Asthma medication use in obese and healthy weight asthma: systematic review/meta-analysis

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Obese asthmatics have higher use of all included asthma medications and take higher ICS doses than healthy-weight subjects, despite similar FEV_1/FVC %, emphasising the need for new, more effective management strategies to be developed for this population. https://bit.ly/2EQtPSi

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ABSTRACT

Background: Obesity is a common comorbidity in asthma and associated with poorer asthma control, more frequent/severe exacerbations, and reduced response to asthma pharmacotherapy.

Objective: This review aims to compare use of all classes of asthma medications in obese (body mass index (BMI) $\geqslant$30 kg·m^{-2}) *versus* healthy-weight (BMI <25 kg·m^{-2}) subjects with asthma.

Design: Databases including CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane, Embase and MEDLINE were searched up to July 2019 for English-language studies that recorded medication use or dose in obese and healthy-weight adults with asthma. A critical appraisal checklist was utilised for scrutinising methodological quality of eligible studies. Meta-analysis was performed and heterogeneity was examined with the use of the Chi-squared test. This review was conducted based on a published protocol (www.crd.york.ac.uk/PROSPERO CRD42020148671).

Results: Meta-analysis showed that obese subjects are more likely to use asthma medications, including short-acting β_2-agonists (OR 1.75, 95% CI 1.17–2.60; p=0.006, I^2=41%) and maintenance oral corticosteroids (OR 1.86, 95% CI 1.49–2.31; p<0.001, I^2=0%) compared to healthy-weight subjects. Inhaled corticosteroid (ICS) dose (μg·day^{-1}) was significantly higher in obese subjects (mean difference 208.14, 95% CI 107.01–309.27; p<0.001, I^2=74%). Forced expiratory volume in 1 s (FEV_1) % predicted was significantly lower in obese subjects (mean difference −5.32%, 95% CI −6.75–−3.89; p<0.001, I^2=42%); however, no significant differences were observed in FEV_1/forced vital capacity (FVC) ratio between groups.

Conclusions: We found that obese subjects with asthma have higher use of all included asthma medication classes and higher ICS doses than healthy-weight asthma subjects, despite lower FEV_1 and a similar FEV_1/FVC %. A better understanding of the factors driving increased medication use is required to improve outcomes in this subgroup of asthmatics.

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Introduction

Asthma is a chronic condition predominantly affecting the lower respiratory tract, characterised by airway hyperresponsiveness, variable airway obstruction, and airway inflammation [1]. Obesity or weight gain often precede asthma onset and existing asthma is further complicated by obesity or increased adiposity [2, 3]. Epidemiological evidence for the relationship between asthma and obesity is well established in the literature [3]. Obesity is associated with both increased asthma incidence and prevalence (particularly in adult females), shown in a meta-analysis conducted in >300 000 adults which reports almost double the odds of incident asthma in obese subjects [2, 3]. The obese asthma phenotype exhibits considerable clinical and molecular heterogeneity, which complicates diagnostic assessment and pharmacological management, which in turn affects therapeutic response.

Obesity appears to be associated with increased asthma severity, as well as worse asthma control [1]. Furthermore, obesity is associated with increased frequency and severity of asthma exacerbations, reduced asthma-related quality of life and reduced response to asthma pharmacotherapies [3]. Due to the complex nature of comorbid obese asthma, contributing mechanisms are yet to be fully elucidated. Proposed factors linking the conditions include both local and systemic inflammation [3], metabolic and microbiome dysregulation [3], unbalanced lifestyle (over-nutrition, poor diet quality, physical inactivity) [4], genetics [5] and mechanical effects [6]. These factors may independently, directly or indirectly trigger inflammatory responses that potentially affect the airways. It has been proposed that two obese-asthma phenotypes exist, early-onset atopic asthma (EOA) and late-onset, nonatopic asthma (LONA), each with different aetiologies and clinical implications. The first, EOA, manifests traditional features of allergic asthma (T-helper cell type 2 (Th2) lymphocyte associated with eosinophilic airway inflammation) and typically responds well to corticosteroid-based treatments that control symptoms. This phenotype may be modified by obesity and symptoms may improve with weight loss, although the disease does not remit. LONA appears to manifest purely due to obesity, as it often resolves or improves with weight loss, with significant changes seen in lung function [7], asthma control [8] and airway hyperresponsiveness [8, 9] following bariatric surgery. Th2 inflammation is less apparent with LONA, and is often associated with innate Th1/Th17-mediated responses, neutrophilic airway inflammation and poor response to corticosteroid-based treatment [10–14].

In all forms, obese asthma is progressive with intermittent exacerbations; thus, effective asthma management plans, including improved pharmacotherapy strategies are warranted. Asthma and obesity both significantly contribute to health resource use and costs. In Australia, more than AUD 300 million per annum is spent on asthma pharmaceuticals, attributed mainly to inhaled corticosteroids (ICS) [15]. Increased obese asthma-related healthcare costs are largely a result of increased prescription medication expenses [16]. Mainstay clinical asthma management typically focuses on pharmacological treatment, although particularly in obese patients, lifestyle interventions and treatment of comorbidities are also important [17].

Asthma medication guidelines do not differ for healthy-weight and obese patients, although obese patients with asthma may not respond as well to standard pharmacotherapies [1]. Efficacy of corticosteroids primarily stems from their broad anti-inflammatory and immunosuppressive effects; promoting synthesis of anti-inflammatory proteins and inhibiting pro-inflammatory cytokines. In the airways, corticosteroids reduce the number of eosinophils, T-lymphocytes, dendritic cells and mast cells and decrease nitric oxide production [18]. However, several studies show attenuated responses to ICS treatment in obese subjects [10, 19, 20]. Combination therapy (ICS and a long-acting β_2-agonist (LABA)) is more likely to achieve asthma control than ICS alone; however, evidence suggests it is also less effective for achieving control in obese compared to healthy-weight subjects [20].

Reduced efficacy of asthma pharmacotherapy in obesity is a major clinical problem considering its paramount role in controlling disease, reducing severity and treating life-threatening exacerbations. Additionally, pharmacotherapies, in particular β_2-agonists, prevent and relieve exercise-induced asthma, necessary to allow safe exercise, which is vital in this population. This review aims to systematically compare use of all classes of asthma medications in obese compared to healthy-weight subjects with asthma, thereby highlighting existing differences in the management of these patient subgroups.

Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [21], and the protocol was registered with the PROSPERO international prospective register of systematic reviews (record no. CRD42020148671), which can be found at www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020148671.

Search strategy

CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane, Embase and MEDLINE databases were searched for English language articles up to July 2019 with the use of keywords and medical subject headings of the National Library of Medicine. The search terms included Abdominal fat or Abdominal obesity or Adipocytes or Adipose tissue or Adiposity or Bariatric surgery or Body composition or Body mass index or Body size or Body weight or Gastric bypass or Gastroplasty or Jejunoileal bypass or Lipectomy or Metabolically benign obesity or Morbid obesity or Obesity or Overnutrition or Overweight or Weight gain or Adipocyte or Adipos or Bariatric or BMI or Body composition or Body mass index or Body size or Body weight or Excess weight or Fat or Fatness or Gynoid or Nonobes or Obes or Overnutrition or Overweight or Weight gain and Status asthmaticus or Asthma or Aspirin-induced asthma, or Exercise-induced asthma or Occupational asthma or Asthma.

