





## Small airway dysfunction and obesity in asthmatic patients: a dangerous liaison?

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### Abstract

Asthma is a chronic condition characterized by inflammation throughout the entire bronchial airways. Recent findings suggest that ventilation inhomogeneity and small airway dysfunction (SAD) play a particularly significant role in asthma development and clinical manifestations. Obesity is a considerable risk factor for asthma development and morbidity in children and adults. A growing body of evidence suggests that SAD is linked to more severe asthma and poor asthma control in obese patients. However, the knowledge about the relationship between peripheral airway compromise and obesity in asthma is limited, mainly because of the historical lack of access to non-invasive assessment methods for studying SAD. Conventional lung function measurements, like spirometry, cannot accurately assess small airway function. However, in recent years, new specialized tests available in outpatient settings have been found to distinguish SAD from large airway obstruction more accurately compared to spirometry. Therefore, understanding the degree of peripheral airway implication in the underlying pathology is critical for effective asthma control and therapeutic decisions. This review highlights recent findings on the impact of SAD on asthma patients who are obese. Additionally, it explores how new diagnostic methods, such as impulse oscillometry (IOS), may be used in outpatient settings to detect small airway impairment in obese asthma at an early stage, potentially leading to improved asthma treatment.

### Keywords

Asthma, obesity, impulse oscillometry, multiple breath washout, small airway dysfunction, small airways

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## Introduction

Asthma is a common chronic condition that affects people of all ages [1, 2].

As is the case with numerous other chronic illnesses, obesity has an adverse impact on patients with asthma. Over the past few decades, there has been a notable rise in both obesity and asthma rates, and evidence indicates a bi-directional relationship between these two chronic conditions [3, 4].

A meta-analysis comprising seven longitudinal cohort studies that involved a sample size of over 300,000 adults demonstrated a dose-response correlation between the odds ratio (OR) of developing asthma and an increase in body mass index (BMI) [5].

However, these results relied on self-reported asthma data, with the risk of overdiagnosis. In studies in which the diagnosis of asthma is supported by a positive reversibility test or bronchial hyperreactivity, the relationship between obesity and asthma becomes less conclusive [5, 6].

Furthermore, obesity can lead to symptoms such as dyspnoea and exercise intolerance that overlap with asthma symptoms, making it difficult to distinguish between them [5].

Obesity has a notable impact on the development and progression of asthma, acting as a significant disease modifier for the condition. Individuals with obesity often experience worse control of their asthma and more severe symptoms compared to lean individuals with asthma [6–9]; this is especially true in females [7, 10].

Recent studies have suggested that chronic inflammation and small airway dysfunction (SAD) contribute to persistent, severe asthma and poor control in obese adults and children [11–13].

While asthma affects the entire bronchial tree, the peripheral airways are recognized as the primary location of airflow obstruction in obstructive lung diseases [14, 15].

Conventional lung function tests, such as spirometry, are ineffective at evaluating SAD and often only detect abnormalities when the disease is already advanced [16, 17].

More specific tests have been developed in recent years that allow for a more accurate diagnosis of SAD [18].

In this review, the latest evidence supporting SAD's impacts on asthma in obese individuals are described and how new diagnostic techniques commonly available in outpatient settings, such as impulse oscillometry (IOS), may guide asthma treatment for obese patients, is explored.

## SAD in asthma

The small airways, defined as those less than 2 mm in diameter, were historically considered the “quiet or silent zone” of the lungs because their normal function did not significantly contribute to total airway resistance [19, 20]. Furthermore, significant small airway disease may exist with minimal abnormality in conventional pulmonary function tests, which are generally insufficient in detecting small airway function [16, 17].

The role of the small airways is crucial in the development and persistence of asthma due to the significant impact of chronic inflammation and obstruction on the distal airways. Anatomopathological studies have shown abnormalities in the small airways of asthma patients, regardless of the level of severity ranging from mild to very severe [21]. In cases of fatal asthma, the outer region of the small airways undergoes extensive remodelling of the extracellular matrix (ECM), which could potentially contribute to the functional alterations and disruption of the interconnection between the airways and lung tissue observed in patients with severe and fatal asthma [21].

Furthermore, subjects with fatal asthma display narrower and more inflamed airways, as well as an increased presence of eosinophils [22].

