Obesity Surgery (2021) 31:1810–1832
https://doi.org/10.1007/s11695-021-05255-7

REVIEW

Is Bariatric Surgery Better than Nonsurgical Weight Loss for Improving Asthma Control? A Systematic Review

Naveed Hossain [1,2] · Chanpreet Arhi [1] · Cynthia-Michelle Borg [1]

Received: 1 November 2020 / Revised: 20 January 2021 / Accepted: 20 January 2021 / Published online: 15 February 2021

Abstract

Obesity is associated with increased severity of asthma. Bariatric surgery can be effective in weight loss and improvement in asthma. Two reviewers conducted a systematic review using search terms: 'weight loss', 'bariatric surgery', and 'asthma'. Adult studies including all bariatric procedures and nonsurgical weight loss regimes were included. Thirty-nine studies, including twenty-six bariatric studies and thirteen nonsurgical studies, were found. No study directly compared bariatric surgery to nonsurgical techniques. Bariatric surgery offered greater weight loss (22–36%) than nonsurgical programmes (4.1–14.2%) and more consistently improved medication use, airway hyperresponsiveness, hospitalisation rate or ED attendance and lung function, while change in inflammatory markers were variable. Bariatric surgery appears to be superior in treating asthma; however, further study on surgery for both mild and severe asthma is required.

Keywords Weight loss · Bariatric surgery · Asthma · Obesity · Morbid

Introduction

Treatment of obesity-related comorbidities is a major factor in the treatment of obesity, such that in the UK, *National Institute for Health and Clinical Excellence* (NICE) guidelines suggest a BMI of ≥ 35 kg/m^2 threshold for patients with at least one comorbidity for access to bariatric surgery [1].

Obesity is associated with both increased severity of asthma and more frequent exacerbations [2–4], while higher BMI has been linked to greater prevalence of asthma with a clear dose-response relationship [4, 5]. Indeed, the Global Initiative for Asthma (GINA) management strategy cites obesity as a modifiable risk factor in asthma management [6].

The pathophysiology of asthma is complex, and several phenotypes have been identified by various authors [7–11]; the 'obesity phenotype' characterised by late-onset, absence of atopy and moderate airway hyperresponsiveness. Bariatric surgery has been demonstrated to result in greater weight loss, more physical activity, and 20% lower mean energy intake compared to nonsurgical control subjects over a 10-year period. Furthermore, 2- and 10-year incidence rates of hypertriglyceridemia and diabetes are more favourable [12].

An analysis of the Michigan Bariatric Surgery Collaborative (MBSC) clinical registry of 13,057 patients [13] found 18.6% of all patients undergoing bariatric surgery to have asthma with the use of at least one medication—a significant disease burden. Reportedoutcomes of bariatric surgery in asthma patients mainly consists of observational studies, some with large numbers; however, no study, including RCTs have directly compared bariatric surgery to nonsurgical weight loss interventions for asthma control, likely due to the logistical and methodological difficulties this would entail.

This systematic review aims to identify and compare the current evidence in support of surgical and nonsurgical weight loss interventions for the purpose of improving asthma outcomes.

Methods

Two reviewers conducted a systematic review according to PRISMA guidelines using the PubMed (MEDLINE) and Google Scholar databases from inception to October 2020.

✉ Naveed Hossain
nhossain@nhs.net

[1] Department of General Surgery, University Hospital Lewisham, Lewisham and Greenwich NHS Trust, Lewisham High Street, London SE13 6LH, UK

[2] Department of General Surgery, Whittington Hospital, Whittington Health NHS Trust, Magdala Avenue, London N19 5NF, UK

The following search terms were used: 'weight loss', 'bariatric surgery' and 'asthma'. All language articles were searched. Review articles reference lists were scanned for further studies to include.

Inclusion criteria included the following: adult age >18 years, patients with obesity and asthma confirmed before intervention and human studies only. All types of bariatric surgery were included such as laparoscopic adjustable gastric banding (LAGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and biliopancreatic diversion duodenal switch (BPD-DS). All nonsurgical weight loss programmes were evaluated including hypocaloric diet regimes with or without exercise programmes. Case series and cohort studies were included where data for an asthma subgroup could be identified.

Population exclusions include mice models, obstructive sleep apnoea and COPD. Comparison exclusions were outcome in patients *without* asthma or obesity. Outcome-based exclusion criteria were use of CPAP or resolution of OSA (Fig. 1).

Results

Thirty-nine original studies were identified between 1993 and 2019, including a total of 5185 patients. Major outcome measures are summarised in Table 1.

Studies of Bariatric Surgery

Twenty-six studies including 4359 patients were identified (Table 5). No RCTs were found. Follow-up ranged from 3 months to 5 years.

Weight loss when reported was significant in all bariatric surgery studies (Table 2) with Baltieri et al. [18]

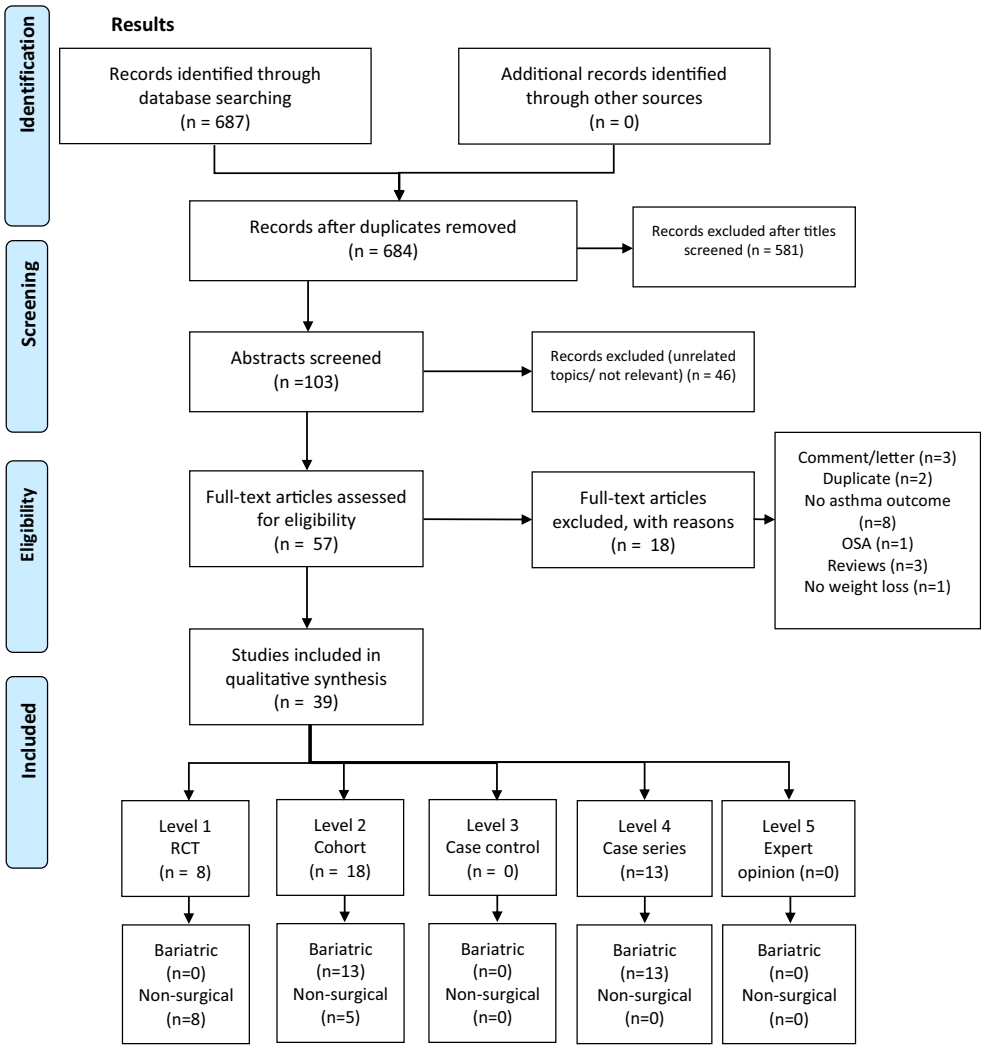

Fig. 1 PRISMA flow chart to demonstrate identification and inclusion of studies used in this systematic review

Table 1 Major outcome measures described in RCTs, cohort studies and case series

(1) Medication use	• Number of asthma medications or dosages prescribed
	• Regular use of
	o inhaled corticosteroids (ICS)
	o short-acting beta agonists (SABA)
	• Use of rescue medications
(2) Symptom scores/quality of life	• Asthma control test (ACT)
	• St George's Respiratory Questionnaire (SGRQ) [14]
	• Visual-analogue scale (VAS)
	• Asthma symptoms utility index (ASUI)
	• Control of Allergic Rhinitis and Asthma Test (CARAT)
	• Asthma severity score (ASS)
	• Asthma control questionnaire (ACQ)
	• Asthma quality of life questionnaire (AQLQ)
	• Asthma life quality (ALQ)
(3) Lung function	• Forced expiratory volume in 1 second (FEV1)
	• Forced vital capacity (FVC)
	• FEV1/FVC ratio
	• Expiratory reserve volume (ERV)
	• Functional residual capacity (FRC)
	• Peak expiratory flow rate (PEFR)
	• Total lung capacity (TLC)
(4) Airway hyperresponsiveness	• Methacholine challenge test (MCT)
	• Provocation dose to achieve ≥15% fall in FEV1 (PD15)
	• Provocation concentration to achieve ≥20% fall in FEV1 (PC20)
(5) Markers or mediators of inflammation	• Adipokines: leptin, adiponectin
	• C-reactive protein (CRP)
	• Exhaled nitric oxide (FeNO)
	• Cytokines: IL 1-6, IL-18, IL-10, tumour necrosis factor (TNF)-a
	• Immunoglobulins: IgE, IgG, IgM, IgA
(6) Healthcare encounters/exacerbations	• ED attendance
	• Hospital admissions
	• Number of exacerbations
(7) Anthropometric measurements	• BMI
	• Weight

demonstrating the greatest average weight loss of 40.52 kg or 40.5% total weight loss (%TWL), p < 0.0001.

Asthma Medication Use

Eighteen studies [9, 13, 16, 17, 20, 21, 25–30, 32–38] demonstrated cessation or reduction in at least one medication. Seven studies [21, 25, 27, 30, 32, 35, 38] reported cessation of all asthma medication in more than 40% of their respective cohorts.

Guerron et al., the largest study (n = 751), reported a reduction in mean number of medications from 1.4 ± 0.6 to 0.8 ± 0.8 at 1 year postoperatively (p < 0.0001). Sikka (n = 40) [29] found mean respiratory prescriptions reduced from 7.0 to 3.8 at one postoperative year (p = 0.002), while Reddy [13] (n = 257) found 101 patients became asthma medication free following bariatric surgery (p < 0.0001).

Reddy et al. [13] reported significantly lower inhaled bronchodilator and ICS use (p < 0.0001); Dixon et al. [9] demonstrated a significant reduction in SABA usage (p = 0.001). Lombardi et al. [28] demonstrated significant reduction in ICS use (p < 0.03), while van Huisstede et al. [20] reported a small reduction in ICS use in their treatment group (BS+A).