Study selection

Original studies with the following designs were included: randomised controlled trials, quasi-experimental studies, cohort studies, case–control studies, before-and-after studies and observational cross-sectional studies. Studies with the following designs were excluded: *in vitro* studies, animal studies, children/adolescent studies, systematic reviews, narrative reviews, case reports, opinion papers and conference abstracts. Review articles were retrieved for the purpose of hand searching the reference list and did not contribute to the final number of included studies. The target subject population was human adults (aged $\geqslant$18 years) with asthma, including all sexes and ethnicities. The exposure of interest was obesity (body mass index (BMI) $\geqslant$30 kg·m^{-2}), which was compared to healthy weight (BMI <25 kg·m^{-2}). The study outcome measures were asthma medication use (any use %), asthma medication dose (µg·day^{-1}) and lung function using forced expiratory volume in 1 s (FEV_1) % predicted values and FEV_1/forced vital capacity (FVC)×100%.

Article citations identified by the search strategy from online databases were imported into the referencing software Endnote X8 (Clarivate Analytic, Philadelphia, PA, USA). All retrieved articles were independently assessed for relevance by two reviewers (CAT and SRE) based on title, abstract and full text using inclusion and exclusion criteria (see supplementary material for PRISMA flowchart). Articles considered not relevant were discarded according to incorrect study population, review exposure not measured, incorrect study outcome or incorrect study design. Following a disagreement on article inclusion, a third independent reviewer (BSB) was involved.

Study quality

Following full-text appraisal, eligible articles were reviewed for methodological quality using the standardised critical appraisal checklist designed by the Academy of Nutrition and Dietetics [22]. This tool combines four relevance questions that address the translation of study findings to practice and 10 validity questions that address scientific rigour. All articles were rated as positive, negative or neutral quality. Studies of negative quality ("no" response to six or more validity questions) were excluded from the review. The level of evidence for each study was determined according to the study design based on the National Health and Medical Research Council of Australia levels of evidence hierarchy [23].

Data extraction and study synthesis

Information from eligible articles was extracted and recorded in a custom-designed database. Data extracted included title, authors, publication year, country, subject characteristics, sample size, BMI, study design, method of asthma diagnosis, comorbidities, limitations and outcomes of interest, including asthma medication use (inhaled short-acting (short-acting β_2-agonist (SABA)) and long-acting (long-acting β-adrenoceptor agonist (LABA), anticholinergic) bronchodilator use, inhaled preventer use (ICS, ICS+LABA), oral preventer use (leukotriene receptor antagonists (LTRA), maintenance oral corticosteroid (OCS), rescue OCS)), ICS dose (µg·day^{-1}) (reported as beclomethasone dipropionate (BDP) in hydrofluoroalkane (HFA) equivalents) and lung function measures (reported as FEV_1 % pred and FEV_1/FVC %).

Statistical methods

Meta-analysis was performed using Review Manager (RevMan, version 5.3; Nordic Cochrane Centre, Copenhagen, Denmark) to analyse the difference between asthma medication use (any use %), asthma medication dose (µg·day^{-1}) and lung function in obese and healthy-weight subjects with asthma. Heterogeneity in meta-analysis models was examined with the use of the Chi-squared test ($p<0.1$ considered to indicate significant heterogeneity) and the I^2 parameter (with 30–60% indicating moderate, 50–90% indicating substantial and 75–100% indicating considerable heterogeneity) [24]. A random-effects model was applied to all meta-analyses. The Mantel–Haenszel statistical method was applied for medication use and the odds ratio (odds ratio effect size) and corresponding 95% confidence intervals were calculated. Subgroup analysis was performed on the meta-analysis examining OCS use, to

individually assess maintenance OCS use and rescue OCS use. The inverse-variance statistical method was used for evaluating differences in ICS dose (μg·day^{-1}) and lung function (FEV_1 % pred, FEV_1/FVC %) by weight status, and the mean difference (effect size) and corresponding 95% confidence intervals were calculated. In assessment of ICS dose, fluticasone propionate (FP) equivalents (μg·day^{-1}) were reported as approximately equivalent to BDP-HFA equivalents (μg·day^{-1}) [25].

Results

The search strategy identified 8941 articles, of which 2603 duplicates were discarded (supplementary material). Next, 6338 article titles were evaluated, based on the review inclusion and exclusion criteria, of which 2380 remained for abstract appraisal. Then, 491 articles were excluded after abstract review, with 1889 retrieved for full-text review. Based on full text, 1854 articles were excluded based on exposure (n=1177), outcomes (n=656) or study design (n=21). Finally, 35 articles were included in the review.

Description of included studies

Of the 35 included studies, cross-sectional design [12, 15, 26–42] was most commonly used (n=19), followed by six retrospective cohort studies [43–48], six prospective cohort studies [49–54], three case–control studies [55–57] and one time-series study [58] (table 1). Included studies were published from 1999 to 2019. Most studies were conducted in the United States of America (n=15) [12, 15, 26–28, 43–47, 49, 50, 54–56], with others from Europe (n=5) [29–31, 51, 52], Asia (n=4) [39–42], Canada (n=4) [32–34, 48], Australia (n=2) [53, 58], South America (n=2) [35, 36], Africa [37], Central America [57] and New Zealand [38].

A total of 31 644 adult subjects (11 294 healthy weight and 20 350 obese) were included in this review (table 1), with 14 928 from retrospective cohort studies, 9180 from prospective cohort studies, 7373 from cross-sectional studies, 128 from case–control studies and 35 from the time-series study. Studies included subjects with varying degrees of asthma severity and control. Prevalences of comorbidities are recorded in table 1 when reported. Such comorbidities include diabetes, obstructive sleep apnoea (OSA), gastro-oesophageal reflux disorder (GORD), hypertension, depression and rhinitis. The methodological quality of 28 of the studies included in this review was positive (80%). These studies were strengthened methodologically by their selection of study subjects, comparability of study groups and clearly definition of the research questions and outcomes. Seven (20%) studies were given a neutral quality rating primarily due to subject selection bias, and lack of consideration to biases and limitations when making conclusions. No studies were assessed as negative quality; thus no studies were excluded based on poor quality. Studies by Sutherland *et al.* [38], Camargo Jr *et al.* [54] and Cohen *et al.* [55] included female subjects only, while Murphy *et al.* [53] exclusively included pregnant women. Bruno *et al.* [29], Desai *et al.* [30] and Gibeon *et al.* [51] exclusively included severe asthma subjects.

Of the 35 studies (table 1), the majority (74%) reported ICS use (n=26) [12, 15, 27, 28, 31–33, 35, 38–40, 42–48, 50, 52–58]. The second most reported asthma medication (46% of studies) included OCS (n=16) [12, 15, 27–31, 33, 36, 39, 40, 44, 48, 49, 51, 52], subgrouped into maintenance OCS use (n=10) (29% of studies) [12, 28, 30, 33, 39, 40, 44, 48, 51, 52] and recue OCS use (n=6) (17% of studies) [15, 27, 29, 31, 36, 49]. 31% reported LTRA use (n=11) [12, 15, 28, 32, 33, 39, 42, 44, 47, 51, 56] and 29% reported LABA use (n=10) [12, 15, 29, 32, 33, 42, 44, 52, 56, 58]. Asthma medications that were reported less often included SABAs in 17% of studies (n=6) [15, 26, 28, 32, 33, 57], ICS+LABA (n=6) [28, 35, 41, 47, 48, 57], and anticholinergics in 11% (n=4) [15, 32, 40, 56]. Of the 35 studies, 29% reported ICS dose (μg·day^{-1}) (n=10) [27, 30, 33, 34, 37, 40, 42, 48, 53, 58], 77% reported FEV_1 % predicted (n=27) [12, 26, 28–35, 37, 38, 40–43, 45, 47, 48, 51–58] and 63% reported FEV_1/FVC % (n=22) [12, 26, 28–33, 37–39, 41–43, 47, 48, 51–53, 56–58] in obese and healthy-weight subjects with asthma.