In lungs specimens obtained by surgical resection from both asthmatic and non-asthmatic individuals, it was found that the expression of interleukin 5 (IL-5) messenger RNA (mRNA) was higher in the small airways compared to the larger airways [23].

Utilizing transbronchial biopsies, it has been demonstrated that inflammation and remodelling of the distal lung can occur even in individuals with mild asthma who exhibit normal or unimpaired lung function [24].

The small airways play a role in producing various T-helper 2 (Th2) cytokines and chemokines that contribute to the initiation and continuation of the inflammatory process. Notably, inflammation in these distal airways has been reported to be more severe compared to inflammation in the larger airways, and there is emerging evidence of remodelling in the peripheral regions of the lungs. Indeed, in asthmatic patients, remodelling of the bronchial airways mainly affects the small rather than the large airways across severities, particularly in severe asthma [25–27].

Mucus plugs are considered a plausible mechanism for chronic airflow obstruction in severe asthma [28].

Dunican et al. [29] discovered that the occurrence of mucus plugging in the small airways was remarkably common among individuals with severe asthma. Those with high mucus scores exhibited air trapping, as indicated by low forced vital capacity (FVC) and high residual volume (RV). Computed tomography (CT) lung imaging techniques, CT & computational fluid dynamics, and magnetic resonance imaging (MRI) can provide information about the location and role of SAD in pathogenesis of asthma, especially in severe asthma [30–33].

However, recent research has shed light on the high incidence and significance of SAD in asthma. For example, research indicates that SAD affects roughly 50–60% of individuals with asthma [34].

In the Assessment of Small Airways Involvement in Asthma (ATLANTIS) study, SAD was strongly evident throughout all levels of Global Initiative for Asthma (GINA) severity. Even if the prevalence varied significantly based on the physiological indicator used to evaluate SAD, it was generally higher in more severe asthma [35].

Several additional cohort studies have reported a high incidence of SAD, diagnosed by IOS, among individuals with asthma [11, 36, 37].

Furthermore, SAD is associated with heightened bronchial hyperresponsiveness, inadequate control of asthma symptoms, and recurrent exacerbations in both adults and children [13, 35, 36, 38–41].

**Table 1.** Available techniques for the assessment of bronchial airways by size (small vs. large airways)

Method	Small airway function	Large airway function
1. Spirometry	FEF25–75%, FVC, FVC/SVC	FEV1, FEV1/FVC
2. IOS	R5–R20, X5, AX, Fres Δ X5 in-esp	R20
3. Single or multiple breath nitrogen washout (SBNW/MBNW) test	Slope phase III, CV, CC, Sacin, Sccond	
4. Body plethysmography	RV, RV/TLC	
5. High resolution CT (HRCT)	Air trapping, airway wall thickness	Airway wall thickness
6. Nuclear medicine (scintigraphy, SPECT, PET)	Regional ventilation defects	
7. 3He-MRI	Non-ventilated lung volume	
8. Bronchoscopy	Transbronchial biopsy, BAL	Endobronchial biopsy
9. Sputum induction	Late phase sputum	Early phase sputum
10. Exhaled nitric oxide (eNO)	Alveolar eNO	
11. CT and computational fluid dynamics	Changes in airway volume and resistance	

AX: reactance area; Fres: resonant frequency; FEV1: forced expiratory volume in 1 s; R5: resistance at 5 Hz; Sacin and Sccond: acinar and conductive airways ventilation heterogeneity; TLC: total lung capacity; FEF25–75%: forced mid-expiratory flow; SVC: slow vital capacity; X5: reactance at 5 Hz; esp: expiratory; CV: closing capacity; CC: closing volume; SPECT: single-photon emission CT; PET: positron emission tomography; BAL: broncho-alveolar lavage

*Note.* Adapted from “Small airway dysfunction and poor asthma control: a dangerous liaison,” by Cottini M, Licini A, Lombardi C, Bagnasco D, Comberiati P, Berti A. Clin Mol Allergy. 2021;19:7 (<https://clinicalmolecularallergy.biomedcentral.com/articles/10.1186/s12948-021-00147-8>), CC-BY.

Despite its clinical significance, SAD has only recently gained recognition in the medical field; this is likely due to the difficulty in evaluating it through the commonly used conventional lung function measures such as spirometry. This is changing in recent years with the increased availability of new specialized tests able to distinguish SAD from large airway obstruction in outpatient clinics (see [Table 1](#) for a summary of available techniques for assessment of small airway function). This is achieved mainly with IOS, which measures pulmonary function during quiet breathing using the well-established, effort-independent, forced oscillation technique [42–45].