Symptom scores and Quality of Life

Ten studies [9, 15, 17–20, 26, 27, 31, 34] considered symptoms, with all but Forno et al. [17], describing significant improvement. Major scoring systems including asthma

Table 2 Summary of changes in weight or BMI

Author (ref)	Study	Weight or BMI reduction (average)	
Bariatric surgery studies			
Santos [15]	Cohort	BMI −11.3 kg/m^2	$p < 0.001$
Guerron [16]	Cohort	BMI −14.5 kg/m^2	–
Forno [17]	Cohort	83–86 lbs (37.6–39.0 kg)	–
Baltieri [18]	Cohort	40.52 kg, (40.5%), BMI from 43.05 to 25.7 kg/m^2	$p < 0.0001$
Maniscalco [19]	Cohort	40.1 kg, BMI −14.8 kg/m^2 intervention group, 2.5 kg, BMI −0.9 kg/m^2 control group	$p < 0.0001$ (between groups)
van Huisstede [20]	Cohort	BMI −14 kg/m^2	–
Chapman [23]	Cohort	BMI −18.5 kg/m^2 TH2-high group, −12 kg/m^2 TH2-low group	$p < 0.0001$
Al-Alwan [24]	Cohort	BMI −9.9 kg/m^2 (asthma subgroup)	–
Toh [26]	Series	BMI (1) −6.1 kg/m2 and (2) −16.6 kg/m2; excess weight loss of (1) 9% (2) 51.6%	–
Boulet [27]	Cohort	51 kg, BMI −16.8 kg/m^2	$p < 0.001$
Dixon [9]	Series	BMI −13.68 kg/m^2	$p < 0.001$
Lombardi [28]	Cohort	BMI −3.7 kg/m^2	$p = 0.001$
Reddy [13]	Cohort	BMI −14 kg/m^2	BMI 49 to 35
Maniscalco [31]	Cohort	Treatment group: 26.3 kg (22%), BMI −10.8; control group: +5 kg gain (4.4%). BMI +1.3 gain	Greater weight loss in treatment group ($p < 0.001$).
Spivak [32]	Series	BMI −10.1 kg/m^2	–
O'Brien [34]	Series	47% mean excess body weight loss	–
Dixon [36]	Series	35.9 kg (28.7%) and BMI −12.8 kg/m^2	–
Macgregor [38]	Series	45kg, 68% excess body weight loss. BMI −16	–
Nonsurgical weight loss studies			
Özbey [14]	RCT	5.2 kg in intervention group, −1.8% body fat	$p < 0.01$, between-group $p = 0.00$
Freitas [39]	RCT	6.1 kg (6.8%) WL+E vs. 2.9 kg (3.1%) WL+S	$p < 0.001$
Ma [40]	RCT	4.0 kg (4.1%) intervention group vs. 2.1 kg (2.1%) control group	$p < 0.01$(kg), $p = 0.005$(%)
Scott [41]	RCT	Greater weight loss achieved in the dietary and combined groups vs. exercise group	$p < 0.001$
Dias-Junior [42]	RCT	7.88 kg, (7.5%). BMI −5.3 kg/m^2 in treatment group	$p < 0.001$ within and between groups
Scott [43]	RCT	8.4 ±4.4 kg (8.5 ± 4.2%) dietary intervention, 1.3 ± 2.2 kg (1.8 ± 2.6%) exercise intervention, 8.2 ± 5.1 kg (8.3 ± 4.9%) combined intervention. Weight loss significantly greater in the dietary vs. combined/exercise groups.	$p < 0.001$ (dietary), $p < 0.01$ (exercise), $p < 0.001$ (combined)
Hernandez Romero [44]	RCT	Diet A: 9.73 kg (10.58%), BMI −3.79 kg/m^2 Diet B: 5.04 kg (6.06%), BMI −1.98 kg/m^2	Greater weight loss in diet A ($p < 0.001$)
Stenius-Aarniala [45]	RCT	Treatment group: 14.2 kg Control group: 0.3 kg (by end of the programme)	Not given
Turner [46]	Cohort	36% achieved 5% total body weight loss, 37% achieved 10% total body weight loss	–
Pakhale [47]	Cohort	16.5 kg (14.2%) treatment group	$p < 0.001$ treatment group, *ns* control group
Johnson [48]	Cohort	8.5 kg (8%)	–
Hakala [49]	Cohort	14 kg. BMI −5.1 kg/m^2	$p < 0.001$

Table 3 Summary of scoring systems used for asthma symptoms and quality of life

ACQ	o 7 domains: 5 for symptoms, 1 for rescue bronchodilator use, 1 for FEV1.
	o A 7-point scale is used in each question (0–6).
	o Total score is the mean of all domains—between 0 (totally controlled) and 6 (severely uncontrolled) [50].
	o A change of >0.5 points is considered clinically significant.
ACT	o 5 domains: restriction of work, waking up at night, shortness of breath, use of rescue medication and patient's overall impression of asthma control.
	o Each domain is scored from 1-5.
	o Total score is the sum of each domain which gives a score out of 25.
	o 19 or less indicates poor control; 20–25 indicates good control.
SGRQ	o 76 items divided into 3 parts measuring symptoms, activity limitation and social and emotional impact of disease. Each item is accorded a weight determined by the degree of distress accorded to each symptom or state described.
	o Overall scores range from 0 (no effect on quality of life) to a maximum score of 100 (maximum perceived distress)
	o A clinically important change in total score is ≥4 units.
CARAT	o 10 questions concerning upper and lower airway symptoms, sleep disturbance, limitation of activity and need for increase in medication over a four-week recall period.
	o Answers are scored on a 4-point Likert scale.
	o Total score ranges from 0 (poor control) to 30 (excellent control).
VAS	o Normally between 0 mm 'best possible' to 100 mm 'worst possible' for patient reported symptoms in a particular domain.
GINA	o Global Initiative for Asthma (GINA) treatment step has been used to give a measure of asthma severity.
	o This ranges from least severe, step 1—as needed low dose ICS formetorol, to most severe, step 6—high dose ICS and LABA ± add on therapy, e.g. tiptropium.
ASS	o A composite of measure of symptoms and treatments used by O'Brien.
	o Higher values indicate poorer control; lower values indicate improvement.
ASUI	o Five domains: cough, wheeze, dyspnoea, sleeplessness and medication side effects.
	o Responses recorded on a 4-point Likert scale.
	o Scoring methodology as described by Revicki [55]
AQLQ [52, 53]	o 32 questions and four domains: symptoms, activity limitation, emotional function and environmental stimuli.
	o Responses are related to the previous 2 weeks
	o Each response is on a 7-point scale (7 = not impaired at all - 1 = severely impaired).
	o Overall score is the mean of all responses; a greater score indicates better quality of life.
	o A change of ≥0.5 points can be considered clinically important.
Mini-AQLQ	o 15 questions in the same 4 domains as the original AQLQ: symptoms, activity limitations, emotional function, and environmental stimuli, also in a 7-point scale.
	o Overall score is the mean of all responses.
	o A change of ≥ 0.5 points can be considered clinically important.
ALQ	o A questionnaire of 20 items with a yes/no response; all questions are weighted equally
	o The sum of all positive answers makes up the total score, ranging from 0 to 20.

control questionnaire (ACQ) [50], asthma control test (ACT) [51], AQLQ [52, 53] and mini-AQLQ [54] (Table 3).

Asthma Control Questionnaire Boulet et al. [27] and Dixon et al. [9] reported statistically and clinically significant ACQ improvement after surgery ($p = 0.03$, $p < 0.001$). van Huisstede et al. [20] demonstrated improvement from baseline ($p < 0.05$) not only in the intervention group (BS+A) but also in the control group (NBS+A) ($p < 0.05$).

Asthma Control Test Baltieri et al. [18] described improvement from 18 to 25 ($p < 0.0001$) and Maniscalco et al. [31] from 18.7 to 22.2 ($p < 0.001$), with the control group unchanged. Maniscalco et al. [19] reported significant

improvement at 1 year after LAGB ($p < 0.0001$), persisting at 5 years. Forno et al. [17], in a large post hoc analysis, found only modest changes from 21.0 at baseline to 20.8 at 60 months; however, it is worth noting that baseline ACT was already considered 'adequate' in this study.

Other Symptom Scores Santos et al. [15] reported CARAT [56] score improved by 3.9 ($p = 0.017$) in upper airways and 4.2 points ($p = 0.027$) in lower airways, and GINA [6] treatment step decreased by 1.8 ($p = 0.017$). Asthma severity score (ASS) was reduced from 44.5 to 14.3 ($p < 0.001$) in one study [34].

Quality of Life Scores Both bariatric studies describing AQLQ showed significant improvement [9, 20]. Improvement in mini-AQLQ [19] ($p = <0.001$) and ALQ [15] ($p = 0.017$) was also reported.

Lung Function

FEV1 and FVC increased in almost all bariatric studies which considered lung function [9, 15, 19, 20, 23, 27, 31], with the exception of Baltieri et al. [18], while Al-Alwan et al. [24] reported significantly increased FEV1 but not FVC. Hewitt et al. reported significant improvement overall in FEV1 and FVC, though this was not associated with asthma status [25].

FEV1/FVC ratio, a marker of airway obstruction, was not found to be changed significantly [9, 18, 20, 23], except by Maniscalco et al. (2017) [19] ($p \leq 0.001$) and only after 5 years follow-up. Chapman et al. and Baltieri et al. found no change in PEFR [18, 23].

van Huisstede et al. and Boulet et al. reported improvement in FRC ($p = 0.02$ and $p < 0.001$) [20, 27] while van Huisstede et al. and Santos et al. demonstrated improvements in TLC ($p = 0.018$, $p = 0.036$) [15, 20]. Boulet et al. [27] also showed vital capacity VC ($p < 0.001$), and ERV ($p = 0.006$) to significantly increase, with no change in the control group.

Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is a pathological hallmark of asthma; it is measured using a stimulus, usually methacholine which acts on muscarinic (M3) receptors [57], known as a methacholine challenge test (MCT). AHR recorded by, for example, PD20 relates to the dose required to achieve a ≥20% fall in baseline FEV1. Six studies reported this outcome [9, 20, 23, 24, 27, 28].

van Huisstede et al. [20], Al-Alwan et al. [24], Boulet et al. [27] and Dixon et al. [9] all demonstrated significant improvement in PD20 or PC20 following bariatric surgery ($p = 0.001$, $p < 0.001$, $p < 0.001$ and $p = 0.03$). Dixon et al. reported significant PC20 increase in those with normal IgE levels ($p = 0.001$) but not those with elevated IgE levels ($p = 0.89$), with similar results by Chapman et al. [23] Conversely, van Huisstede et al. reported PD20 increase only in their IgE-high subgroup ($p = 0.003$). Boulet et al. found improvement of PC20 to be *independent* of atopic status.