Findings from the meta-analysis

Meta-analyses were performed using all studies to examine the difference in asthma medication use (any use %) and dose (μg·day^{-1}) by categories: inhaled short-acting (SABA) and long-acting (LABA, anticholinergic) bronchodilator asthma medication use (figure 1); inhaled preventer asthma medication use and dose (ICS, ICS+LABA, ICS dose (μg·day^{-1}) (in BDP-HFA equivalents)) (figure 2); oral preventer asthma medication use (OCS use: subgrouped into maintenance OCS and rescue OCS, LTRA) (figure 3); and lung function (FEV_1% predicted, FEV_1/FVC%) (figure 4) between obese and healthy-weight subjects with asthma. Meta-analyses demonstrated that obese subjects with asthma are significantly more likely to use all classes of asthma medications included in this review, use a higher ICS dose (μg·day^{-1}), have a lower FEV_1 % predicted and a similar FEV_1/FVC % compared to healthy-weight subjects with asthma. The number of studies performed in only females, pregnant women and severe asthma was too limited to perform subgroup analyses and thus were represented within larger meta-analyses. Significant heterogeneity was found in the meta-analyses examining LABA use (figure 1) and ICS use (figure 2), ICS

TABLE 1 Summary of included studies that reported asthma medication use, dose and lung function in adults with asthma

First author, year (location) [reference]	Study population n sex age BMI kg·m^{-2} healthy/obese	Design/evidence level[#]	Quality[¶]	Method of asthma diagnosis	Outcomes (asthma medication class)	Comorbidities (excluded comorbidities)	BMI kg·m^{-2} <25	BMI kg·m^{-2} ⩾30
Adeyeye, 2013 (Lagos) [39]	118 M/F ⩾18 years <25/⩾30	Cross-sectional/IV	Ø	Dr-dx (NHLBI guidelines)	ICS LTRA mOCS FEV_1/FVC %	Not listed		
Bruno, 2014 (Europe) [29]	66 M/F ⩾18 years 22.7±2.3/32.3±3.3	Cross-sectional/IV	+	Severe asthma outpatients (ATS criteria)	LABA rOCS FEV_1 % predicted FEV_1/FVC%	Type II diabetes OSA GORD Systemic hypertension Left ventricle failure Osteoporosis Bronchiectasis Tuberculosis Psychological factors (COPD)	0 0 33 12 5 21 2 5 7	38 17 53 33 13 29 8 4 4
Camargo, 1999 (USA) [54]	901 F ⩾18 years <22.5/⩾30	Prospective cohort/III-2	+	Dr-dx (guidelines not specified)	ICS FEV_1 % predicted	Not listed		
Chen, 2016 (China) [40]	136 M/F ⩾18 years Acute: 22.2±1.6/36±6.1 Stable: 22.5±1.7/35.9±4.4	Cross-sectional/IV	+	Acute asthma+stable asthma (GINA guidelines)	Anticholinergic ICS ICS (BDP equivalent) dose µg·day^{-1} FEV_1 % predicted mOCS	OSA GORD Depression BDI score ⩾14	10 21 23	20 39 36
Clerisme-Beaty, 2009 (USA) [26]	227 M/F ⩾17 years 18.5–24.9/⩾30	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	SABA FEV_1 % predicted FEV_1/FVC %	GORD Rhinitis Sinusitis Chronic bronchitis (Comorbidities interfering with study)	42 69 39 28	54 53 59 33
Cohen, 2019 (USA) [55]	32 F 18–50 years 22.8±11.6/35.9±24.7	Case–control/III-2	+	Dr-dx childhood-onset asthma (age <12 years) (guidelines not specified)	ICS FEV_1 % predicted	(Any comorbidity ↑ systemic inflammation, active infection, diabetes, OSA, hepatic disease, cardiac disease)		
Cortés-Télles, 2015 (Mexico) [57]	28 M/F ⩾18 years 23.0±1.0/33.0±3.0	Case–control/III-3	+	Dr-dx (well controlled) (NHLBI guidelines +GINA guidelines+Asthma Control Test)	ICS ICS+LABA SABA FEV_1 % predicted FEV_1/FVC %	(Any comorbidities interfering with exercise testing)		
Deesomchok, 2010 (Canada) [32]	96 M/F 20–60 years 22.4±1.9/35.8±5.5	Cross-sectional/IV	+	Dr-dx (stable) (guidelines not specified)	Anticholinergic ICS LABA LTRA SABA FEV_1 % predicted FEV_1/FVC %	Hypertension Heart disease Anxiety Depression Severe allergic reaction	3 0 14 11 9	19 5 17 26 5

Continued

TABLE 1 Continued

First author, year (location) [reference]	Study population n sex age BMI kg·m^{-2} healthy/obese	Design/evidence level[#]	Quality[¶]	Method of asthma diagnosis	Outcomes (asthma medication class)	Comorbidities (excluded comorbidities)	BMI kg·m^{-2}	
							<25	⩾30
de Lima Azambuja, 2015 (Brazil) [35]	50 M/F ⩾18 years 18.5–24.9/⩾30	Cross-sectional/IV	+	Dr-dx (ATS/ERS criteria)	ICS ICS+LABA FEV_1 % predicted	Hypertension Type II diabetes GORD Metabolic syndrome	36 4 20 28	60 16 40 52
Desai, 2013 (England) [30]	83 M/F ⩾18 years 22.0±2.1/36.2±5.9	Cross-sectional/IV	+	Dr-dx (severe) (GINA step 4 or 5)	ICS (BDP equivalent) dose µg·day^{-1} mOCS FEV_1 % predicted FEV_1/FVC %	Not listed		
Dixon, 2006 (USA) [43]	361 M/F ⩾18 years 22.0±2.0/38.0±7.0	Retrospective cohort/III-2	Ø	Dr-dx (mild-to-moderate persistent) (guidelines not specified)	ICS FEV_1 % predicted FEV_1/FVC %	Rhinitis Sinusitis GORD	71 41 21	69 50 36
Farah, 2011 (Australia) [58]	35 M/F ⩾18 years 18.5–24.9/⩾30	Time series/III-2	+	Dr-dx (guidelines not specified)	LABA ICS (BDP equivalent) dose µg·day^{-1} FEV_1 % predicted FEV_1/FVC %	(Lung diseases other than asthma)		
Gibeon, 2013 (UK) [51]	471 M/F ⩾18 years 22.8±4.4/34.2±5.3	Prospective cohort/III-2	Ø	Severe refractory asthma (ATS criteria)	LTRA mOCS FEV_1 % predicted FEV_1/FVC %	Perennial rhinitis Seasonal rhinitis Eczema Nasal polyps GORD Central bronchiectasis Other bronchiectasis Emphysema	35 39 23 18 40 18 28 6	33 42 32 11 54 7 21 5
Giouleka, 2011 (Greece) [52]	66 M/F ⩾18 years 22.6±2.0/34.0±3.0	Prospective cohort/III-2	+	Dr-dx (GINA guidelines)	ICS LABA mOCS FEV_1 % predicted FEV_1/FVC %	(Illnesses (*e.g.* OSA) that could interfere with proposed tests)		
Hasegawa, 2014 (USA) [44]	904 M/F 18–54 years <25/⩾30	Retrospective cohort/III-2	Ø	Dr-dx (guidelines not specified)	ICS LABA LTRA mOCS	(COPD)		
Holguin, 2010 (USA) [56]	68 M/F ⩾18 years ⩽25/⩾30	Case control/III-2	+	Dr-dx (guidelines not specified)	Anticholinergic ICS LABA LTRA FEV_1 % predicted FEV_1/FVC %	Not listed		