Several obstacles have hindered the widespread adoption of IOS in clinical settings. However, with the advancement of modern computing technology and the availability of pressure transducers capable of accurately monitoring high-frequency pressure changes, commercial systems for IOS have been successfully developed [45].

## Obesity and asthma

When the body accumulates flesh (*polisarkos*), “The person cannot walk without sweating...neither breathe easily... I have made any sufficiently stout patient moderately thin in a short time by compelling him to do rapid running...” [46].

Obesity is a pressing public health problem on a global scale, with a particular impact on developed countries. The detrimental effects on respiratory health should be mentioned among the associated complications [47]. Obesity has a considerable effect on lung function, including spirometric measurements and lung volumes [48].

An increase in BMI is indeed associated with a more rapid decline in FEV1 and FVC in overweight and obese asthmatic adults than in their normal-weight counterparts [49]. More than 60 percent of adults with severe asthma also have obesity [7, 50], leading to a significant increase in medication use and hospital admissions [51, 52].

Obese individuals with asthma exhibit distinctive phenotypic traits [53]. Presently, obesity-related asthma is categorized into two distinct forms, both of which are associated with more severe asthma symptoms. The first form is characterized by a late-onset non-type 2 phenotype, which encompasses adults and older children. The second form is an early-onset type 2 phenotype, which may involve pre-existing asthma that is further complicated by obesity [54].

Both phenotypes exhibit airway hyperresponsiveness (AHR) to methacholine challenge [55], while obese non-asthmatic individuals are not hyperresponsive [56]. In both phenotypes, obesity leads to a worsening of disease severity and control. However, especially in patients with late-onset non-allergic (LONA), becoming obese is a “causal” factor for the onset of asthma.

Indeed, it appears that LONA is a direct result of obesity. Individuals with asthma who are obese experience minimal inflammation in their airways. One of the reasons behind this type of asthma seems relatively straightforward: Obese patients with asthma breathe with reduced lung capacity due to the added weight on their chest wall, which leads to increased AHR. Furthermore, obese individuals with LONA asthma have more flexible and easily collapsible peripheral airways compared to obese individuals without asthma [6, 57]. This increased collapsibility may be a result of decreased stiffness in the distal airway walls [8].

Certainly, there exists a subgroup of individuals with both asthma and obesity who demonstrate, with IOS, a high reactance. This subgroup experiences considerable dysfunction in their peripheral airways even under normal conditions, and this dysfunction further deteriorates when exposed to methacholine. Notably, this particular subgroup mainly consists of women and exhibits a higher prevalence of gastroesophageal reflux disease. Additionally, these individuals tend to experience more severe asthma symptoms compared to other groups. Interestingly, when comparing lung function parameters between the low and high reactance subgroups identified by the IOS system, the differences observed were in terms of absolute values rather than percentage values, indicating that these distinctions already existed at the baseline level (see also in the “[SAD in asthmatic patients with obesity](#)” section below).

A very recent study showed that obesity is associated with worse peripheral airways dysfunction in moderate-to-severe asthma, including a patient cluster who were older, obese and female with more frequent exacerbations [58].

Another factor is the abnormal function of surfactant, a substance that helps maintain stability in the alveoli. In individuals with obesity, surfactant dysfunction can lead to increased alveolar instability and collapse. Lastly, adipose tissue in the body can produce mediators that have direct or indirect effects on the airways, potentially contributing to the development of asthma symptoms.

There are several potential mechanisms that explain how obesity may contribute to the development of asthma. These mechanisms include a shared genetic component, dietary and nutritional factors, changes in the gut microbiome, systemic inflammation, metabolic abnormalities, and alterations in lung anatomy and function. These factors probably play a collective role in the association between obesity and asthma [54].

### **Mechanical effects**

Obesity has a profound impact on normal lung physiology. One notable effect is that obese individuals tend to breathe at lower lung volumes. This is primarily due to the excessive accumulation of fat in the thoracic and abdominal cavities, which compresses the lungs and reduces their overall volume. Two significant changes associated with obesity include a decrease in functional residual capacity (FRC) and expiratory reserve volume (ERV). Furthermore, obesity increases the susceptibility of the peripheral airways and lung tissue to collapse, particularly in individuals with late-onset asthma [7].

