AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

# OBESITY IN SEVERE ASTHMA: UNVEILING CHALLENGES AND EXPLORING NEW THERAPEUTIC OPTIONS

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**Abstract:**

**Background.** Obesity has emerged as one of the most prevalent comorbidities in severe asthma, affecting up to half of patients in some severe asthma cohorts and profoundly modifying disease expression, treatment response and prognosis.

**Objective.** This narrative review summarizes current evidence on the epidemiology and pathobiology of obesity-associated severe asthma, highlights diagnostic and therapeutic challenges, and discusses emerging pharmacologic and non-pharmacologic strategies with a focus on weight-targeted interventions.

**Methods.** A non-systematic literature search of PubMed, Scopus and Web of Science was performed for English-language publications from 2010 to November 2025 using terms including severe asthma, obesity, obese asthma, GLP-1 receptor agonists and bariatric surgery. Key guidelines, large observational cohorts, randomized controlled trials, meta-analyses and high-impact narrative reviews were prioritized.

**Results.** Obesity increases the risk of developing asthma and is over-represented in severe asthma phenotypes. Obese individuals with severe asthma exhibit distinct clinical and inflammatory features, including poorer symptom control, more frequent exacerbations, reduced quality of life, altered lung mechanics and a greater burden of comorbidities. Systemic low-grade inflammation, adipokine imbalance, mechanical constraints, metabolic dysregulation and microbiome alterations contribute to a complex “obese asthma” endotype that is often T2-low and relatively corticosteroid-resistant. Established interventions—structured lifestyle modification and bariatric surgery—can substantially improve asthma control, lung function and quality of life in selected patients. Emerging data suggest that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and other anti-obesity pharmacotherapies may confer additional benefits beyond weight loss, potentially reducing exacerbations and improving asthma control in obese individuals.

**Conclusion.** Obesity in severe asthma represents a distinct, heterogeneous and therapeutically challenging endotype. Optimal management requires a treatable-traits framework that integrates aggressive weight management, optimization of inhaled and biologic therapy, and targeted use of novel anti-obesity agents. High-quality phenotype-driven trials are needed to define which patients derive the greatest benefit from specific weight-centred interventions.

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**Keywords:** severe asthma; obesity; obese asthma phenotype; treatable traits; GLP-1 receptor agonists; bariatric surgery; systemic inflammation.

## 1. Introduction

Asthma and obesity are two converging global epidemics. Obesity not only increases the risk of incident asthma but is also disproportionately prevalent among patients with severe, difficult-to-treat disease. In severe asthma cohorts, obesity frequently exceeds 40–50 %, and in some registries nearly half of patients with severe or uncontrolled asthma are obese.

The coexistence of obesity and severe asthma is associated with increased healthcare utilization, more frequent exacerbations, impaired health-related quality of life and higher mortality. Yet, clinical guidelines have only recently begun to address obesity as a modifiable “treatable trait”. This review aims to synthesize emerging evidence on obesity-associated severe asthma, focusing on epidemiology, mechanisms, diagnostic challenges and both current and future therapeutic strategies.

## 2. Epidemiology and clinical burden

### 2.1 Prevalence of obesity in severe asthma

Epidemiologic studies consistently demonstrate a strong association between increased body mass index (BMI) and asthma prevalence, particularly among women and individuals with late-onset disease. Severe asthma registries report obesity in approximately 40–60 % of participants, with higher BMI correlating with worse symptom scores and more frequent exacerbations.

### 2.2 Impact on clinical outcomes

Obese individuals with severe asthma experience:

- **More symptoms and poorer control** (higher ACQ/ACT scores, more nocturnal symptoms).
- **Increased exacerbation rates** and hospitalizations.
- **Reduced quality of life**, including physical and emotional domains. **Higher healthcare costs and polypharmacy** driven by multimorbidity (sleep apnoea, GERD, depression, osteoarthritis).

These observations underscore the need to regard obesity not merely as a coincidental comorbidity but as a key modifier of the severe asthma phenotype.