Markers or Mediators of Inflammation

Markers or mediators of inflammation are reported by seven bariatric studies (Table 4). Leptin was significantly decreased [18, 20] or unchanged [9], while adiponectin was significantly increased [9, 18, 20]. IL-6 was significantly increased and IL-8 decreased in two studies [9, 18], though van Huisstede et al. [20] found no significant change in IL-6 or IL-8. CRP [18] and hs-CRP [20, 27] were significantly reduced; IgE [9, 20] was unchanged and exhaled nitric oxide (FeNO) was either unchanged [20, 31] or decreased [28]. The effect on TNF-α was variable [9, 18, 20].

Healthcare Encounters/Exacerbations

Hasegawa et al. [22] ($n = 2261$) demonstrated ED attendance or hospitalisation decreased significantly from 22.0 to 10.9% at 12 months (OR 0.42, 95% CI 0.35–0.50, $p < 0.001$). Other studies [34, 36] reported asthma-related hospitalisation in 27.2% and 21.2% of patients 12 months preceding surgery, and none 12 months postoperatively (p values not given). Lombardi et al. ($n = 14$) [28] stated no patients experienced asthma-related hospitalisations at 12 months postoperatively (Table 5).

Macgregor et al. [38] found 12.5% ($n = 5$) reported no asthma attacks, 18.5% ($n = 7$) fewer attacks and 12.5% ($n = 5$) only seasonal/allergy-related attacks postoperatively with significant correlation between weight loss and improvement in asthma symptoms ($p = 0.0093$).

Studies of Nonsurgical Weight Loss

Thirteen studies [14, 39–49, 58] including eight RCTs [14, 39–45] describe nonsurgical weight loss interventions in 826 patients, with follow up time ranging from 40 days to 24 months (Table 6).

Of the RCTs, only Stenius-Aarniala et al. [45] and Hernandez-Romero et al. [44] demonstrated a greater than 10% total body weight loss, while Ma et al. [40] demonstrated the most modest weight loss of 4.0%. Of other studies, Pakhale et al. [47] and Hakala et al. [49] reported a greater than 10% weight loss ($p < 0.001$) (Table 2).

Asthma Medication Use

Stenius-Aarniala et al. [45] reported a decrease in rescue medication of 0.5 doses in their treatment group ($p = 0.002$) (vs. 0

Table 4 Summary of changes in markers or mediators of inflammation in Bariatric surgery and nonsurgical weight loss studies

Author (ref.), study group(s)	Leptin	Adiponectin	IL-6, IL8	CRP/hs-CRP	TNF-α	IgE	FeNO
Bariatric surgery studies							
Baltieri [18]	↓ $p = 0.001$	↑ $p = 0.025$	↑ IL-6 $p = 0.004$ ↓ IL-8 $p = 0.002$	↓ CRP $p = 0.003$	↓ $p = 0.007$		
	Other results: ↔ resistin, $p = 0.769$						
van Huisstede [20], *BS+A group*	↓ $p < 0.001$	↑ $p < 0.001$	↔ IL-6 $p = 0.211$ ↔ IL-8 $p = 0.124$	↓ hs-CRP $p < 0.001$	↔ $p = 0.715$		↔ $p = 0.447$
	Other results: ↔ granulocyte macrophage colony stimulating factor (GM-CSF), $p = 0.401$.						
Chapman [23], *TH2-high group*						↔ $p = 0.06$	
	Further results: IgE median 283 to 251 IU/mL (trend toward reduction)						
Boulet [27], intervention group/control group				↓ hs-CRP $p < 0.001$ (intervention group) ↔ hs-CRP $p = 0.67$ (control group)			
	Other results: ↔ neutrophils, ↔ eosinophils (no p value given)						
Dixon [9]	↔ $p = 0.096$	↑ $p = 0.003$	↑ IL-6 $p = 0.02$ ↓ IL-8 $p = 0.002$		↑ $p = 0.02$	↔ $p = 0.95$	
	Other results: *BAL fluid:* ↑ adiponectin ($p = 0.01$), ↔ leptin ($p = 0.63$), ↓ lymphocytes ($p < 0.01$), ↔ macrophages (0.13), ↔ neutrophils ($p = 0.18$), ↔ eosinophils ($p = 0.27$). *Serum:* ↑ IL-5 ($p = 0.02$), ↑ IL-13 ($p = 0.048$), ↑ IL-17 ($p = 0.03$).						
Lombardi [28], *asthma group*							↓ $p = 0.04$
	Further results: FeNO ↓4.86 ppb in asthma group vs. ↑0.27 ppb in nonasthma group ($p = 0.04$)						
Maniscalco [31], *OB/CG*							↔ $p = 0.42$ (OB) ↔ $p = 0.46$ (CG)
Nonsurgical weight loss studies							
Freitas [39], *WL+E vs. WL+S: (group × time interaction)*	↓ $p = 0.003$	↑ $p = 0.027$	↓ IL-6 $p = 0.008$	↔ CRP $p = 0.295$	↓ $p = 0.018$		↓ $p < 0.001$
	Other results: ↓ IL-4 ($p = 0.004$), ↑ IL-10 ($p = 0.003$), ↑ vitamin D ($p = 0.012$), ↓ CCL2 ($p = 0.024$), ↔ CXCL9 ($p = 0.082$), ↔ CXCL10 ($p = 0.267$) , ↓ leptin/adiponectin ratio ($p = 0.009$)						
Dias-Junior [42], *treatment group vs. control group*	↔ p = ns			↔ CRP p = ns		↔ p = ns	↔ p = ns
	Other results:*Serum*: ↔ eotaxin p = ns, ↔ transforming growth factor (TGF)-β1 p = ns; *sputum*: ↔ eosinophils, neutrophils, lymphocytes, macrophages, epithelial cells (p = ns)						
Scott [43], *dietary/combined*	↓ $p < 0.01$ (*dietary/combined*)	↔ p = ns (*dietary/combined*)	↓ IL-6 $p < 0.05$ (combined)	↔ p = ns (all groups)			
	Other results: *Sputum*: ↓ eosinophils ($p = 0.028$, exercise group), ↔ all other sputum markers.						
Hernandez Romero [44], *diet A/diet B*			↓ IL-6 $p < 0.001$ (*diet A/diet B*)		↓ $p < 0.001$ (*diet A/diet B*)	↓ $p < 0.029$ (*diet A*)	

Table 4 (continued)

Author (ref.), study group(s)	Leptin	Adiponectin	IL-6, IL8	CRP/hs-CRP	TNF-α	IgE	FeNO
Johnson [48]	↔ (p = ns)	**Other results:** ↓ IL-1, ↓ IL-2, ↓ IL-4, ↓ IL-5, ↓ IL-10, ↓ IL-13 ($p < 0.001$) both diets; ↔ IgE: diet B; ↔ IgG, IgM, IgA both diets.	↓ IL-8 $p < 0.001$ (*diet A/diet B*)	↔ CRP $p = 0.2777$	↓$p < 0.01$ (by week 4)		
		Other results: ↓ BDNF ($p < 0.01$) by 2 weeks; *ceramides*: ↓ C16:0, ↓ C18:0, and ↓ C24:0 ($p < 0.05$) by 2 weeks, ↓ C22:0 ($p < 0.05$) by 4 weeks. ↓ protein carbonyls, ↓ nitrotyrosine and ↓ 8-isoprostane ($p < 0.05$) by 2 weeks. ↓ lysine and histidine adducts of 4-hydroxynonenal ($p < 0.05$) by 4 weeks. ↑ uric acid ($p < 0.05$).					

'↑' significant increase; '↓' significant decrease; '↔' no significant change; *IL*, interleukin; *CRP*, c-reactive protein; *hs-CRP*, high-sensitivity CRP; *TNF-α*, tumour necrosis factor alpha; *IgE*, immunoglobulin E; *FeNO*, exhaled nitric oxide; *BAL*, bronchoalveolar lavage; *ns*, nonsignificant; *OB*, obesity and asthma undergoing bariatric surgery; *CG*, control group; *WL+E*, weight loss + exercise group; *WL+S*, weight loss + sham exercise group; *CCL2*, chemokine (C–C– motif) ligand 2; *CXCL9*, chemokine (C–X–C motif) ligand 9; *CXCL10*, chemokine (C–X–C motif) ligand 10; *BDNF*, brain-derived neurotrophic factor

in the control group), fewer exacerbations ($p = 0.001$), but no significant decrease in oral steroid courses ($p = 0.07$).

Hernandez-Romero et al. [44] demonstrated use of rescue medication to be 20–30% less for salbutamol, theophyllin and ICS in diet A (1200–1500 kcal/ day of powdered feed) but was unchanged in diet B (1200–1500 kcal/day personalised meal regime) except for a 10% reduction in salbutamol, despite both diet regimes having the same calorie content.

Ma et al. [40] found no statistically significant difference in medication, including the number of asthma exacerbations requiring systemic corticosteroids.

Turner et al. [46] ($n = 48$) demonstrated 23 patients (48%) requiring reduced dosages (no p value given); Pakhale et al. [47] and Hakala et al. [49] did not demonstrate any significant change in medication use.

Symptom Scores and Quality of Life

Asthma Control Questionnaire RCTs demonstrated some conflicting results: Scott et al. [43] found statistically and clinically significant (>0.5 points) improvement in 'dietary' and 'combined' treatment arms ($p < 0.001$ and $p \leq 0.05$), but not in the 'exercise' arm, while Freitas et al. [39] recorded improvement in combined weight loss and exercise (WL+E) ($p < 0.001$) but no change in the weight loss-only (WL+S) group.

Dias-Junior et al. [42] showed within- and between-group improvement ($p < 0.001$); however, Ma et al. [40] reported no changes in ACQ within or between groups ($p = 0.92$) but describe clinically significant improvement in ACQ (>0.5 points) with a weight loss of 5–10% or ≥10%. Other studies by Pakhale et al. [47] and Johnson et al. [48] describe significant improvement ($p < 0.001$, $p < 0.0015$).

Asthma Control Test Dias-Junior et al. [42] and Özbey et al. [14] reported a mean improvement of 5.17 points ($p < 0.001$) and 2 points ($p < 0.001$) respectively with significant between-group improvement in ACT. Ma et al. [40] found no significant change.

St George's Respiratory Questionnaire [59] Stenius-Aarniala et al. [45] and Dias-Junior et al. [42] found significant between-group improvements in *total* St George's Respiratory Questionnaire (SGRQ) score ($p = 0.02$, $p = 0.011$)). Dias-Junior et al. [42] found significant improvement within the intervention group ($p < 0.001$) in all domains, and between-groups improvement for activity ($p = 0.005$) and impact ($p = 0.028$) domains.