The risk for AHR increases with BMI, and weight gain is a risk factor for developing AHR [59].

The increased AHR observed in obesity is likely attributed to a decrease in the tethering forces exerted by the lung tissue on the connected airways. As a result, the airways become narrower and experience early closure in the peripheral regions. This narrowing of the airways leads to elevated airway resistance, which causes limitations in expiratory flow, especially when an individual is in a sitting position. Furthermore, these limitations in expiratory flow become even more pronounced when the individual is lying down in a supine position [60].

### **Inflammatory changes**

Obese individuals with asthma exhibit a distinct pattern of inflammation compared to non-obese individuals with asthma. Obesity is a multifaceted condition characterized by a chronic low-grade inflammatory state, accompanied by an elevation in various inflammatory markers. Adipocytes in obese individuals release proinflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), IL-1 $\beta$ , and IL-6, while the production of anti-inflammatory mediators like adiponectin is reduced. These alterations in inflammatory mediators likely contribute to heightened airway reactivity and inflammation observed in individuals with obesity-related asthma [61].

In obese patients with early-onset asthma, the disease is characterized as a Th2-high condition, exhibiting elevated levels of serum immunoglobulin E (IgE), eosinophils in both peripheral blood and tissues, and increased production of pro-inflammatory cytokines such as IL-4, IL-13, and IL-5. However, the pro-inflammatory Th2 state observed in early-onset asthma among obese individuals is counteracted by immune suppression seen in these patients [62].

A recent systematic review and meta-analysis examined 40 studies to investigate the impact of obesity on airway and systemic inflammation in adults with asthma; the findings revealed that obese individuals with asthma exhibit a distinct pattern of inflammation compared to non-obese individuals with asthma [63]. Specifically, sputum neutrophil levels were found to be 5% higher in obese asthmatics compared to non-obese asthmatics. Additionally, obese individuals showed elevated blood neutrophil counts along with higher levels of C-reactive protein, IL-6, and leptin. Conversely, fractional eNO (FeNO) levels were found to be 4.5 parts per billion (ppb) lower in obese individuals [63].



## Role of macrophages

Adipose tissue macrophages have a significant role in promoting the inflammatory state associated with obesity. In obesity, there is an increase in the number of adipose tissue macrophages, and there is also a shift from M2 macrophages (with anti-inflammatory properties) to M1 macrophages (with pro-inflammatory properties). As a result of this shift, pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 are produced, further contributing to the inflammatory environment in obesity. The presence of M1 macrophages and the release of these pro-inflammatory cytokines play a crucial role in the perpetuation of inflammation in adipose tissue [52, 62].

## Oxidative stress and nitric oxide metabolism

Increased oxidative stress and altered nitric oxide (NO) metabolism are also among the factors contributing to altered airway structure and function observed in obese individuals with asthma. In obese patients with asthma, there is evidence of increased airway oxidative stress, which can be measured by elevated levels of 8-isoprostanes in exhaled breath condensate. This oxidative stress is associated with decreased levels of airway NO, especially in individuals with later-onset asthma [64].

Mitochondrial dysfunction contributes to the elevation of specific metabolites like homocysteine and asymmetric dimethyl arginine (ADMA). These metabolites, in turn, reduce the availability of arginine, which interferes with NO synthesis. This disruption in NO synthesis leads to oxonitrative stress, particularly affecting epithelial and vascular endothelial cells. The impaired mitochondrial function and resulting alterations in metabolite levels play a role in the development of oxonitrative stress and contribute to the pathophysiology of airway and vascular dysfunction observed in conditions such as obesity-associated asthma [62].

## Metabolic dysregulation

Metabolic dysregulation, beyond obesity alone, can independently contribute to the development of asthma. Factors such as hyperinsulinemia, dyslipidemia, and hypertension have been identified as potential links to asthma and should be considered even in non-obese individuals. These metabolic abnormalities can have a significant impact on asthma pathogenesis and should be taken into account when evaluating and managing patients with asthma, regardless of their weight status [54].

## Microbiome

Obese individuals tend to have a less diverse gut microbiome compared to lean individuals. This is detrimental to these patients as a greater diversity of the microbiome is associated with a stronger mucosal immune defense [62].