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## 3. Pathobiological mechanisms

Obesity-associated severe asthma is mechanistically heterogeneous. Multiple overlapping mechanisms link excess adiposity to asthma onset and severity.

### 3.1 Systemic low-grade inflammation and adipokines

Adipose tissue in obesity is metabolically active and secretes pro-inflammatory cytokines (IL-6, TNF-α, IL-1β) and chemokines (e.g. CCL2), together with adipokines such as leptin, while anti-inflammatory mediators such as adiponectin are down-regulated. This chronic systemic inflammation can amplify airway inflammation, promote steroid resistance and contribute to airway remodeling.

Leptin may enhance Th2 and ILC2 responses and promote eosinophilic and neutrophilic inflammation, whereas low adiponectin has been associated with worse airflow obstruction in obese asthma.

### 3.2 Altered inflammatory endotypes

Obesity-associated asthma often displays a T2-low or mixed inflammatory pattern, with reduced eosinophilia and elevated neutrophils, in contrast to classic early-onset atopic asthma. This may partially explain the attenuated response to inhaled corticosteroids and some biologics targeting T2 pathways in obese patients.

### 3.3 Mechanical and functional changes

Excess adiposity around the chest wall and abdomen reduces functional residual capacity and expiratory reserve volume, increasing airway closure and ventilation heterogeneity. These mechanical constraints can produce dyspnoea, wheezing and reduced exercise tolerance independent of bronchial inflammation, complicating symptom interpretation in obese individuals.

### 3.4 Metabolic and endocrine dysregulation

Insulin resistance, dyslipidaemia and alterations in glucocorticoid metabolism are increasingly recognized in obese asthma. Hyperinsulinaemia and altered glucocorticoid receptor function may contribute to steroid resistance and persistent airway hyperresponsiveness. Additionally, obesity-related comorbidities such as obstructive sleep apnoea, non-alcoholic fatty liver disease and polycystic ovary syndrome may further aggravate airway inflammation and symptom perception.

### 3.5 Microbiome, genetics and epigenetics

Emerging data implicate gut and airway microbiome dysbiosis in obesity-associated asthma, with diet-induced changes in microbial composition modifying systemic and airway immune responses. Epigenetic mechanisms, including DNA methylation changes in obesity and asthma-

AMERICAN ACADEMIC PUBLISHER
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related genes, may help explain the persistence of the obese asthma phenotype despite weight loss in some patients, though this area remains under-explored.

## 4. Obesity-associated severe asthma phenotype

### 4.1 Clinical features

Obesity-associated severe asthma is frequently **adult-onset**, often non-atopic, with:

- Predominance in women;
- Lower $FEV_1$/FVC ratios but relatively preserved DLCO;
- Prominent dyspnoea and exercise limitation;
- High symptom burden despite maximal inhaled therapy.

Fixed airflow obstruction and small airway dysfunction are more common in obese severe asthma, and lung function may improve substantially after weight loss, highlighting a strong mechanical component.

### 4.2 Inflammatory and molecular signature

Compared with lean counterparts, obese severe asthmatics show higher systemic inflammatory markers, but often lower airway eosinophilia and fractional exhaled nitric oxide (FeNO). Transcriptomic and proteomic studies suggest distinct pathways involving innate immunity, metabolism and oxidative stress, supporting the concept of a specific **"obese asthma syndrome"** or endotype.

### 4.3 Pediatric considerations

In children, obesity increases asthma risk and may promote a similar high-symptom, low-eosinophil phenotype, but growth, pubertal changes and developmental lung trajectories add complexity. Interventions must therefore be tailored to developmental stage and family environment.

## 5. Diagnostic and management challenges

### 5.1 Distinguishing asthma from obesity-related dyspnoea

Dyspnoea, chest tightness and reduced exercise tolerance in obesity are not specific to asthma and can be driven by deconditioning, restrictive mechanics or comorbidities such as heart failure or sleep apnoea. Objective confirmation of variable airflow limitation (spirometry with bronchodilator testing, peak-flow variability, bronchial provocation) is essential to avoid over-diagnosis.