Visual Analogue Scale and ASUI Using Visual Analogue Scale (VAS), Stenius-Aarniala et al. [45] demonstrated improvement in dyspnoea ($p = 0.03$) but not cough ($p = 0.67$)

Table 5 Summary of adult studies on effect of bariatric surgery in asthma * = Primary outcome measure (if given)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and Results
Santos LM, 2019 Cohort	8 patients with asthma and obesity within a total cohort of 26 obese patients undergoing bariatric surgery	8	Laparoscopic gastric bypass or laparoscopic vertical gastrectomy (65.4% to 34.6% for total cohort)		6 - 9 months	**(1) Lung function:** increase in VC (268mL p=0.107), FVC (303mL, p=0.04), FEV1 (295mL p=0.017), TLC (659mL p=0.036). Significant improvement in FEF75% (291mL p=0.018), FEF25-75% (428mL p=0.012) and Rtot (-0.17kPa*s/L p=0.035); **(2) Symptom scores:** CARAT score increase of 3.9 (p=0.017) in upper airways and 4.2 (p=0.027) in lower airways; mean decrease of 1.8 (p=0.017) in GINA treatment step; ALQ improved significantly from 9.6 to 4.1 (p=0.017).
Guerron, 2019 Cohort	751 patients undergoing bariatric surgery with ≥1 prescribed asthma medication	751	RYGB, SG, gastric band, duodenal switch		3 years	**(1) Asthma medication use:** average of 1.4 ± 0.6 preoperatively, reduced to 0.8 ± 0.8 at 1 year. Significant reduction post bariatric surgery (p<0.0001): 46% lower at 3 years (RR 0.54, 95% CI 0.45–0.65)
Forno, 2019 Cohort	Post hoc analysis of 555 patients with asthma participating in the LABS-2 study (Longitudinal Assessment of Bariatric Surgery)	555	RYGB (72.3%), LAGB (22.7%), SG (3.2%), other (1.8%)		5 years	**(1) Lung function:** post-operative results not given **(2) Symptom score:** ACT score 21 at baseline, increased to 21.5 ±0.17 at 12 months, decreased to 20.8 ±0.30 at 60 months (p=0.017 change over time after weight adjustment). Metabolic syndrome at each visit significantly associated with lower ACT score at the next visit (p=0.011 after weight adjustment). **(3) Asthma medication use**: concomitant asthma medication use at baseline was 227/534 (43%); not used for the purpose of demonstrating asthma control **(4) Serum blood markers:** proportion of patients with low HDL or high triglycerides dropped by >50% with a similar reduction in hyperglycaemia.
Baltieri, 2018 Cohort	19 females with asthma undergoing bariatric surgery BMI≥35	19	RYGB		12 months	**(1) Lung function;** FEV1, FVC, FEV1/FVC, PEF, FEF25-75 - no significant change over time **(2) Symptom score:** ACT score improved over time from 18 to 25 (p<0.0001) **(3) Inflammatory markers**- see table 4
Maniscalco M, 2017 Cohort	26 subjects with severe obesity and intermittent or mild-to-moderate asthma being evaluated for LAGB	26	15 obese adults underwent LAGB,	11 non-operated controls	Five years (60 months)	**(1) Lung function:** increase in FEV1, FVC and FEV1/FVC ratio compared to control group at 5 years follow up (p≤0.001); no significant difference noted at 1 year follow up **(2) Symptom score:** ACT score increased in treatment group (17.8 to 21.8) compared to no change in control group (19.0 to 19.1) at five years (p=0.018) **(3) Quality of life:** Mini-AQLQ - increase in treatment group (4.1 to 5.3) compared to slight decrease in control group (4.1 to 3.9) at five years (p≤0.001) **(4) BMI**
van Huisstede A, 2015 Cohort	39 patients with asthma in a cohort of 78 patients with obesity (BMI > 35)	39	BS+A: Bariatric surgery (n=27); 63% of BS+A underwent SG, 37% underwent RYGB.	NBS+A: no bariatric surgery (n=12) [BS-A bariatric surgery patients without asthma (n=39)]	12 months	**(1) Lung function:** FEV1 improved from 86 to 95 %pred (p<0.001), FVC improved from 96 to 105 %pred, TLC and FRC %pred improved significantly (p=0.018, 0.008), FEV1/FVC and RV/TLC (representing hyperinflation) did not change (p=0.246, 0.767). **(2) Airway hyperresponsiveness (AHR)** - Methacholine challenge test PD20: positive in 24 patients at baseline, negative in 13 of these at 12 months (no p value given) **(3) Asthma medication use:** in BS+A group, 6 subjects used ICS at baseline, compared to 4 at 12 month follow up. In NBS+A group, 12 patients continued using ICS **(4) Symptom score**- ACQ improved from 1.2 to 0.4 (p<0.05) in BS+A group, also improved significantly in NBS+A group **(5) Quality of life**: AQLQ improved from 5.6 to 6.7 (p<0.05) in BS+A group, no significant change in NBS+A group

Table 5 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and Results
						(6) Cellular infiltrates in bronchial biopsies; Only mast cells decreased significantly from 118 to 61 cells/mm^2 (p=0.036), eosinophils (EG2), neutrophils (NE), B cells (CD20), macrophages (CD68), CD4+ and CD8+ T cells showed no change at 12 months **(7) Inflammatory markers:** see table 4
Abbas M, 2015 Series	25 asthma patients aged 60+ among 83 undergoing bariatric surgery,	25	LSG or LRYGB		3-12 months	**(1) Asthma medication use:** cessation: 12 patients (47%) reported resolution; reduction: 8 patients (30%) reported improvement
Hasegawa K, 2015 Series	Asthma patients undergoing bariatric surgery with ≥1 prior hospitalisation/ ED visit for asthma exacerbation	2261	Bariatric surgery (operation not defined)		24 months	**(1) ED attendance or hospitalisation:** Risk 22% 13-24 months before surgery, 21.7% 0-12 months before surgery (p=0.80), 10.9% 0-12 months after surgery (p<0.001), 10.9% 13-24 months after surgery (p<0.001)
Chapman DG, 2014 Cohort	22 patients with obesity and asthma (10 early onset IgE-high, 12 late onset IgE-low)	22	Bariatric surgery (operation not defined)		12 months	**(1) Lung function:** FEV1 and FVC improved in both TH2-low and TH2-high groups (p<0.001 and p=0.001). No change in FEV1/FVC or PEFR (p=0.35, p=0.28) **(2) Airway hyperresponsiveness:** AHR and sensitivity to airway closure (logDRSFVC) improved in the TH2-low group but not in the TH2-high group (interaction p=0.04), in spite of no change in sensitivity to airway narrowing (logDRSFEV1/FVC) in either group (p=0.79). **(3) Inflammatory markers** – see table 4
Al-Alwan A, 2014 Cohort	10 females with obesity and non-allergic late onset asthma in a cohort of 23 bariatric surgery patients	10	Bariatric surgery (operation not defined)		12 months	**(1) Lung function:** FEV1 improved significantly (79.8 to 87.2 p=0.03), no significant change in FVC, FEV1/FVC, FRC, ERV **(2) Airway hyperresponsiveness (AHR):** PC20 increased- 4.7 to 9.9mg/ml (p<0.001) **(3) Lung resistance:** asthma patients exhibited a decrease in frequency dependence of resistance such that change in resistance was greater at 5Hz compared to 35Hz **(4) Lung reactance** became less negative at 5 Hz with weight loss p<0.01
Hewitt S, 2014 Cohort	27 patients with asthma out of 113 bariatric surgery patients: BMI>40 or >35 with ≥1 comorbidity	27	LRYGB, LSG, BPD-DS		5 year	**(1) Lung function:** No data available specifically for asthma subgroup; change in FEV1 and FVC not significantly associated with asthma status **(2) Asthma medication use:** resolution of all asthma medication in 48% (p<0.001), 38% reduction in asthma mean number of medications in persistent asthmatics (p=0.001).
Toh JJ, 2014 Series	Two patients with asthma in a series of 3 with treatment-resistant asthma	2	Mini-gastric bypass		3-33 months	**(1) Asthma medication use:** reduced in 1 patient, cessation of all in 1 patient **(2) Emergency hospital visits:** reduced from 4 and 5 in the year preceding surgery to 1 and 0 post op **(3) Symptom score:** ACT measured in 1 patient, improved from 10 to 25
Boulet LP, 2012 Cohort	12 patients with asthma and BMI >40 or BMI >35 with one comorbidity; 11	23	12 underwent BPD-DS	11 did not undergo surgery	12 months	**(1) Airway hyperresponsiveness (AHR)*** –PC20 improved by 2.7 doubling concentrations at 12 months (p<0.001) in the intervention group, stable in the control group (p=0.49)

Table 5 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and Results
	patients with severe obesity and asthma (considered as controls) underwent the same evaluations.					**(2) Lung function:** Improvement from baseline in FVC ($p<0.001$), FEV1 ($p<0.001$), FRC ($p<0.001$), ratio FRC/Total lung capacity TLC ($p=0.003$), vital capacity VC ($p<0.001$), ERV ($p=0.006$) in intervention group; no significant change in control group **(3) Symptom score** - ACQ: total score reduced from 5.6 to 0.3 in intervention group ($p=0.03$); score increased from 7.1 to 7.5 in the control group ($p=0.56$) **(4) Asthma medication use**: reduced from 12 to two patients remaining on asthma medication in intervention group; no change in medication use in control group **(5) Inflammatory markers:** see table 4
Dixon AE, 2012 Series	23 patients with asthma in a total of 44 patients undergoing bariatric surgery	23	Open or Laparoscopic RYGB, LAGB		12 months	**(1) Airway hyperresponsiveness (AHR)*** - PC20 increased from 3.90 to 7.28 ($p=0.03$). Post-hoc analysis: improvement in patients with normal IgE levels ($p=0.001$), but not with increased IgE levels ($p=0.89$) **(2) Lung function:** improvement in FEV1 from 82.4 to 90.4 %pred ($p<0.01$), FVC improved from 84.1 to 93.9 %pred ($p<0.001$), FEV1/FVC remained unchanged $p=0.74$ **(3) Symptom scores** - AQLQ increased from 4.87 to 5.87 ($p<0.01$): ACQ reduced from 1.64 to 0.63 ($p<0.001$); **(4) Asthma medication use:** Significant reduction in short acting β-agonist usage ($p=0.001$). No significant change in ICS, fluticasone, LABA or leukotriene modifier. **(5) Inflammatory markers** – table 4
Lombardi C, 2011 Cohort	14 patients with asthma in a cohort of 29 patients with obesity undergoing bariatric surgery	14	BPD-DS		12 months	**(1) Airway hyperresponsiveness (AHR):** PD20 positive reduced from eight to three patients at 12 months; **(2) Lung function:** FVC increase ($p=0.043$) in total cohort- data for asthma subgroup not given. No difference between asthmatics and non-asthmatics for FEV1 and FVC. **(3) Asthma medication use:** ICS use reduced from beclomethasone-equivalent intake of 406 to 218 micrograms ($p<0.03$) **(4) Symptom score:** Asthma severity questionnaire: 5 point scale – full results not given. No exacerbations or hospitalisations at 12 months follow up. **5) Inflammatory markers** – table 4
Reddy RC, 2011 Cohort	257 patients with asthma; in a total of 2562 undergoing bariatric surgery	257	Lap/open RYGB, LAGB, BPD-DS, SG		12 months	**(1) Asthma medication use:** 101 patients medication-free at 12 months compared to *zero* pre-op ($p<0.0001$). Significant reduction in inhaled bronchodilators: 35% to 20.2% ($p<0.0001$) and ICS: 49.8% to 29.6% ($p<0.0001$). Non-significant reduction in anti-leukotriene and oral corticosteroid medication **(2) Quality of life:** results not given
Sikka N, 2010 Series	40 patients with asthma out of 320 patients undergoing bariatric surgery	40	RYGB		24 months	**(1) Asthma medication use:** mean respiratory prescriptions reduced from 7.0 to 3.8 ($p=0.002$)
Sultan S, 2009 Series	8 patients with asthma out of 53 patients undergoing bariatric surgery with BMI <35	8	LAGB		24 months	**(1) Asthma medication use** - medication stopped in 5/8 patients (p value not given)

