Neutrophilic Phenotypes:**
Respond better to weight loss due to reduced systemic inflammation.

- Markers of Airway Inflammation:**

- Exhaled Nitric Oxide (eNO):**
Significant reductions of 15–20% with combined diet and exercise.

- **Neutrophilic Inflammation:**
Gynoid fat loss in women is linked to a 25% decrease in airway neutrophilic inflammation.
- **Saturated Fat Intake:**
Reduced intake correlates with improvements in airway inflammation.

10–15% improvement in quality of life (QoL).

PAEDIATRIC WEIGHT LOSS INTERVENTIONS AND ASTHMA

Effects on Lung Function and Asthma Control

- **Non-Controlled Studies:**
Improvements in FEV1, ERV, and total lung capacity (TLC) with BMI reduction.
- **Adipokine Changes:**
 - Increase in adiponectin and decrease in leptin linked to improved lung function (FVC, FEV1).
 - Enhanced exercise-induced bronchoconstriction (EIB) control.
- **Randomized Controlled Trials (RCTs):**
 - **Dietary Intervention:**
Increased ERV by 10–12%, but not statistically significant compared to controls.
 - **FVC Improvement:**
15% greater improvement in the intervention group despite similar BMI changes.
 - **Exacerbations and Quality of Life:**
20% reduction in exacerbations, with

THE IMPACT OF EXERCISE ON ASTHMA

Exercise may be part of a lifestyle intervention to reduce weight in asthma, or could be considered as an intervention by itself. Studies suggest that exercise can reduce allergic airway inflammation, but only small studies have examined exercise in the treatment of human asthma. These small studies are likely underpowered to see significant differences in asthma outcomes. One study investigated the role of exercise as part of a three-arm randomized trial in which obese asthmatics were randomized to dietary intervention, exercise, or exercise and dietary intervention for the treatment of asthma. Only the patients in the dietary intervention and exercise plus dietary intervention (both of these groups achieved significant weight loss) experienced significant improvements in asthma control. The exercise group maintained a stable weight and did not experience a significant improvement in asthma control, but did have a significant decrease in airway eosinophilia (which is consistent with earlier findings from allergic airway inflammation and asthma). There are currently no large studies of exercise as an intervention to improve asthma control in obesity, though preliminary data from small

studies suggest it may be particularly helpful to treat obese asthmatics as part of a lifestyle intervention including weight loss.

BARIATRIC SURGERY: THE MOST EFFECTIVE WEIGHT LOSS INTERVENTION

Bariatric Surgery and Asthma

Improvements

- **Sustained Weight Loss:**
20–30% weight loss achieved through bariatric surgery.
- **Asthma Control:**
50–60% improvements in asthma control and lung function.
- **Lung Function Enhancements:**
 - Forced expiratory volume (FEV1) and peak expiratory flow (PEF) improved by 20–25%.
 - Airway hyperreactivity (AHR) reduced by 30–40%.
- **Exacerbation Reduction:**
Bariatric surgery reduces asthma exacerbation risk by 58% (baseline risk 22%).

Mechanisms Behind Asthma

Improvement

- **Visceral Fat Reduction:**
Decreases in pro-inflammatory cytokines (e.g., IL-6, TNF- α) and leptin, with increased adiponectin.

- **Gut-Lung Axis:**

Weight loss restores gut microbiota diversity, reducing pro-inflammatory metabolites like short-chain fatty acids.

- **Infection Sensitivity:**

Bariatric surgery improves immune responses, reducing risks of asthma exacerbations triggered by infections.

COMORBIDITIES ASSOCIATED WITH OBESITY AND ASTHMA

Aside from asthma, obese patients may have several other co-morbid conditions, including gastroesophageal reflux disease (GERD), hypertension, obstructive sleep apnoea, insulin resistance, and dyslipidaemia. These conditions may complicate asthma in the obese, and there is evidence that at least some of these co-morbidities may contribute to severe obese asthma. For example, GERD is very common in severe asthma, especially in patients who are obese; patients in the obese asthma clusters have more GERD than those in the other severe asthma group.

Reflux can cause bronchoconstriction, and GERD is an important risk factor for asthma exacerbations in patients with severe asthma. Several studies have evaluated the ability of proton pump inhibitors to ameliorate asthma symptoms, but most identified only a modest effect or no effect of treatment, although none of the studies focused specifically on obese

asthmatics.