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### 5.2 Lung function interpretation

Reduced FVC and ERV may mimic a restrictive pattern, and airway hyperresponsiveness may be influenced by mechanical rather than inflammatory factors. Clinicians must interpret spirometry and plethysmography in the context of BMI and body composition, and incorporate impulse oscillometry or nitrogen washout where available to assess small airway involvement.

### 5.3 Therapeutic resistance

Obesity is associated with attenuated response to inhaled corticosteroids and possibly to some biologics, although results are inconsistent. Pharmacokinetics, altered distribution volumes, systemic inflammation and co-existent T2-low disease may all contribute.

### 5.4 Multimorbidity and polypharmacy

Patients with obesity-associated severe asthma have a high burden of comorbidities—obstructive sleep apnoea, GERD, depression, osteoarthritis, type 2 diabetes—which require careful assessment and integrated management. These conditions can both mimic and exacerbate asthma symptoms, and their treatment may interact with asthma pharmacotherapy.

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## 6. Established therapeutic options

### 6.1 Lifestyle interventions and structured weight loss

Lifestyle interventions combining calorie restriction, improved diet quality and increased physical activity can result in 5–10 % weight loss, which is often sufficient to improve asthma control, lung function and quality of life. Even modest weight loss has been associated with reductions in exacerbations and use of rescue medication in obese asthmatics.

For severe asthma, weight-management programmes should be embedded within multidisciplinary severe asthma clinics, involving dietitians, physiotherapists, psychologists and sleep specialists.

### 6.2 Bariatric surgery

Bariatric surgery offers substantial and often sustained weight reduction for individuals with morbid obesity and can profoundly impact asthma outcomes:

- Improvements in asthma control scores and symptom burden;
- Increases in $FEV_1$, FVC and ERV;
- Reductions in systemic inflammatory markers and airway mast cells in some cohorts.

AMERICAN ACADEMIC PUBLISHER
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However, not all patients benefit equally; improvements may attenuate after the first postoperative year, and those without metabolic syndrome may experience more durable gains in asthma control. Careful selection and long-term follow-up are essential.

### 6.3 Optimization of standard asthma therapy

Obesity-associated severe asthma still requires adherence to guideline-directed pharmacotherapy: high-dose inhaled corticosteroids with long-acting bronchodilators, with add-on long-acting muscarinic antagonists and biologics as indicated.

Given the higher prevalence of non-T2 inflammation, biomarkers (blood eosinophils, FeNO, IgE) and sputum phenotyping, where available, are particularly important in selecting biologics. Early identification and aggressive management of comorbidities such as sleep apnoea and GERD may enhance treatment response.

## 7. Emerging therapeutic options

### 7.1 GLP-1 receptor agonists and other anti-obesity agents

GLP-1 receptor agonists (GLP-1 RAs) and dual agonists (e.g. GLP-1/GIP) have transformed obesity management and are under active investigation in respiratory disease. Observational studies and real-world analyses suggest that, in individuals with obesity and asthma, GLP-1 RAs may:

- Improve asthma control scores;
- Reduce exacerbation frequency;
- Offer benefits beyond weight loss, possibly via anti-inflammatory and immunomodulatory mechanisms.

Mechanistically, GLP-1 RAs may modulate systemic inflammation, oxidative stress and autonomic tone, though the exact pathways in asthma remain to be clarified.

Other anti-obesity pharmacotherapies (e.g. combination agents targeting appetite and energy expenditure) are likely to be evaluated in obese asthma, but robust asthma-specific outcomes are currently lacking.

### 7.2 Biologics and targeted therapies in obese severe asthma

Data on the impact of obesity on response to asthma biologics (anti-IgE, anti-IL-5/5R, anti-IL-4Rα, anti-TSLP) are mixed. Some cohorts suggest attenuated improvements in lung function or exacerbation reduction among obese patients, while others show comparable efficacy when selected according to T2 biomarkers.

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Future research should clarify whether specific biologics perform better in obese phenotypes, whether dose adjustments are needed based on body weight, and how to integrate biologics with intensive weight-loss strategies.