Table 5 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and Results
Maniscalco M, 2008 Cohort	22 females with asthma and obesity, 12 undergoing bariatric surgery, 10 controls	22	12 underwent LAGB (OB)	10 Non-operated controls (CG)	12 months	**(1) Lung function:** Improvement in FEV1 from 83.0 to 87.2 %pred (p=0.009), FVC from 87.8 to 95.2 %pred (p=0.001) in treatment group. No change in control group. **(2) Symptom scores:** Asthma control test (ACT): in the OB group, increased from 18.7 to 22.2 (p<0.001), no change in the control group (CG). **(3) Inflammatory markers:** see table 4
Spivak H, 2005 Series	11 patients with asthma in a cohort of 163 undergoing bariatric surgery	11	LAGB		18 months	**(1) Asthma medication use:** Medication use resolved in 9 patients (81.8%), improved in zero patients, no improvement in 2 patients (18.2%) p<0.05
He M, 2004 Series	82 patients with asthma out of 310 patients undergoing bariatric surgery	82	Silastic Ring Gastric Bypass (SRGB), Fobi pouch		60 (mean; range 1-12 yrs)	**(1) Asthma medication use**: 47 (67%) "cured" taking no medication, 21 (28%) "improved" better control of symptoms with same or less medication, eight (10%) remained unchanged.
O'Brien PE, 2002 Series	33 patients with asthma out of 709 patients with obesity undergoing bariatric surgery	33	LAGB / Open		12 months	**(1) Symptom scores:** Asthma severity score (ASS) reduced from 44.5 to 14.3 (p<0.001) **(2) Asthma medication use:** patients taking daily medication reduced from 18 to 8 at follow up. 11 of 33 regarded as having no clinical signs of asthma **(3) Asthma exacerbations / hospitalisations:** nine patients had one or more admissions for asthma pre-op; no admissions in the 12 months post-op.
Dhabuwala, A, 2001 Series	34 patients with asthma in a cohort of 157 undergoing bariatric surgery.	34	Silastic Ring Gastric Bypass (SRGB)		24 months	**(1) Asthma medication use:** 17 (50%) resolved - no medication, 9 (26.5%) improved - fewer medications, 5 (14.7%) unchanged, 3 (8.8%) unknown (lost to follow up).
Dixon JB, 1999 Series	32 patients with asthma and obesity followed up from a cohort of 33 patients undergoing bariatric surgery	32	LAGB "Lap Band" *Assessment by pre- and post-op surveys*		12 months	**(1) Patient-assessed asthma severity, daily impact of asthma on ADLs**: both improved significantly (p<0.001) **(2) Asthma medication use:** 20 patients using "much less", 6 using "less", 6 "the same" (p<0.001). 14 using daily medication pre-op, 6 at follow-up. Fewer using ICS. **(3) Hospitalisations/ED visits:** 7 patients required hospital admission on one or more occasions in the year prior to surgery, 0 in the year after (no p value given)
Murr MM, 1994 Series	6 patients with asthma and obesity in series of 62 bariatric surgery patients ≥ age 50	6	RYGB, Vertical banded gastro-plasty		20 months	**(1) Asthma medication use:** a "marked decrease" in 100% (n=6)
Macgregor AM, 1993 Series	40 patients with asthma and morbid obesity undergoing bariatric surgery	40	RYGB, Vertical banded gastroplasty		48 months	**(1) Asthma severity** - frequency of attacks: 28 patients had > 10 per year (severe), 12 patients >6 per year (moderate). Post-op: 24 reported no attacks (19 of which came off all asthma medication), 7 had fewer attacks, 5 had attacks only on a seasonal basis, 3 were "unchanged" and 1 was worse **(2) Asthma medication use:** 29 (72.5%) used bronchodilators daily; at follow up 12 (42%) no longer used medication for asthma, 10 (34%) used bronchodilators daily, 7 (24%) as-needed.

%pred (% predicted); ACT (asthma control test); ADLs (activities of daily living); ACQ (Asthma Control Questionnaire); ALQ (asthma life quality); AQLQ (Asthma Quality of Life Questionnaire); BMI (body mass index – kg/m^2); CARAT (Control of Allergic Rhinitis and Asthma Test); FEF25-75% (forced expiratory flow at 25-75% of FVC); FEF75% (flow when 75% of FVC has been exhaled); FEV1 (forced expiratory volume in 1 second); FRC (functional residual capacity); FVC (forced vital capacity); GINA step (Global Initiative for Asthma treatment step); HDL (high density lipoprotein); ICS (inhaled corticosteroids); LABA (long acting beta agonist); Mini-AQLQ (mini-Asthma Quality of Life Questionnaire); PC20 (provocative concentration of methacholine that results in a 20% fall in FEV_1); PD20 (provocative dose of methacholine that results in a 20% fall in FEV_1); RR (relative risk); Rtot (total lung resistance); TH-2 (CD4+ T helper-2 cytokines); TLC (total lung capacity); VC (vital capacity)

ompared with controls. Hakala et al. [49] found a similar improvement in 'dyspnoea' ($p < 0.001$) but not 'cough'. Johnson et al. [48] reported asthma symptom utility index (ASUI) [60] improved by 0.25 ($p < 0.002$).

Quality of Life Pakhale et al. [47] and Özbey et al. [14] showed that AQLQ improved overall ($p = 0.003$, $p < 0.001$) with no change in their controls. Scott et al. [43] reported significant within-group improvement in dietary ($p < 0.01$) exercise ($p \leq 0.05$) and combined ($p < 0.01$) groups.

Freitas et al. [39] demonstrated significant AQLQ improvement in all domains from baseline for the WL+E group, but only in the 'environmental stimuli' domain for the weight loss only (WL+S) group; between-group improvement was only found in 'activity limitation' ($p = 0.007$).

Johnson et al. [48] demonstrated an improvement in mini-AQLQ [54] ($p < 0.004$), while Ma et al. [40] found no change.

Lung Function

FEV1 and FVC showed significant between-group increase in RCTs by Özbey et al., Stenius-Aarniala et al. [14, 45], Freitas et al. (which includes an exercise intervention) [39], and two other studies [47, 49]. Another RCT, Dias-Junior et al. [42], reported FVC increased compared to a control group ($p = 0.006$) but found no change in FEV1. RCTs by Scott et al. [43] and Ma et al. [55] showed no significant improvement in FEV1 and FVC, while Johnson et al. [48] found no significant change in FEV1.

Improvement in FEV1/FVC was only reported by Özbey et al. [14]; all other studies showed no improvement [42, 47, 49, 55].

Scott et al. [43] showed no increase in FRC between groups; however, TLC increased in the exercise and combined intervention groups compared to dietary intervention ($p = 0.037$); they also found >10% weight loss resulted in significantly increased FRC ($p = 0.018$) and ERV ($p = 0.008$). Within their dietary group, ERV improved significantly ($p < 0.05$). Freitas et al. [39] found between group improvement in WL+E compared to WL+S ($p = 0.038$) for ERV; however, TLC remained unchanged while Dias Junior showed no change in ERV.

Airway Hyperresponsiveness

Decrease in AHR was mostly not significant within the nonsurgical studies, including studies which demonstrated significant symptom score improvement [42].

Scott et al. [43] found AHR decreased significantly only within the combined exercise and dietary intervention

group, from 100 to 66.7% ($p = 0.027$). Dias-Junior et al. [42] demonstrated a nonsignificant increase in PD20 of 1.20 mg in their treatment group, while Pakhale et al. [47] found PC20 improvement in their intervention group approaching significance ($p = 0.051$). Hakala et al. [49] and Aaron et al. [58] found no significant improvement in AHR.

Markers or Mediators of Inflammation

These are reported by five studies (Table 4). Leptin was either decreased [39, 43] or unchanged [42, 48], while adiponectin was either increased [39] or unchanged [43]. IL-6 was significantly decreased [39, 43, 44], as was IL-8 [44] and TNF-α [39, 44, 48]. CRP was unchanged [39, 42, 43, 48], while IgE was unchanged [39, 42] or decreased [44]. FeNO was unchanged [42] or decreased [39].

Healthcare Encounters/Exacerbations

Only Dias-Junior et al. [42] report a statistically significant reduction in ED visits ($p = 0.0095$) in the treatment group. Ma et al. [40] ($n = 330$) found no significant change in asthma-related hospitalisations or ED visits ($p = 0.40$, $p = 0.26$, respectively).

Stenius-Aarniala et al. [45] report a statistically significant reduction in exacerbations in their treatment group, median 1 (range 0–4) compared to 4 (range 0–7) in the controls ($p = 0.001$).

Discussion

This review demonstrates significant improvement in asthma outcomes with weight loss, while bariatric surgery seems to offer more consistent clinical improvement in medication use, symptom scores, exacerbations and hospital attendance and AHR compared to nonsurgical programmes, as well as greater total body weight loss (22–36% vs 4.1–14.2%).

Clinical Implications

Arguably the most important clinical finding is the reduction in asthma medication use following bariatric surgery. Guerron et al. [16] found that preoperative BMI has a significant effect on asthma medication use and showed significant improvement with surgery, as did Reddy et al. [13] ($n = 257$). Bariatric surgery also dramatically reduced the risk of hospital admission or ED attendance for asthma by between 50% [22] and 100% within 12 months [28, 34, 36]. This may reduce the economic burden of asthma both on health systems and individuals. In clinical practice, it may be worthwhile to include respiratory or primary care clinicians in the perioperative process, analogous to the way diabetes specialists are currently involved, on the understanding that asthma medication doses will be titrated down or stopped altogether.

That symptom scores and quality of life were significantly improved in all but one bariatric study is important; these outcomes can be discussed preoperatively with patients as a possible benefit of surgery, especially for those whose main comorbidity is asthma. Routine preoperative symptom scoring for these patients may be worthwhile. Nonsurgical studies showed some improvement with weight loss, although not uniformly and many included an exercise component which may have improved symptom scores and respiratory function independently of weight loss.

A target weight loss may be relevant, with larger weight losses being achievable through surgery. Indeed, the largest RCT of nonsurgical weight loss [40] described clinically significant improvement in ACQ scores only with weight loss >5% [40], while studies reporting >10% weight loss [45, 47, 49] showed improvement in symptom scores. Interestingly, Forno et al. describe patients who underwent RYGB had significantly greater improvement on ACT scores than those who underwent other types of bariatric surgery ($p = 0.002$); this may influence the type of bariatric surgery offered to patients after multidisciplinary team (MDT) discussion.