Continued

TABLE 1 Continued

First author, year (location) [reference]	Study population n sex age BMI kg·m^{-2} healthy/obese	Design/evidence level[#]	Quality[¶]	Method of asthma diagnosis	Outcomes (asthma medication class)	Comorbidities (excluded comorbidities)	BMI kg·m^{-2}	
							<25	⩾30
Holguin, 2011 (USA) [12]	769 M/F ⩾18 years 35.8±5.5/22.4±2.3	Cross-sectional/IV	+	Questionnaires and respiratory tests (mild, moderate or severe asthma) (guidelines not specified)	ICS LABA LTRA mOCS FEV_1 % predicted FEV_1/FVC %	Not listed		
Jesus, 2018 (Brazil) [36]	605 M/F ⩾18 years <25/⩾30	Cross-sectional/IV	+	Dr-dx (mild-to-moderate or severe) (guidelines not specified)	rOCS	Hypertension/diabetes/dyslipidaemia Rhinitis GORD Severe depression (Any disease severe enough to make it difficult to assess asthma symptoms or any other disease that causes dyspnoea)	21 91 35 4	57 93 66 9
Kwon, 2012 (Korea) [41]	619 M/F ⩾18 years <25/⩾30	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS+LABA FEV_1 % predicted FEV_1/FVC %	Allergic rhinitis	77	75
Lavoie, 2006 (Canada) [33]	233 M/F ⩾18 years <25/⩾30	Cross-sectional/IV	Ø	Dr-dx (guidelines not specified)	ICS ICS (FP equivalent) dose μg·day^{-1} LABA LTRA mOCS SABA FEV_1 % predicted FEV_1/FVC %	Hypertension Diabetes Hypercholesterolaemia (Comorbid diseases (disease types not specified))	23 3 19	28 8 22
Liu, 2018 (China) [42]	33 M/F ⩾18 years 22.2±1.8/31.7±1.9	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS ICS (BDP equivalent) dose μg·day^{-1} LABA LTRA FEV_1 % predicted FEV_1/FVC %	(Chronic respiratory disease+severe systemic disease (lung cancer, bronchiectasis, heart disease, hypertension, diabetes or psychiatric disorders))		
Lugogo, 2018 (USA) [45]	454 M/F ⩾18 years ⩽24.9/⩾30	Retrospective cohort/IV	+	Dr-dx (guidelines not specified)	ICS FEV_1 % predicted	(Presence of other lung diseases)		
Maalej, 2012 (Tunisia) [37]	137 M/F ⩾18 years 18.5–24.9/⩾30	Cross-sectional/IV	Ø	Inpatient and outpatient respiratory departments (GINA criteria) (intermittent, mild persistent, moderate persistent or severe persistent asthma)	ICS (BDP equivalent) dose μg·day^{-1} FEV_1 % predicted FEV_1/FVC %	Diabetes Hypertension Hypercholesterolaemia GORD Rhinitis Sinusitis (Any additional respiratory disease excluded)	4 3 0 1 59 13	17 18 8 10 8 3

Continued

TABLE 1 Continued

First author, year (location) [reference]	Study population n sex age BMI kg·m^{-2} healthy/obese	Design/evidence level[#]	Quality[¶]	Method of asthma diagnosis	Outcomes (asthma medication class)	Comorbidities (excluded comorbidities)	BMI kg·m^{-2}	
							<25	⩾30
Mosen, 2008 (USA) [27]	703 M/F >35 years <25/⩾30	Cross-sectional/IV	+	Healthcare use suggestive of active asthma (guidelines not specified)	ICS ICS (BDP equivalent) dose µg·day^{-1} rOCS	GORD	34	43
Murphy, 2017 (Australia) [53]	111 Pregnant females ⩾18 years 22.3±2.1/33.6±6.1	Prospective cohort/III-2	+	Dr-dx (guidelines not specified)	ICS ICS (BDP equivalent) dose µg·day^{-1} FEV_1 % predicted FEV_1/FVC %	(Presence of a chronic medical disease (other than asthma))		
Nathell, 2002 (Sweden) [31]	160 M/F ⩾18 years 19.9±2.3/33.7±3.7	Cross-sectional/IV	+	Questionnaire, phone interview+clinical examination (guidelines not specified)	ICS rOCS FEV_1 % predicted FEV_1/FVC %	Not listed		
Rastogi, 2017 (USA) [28]	792 M/F ⩾18 years 18.5–24.9/⩾30	Cross-sectional/IV	+	Self-reported current Dr-dx (guidelines not specified)	ICS ICS+LABA LTRA mOCS SABA FEV_1 % predicted FEV_1/FVC %	COPD Coronary heart disease Congestive heart failure	15 3 1	18 5 5
Schatz, 2013 (USA) [46]	12 137 M/F 18–65 years <25/⩾30	Retrospective cohort/III-2	+	Persistent asthma (HEDIS criteria)	ICS	(COPD, emphysema or chronic bronchitis)		
Schatz, 2015 (USA) [49]	7229 M/F 18–56 years <25/⩾30	Prospective cohort/III-3	+	Persistent asthma (HEDIS criteria)	rOCS	Reported as total: GORD Depression		28 28
Sutherland, 2008 (New Zealand) [38]	39 F 18–50 years 22.8±1.9/37.2±4.4	Cross-sectional/IV	+	Respiratory symptoms+respiratory tests (guidelines not specified)	ICS FEV_1 % predicted FEV_1/FVC %	(Any disease that could potentially ↑ systemic inflammation)		
Tang, 2019 (USA) [47]	924 M/F ⩾18 years <25/⩾30	Retrospective cohort/IV	+	Dr-dx (guidelines not specified)	ICS ICS+LABA LTRA FEV_1 % predicted FEV_1/FVC %	GORD OSA Diabetes	13 2 0	33 14 9
Taylor, 2008 (USA) [15]	2102 M/F ⩾18 years <25/⩾30	Cross-sectional/IV	+	Self-reported Dr-dx (guidelines not specified)	Anticholinergic ICS LABA LTRA rOCS SABA	Not listed		

Continued

TABLE 1 Continued

First author, year (location) [reference]	Study population n sex age BMI kg·m^{-2} healthy/obese	Design/evidence level[#]	Quality[¶]	Method of asthma diagnosis	Outcomes (asthma medication class)	Comorbidities (excluded comorbidities)	BMI kg·m^{-2}	
							<25	⩾30
Thomson, 2003 (USA/Canada) [50]	402 M/F 18–54 years <25/⩾30	Prospective cohort/III-2	+	Dr-dx (acute asthma) (guidelines not specified)	ICS	COPD	3	3
Vermette, 2016 (Canada) [48]	148 M/F ⩾18 years 22.6±1.6/35.2±5.2	Retrospective cohort/III-2	Ø	Dr-dx (Canadian Asthma Consensus guidelines)	ICS ICS (BDP equivalent) dose µg·day^{-1} ICS+LABA mOCS FEV_1 % predicted FEV_1/FVC %	(Associated comorbidities causing dyspnoea)		
Wright, 2010 (Canada) [34]	405 M/F 18–75 years 22.7±1.6/33.8±3.6	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS (FP equivalent) dose µg·day^{-1} FEV_1 % predicted	(Conditions that conferred greater morbidity than asthma)		
Total subjects n	31 644							