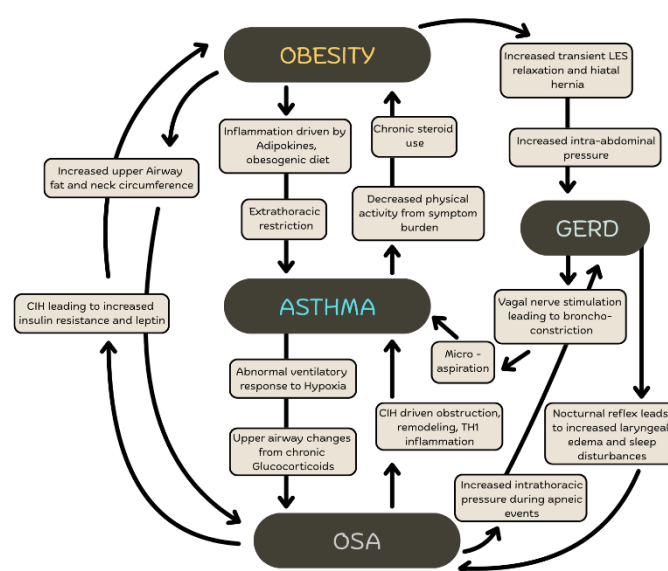
There is also a high prevalence of obstructive sleep apnoea (OSA) in patients with severe asthma, with rates as high as 80%, and the frequency of severe asthma exacerbations is higher in asthmatics with OSA than those without OSA. Importantly, these patients have greater sputum neutrophils, consistent with the link between sputum neutrophils and severe asthma.

OSA is associated with systemic inflammation, and in the obese, the intermittent hypoxemia associated with repeated obstructive episodes may exacerbate already existing adipose tissue hypoxia, worsening adipocyte death, macrophage infiltration, and consequent systemic inflammation characteristic of obesity. There is evidence that continuous positive airway pressure (CPAP), a treatment for OSA, reduces systemic inflammation in asthmatics and also reduces airway responsiveness, asthma symptoms, and 2-agonist use. Bariatric surgery also improves both asthma and OSA.

Type 2 diabetes is also a major complication of obesity, and there is some evidence that obesity, coupled with insulin resistance, may interact to promote asthma. Several studies observed a strong association between obesity and current asthma, but this relationship was stronger in patients in the highest than the lowest of insulin resistance. Insulin resistance also amplifies reductions in lung function in

overweight or obese adolescents.

Exactly how insulin resistance might promote asthma in the obese has not been established, but there is evidence of effects of insulin both on the immune system and on airway smooth muscle. A retrospective analysis of data from patients with asthma and diabetes indicated lower risk of asthma hospitalization in patients who were taking metformin for treatment of their diabetes than in those who were not. However, a randomized controlled trial of treatment with another type 2 diabetes therapeutic, pioglitazone, indicated little benefit in obese asthmatics. Moreover, pioglitazone treatment caused additional weight gain in these patients [10, Rank 2]



HOW DIFFERENT COMORBIDITIES ASSOCIATE WITH ASTHMA

Asthma, a prevalent chronic respiratory disorder affecting over 300 million people

globally, presents as a heterogeneous syndrome with various phenotypes, influenced by age of onset and underlying comorbidities. The prevalence of asthma in adults ranges from 0.2% to 21%, with distinct phenotypic differences based on the age at which asthma develops. Early-onset asthma, typically seen in childhood, is often atopic with Th2-predominant inflammation, good response to glucocorticoids, and a favourable prognosis. On the other hand, adult- or late-onset asthma, often associated with nonatopic individuals (predominantly females), tends to have a less favourable prognosis, with a higher likelihood of persistent airflow limitation.

Recent research has challenged the traditional view that asthma predominantly begins in childhood, revealing that adult-onset asthma is more common in women over 40 in the United States. This adult-onset asthma has been linked to a variety of factors, including obesity, occupational exposures, rhinitis, respiratory infections, smoking, and stressful life events, all of which may contribute to the development of asthma in adulthood. These factors also correlate with metabolic and inflammatory disorders such as obesity, metabolic syndrome, type 2 diabetes, cardiovascular diseases, and psychiatric conditions, which further complicate asthma management.

In clinical practice, comorbidities are a significant concern, particularly in older or

obese patients. Studies indicate that 35% of adults in the U.S. are obese, and multimorbidity (the presence of multiple comorbid conditions) is common. In early-onset asthma, common comorbidities include food allergies, atopic eczema, and allergic rhinitis, which are well-characterized and often overlap with asthma. Gastroesophageal reflux disease (GERD) has gained attention as a contributing factor to asthma exacerbations, with studies indicating its higher prevalence in asthmatic individuals. In contrast, chronic obstructive pulmonary disease (COPD), typically affecting individuals over 40, shares many features with asthma, including chronic airway obstruction, although it exhibits less reversibility in airway obstruction compared to asthma. The coexistence of asthma and COPD, often referred to as asthma-COPD overlap syndrome (ACOS), poses unique challenges in diagnosis and treatment.