Lung Function and Physiology

Obesity significantly reduces ERV, and FRC, the resting lung volume, due to lung compression which leads to narrowing of airways and alveolar de-recruitment, while FEV1 and FVC are also slightly reduced; FEV1/FVC ratio and VC normally remains the same [61]. This review has largely shown these changes in FEV1, FVC and ERV to be reversed with weight loss, although more consistently with bariatric surgery. Improvement in these mechanical effects on lung function has also been demonstrated in nonasthmatics [20].

That weight loss has been demonstrated to improve asthma outcomes can be explained further in two main ways. Firstly, in the 'obesity phenotype' of asthma [7–11, 62–64], individuals experience abnormal collapse and increased sensitivity to closure of peripheral airways at a higher body mass; thought to be related to decreased airway wall thickness [65] and increased elastance of the peripheral airway [24, 66]. In this phenotype, characterised by late-onset, reduced IgE and CD4+ T helper 2 cytokines (TH2-low), weight loss has a greater effect than in early-onset atopic asthma, characterised by elevated IgE and CD4+ T helper 2 cytokines (TH2-high).

Dixon et al. found that AHR improved significantly in 'low IgE' patients ($p = 0.001$) but not those with normal IgE levels ($p = 0.89$) [9], with similar results found by Chapman et al. They postulate that obesity reduces tethering forces of the

Table 6 Summary of adult studies on effect of non-surgical intervention in asthma

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
Ozbey U, 2019 RCT	Adults with controlled asthma and obesity	72	A nutrition and 10-week weight loss diet program. *n*=37	No intervention. *n*=35	10 weeks	**(1) Lung function:** FEV1, FVC and FEV1/FVC: significant between-group improvement (p=0.00, p=0.00, p<0.042 respectively), PEFR showed non-significant improvement and MEF significantly improved in the intervention group compared to the controls. **(2) Symptom scores**: ACT and AQLQ increased in intervention group vs. control group (p=0.00)
Freitas PD, 2016 RCT	Age 30-60 with mod/ severe asthma, BMI ≥35 to <40, under optimal medical treatment	55	WL+E: weight loss program incorporated with aerobic and resistance exercises. *n*=28	WL+S: Diet counselling sessions and behavioural techniques plus sham exercises - stretching *n*=27	3 months in total; exercise sessions twice weekly, counselling sessions weekly	**(1) Symptom scores:** ACQ*: significant decrease in WL+E from 2.0 to 1.1 (p<0.001), no change in WL+S group; between groups more improvement in WL+E (p=0.003), AQLQ: significant improvement in all domains for WL+E, only significant improvement in "environmental stimuli" domain for WL+S, between group improvement only in activity limitation domain (p=0.007); Exacerbations: experienced by 53% in the WL+E group and 20% in the WL+S group (p = 0.03). **(2) Lung function:** FEV1 and FVC showed within-group improvement in WL+E but no between group improvement, TLC showed no significant between or within group change; significant between-group improvement in ERV in WL+E compared to WL+S (p=0.038) **(3) Inflammatory markers** – table 4
Ma, J, 2015 RCT	Adults (BMI ≥ 30) with uncontrol-ed asthma	330	Theory-based and goal-oriented lifestyle intervention targeting weight loss and increased physical activity (*n*=165)	Usual care, plus a list of weight management services, pedometer, scales, and asthma self-management DVD (*n*=165)	12 months with assessments at 6 months	**(1) Symptom scores** – ACQ*: mean adjusted change in intervention group was -0.3 ±0.1 vs -0.2 ±0.1 in control subjects at 12 months, this was not significant (p=0.92), weight loss of 5-10% (OR 2.19 95%CI 1.08-4.46) or ≥10% (OR 3.78 95%CI 1.72-8.31) was associated with clinically significant improvement in ACQ scores; ACT and mini-AQLQ: no significant between group difference at 6 or 12 months; **(2) Lung function -** FEV1, FVC, FEV1/FVC: no between-group difference at 6 or 12 months **(3) Asthma medication use:** no statistically significant differences in medication use including ICS, LTRA, LABA, SABA and beclomethasone both between-group and pre-and post-randomisation

Table 6 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
						(4) Healthcare encounters: no significant differences in number of asthma exacerbations, ED visits and hospitalisations at 6 or 12 months
Scott HA, 2015 RCT	BMI 28–40 non-smoking adults with stable asthma.	38	Three-armed study: (1) Dietary: 885–1170 kcal/day- two meal replacements per day. Dietician, clinic and phone consultation. (n=15)	(2) Exercise: 12-week gym (n=10) (3) Combined dietary and exercise programme (n=13)	10 weeks, 3x weekly exercise sessions	**(1) Symptom scores:** ACQ: baseline measurements did not influence degree of weight loss, AQLQ: lower baselines values resulted in greater weight loss (p=0.027) and change in AQLQ was associated with greater weight loss (p=0.048); **(2) Lung function:** Lower FEV1/FVC at baseline correlated with greater weight loss (rs = 0.398, P = 0.015) and fat loss (rs = 0.455, P = 0.005), however changes in lung function did not correlate with greater weight loss (data not given)
Dias-Junior SA; 2014 RCT	Adults (BMI ≥ 30) with severe asthma	33	Hypocaloric weight loss programme with the use of sibutramine (10mg per day) and orlistat (120mg per day)	Bi-monthly consultations without weight loss programme	6 months, bimonthly consult-ations	**(1) Symptom scores:** ACQ*: improvement of 1.4 in treatment group (p<0.001)- significant between group improvement (p<0.001), ACT: improvement of 5.17 in the treatment group (p<0.001) and significant between group improvement (p<0.001), SGRQ: significant decrease in treatment group (p<0.001) and between-groups for all domains except symptoms, **(2) Lung function:** FVC: significant improvement in treatment group 0.24L (p=0.002) and also between groups (p=0.006); FVC also improved significantly all in those who achieved >10% weight loss (p<0.05); FEV1, IC, TLC, ERV, RV, showed no change **(3) Airway hyperresponsiveness:** PD20 - non-significant improvement: 1.20mg in treatment group **(4) Inflammatory markers** – see table 4
Scott HA, 2013 RCT	Adults (BMI 28–40) non-smoking with stable asthma.	46	Three-armed study (1) Dietary: 885–1170 kcal/ day) including two meal replacements per day and one main meal. Dietician, clinic visits, phone consultations(n=18)	(2) Exercise: gym attendance at least 3 times per week for 12-weeks (n=14) (3) Combined dietary and exercise programme (n=14)	10 weeks, 3x weekly exercise sessions	**(1) Symptom scores-** ACQ: significant reduction in dietary and combined groups by 0.6 ±0.5 (p<0.001) and 0.5 ±0.7 (p≤0.05) respectively, non-significant reduction in exercise group by 0.3 ±0.5; AQLQ: significant within-group reduction in all three groups, greatest in the dietary group by 0.9 (p<0.01) compared to 0.49 (p≤0.05) and 0.5 (p<0.01) for exercise and combined groups;

Table 6 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
						(2) Lung function: TLC was improved significantly after exercise and combined interventions relative to dietary intervention (p=0.037), ERV was improved within the dietary group only (p<0.05), FEV1, FVC, FRC, RV showed no significant change between groups. >10% weight loss resulted in significantly improved FRC (p=0.018) and ERV (p=0.008); **(3) Airway hyperresponsiveness -** The proportion of subjects with AHR (PD15) decreased significantly from pre- to post-intervention in the combined group (100% vs. 66.7% respectively, p= 0.027), non-significant reductions were noted within the other groups **(4) Inflammatory markers:** table 4
Hernandez Romero A, 2008 RCT	Adults BMI ≥27.5 with moderate persistent asthma	96	Diet A: 1,200 to 1,500 kcal / day of powdered feed of milled rice, ground soybean, sesame and milled fiber tuna (n=49)	Diet B: 1,200 to 1,500 kcal / day Miami Heart Institute diet: a three-day repeating diet (n=47)	40 days, recordings made at 0, 7, 14, 21, 28, 35 and 40 days	**(1) Symptoms:** cough - improved by 80% in diet A, 60% in diet B, wheeze - 100% improvement in diet A, 75% improvement in diet B, fatigue - 100% improvement in diet A, 70% improvement in diet B, shortness of breath - 100% improvement in diet A, 70% improvement in diet B; **(2) Use of rescue medications** - 20-30% improvement in salbutamol, theophylline and ICS in diet A, largely unchanged except 10% reduction in salbutamol in diet B; **(3) Lung function:** airway reversibility: improved by 35% in diet A, improved by 10% in diet B; **(4) Inflammatory markers**: table 4 **(5) Other biochemical tests**: lipids, LFTs, Amylase, Lipase, TFTs- significance not reported. **(6) Weight loss**
Stenius-Aarniala B, 2000 RCT	Adults with asthma (BMI 30 to 42 kg/m2) recruited through newspaper advertisements.	38	12 group sessions- 14 weeks: eight weeks "dieting period"-participants take a very low energy 1760 kJ diet containing daily allowances of all essential nutrients. (n=19)	Sessions at the same intervals as treatment group; each half an hour. Received normal medical care throughout. (n=19)	12 months: 12 group sessions in 14 weeks for all participants	**(1) Symptom scores:** SGRQ: improved in treatment group in all subscales compared to controls. At 1 year the difference between groups in total score was −10 (p=0.02), VAS: significant decrease in dyspnoea (p=0.03) but not cough (p=0.67) compared to controls; **(2) Lung function:** PEFR increase was not significant (p=0.06), FEV1 %pred increased by 7.6% in the treatment group compared to

Table 6 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
						controls (p=0.02), FVC %pred was also significantly greater in the treatment group by 7.6% compared to controls (p=0.001); **(3) Medication use:** overall reduction in rescue medication was 0.5 doses in the treatment group vs. 0 in the control group (p=0.002). Exacerbations were also significantly fewer in the treatment group (p=0.001), but number of oral steroid courses was not significantly fewer (p=0.07) **(4) Laboratory values:** Mean urinary excretion of sodium and magnesium significantly reduced in treatment group vs control (p=0.01, p=0.004); other lab values (cortisol, potassium, calcium, triglycerides, cholesterol) showed no significant change
Turner D, 2015 Cohort	48 asthma patients out of 180 with BMI≥35	48	Attendance at a multidisciplinary weight management clinic		6 - 24 months; 4-6 weekly attendance	**(1) Asthma medication use:** 23 out of 48 (48%) patients report taking reduced dosages of asthma medication (no p values given)
Pakhale S, 2015 Cohort	22 adults aged 18 to 75 years with a BMI ≥32.5 and self-reported physician-diagnosed asthma.	22 (n=16)	Behavioural weight management program comprising three daily liquid meal replacements and weekly group sessions to discuss progress and listen to presentations by health professionals	Control group (n=6)	3 months	**(1) Airway hyperresponsiveness** - PC20 improved from 5.02 mg/mL to 10.2 mg/mL in the intervention group (p=0.051), non-significant increase from 6.6 to 7.7 mg/mL in the control group; At three months, MCT was negative for eight (50%) in the intervention group compared to two (33.3%) in the control group **(2) Lung function:** FEV1 and FVC improved by 5% in intervention group (p<0.01), decreased by 7% in the control group (non-significant), FEV1/FVC ratio unchanged in both groups (p>0.05); **(3) Symptom score:** ACQ reduced in intervention group (p<0.001), unchanged in control group **(4) Quality of life:** AQLQ improved in the intervention group for overall mean scores (p=0.003), and for three AQLQ subscales (p≤0.002). Scores in the control group remained unchanged. **(5) Asthma medication use:** One patient (6.3%) in the intervention group stopped taking asthma medication compared with none in the control group.