Data are presented as mean±SD or %, unless otherwise stated. BMI: body mass index; M: male; F: female; IV: inverse variance; Dr-dx: doctor diagnosed; NHLBI: National Heart, Lung, and Blood Institute; ICS: inhaled corticosteroids; LTRA: leukotriene receptor antagonists; mOCS: maintenance oral corticosteroids; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ATS: American Thoracic Society; LABA: long-acting β_2-agonists; rOCS: rescue oral corticosteroids; OSA: obstructive sleep apnoea; GORD: gastro-oesophageal reflux disorder; GINA: Global Initiative for Asthma; BDP: beclomethasone dipropionate; BDI: Beck Depression Inventory; SABA: short-acting β_2-agonists; ERS: European Respiratory Society; FP: fluticasone propionate; HEDIS: Healthcare Effectiveness Data and Information Set. [#]: evidence levels are defined by the National Health and Medical Research Council [23]; [¶]: Ø: neutral study quality; +: positive study quality; methodological study quality was determined with the use of the Academy of Nutrition and Dietetics critical appraisal checklist [22].

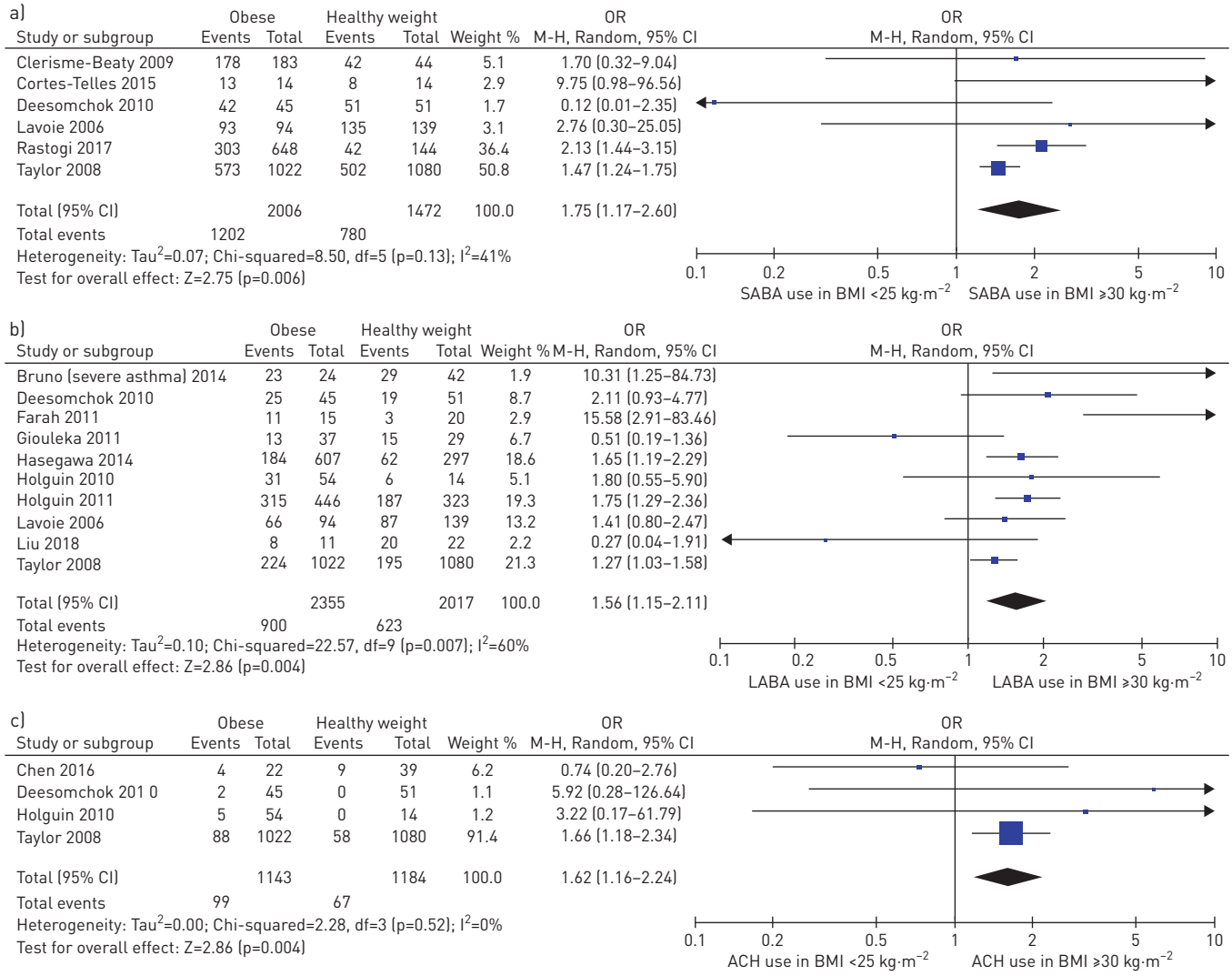

FIGURE 1 Effect of obesity on inhaled short- and long-acting bronchodilator asthma medication use. Forest plots of studies showing the difference in inhaled a) short-acting (short-acting β_2-agonists (SABA)) and b) long-acting β_2-agonists (LABA), c) anticholinergic (ACH) bronchodilator use, between obese (body mass index (BMI) ⩾30 kg·m^{-2}) and healthy-weight (BMI <25 kg·m^{-2}) subjects with asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% confidence intervals determined with the use of generic Mantel–Haenszel (M-H) random-effects models. Heterogeneity was quantified by I^2 at a significance of p<0.10. df: degree of freedom.

dose (figure 2), reported FEV_1 % predicted (figure 4) and reported FEV_1/FVC % (figure 4); thus, a random effects model was applied to all meta-analyses.

Meta-analysis: inhaled short- and long-acting bronchodilator asthma medication use

Inhaled short-acting (SABA) and long-acting (LABA, anticholinergic) bronchodilator asthma medication use was examined according to the asthma medication categories reported in the selected studies (figure 1). Information on SABA use by weight status was available from six studies including a total of 3478 subjects. The pooled odds ratio was significant, indicating higher SABA use in obese *versus* healthy-weight subjects (OR 1.75, 95% CI 1.17–2.60; p=0.006, I^2=41%). 10 studies (including 4372 subjects) reported data on LABA use by weight status. The pooled odds ratio was significant, showing higher LABA use in obese *versus* healthy-weight subjects (OR 1.56, 95% CI 1.15–2.11; p=0.004, I^2=60%). Moderate heterogeneity was detected across the included studies. Four studies (including 2327 subjects) reported on anticholinergic medication use by weight status. The pooled odds ratio was significant, demonstrating higher anticholinergic medication use in obese *versus* healthy-weight subjects (OR 1.62, 95% CI 1.16–2.24; p=0.004, I^2=0%).