These comorbidities highlight the complex, multifactorial nature of asthma, necessitating a comprehensive approach to diagnosis and treatment, considering not just asthma itself but also the interplay with other chronic conditions.

The Association Between Early Life Exposures and Asthma

Early life exposures including maternal diet, maternal smoking, air pollution, and

complications during pregnancy can profoundly influence an offspring's metabolic health and risk of developing chronic diseases such as asthma. These exposures during critical windows of development may trigger structural, metabolic, or epigenetic changes in the foetus, increasing vulnerability to diseases later in life. For instance, maternal obesity has been linked to a higher risk of both insulin resistance and childhood asthma in offspring. Similarly, low birthweight is associated with elevated risks of asthma, hypertension, type 2 diabetes, and cardiovascular disease by middle age.

Adverse intrauterine environments may permanently alter developmental trajectories, predisposing children to chronic inflammatory conditions. One of the most potent contributors to this risk is early life psychological stress. Severe early life stress such as neglect, abuse, or trauma has been independently associated with an increased likelihood of developing both asthma and depression in adulthood. This connection is believed to be mediated by sustained systemic inflammation. Studies show that individuals who experienced adverse childhood events have persistently elevated levels of pro-inflammatory cytokines. Moreover, these individuals exhibit heightened inflammatory responses when exposed to stress in adulthood, compared to those without such a history.

The chronic activation of inflammatory pathways driven by early life adversity may contribute to heightened susceptibility not only to asthma but also to a wide spectrum of other chronic inflammatory diseases. These findings underscore the importance of maternal and early childhood health as foundational to lifelong respiratory and metabolic health.

The Association Between Obese Asthma and Insulin Resistance

Obese children, especially those from ethnic minority backgrounds, are at heightened risk of developing insulin resistance, a key precursor to type 2 diabetes that is characterized by systemic hyperinsulinemia. Increasing evidence indicates that metabolic dysregulation, particularly insulin resistance, plays a central role in the pathophysiology of obesity-related asthma in children. Studies have demonstrated a higher prevalence and severity of insulin resistance, metabolic syndrome, and clinical indicators such as acanthosis nigricans among asthmatic children when compared to non-asthmatic peers.

Insulin resistance is closely associated with elevated levels of pro-inflammatory markers such as leptin and interleukin-6 (IL-6), which may contribute to both the development and worsening of asthma symptoms. Notably, insulin resistance has been identified as a predictor of reduced lung function, specifically

through lower airway obstruction and decreased lung volumes. These associations are independent of both overall and central adiposity, suggesting that insulin resistance itself, rather than body fat alone, is a key driver of pulmonary impairment.

The systemic inflammation accompanying insulin resistance is thought to contribute directly to the airway inflammation observed in obese asthma phenotypes. While insulin primarily regulates glucose metabolism, it also exhibits anti-inflammatory properties under normal conditions. However, in states of insulin resistance, this protective anti-inflammatory role may be blunted or lost, potentially exacerbating airway inflammation and bronchial hyperresponsiveness.

Overall, the interplay between insulin resistance and asthma underscores the importance of early identification and management of metabolic dysfunction in obese children with asthma, especially in vulnerable populations. Addressing insulin resistance may be a crucial component of optimizing asthma control and improving long-term respiratory outcomes.

The Association Between Obese Asthma and Dyslipidaemia

Dyslipidaemia, characterized by abnormal lipid profiles such as elevated triglycerides and low high-density lipoprotein (HDL) levels, has emerged as a significant metabolic factor linked

to asthma, paralleling the role of insulin resistance. Several studies have demonstrated associations between dyslipidaemia and respiratory symptoms, including wheezing in adults and asthma in children. In obese urban adolescents, higher HDL levels have been associated with better pulmonary function, suggesting a protective role of HDL against asthma-related airway dysfunction. This protective effect may be partially attributed to HDL's ability to reduce monocyte activation and thereby modulate systemic inflammation.

Emerging research indicates that the relationship between dyslipidaemia and asthma may begin as early as in utero. For example, maternal diets low in polyunsaturated fatty acids (PUFAs) during pregnancy have been associated with an increased risk of asthma in offspring. This highlights the role of prenatal nutrition and early metabolic programming in determining long-term respiratory outcomes. Even in the absence of obesity, altered fat intake and lipid imbalance can contribute to airway inflammation and bronchial hyperreactivity.

Multiple pathophysiological mechanisms are believed to underlie the association between dyslipidaemia and asthma. In adults, high dietary fat intake has been correlated with increased neutrophilic airway inflammation and diminished responsiveness to bronchodilator therapy, both of which are features commonly

seen in non-eosinophilic, obesity-related asthma phenotypes.