The reduced diversity of the gut microbiome in obese individuals, along with increased intestinal permeability, can lead to the activation of inflammatory pathways, such as nuclear factor kappa B (NF- $\kappa$ B). This activation results in increased expression of pro-inflammatory cytokines like IL-6 and TNF- $\alpha$  [65].

There is evidence suggesting a reciprocal relationship between childhood obesity and asthma. Childhood obesity is associated with a higher likelihood of developing asthma, while childhood asthma can increase the risk of obesity in children and adolescents. In fact, asthma in children increases the relative risk of obesity by 1.5–1.7 times [4, 66, 67].

A recent study demonstrated that adults with asthma are at a greater risk of developing obesity compared to those without asthma, particularly among non-atopic individuals, those with longer disease duration, or those receiving oral corticosteroid treatment [68]. The link between asthma and obesity is influenced by the use of oral corticosteroids and is more pronounced in individuals taking these medications [68].

The association between asthma and obesity has been extensively researched and widely recognised, with overweight individuals more susceptible to worse asthma control and a more severe form of the disease. In addition, studies have found that in asthmatic patients, obesity is commonly associated with low physical activity [69].

Furthermore, in obese patients, asthma is associated with reduced responsiveness to several of the commonly used therapies, which may have significant implications for clinical management [7].

Investigating the underlying mechanisms of this link between obesity and asthma may have crucial public health implications and can provide insights for the development of future therapies to improve asthma control in obese patients.

## SAD in asthmatic patients with obesity

Obesity significantly affects both distal and central airway function [70–72]. By detecting small airway abnormalities present to a greater extent than in healthy obese individuals, IOS may be an early functional marker of asthma, especially in obese individuals who report symptoms despite having normal airflow [73]. SAD has been previously linked to specific characteristics of asthmatic patients such as smokers, older individuals with long-standing disease and fixed airflow obstruction, those with exercise- and nocturnal-induced symptoms, and those with severe and uncontrolled asthma spirometry [74, 75].

Recent studies, including multivariate analyses and structural equation modeling, have shown that obesity is also a significant independent predictor of SAD in patients with asthma that is managed in the community [11, 36]. A study from Italy showed that overweight was among the strongest predictors of IOS-defined SAD [36]. Specifically, the decision tree analysis showed that overweight asthmatic patients with exercise-induced symptoms have a 94% prevalence of SAD [36]. Recently, Abdo et al. [11] showed a close association of IOS-defined SAD with overweight and obesity. Interestingly, this study also indicates an indirect contribution to SAD through systemic inflammation [11].

Both of these studies showed that overweight and obese asthma patients exhibit more severe SAD and poorer symptom control [11, 36].

Obesity can cause increased airway resistance, particularly in the peripheral airways, leading to difficulty breathing and reduced functional capacity. Despite having normal large airway function determined by spirometry, obesity is often linked to respiratory symptoms. Reduced FRC and reduced ERV indicate peripheral airway dysfunction, and are prevalent among individuals suffering from both obesity and asthma.

LONA asthma in obese patients results from mechanical factors: breathing at low lung volumes, and peripheral airway narrowing. In LONA asthma, an excessive collapse of the central airways is related to obesity [76].

Recently, Dixon et al. [8] demonstrated that airway hyper-reactivity in the peripheral airways, as measured by oscillometry, is prevalent among obese individuals and those with obesity and asthma. There is a subgroup of obese asthma patients who exhibit a disproportionate amount of peripheral airway dysfunction as revealed by oscillometry compared to what is shown by spirometry. This peripheral airway dysfunction indicates a significant respiratory condition that cannot be easily detected through spirometry alone. This study suggests that small airway inflammation and dysfunction, as detected by advanced techniques, increases the risk of persistent asthma, severe asthma, and poor asthma control in obese adults and children [8].

Chronic lung compression characterizes obese subjects, as evidenced by a decrease in plethysmographic FRC. In particular, in obese subjects with LONA asthma, the decrease in FVC signals a greater tendency for small airways closure [61]; these patients therefore tend to present increased air trapping, indicating a dysfunction of the small airways resulting in the collapse of the airways at a higher volume prior to complete expiration. The greater air trapping found in LONA asthma is significantly influenced by age, indicating that this condition is related to both obesity and aging [77].