Meta-analysis: inhaled preventer asthma medication use and dose

Inhaled preventer asthma medication use and dose was examined according to the asthma medication categories reported in the selected studies (figure 2). Data on ICS use according to weight status was

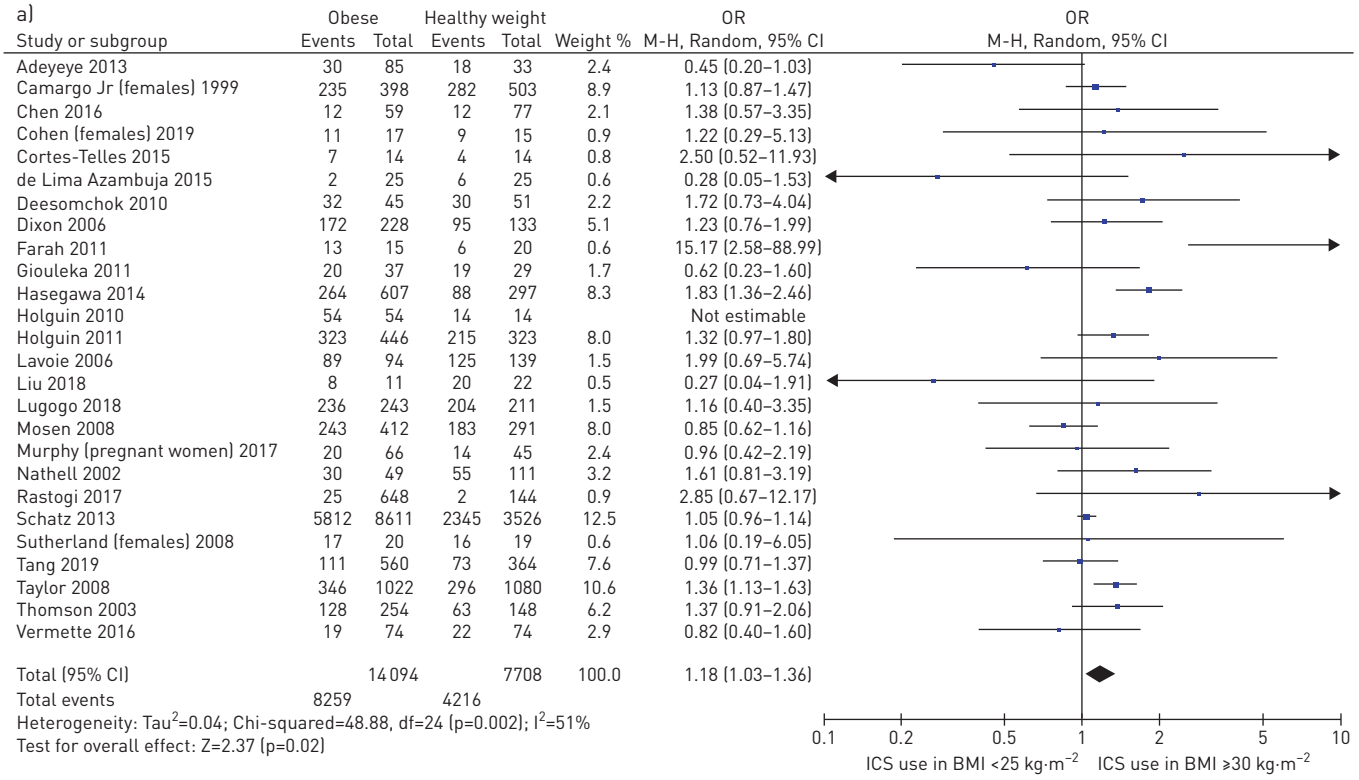

FIGURE 2 Effect of obesity on inhaled preventer asthma medication use and dose. Forest plots of studies showing the difference in a) inhaled corticosteroid (ICS) use, b) ICS+long-acting β_2-agonists (LABA) use, and c) ICS (beclomethasone dipropionate hydrofluoroalkane equivalent) dose ($\mu g \cdot day^{-1}$) between obese (body mass index (BMI) $\geqslant 30\ kg \cdot m^{-2}$) asthma and healthy-weight (BMI $<25\ kg \cdot m^{-2}$) asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. For graphs a) and b), values are odds ratios with 95% confidence intervals determined with the use of generic Mantel–Haenszel (M-H) random-effects models. For graph c), values are mean differences with 95% confidence intervals determined with the use of generic inverse variance (IV) random-effects models. Heterogeneity was quantified by I^2 at a significance of p<0.10. df: degree of freedom.

available from 26 studies including a total of 21 802 subjects. The pooled results were significant, demonstrating increased ICS use in obese *versus* healthy-weight subjects (OR 1.18, 95% CI 1.03–1.36; p=0.020, I^2=51%), however, moderate heterogeneity was found across the pooled studies. We identified six