Table 6 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
						(6) Physical activity increased in the intervention group from 15.5 to 25.7 METs (p=0.47) and decreased from 4.6 to 1.8 METs in the control group (p=0.335)
Johnson JB, 2007 Cohort	10 subjects (8F: 2M) BMI >30, inactive lifestyles, stable moderate persistent asthma.	10	Alternate day calorie restriction, comprising less than 20% of normal calorie intake on alternate days for 8 weeks.		8 weeks	**(1) Symptom scores:** ACQ improved by 1.3 (p<0.0015), ASUI scores improved by 0.25 (p<0.002), mini-AQLQ change was 2.1 (p<0.004) **(2) Lung function:** PEFR increased from 334.7 L/min to 379.3 L/min (p=0.0081), FEV1 showed no significant change, however FEV1 after albuterol was significantly greater at 8 weeks compared to baseline suggesting improvement in bronchial responsiveness (p=0.0156) **(3) Lipid markers:** Total cholesterol and triglycerides were significantly lower at 8 weeks compared to baseline (p=0.048, p=0.039); HDL cholesterol was significantly increased at 8 weeks (p=0.011). LDL, glucose, ghrelin and insulin were unchanged. **(4) Inflammatory markers:** Table 4
Aaron, 2004 Cohort	24 asthma patients in cohort of 58 women - BMI >30	24	Liquid meal replacement of 900 kcal per day for (i) 6 weeks if BMI>30 (ii) 12 weeks if BMI>35		6 months	**(1) Airway hyperresponsiveness:** subgroup analysis of asthma patients found that PC20 did not show any improvement with weight loss. For every 10% weight loss, the change in PC20 was only one fifth of a doubling dilution (p=0.66) **(2) Lung function and (3) Symptom score:** reported for total cohort, not specific for asthma group
Hakala K, 2000 Cohort	14 asthma patients (11M: 3F age 25-62), BMI range 32.5 - 42.5	14	Very low calorie diet (VLCD) for 8 weeks		8 weeks	**(1) Lung function:** PEF - morning, evening and lowest morning PEF all significantly increased (p<0.001, p<0.005, p<0.001), FEV1 (77-83% predicted) and FVC (88-93% predicted) increased (p<0.05) FEV1/FVC unchanged, FRC, VC and TLC -significant increase with weight reduction **(2) Airway hyperresponsiveness:** Histamine challenge test - mean PD15 increased from 0.20mg to 0.30mg (non-significant).

Table 6 (continued)

Author, Year, Study type	Population	n	Intervention	Control	Follow up	Outcomes and results
						(3) Symptom score: VAS dyspnoea 14.6 to 8.6 $p<0.001$, VAS cough 8.8 to 8.6 (non-significant). **(4) Use of rescue medication:** Reduced from 0.6 to 0.4 doses/day (non-significant change)

ACQ (asthma control questionnaire); ACT (asthma control test); AHR (airway hyper-responsiveness); ASUI (Asthma Symptom Utility Index); BMI (body mass index – kg/m^2); ERV (expiratory reserve volume); FEV1 (forced expiratory volume in 1 second); FEV1/FVC (forced vital capacity in 1 second/forced vital capacity); FRC (functional residual capacity); FVC (forced vital capacity); HDL (high density lipoprotein); ICS (inhaled corticosteroids); LABA (long acting beta agonist); LDL (low density lipoprotein); LFTs (liver function tests); LTRA (leukotriene receptor antagonist); MCT (methacholine challenge test); MEF (mid expiratory flow); METs (metabolic equivalent tasks); Mini-AQLQ (mini asthma quality of life questionnaire); OR (odds ratio); PC20 (provocative concentration of methacholine that results in a 20% fall in FEV_1); PD15 (provocative dose that results in a 20% fall in FEV_1); PEFR (peak expiratory flow rate); SABA (short acting beta agonist); SGRQ (St George's Respiratory Questionnaire); TFTs (thyroid function tests); TLC (total lung capacity); VAS (visual-analogue scale); VC (vital capacity)

*= Primary outcome measure (if given)

lung parenchyma on the small airways and predisposes them to closure [23].

Secondly, increased adiposity causes increased airway inflammation due to low-grade systemic inflammation from adipose tissue breakdown resulting in macrophage activation and generation of proinflammatory cytokines, which impact the lung [67]. Inflammatory mediators such as CRP [68, 69], IL-6 [70] and tumour necrosis factor alpha (TNF-α) [71] have been demonstrated in higher levels in obese patients. Furthermore, adipose tissue gives rise to adipokines which are implicated in the inflammatory response: leptin being proinflammatory and increased in obesity, and adiponectin anti-inflammatory and decreased in obesity [72]. Mice models have shown increased AHR when exogenous leptin is administered [73], while exogenous adiponectin reduced AHR and airway inflammation [74]. Airway epithelial cells express both leptin and adiponectin receptors [75–77]; it has been suggested that these offer an alternative route of pathogenesis of airway reactivity separate from systemic inflammation, by promoting alteration of alveolar macrophage function and airway remodelling in late-onset, TH2-low, asthma [78].

Significant reductions in leptin [18, 20, 39, 43] and increases in adiponectin [18, 20, 39] in both bariatric and some nonsurgical interventions were demonstrated while CRP was significantly reduced in mostly bariatric studies [18, 20, 27, 48]. Other inflammatory markers showed variable responses which may suggest their lack of specificity to asthma and its various phenotypes [11].

Other routes of pathogenesis of airway reactivity exist which have not been described in studies in this review, such as the advanced glycation end products (AGE) pathway mediated by arginine dysregulation in obesity and metabolic syndrome and may be modulated by incretins such as glucagon-like peptide 1 (GLP-1) [79]. These represent areas of further study in obesity-related asthma.

Quality of Studies

The quality of the evidence available for bariatric surgery includes cohort studies and case series. There were no RCTs; therefore, all studies in this group may have confounding factors which are not accounted for. For example, those with severely uncontrolled asthma may not pass anaesthetic assessment for surgery or may undergo pre-optimisation. Many bariatric series included subgroups of asthmatic patients from which outcome data was extracted, though these were usually not primary outcome measures. Nonsurgical studies were fewer in number, but higher quality evidence; most being RCTs with clear selection criteria and outcome measures.

Limitations of This Review

There is much heterogeneity between studies. They differ in populations, specific outcome measures, reporting (e.g. between-group and within-group/from baseline changes) and units used (e.g. litres vs. %pred); therefore, only a narrative review, rather than a quantitative synthesis, was possible.

Conclusion and Future Direction

The relationship between asthma and obesity is complex and likely mediated by a combination of susceptibility to weight-related peripheral airways collapse, systemic inflammation and adipokine imbalance resulting in increased airway hyperresponsiveness. Notwithstanding the limitations of the review and the quality of the studies, it appears that bariatric surgery is more effective in treating asthma. We do, however, require good-quality studies which focus on the effect of bariatric surgery on mild and severe asthma. Should patients with BMI >35 kg/m^2 with mild asthma as their only comorbidity be offered bariatric surgery? Similarly, should patients with severe life-threatening asthma be considered for bariatric surgery in spite of anaesthetic risks? These questions may need to be answered with future research.

Code Availability Not applicable.

Author Contributions All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Naveed Hossain and Chanpreet Arhi. The first draft of the manuscript was written by Naveed Hossain, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability Raw data available on request.

Declarations

Ethics Approval and Consent to Participate Our study did not require ethical approval. No patient identifiable information or images are included in the study.

Consent for Publication No patient identifiable information or images are included in the study.

Conflict of Interest The authors declare no conflict of interest.

References

1. Obesity: identification, assessment and management. Clinical guideline CG189. National Institute for Health and Care Excellence [NICE]. 2014.
2. Fitzpatrick S, Joks R, Silverberg JI. Obesity is associated with increased asthma severity and exacerbations, and increased serum immunoglobulin E in inner-city adults. Clin Exp Allergy. 2012;42(5):747–59.
3. Denlinger LC, Phillips BR, Ramratnam S, et al. Inflammatory and comorbid features of patients with severe asthma and frequent exacerbations. Am J Respir Crit Care Med. 2017;195(3):302–13.
4. Barros R, Moreira P, Padrao P, et al. Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. Clin Nutr. 2017;36(4):1068–74.
5. Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med. 2007;175(7):661–6.
6. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Available from: www.ginaasthma.com. 2019.
7. Haldar P, Pavord ID, Shaw DE, et al. Cluster analysis and clinical asthma phenotypes. Am J Respir Crit Care Med. 2008;178(3):218–24.
8. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. Am J Respir Crit Care Med. 2010;181(4):315–23.
9. Dixon AE, Pratley RE, Forgione PM, et al. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. J Allergy Clin Immunol. 2011;128(3):508–15 e1-2.
10. Sutherland ER, Goleva E, King TS, et al. Cluster analysis of obesity and asthma phenotypes. PLoS One. 2012;7(5):e36631.
11. Carr TF, Kraft M. Use of biomarkers to identify phenotypes and endotypes of severeasthma. Ann Allergy Asthma Immunol. 2018;121(4):414–20.
12. Sjöström L, Lindroos A-K, Peltonen M, et al. Lifestyle, Diabetes, and cardiovascular risk factors 10 years after bariatric surgery. 2004;351(26):2683–93.
13. Reddy RC, Baptist AP, Fan Z, et al. The effects of bariatric surgery on asthma severity. Obes Surg. 2011 Feb;21(2):200–6.
14. Özbey Ü, Balaban S, Sözener Z, et al. The effects of diet-induced weight loss on asthma control and quality of life in obese adults with asthma: a randomized controlled trial. J Asthma. 2020;57(6):618–26.
15. Santos LM, Ramos B, Almeida J, et al. The impact of weight loss beyond lung function: benefit with respect to asthma outcomes. Pulmonology. 2019;25(6):313–9.
16. Guerron AD, Ortega CB, Lee H-J, et al. Asthma medication usage is significantly reduced following bariatric surgery. Surg Endosc. 2019;33(6):1967–75.
17. Forno E, Zhang P, Nouraie M, et al. The impact of bariatric surgery on asthma control differs among obese individuals with reported prior or current asthma, with or without metabolic syndrome. PLoS One. 2019;14(4):e0214730.
18. Baltieri L, Cazzo E, de Souza AL, et al. Influence of weight loss on pulmonary function and levels of adipokines among asthmatic individuals with obesity: one-year follow-up. Respir Med. 2018;145:48–56.
19. Maniscalco M, Zamparelli AS, Vitale DF, et al. Long-term effect of weight loss induced by bariatric surgery on asthma control and health related quality of life in asthmatic patients with severe obesity: a pilot study. Respir Med. 2017;130:69–74.
20. van Huisstede A, Rudolphus A, Castro Cabezas M, et al. Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma. Thorax. 2015;70(7):659–67.
21. Abbas M, Cumella L, Zhang Y, et al. Outcomes of laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass in patients older than 60. Obes Surg. 2015;25(12):2251–6.
22. Hasegawa K, Tsugawa Y, Chang Y, et al. Risk of an asthma exacerbation after bariatric surgery in adults. J Allergy Clin Immunol. 2015;136(2):288–94. e8