Dynamic hyperinflation occurs when the expiratory flow has not emptied alveoli to their resting FRC values by the end of exhalation. Persistent small airway inflammation appears to be important in developing dynamic hyperinflation and limitation of daily exercise in some asthmatic patients. Interestingly, dynamic hyperinflation is greater in obese asthmatic patients than non-obese patients, emphasising the importance of considering obesity when assessing dynamic hyperinflation in asthma [78].

Some studies have shown that distal airway function is affected by obesity as measured by IOS, which is not reflected by spirometry [79]. For example, Skloot et al. [79] showed that obesity is characterized by peripheral airway dysfunction with increased small airway resistance and low-frequency AX, which reflects lung stiffness. Moreover, obesity was also marked by increased methacholine responsiveness, especially in small airways.

Many studies show that reductions in FVC following methacholine challenge may indicate peripheral airway closure, with clinically important implications in asthma [80, 81]. These changes in FVC also correlate with measures of SAD assessed by IOS [80]. Airway closure following methacholine challenge is a frequent occurrence among asthmatics, especially among elderly and obese individuals [81].

In conclusion, IOS is considered a reliable method for identifying airway abnormalities in overweight individuals, even in cases where spirometry results and inflammation of the airways as established by FeNO are normal.

Thus, the use of both spirometry and oscillometry may uncover lung mechanical abnormalities that are particularly relevant to individuals with both obesity and asthma.

## **The impact of SAD on asthma management in patients with obesity**

Proper assessment of the clinical phenotypes and inflammatory endotypes involved in asthma appears essential for desirable precision medicine in obese asthmatics.

Inhaled corticosteroids (ICSs) are widely recognized as an effective treatment for asthma [82], and assessing the inflammatory endotype in patients with obesity can help predict their response to ICS therapy.

Indeed, patients with obesity and eosinophilic inflammation are more likely to respond positively to ICS, unlike those with neutrophilic inflammation and reduced FVC, who most likely do not respond to ICS and may even experience worsening of symptoms with increasing ICS therapy [83].

In addition, a lower response to ICSs combined with long-acting beta-agonists (LABAs), both in terms of FEV1 and FEV1/FVC ratio, has been shown in obese asthmatics in some studies, along with a more limited response of FeNO to ICSs [62, 84].

Obese patients are also less likely to achieve asthma control using ICS or ICS plus LABA than non-obese patients, with a 2.7-fold lower probability of achieving control than those with an average BMI [85].

Of the 307 patients analyzed in the Severe Asthma Research Program 3 (SARP-3), 55% ( $n = 170$ ) were classified as obese, while 46% ( $n = 140$ ) had insulin resistance (IR). IR is a frequent issue amongst asthmatic patients and has been linked to reduced lung function, a more rapid functional decline, and insufficient effect of traditional treatments such as bronchodilators and corticosteroids [86].

Determining a specific SAD phenotype may significantly impact therapeutic decisions. In this regard, IOS may be a valuable tool for better characterizing peripheral airway dysfunction as a treatable aspect of pulmonary disease, leading to more personalized treatment plans for asthma patients.

Recent technological advances have paved the way for developing new drug delivery systems and formulations that improve drug deposition and overall efficacy, safety, and effectiveness. Real-world studies have demonstrated that extra-fine formulations of ICS, ICS and LABA, and long-acting muscarinic antagonists (LAMA) have a much better likelihood of resulting in asthma control, even in patients with SAD phenotypes, and including those with obese asthma [87–94]. A study conducted recently reported that individuals with asthma who used ICS had an increased risk of developing higher BMI trajectories over time, and they also required more antidiabetic and cholesterol-lowering medications [95]. The risk of these outcomes increased in a dose-dependent manner with the use of ICS. The findings of this study suggest that long-term use of medium- to high-dose ICS may have systemic effects [95]. It is therefore especially important in obese patients to treat the peripheral airways with extra-fine molecules, as this allows a reduction in the daily dose of ICS compared to large particles [20].



Interestingly, SAD may be impacted by biological drugs, which have demonstrated improvement not only in controlling asthma symptoms, reducing oral corticosteroid usage, and decreasing exacerbation frequency but also in small airway function [96, 97]. Due to the diverse inflammatory endotypes observed in obesity-associated asthma, the effectiveness of biological treatments may vary among patients with both conditions. It is not surprising that biologics may not yield equal efficacy in all individuals with obesity and asthma, considering the heterogeneity within this patient population [62].