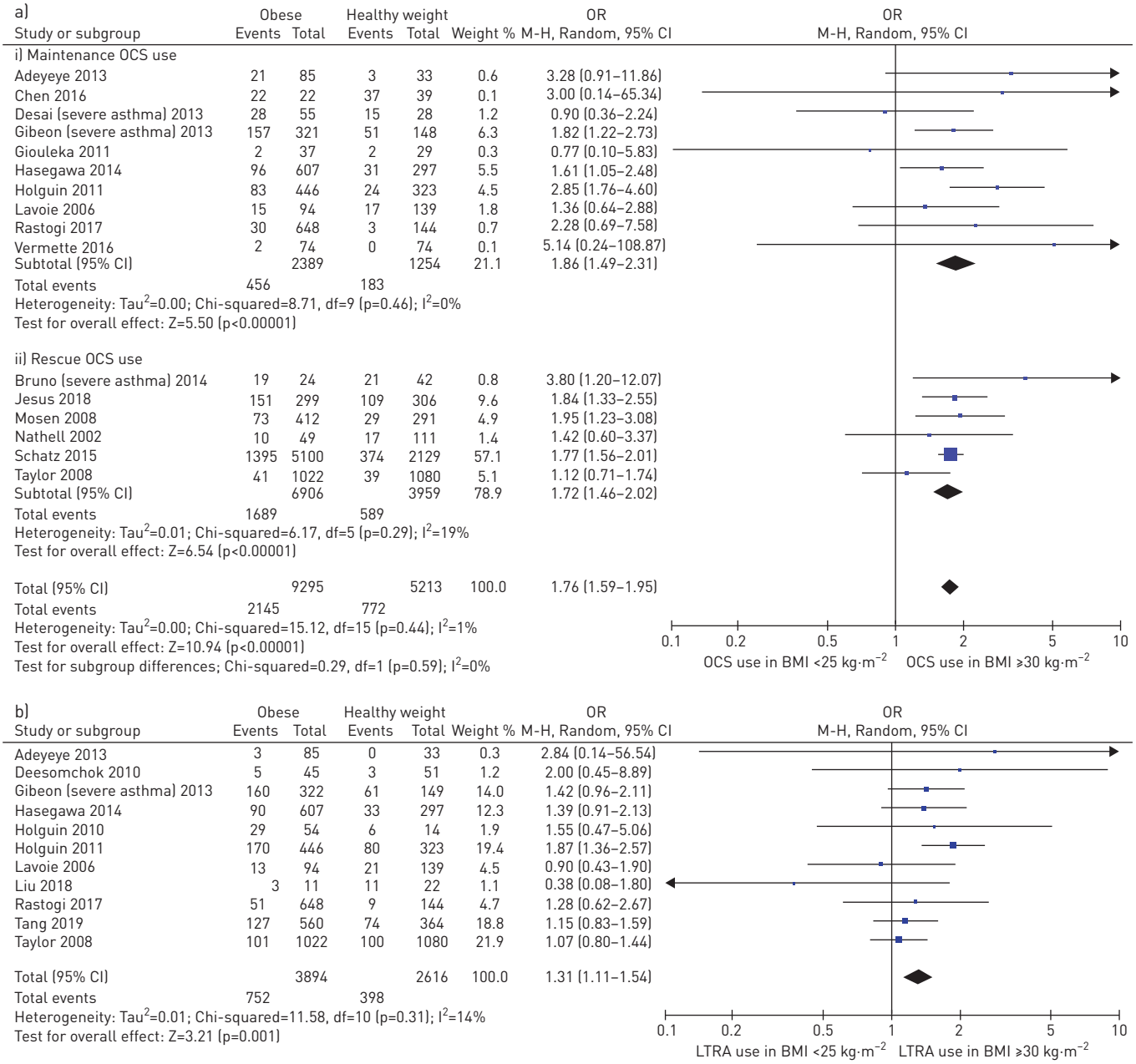

FIGURE 3 Effect of obesity on oral preventer asthma medication use. Forest plots of studies showing the difference in a) oral corticosteroid (OCS) use subgrouped into i) maintenance OCS use and ii) rescue OCS use, and b) leukotriene receptor antagonist (LTRA) use between obese (body mass index (BMI) ⩾30 kg·m^{-2}) asthma and healthy-weight (BMI <25 kg·m^{-2}) asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% confidence intervals determined with the use of generic Mantel–Haenszel (M-H) random-effects models. Heterogeneity was quantified by I^2 at a significance of p<0.10. df: degree of freedom.

studies (including 2561 subjects) reporting on ICS+LABA use in obese and healthy-weight subjects. The pooled OR was significant, demonstrating increased ICS+LABA use in obese subjects (OR 1.75, 95% CI 1.19–2.58; p=0.005, I^2=44%). Information on ICS dose in obese and healthy-weight subjects was available from nine studies including a total of 1321 subjects. The pooled results showed obese subjects with asthma use ∼208 µg more ICS (BDP-HFA equivalents) per day (mean difference 208.14, 95% CI 107.01–309.27; p<0.001, I^2=74%) compared to healthy-weight subjects with asthma. Study pooling demonstrated substantial heterogeneity in this model. Eight [27, 30, 37, 40, 42, 48, 53, 58] out of the 10 studies reported ICS dose in the form of BDP-HFA equivalents (µg·day^{-1}) and two [33, 34] reported ICS dose in the form of FP equivalents (µg·day^{-1}), which were equated to BDP-HFA equivalents before analysis.

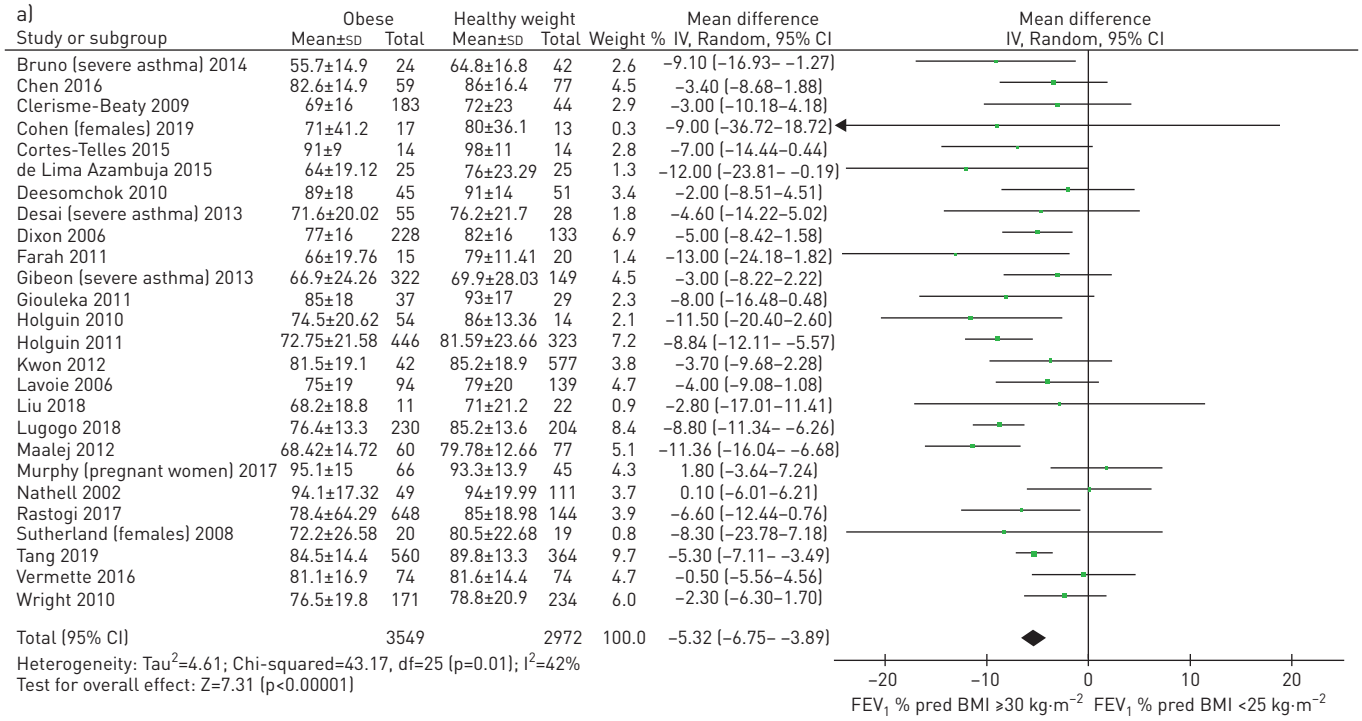

FIGURE 4 Effect of obesity on lung function. Forest plot of studies showing the difference in lung function between obese (body mass index (BMI) ⩾30 kg·m^{-2}) asthma and healthy-weight (BMI <25 kg·m^{-2}) asthma a) forced expiratory volume in 1 s (FEV_1 % predicted) and b) FEV_1/forced vital capacity (FVC) %. The pooled effect estimate (diamond) for each meta-analysis is shown. Values are mean differences with 95% confidence intervals determined with the use of generic inverse variance (IV) random-effects models. Heterogeneity was quantified by I^2 at a significance of p<0.10. df: degree of freedom.

Meta-analysis: oral preventer asthma medication use

Oral preventer asthma medication use was examined according to the asthma medication categories reported in the selected studies (figure 3). 16 studies (including 14 508 subjects) reported data on OCS use by weight status. The pooled OR was significant, showing higher OCS use in obese *versus* healthy-weight subjects (OR 1.76, 95% CI 1.59–1.95; p<0.001, I^2=1%). Subgroup analysis was then performed to examine the difference in maintenance OCS and rescue OCS in obese and healthy-weight subjects with asthma. Information on maintenance OCS use by weight status was available from 10 studies including a total of

3643 subjects. The pooled odds ratio was significant, indicating higher maintenance OCS in obese *versus* healthy-weight subjects (OR 1.86, 95% CI 1.49–2.31; p<0.001, I^2=0%). Data on rescue OCS use in obese and healthy-weight subjects was available from six studies including a total of 10 865 subjects. The pooled odds ratio was significant, indicating higher rescue OCS in obese *versus* healthy-weight subjects (OR 1.72, 95% CI 1.46–2.02; p<0.001, I^2=19%). A total of 11 studies (including 6510 subjects) provided data on LTRA use by weight status. The pooled odds ratio was significant, indicating increased LTRA use in obese *versus* healthy-weight subjects (OR 1.31, 95% CI 1.11–1.54; p=0.001, I^2=14%).