Collectively, these findings suggest that dyslipidaemia is more than just a metabolic comorbidity—it may actively contribute to the development and persistence of asthma through inflammation-driven airway changes. Addressing lipid abnormalities in obese individuals with asthma could represent a valuable therapeutic avenue for improving respiratory health and disease control.

The Association Between Mental Disorders and Asthma

The relationship between asthma and mental health has been acknowledged for centuries, with psychosocial factors recognized as both contributors to asthma onset and modifiers of its clinical course. These influences manifest through both direct physiological pathways, such as modulation of the autonomic nervous system, endocrine function, and inflammatory responses, and indirect mechanisms, including adherence to treatment regimens, perception and misperception of symptoms, and overall health-related behaviours.

A substantial body of evidence indicates a bidirectional association between asthma and psychiatric disorders, particularly anxiety and depressive disorders. Notably, patients with severe or poorly controlled asthma display significantly higher rates of panic disorder,

generalized anxiety disorder (GAD), agoraphobia, and depression than the general population. However, heterogeneity in study design, such as variability in asthma diagnostic criteria and inconsistent use of DSM-based psychiatric assessments, has led to some inconsistency in findings.

Recent epidemiological studies demonstrate that individuals with depression are at increased risk of developing asthma, and conversely, asthma patients are more likely to experience depressive symptoms. Among individuals with asthma, factors associated with anxiety include older age, the presence of comorbidities, and frequent general practitioner (GP) visits. For depression, predictors include female sex, older age, poor self-rated health, multiple comorbidities, non-drinking status, and recent emergency department visits.

Severity of asthma appears to correlate with the extent of psychiatric comorbidity. Patients with **lifetime severe asthma** show a significantly elevated risk for several anxiety disorders (including panic disorder, social phobia, and GAD), bipolar disorder, and other severe mental health conditions. Even **non-severe asthma** is associated with increased rates of anxiety and somatoform disorders. These patterns are not confined to adults; children and adolescents with asthma also show elevated risks for anxiety and depression.

An additional dimension of this association is

the link between asthma, personality disorders, and chronic noninflammatory pain conditions such as fibromyalgia and persistent musculoskeletal pain. These individuals often demonstrate high primary care utilization and frequently use non-prescribed analgesics, suggesting a potentially under-recognized comorbidity cluster.

The impact of asthma on quality of life is profound and multifactorial, contributing to sleep disturbances, fatigue, reduced physical activity, academic and occupational impairment, and emotional distress. These outcomes, in turn, may increase susceptibility to suicidal ideation and behaviours, an emerging area of concern in asthma management.

Behavioural pathways, such as smoking, may mediate the relationship between mood or anxiety disorders and poor asthma control. Recent research supports the independent associations of current smoking, mood disorders, and anxiety disorders with suboptimal asthma outcomes. Additionally, depressive symptoms have been proposed as potential mediators of the relationship between elevated BMI and asthma control, though this hypothesis requires further validation.

CONCLUSION

Obesity is a significant and independent risk factor for the development and progression of

asthma across both paediatric and adult populations. Although commonalities exist in clinical presentation across age groups, distinct pathophysiological and phenotypic differences also emerge. The underlying mechanisms linking obesity and asthma are multifactorial, involving shared genetic predispositions, dietary patterns, nutritional deficiencies, gut microbiome alterations, systemic low-grade inflammation, metabolic dysregulation, and structural changes in lung function.

Mounting evidence supports the effectiveness of weight loss interventions, both lifestyle-based and surgical, in improving asthma control and reducing disease burden. However, there is a critical need to move beyond the traditional reliance on body mass index (BMI) as the sole metric of obesity. Future research should incorporate diverse anthropometric indices (e.g., waist-to-hip ratio, fat distribution) and metabolic biomarkers to better characterize obesity phenotypes relevant to asthma pathogenesis and treatment.

Obesity is inherently a multifaceted disorder characterized by maladaptive exposures and behaviours, including poor diet quality, sedentary lifestyle, and disrupted energy homeostasis. Excess adiposity contributes to a state of immunometabolism imbalance, increased oxidative stress, and impaired nitric oxide bioavailability, all of which may exacerbate airway inflammation and reduce

responsiveness to conventional asthma therapies originally developed for lean individuals.

This evolving epidemic of obesity-associated airway disease underscores the urgency of understanding the intricate interactions between metabolic dysfunction, systemic inflammation, and respiratory physiology. Advancing our knowledge in this domain will not only clarify the bidirectional relationship between metabolism and lung function but will also pave the way for more targeted, phenotype-specific interventions to improve outcomes in patients living with both obesity and asthma.

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