The effectiveness of biologics targeting allergic pathways, such as omalizumab, in obese patients with type 2 inflammation of asthma has yielded mixed results according to studies [98–101]. A retrospective review of 340 severe asthma patients treated with omalizumab revealed that obese individuals had poorer outcomes compared to those with normal weight [99]. Specifically, obesity was significantly associated with more exacerbations, reduced asthma control as indicated by the Asthma Control Test (ACT) score and the GINA guidelines, even after considering other factors that could confound the results. Additionally, obese asthmatics taking omalizumab were less likely to experience improved lung function (FEV1) compared to those of normal weight [99].

In contrast, the efficacy of dupilumab in obese individuals with asthma seems to be more promising. A post-hoc analysis of the phase 3 QUEST study, which included 1,584 patients with elevated peripheral eosinophil counts and FeNO, demonstrated a decrease in the annualized rate of asthma exacerbations [102]. This reduction was observed regardless of demographic factors, including BMI. The study also revealed that the greatest treatment effects were observed in subjects with higher levels of eosinophils and FeNO [102].

To a similar extent, mepolizumab shows favourable data for obese asthmatics [102–105]. A post-hoc meta-analysis in 2021 of all phase IIb/III studies of mepolizumab, in which 32% of subjects reported obesity, showed a reduction in the rate of clinically significant exacerbations, health-related quality of life and asthma control independent of comorbidities [104].

For obese patients with non-type-2 inflammation (neutrophilic asthma or altered IL-17, IL-22, or IL-6 pathways), existing biologics are not applicable. Emerging biologics, such as the recently approved tezepelumab, which targets the upstream thymic stromal lymphopoietin (TSLP) pathway, may have a role for obese asthmatics with non-type 2 inflammation. Indeed, tezepelumab improves the rate of exacerbations regardless of eosinophil count, which may suggest that it could be a promising tool in the treatment of obese asthmatics with non-eosinophilic asthma [106].

## Weight loss approaches

Since obesity has such a significant impact on asthma, weight loss may play an important role in improving asthma management. Research has shown that adequate weight loss can lead to significant improvements in asthma control and lung function [7]. Weight loss can be achieved through non-surgical or surgical means, with bariatric surgery being particularly effective in reversing peripheral abnormalities associated with obesity and asthma [57, 107]. Studies have shown that bariatric surgery can alleviate lung compression in both control subjects, obese individuals without asthma, and obese individuals with asthma [57]. Notably, weight loss through bariatric surgery had a greater impact on lung elastance in asthmatic patients, which implies that the distal lung is more prone to collapse in individuals with asthma [57].

## Conclusions

Despite the availability of effective therapies, many obese asthma patients still experience poor control in real-life. Obesity is a strong independent factor predicting SAD in community-managed asthma patients, particularly those with LONA asthma. Given SAD's significant impact on asthma control, it is essential to actively search for it as part of the management of obese asthma patients. As a result, we believe incorporating IOS into the routine diagnostic process for obese asthma patients in a clinical setting would be beneficial. Identifying SAD through IOS can help healthcare providers determine the likelihood of an

asthma exacerbation and make informed treatment decisions, resulting in more personalized and specifically tailored asthma management. By better characterizing SAD as a “pulmonary treatable trait” in obese asthmatics, IOS can significantly improve the quality of care for these patients.

## Abbreviations

AHR: airway hyperresponsiveness

BMI: body mass index

CT: computed tomography

eNO: exhaled nitric oxide

FeNO: fractional exhaled nitric oxide

FEV1: forced expiratory volume in 1 s

FRC: functional residual capacity

FVC: forced vital capacity

ICSs: inhaled corticosteroids

IL-5: interleukin 5

IOS: impulse oscillometry

LABAs: long-acting beta-agonists

LONA: late-onset non-allergic

NO: nitric oxide

RV: residual volume

SAD: small airway dysfunction

Th2: T-helper 2

TNF- $\alpha$ : tumor necrosis factor  $\alpha$

## Declarations

### Author contributions

JP: Conceptualization, Writing—original draft, Writing—review & editing. CL, PC, ML, AB, EH, and GP: Writing—original draft, Writing—review & editing. MC: Conceptualization, Writing—original draft, Writing—review & editing, Supervision.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

### Ethical approval

Not applicable.

### Consent to participate

Not applicable.

### Consent to publication

Not applicable.

### Availability of data and materials

Not applicable.

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