23. Chapman DG, Irvin CG, Kaminsky DA, et al. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. Respirology. 2014;19(8):1170–7.
24. Al-Alwan A, Bates JH, Chapman DG, et al. The nonallergic asthma of obesity. A matter of distal lung compliance. Am J Respir Crit Care Med. 2014;189(12):1494–502.
25. Hewitt S, Humerfelt S, Sovik TT, et al. Long-term improvements in pulmonary function 5 years after bariatric surgery. Obes Surg. 2014;24(5):705–11.
26. Toh JJ, Pasupathy S, Poopalalingam RA, et al. Can bariatric surgery be performed safely in patients with severe treatment-resistant asthma? Obes Surg. 2014;24(2):334–6.
27. Boulet LP, Turcotte H, Martin J, et al. Effect of bariatric surgery on airway response and lung function in obese subjects with asthma. Respir Med. 2012;106(5):651–60.
28. Lombardi C, Gargioni S, Gardinazzi A, et al. Impact of bariatric surgery on pulmonary function and nitric oxide in asthmatic and non-asthmatic obese patients. J Asthma. 2011;48(6):553–7.
29. Sikka N, Wegienka G, Havstad S, et al. Respiratory medication prescriptions before and after bariatric surgery. Ann Allergy Asthma Immunol. 2010;104(4):326–30.
30. Sultan S, Parikh M, Youn H, et al. Early U.S. outcomes after laparoscopic adjustable gastric banding in patients with a body mass index less than 35 kg/m2. Surg Endosc. 2009;23(7):1569–73.
31. Maniscalco M, Zedda A, Faraone S, et al. Weight loss and asthma control in severely obese asthmatic females. Respir Med. 2008;102(1):102–8.
32. Spivak H, Hewitt MF, Onn A, et al. Weight loss and improvement of obesity-related illness in 500 U.S. patients following laparoscopic adjustable gastric banding procedure. Am J Surg. 2005;189(1):27–32.
33. He M, Stubbs R. Gastric bypass surgery for severe obesity: what can be achieved? N Z Med J. 2004;117(1207):U1207.
34. O'Brien PE, Dixon JB, Brown W, et al. The laparoscopic adjustable gastric band (Lap-Band): a prospective study of medium-term effects on weight, health and quality of life. Obes Surg. 2002;12(5):652–60.
35. Dhabuwala A, Cannan RJ, Stubbs RS. Improvement in comorbidities following weight loss from gastric bypass surgery. Obes Surg. 2000;10(5):428–35.
36. Dixon JB, Chapman L, O'Brien P. Marked improvement in asthma after Lap-Band surgery for morbid obesity. Obes Surg. 1999;9(4):385–9.
37. Murr MM, Siadati MR, Sarr MG. Results of bariatric surgery for morbid obesity in patients older than 50 years. Obes Surg. 1995;5(4):399–402.
38. Macgregor AM, Greenberg RA. Effect of surgically induced weight loss on asthma in the morbidly obese. Obes Surg. 1993;3(1):15–21.
39. Freitas PD, Ferreira PG, Silva AG, et al. The role of exercise in a weight-loss program on clinical control in obese adults with asthma. A Randomized Controlled Trial. Am J Respir Crit Care Med. 2017;195(1):32–42.
40. Ma J, Strub P, Xiao L, et al. Behavioral weight loss and physical activity intervention in obese adults with asthma. A randomized trial. Ann Am Thorac Soc. 2015;12(1):1–11.
41. Scott HA, Gibson PG, Garg ML, et al. Determinants of weight loss success utilizing a meal replacement plan and/or exercise, in overweight and obese adults with asthma. Respirology. 2015;20(2):243–50.
42. Dias-Junior SA, Reis M, de Carvalho-Pinto RM, Stelmach R, Halpern A, Cukier A. Effects of weight loss on asthma control in obese patients with severe asthma. Eur Respir J 2014;43(5):1368-1377.
43. Scott HA, Gibson PG, Garg ML, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clin Exp Allergy. 2013;43(1):36–49.
44. Hernandez Romero A, Matta Campos J, Mora Nieto A, et al. Clinical symptom relief in obese patients with persistent moderate asthma secondary to decreased obesity. Rev Alerg Mex (Tecamachalco, Puebla, Mexico : 1993). 2008;55(3):103–11. Alivio de sintomas clinicos en pacientes obesos con asma moderada persistente secundario a la disminucion de obesidad. spa.
45. Stenius-Aarniala B, Poussa T, Kvarnstrom J, et al. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ. 2000;320(7238):827–32.
46. Turner D, Haboubi N. Qualitative and quantitative outcomes of a 1:1 multidisciplinary weight management clinic. Healthcare (Basel). 2015;3(2):429–51.
47. Pakhale S, Baron J, Dent R, et al. Effects of weight loss on airway responsiveness in obese adults with asthma: does weight loss lead to reversibility of asthma? Chest. 2015;147(6):1582–90.
48. Johnson JB, Summer W, Cutler RG, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic Biol Med. 2007;42(5):665–74.
49. Hakala K, Stenius-Aarniala B, Sovijarvi A. Effects of weight loss on peak flow variability, airways obstruction, and lung volumes in obese patients with asthma. Chest. 2000;118(5):1315–21.
50. Juniper EF, O'Byrne PM, Guyatt GH, et al. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902–7.
51. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. J Allergy Clin Immunol. 2004;113(1):59–65.
52. Juniper EF, Guyatt GH, Ferrie PJ, et al. Measuring quality of life in asthma. Am Rev Respir Dis. 1993;147(4):832–8.
53. Juniper EF, Bousquet J, Abetz L, et al. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med. 2006;100(4):616–21.
54. Juniper E, Guyatt G, Cox F, et al. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J. 1999;14(1):32–8.
55. Ma J, Strub P, Camargo Jr CA, et al. The Breathe Easier through Weight Loss Lifestyle (BE WELL) Intervention: a randomized controlled trial. BMC Pulm Med. 2010;10:16.
56. Azevedo P. Correia de Sousa J, Bousquet J, Bugalho-Almeida A, Del Giacco SR, Demoly P, et al. Control of Allergic Rhinitis and Asthma Test (CARAT): dissemination and applications in primary care. Prim Care Respir J. 2013;22(1):112–6.
57. Brannan J, Lougheed MD. Airway hyperresponsiveness in asthma: mechanisms, clinical significance, and treatment. Front Physiol. 2012;3(460) English
58. Aaron SD, Fergusson D, Dent R, et al. Effect of weight reduction on respiratory function and airway reactivity in obese women. Chest. 2004;125(6):2046–52.
59. Jones PW, Quirk FH, Baveystock CM. Littlejohns P. A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. Am Rev Respir Dis. 1992;145(6):1321–7.
60. Revicki DA, Kline Leidy N, Brennan-Diemer F, et al. Integrating patient preferences into health outcomes assessment: the Multiattribute Asthma Symptom Utility Index. Chest. 1998;114(4):998–1007.
61. Dixon AE, Peters U. The effect of obesity on lung function. Expert Rev Respir Med. 2018;12(9):755–67.
62. Bates JHT, Poynter ME, Frodella CM, et al. Pathophysiology to phenotype in the asthma of obesity. Ann Am Thorac Soc. 2017;14(Supplement_5):S395–s8.

63. Bates JHT. Physiological mechanisms of airway hyperresponsiveness in obese asthma. Am J Respir Cell Mol Biol. 2016;54(5):618–23.
64. Holguin F, Bleecker ER, Busse WW, et al. Obesity and asthma: an association modified by age of asthma onset. J Allergy Clin Immunol. 2011;127(6):1486–93.e2.
65. Bates JHT, Dixon AE. Potential role of the airway wall in the asthma of obesity. J Appl Physiol. 2015;118(1):36–41.
66. Dixon AE, Poynter ME. Mechanisms of asthma in obesity. Pleiotropic aspects of obesity produce distinct asthma phenotypes. Am J Respir Cell Mol Biol. 2016;54(5):601–8.
67. Tashiro H, Shore SA. Obesity and severe asthma. Allergol Int. 2019;68(2):135–42.
68. Ford ES. Body mass index, diabetes, and C-reactive protein among U.S. adults. Diabetes Care. 1999;22(12):1971–7.
69. Scott HA, Gibson PG, Garg ML, et al. Airway inflammation is augmented by obesity and fatty acids in asthma. Eur Respir J. 2011;38(3):594–602.
70. Peters MC, McGrath KW, Hawkins GA, et al. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. Lancet Respir Med. 2016;4(7):574–84.
71. Kern PA, Saghizadeh M, Ong JM, et al. The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest. 1995;95(5):2111–9.
72. Kim S-H, Sutherland ER. Gelfand EW. Is there a link between obesity and asthma? Allergy, Asthma Immunol Res. 2014;6(3):189–95.
73. Shore SA, Schwartzman IN, Mellema MS, et al. Effect of leptin on allergic airway responses in mice. J Allergy Clin Immunol. 2005;115(1):103–9.
74. Shore SA, Terry RD, Flynt L, et al. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol. 2006;118(2):389–95.
75. Bergen HT, Cherlet TC, Manuel P, et al. Identification of leptin receptors in lung and isolated fetal type II cells. Am J Respir Cell Mol Biol. 2002;27(1):71–7.
76. Bruno A, Pace E, Chanez P, et al. Leptin and leptin receptor expression in asthma. J Allergy Clin Immunol. 2009;124(2):230–7.7.e1-4
77. Miller M, Cho JY, Pham A, et al. Adiponectin and functional adiponectin receptor 1 are expressed by airway epithelial cells in chronic obstructive pulmonary disease. J Immunol. 2009;182(1):684–91.
78. Sideleva O, Suratt BT, Black KE, et al. Obesity and asthma: an inflammatory disease of adipose tissue not the airway. Am J Respir Crit Care Med. 2012;186(7):598–605.
79. Nguyen D-V, Linderholm A, Haczku A, et al. Glucagon-like peptide 1: a potential anti-inflammatory pathway in obesity-related asthma. Pharmacol Ther. 2017;180:139–43.

Publisher's NotePublisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.