### 7.3 Treatable-traits and precision medicine approaches

A "treatable-traits" framework—systematically assessing airway inflammation, lung mechanics, extrapulmonary comorbidities and behavioural factors—provides a rational basis for managing obesity-associated severe asthma. Within this paradigm, obesity is one of several modifiable traits, alongside sleep apnoea, dysfunctional breathing, anxiety/depression and environmental exposures.

Digital tools, remote monitoring and structured rehabilitation programmes may further support sustained weight loss and improve adherence in this complex population.

## 8. Gaps in knowledge and research priorities

Despite rapid advances, key evidence gaps remain:

1. Phenotypic heterogeneity. The obese asthma population includes early- and late-onset, T2-high and T2-low, and child vs adult phenotypes; more granular endotyping is needed.
2. Causality and reversibility. It remains unclear to what extent obesity-induced changes in airway structure and function are reversible with weight loss, and which patients are "weight-sensitive".
3. Mechanistic studies of new anti-obesity agents. High-quality randomized controlled trials with asthma-specific endpoints are required to confirm the benefits and elucidate mechanisms of GLP-1 RAs and related drugs in severe asthma.
4. Biologic therapy in obesity. Data on biologics in obese severe asthma are limited; prospective studies stratified by BMI, inflammatory endotype and body composition are urgently needed.
5. Long-term outcomes. Few studies extend beyond 3–5 years; the durability of benefits from bariatric surgery, pharmacologic weight loss and combined approaches remains uncertain.

### Author's Clinical Perspective

In my clinical practice, which includes adult patients aged 18–60 years with obesity-associated severe asthma, several consistent patterns have emerged. A major challenge is the low response rate to biologic therapy, which reaches only about 10% in this patient population, markedly lower than expected based on clinical trial data. Similarly, the overall response to standard ICS/LABA or ICS/LABA plus biologic therapy remains modest, with only 40–45% of patients demonstrating clinically meaningful improvement in symptom control or lung function.

AMERICAN ACADEMIC PUBLISHER
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Weight reduction, however, has shown the most reliable and clinically significant benefit. Patients achieving intentional weight loss—typically ≥7–10% of baseline body weight—frequently experienced improvements in asthma control, exertional tolerance and reduction in exacerbations. In many cases these improvements exceeded those observed with pharmacological intensification alone, supporting the growing recognition of obesity as a central modifiable trait in severe asthma.

Diagnostic evaluation in this cohort is often complicated by obesity-related physiologic factors. Reduced functional capacity and mechanical restriction may mimic asthma worsening, making the assessment of weight-related symptoms a critical component of diagnostic accuracy. Moreover, the high prevalence of comorbidities, including obstructive sleep apnea, gastroesophageal reflux disease, metabolic syndrome and psychological factors, adds additional layers of clinical complexity and frequently contributes to both symptom perception and poor therapeutic response.

Overall, these real-world observations underscore the need for a comprehensive, weight-centered management strategy and support the integration of obesity-targeted interventions within severe asthma treatment pathways.

## 9. Conclusion

Obesity in severe asthma constitutes a distinct and increasingly prevalent endotype characterized by high symptom burden, multimorbidity, altered inflammatory pathways and frequent therapeutic resistance. Recognition of obesity as a central treatable trait has profound implications for assessment and management, mandating systematic evaluation of body composition, metabolic health and comorbid conditions in all patients with severe asthma.

Lifestyle-based weight management and bariatric surgery can markedly improve asthma outcomes in selected individuals, while emerging anti-obesity pharmacotherapies—particularly GLP-1 RAs—represent promising additions to the therapeutic armamentarium. Integration of these weight-targeted strategies with optimized inhaled therapy, judicious use of biologics and multidisciplinary care offers the best prospect for improving prognosis in this challenging population.

Future research should prioritise phenotype-driven, long-term trials to identify which patients with obesity-associated severe asthma derive the greatest benefit from specific interventions, moving the field closer to true precision medicine.

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