Meta-analysis: lung function

Lung function was examined using reported FEV_1 % predicted and FEV_1/FVC % in the selected studies (figure 4). FEV_1 % predicted in obese and healthy-weight subjects was reported in 26 studies including a total of 6521 subjects. The pooled mean difference showed a significant inverse association between obesity and FEV_1 % predicted; obese subjects with asthma had ~5.32% lower FEV_1 % predicted compared to healthy-weight subjects with asthma (mean difference −5.32%, 95% CI −6.75–−3.89; p<0.001, I^2=42%). Study pooling demonstrated moderate heterogeneity in this model. Data on FEV_1/FVC % by weight status was available from 22 studies including a total 5584 of subjects. The pooled mean difference did not show a significant difference in FEV_1/FVC % between obese and healthy-weight subjects with asthma (mean difference −0.10%, 95% CI −1.21–1.02; p=0.86, I^2=59%). Study pooling demonstrated moderate heterogeneity in this model.

Discussion

This systematic review and meta-analysis is the first, to our knowledge, to investigate the effect of obesity on asthma medication use and dose in adults. Our meta-analyses findings indicate that obesity is significantly associated with increased odds of asthma medication use (any use %), including inhaled short-acting (SABA) and long-acting (LABA, anticholinergic) bronchodilator asthma medication use, inhaled preventer asthma medication use (ICS, ICS+LABA) and oral preventer asthma medication use (OCS use; subgrouped into maintenance OCS and rescue OCS, LTRA). Meta-analyses conducted as part of this review also indicate that obese subjects with asthma use higher daily ICS doses (reported as BDP-HFA equivalents), have lower FEV_1 % predicted and similar FEV_1/FVC % compared to healthy-weight subjects with asthma.

Mounting evidence demonstrates an inverse relationship between obesity and response to asthma medications, such as ICS [10, 20, 59–61]; however, the pathobiological mechanisms contributing to this phenomenon remain largely unknown [14]. *Post hoc* analyses of clinical trials [10, 19, 61–63] have supported this finding, providing evidence of altered responses to standard asthma treatment across BMI categories. In fact, publications [10, 20] have specifically reported that obese subjects, particularly the morbidly obese (BMI $\geqslant$40 kg·m^{-2}) are less likely to achieve control using standard asthma treatments. In the study by Telenga *et al.* [59], pooled patient data from four well-defined asthma cohorts (n=423) demonstrated that after commencing ICS treatment, improvement in FEV_1 % predicted was lower and sputum neutrophils were higher in obese compared to nonobese asthma subjects. Similarly, Farah *et al.* [58] assessed clinical features in 49 asthma subjects before and after 3 months of daily treatment with 1500 µg ICS (beclomethasone) and showed a strong correlation between BMI and residual asthma symptoms, despite high-dose ICS treatment [58]. In general, ICS and combination ICS+LABA appear superior to montelukast (a LTRA) for the treatment of asthma in obese patients [61, 63]. According to the *post hoc* analysis of 1052 persistent asthma patients by Sutherland *et al.* [63], ICS (inhaled fluticasone diproprionate) compared to montelukast led to greater symptom reduction and a statistically greater improvement in clinical features within all weight groups, including the subgroup who were obese (BMI $\geqslant$30 kg·m^{-2}). In addition, Camargo *et al.* [61] investigated the relationship between BMI and response to treatment with ICS+LABA (inhaled FP +salmeterol 100/50 µg) *versus* montelukast (10 mg) in a retrospective analysis of four pooled published clinical trials. Observations showed that, in comparison to healthy-weight subjects, the time to peak FEV_1 was longer in the very obese subjects, and responses to ICS+LABA were superior compared to montelukast. A study with conflicting results, Peters-Golden *et al.* [10], examined the effect of overweight/obesity on therapeutic responsiveness to either ICS (inhaled beclomethasone 200 µg four puffs twice daily) or montelukast (oral 10 mg once daily) in 3073 patients with moderate asthma. In this study, overweight/obese subjects showed a reduced response to ICS, with fewer days where asthma control was achieved, whereas responsiveness to montelukast remained unaffected by BMI. Findings from the meta-analysis included in this review showed that obese asthma subjects were more likely to use LTRA compared to healthy-weight subjects; however, there is currently no evidence to suggest that response to LTRA is reduced in obese asthma. Furthermore, as reflected in the literature and in this review, increasing corticosteroid doses in obese subjects based on poor asthma control, as currently recommended in guidelines, may lead to overtreatment with corticosteroids in this population.

In regard to OCS use, a similar pattern of agent insensitivity has been observed, although it is not as commonly investigated. Gibeon *et al.* [51] and Mosen *et al.* [27] have shown that maintenance treatment with high-dose oral prednisolone is more prevalent in obese subjects despite displaying a similar degree of airway obstruction and eosinophilic airway inflammation to nonobese subjects. Caution is warranted with regards to increasing maintenance OCS treatment in obese subjects, as it is unlikely to improve corticosteroid-unresponsive factors, and may contribute to the development of side-effects such as insulin resistance [64]. Furthermore, in agreement with the findings from our meta-analysis, other studies also report higher SABA use in obese compared to healthy-weight asthma. Two cross-sectional studies by Taylor *et al.* [15] and Rastogi *et al.* [28], together reporting on data from 2894 asthma subjects, displayed increased use of SABA in obese subjects compared to nonobese subjects. Again, suggesting that obese subjects are experiencing worse symptoms and/or reduced bronchodilator efficacy.

Mechanisms explaining why obese asthmatics use asthma medications more often and in higher doses remain unclear, although may be the result of obesity-induced changes influencing the airways such as systemic inflammation, altered airway inflammatory profile, mechanical effects (lung restriction and airway closure), genetics and/or treatment insensitivity factors [3, 65]. Another plausible hypothesis includes the misinterpretation of obesity-related symptoms/comorbidities by the patient or physician being attributed to asthma. It is likely that multiple factors are important, implying that multiple approaches may be required to improve medication efficacy and disease control in this population.

A growing pool of evidence supports the hypothesis that obesity induces a unique pattern of airway inflammation, which may respond poorly to corticosteroids. Obese asthmatic airways typically demonstrate a noneosinophilic, neutrophilic inflammatory phenotype [59, 66, 67], demonstrated by low reduced fractional exhaled nitric oxide levels and high sputum neutrophils [45, 68–71]. This is consistent with the findings from the cluster analysis by Haldar *et al.* [72], which identified a clinical asthma phenotype defined by obesity, noneosinophilic inflammation, high level of symptoms and poorer response to steroid-based treatment. Current therapies have largely been developed to target Th2-high type, allergy driven asthma in lean subjects, using lean animal models of asthma and conducting clinical trials in leaner populations, not accounting for the variability seen in obese patients [14]. Hence, it is not surprising that existing therapies are not optimal for obese asthma subjects and alternative approaches to therapy are needed.

Adipose tissue is metabolically active and its accumulation stimulates chronic low-grade systemic inflammation and alters immune system functioning, which can have direct negative effects on the airways [73]. Rapid enlargement of adipose tissue creates a hypoxic environment accompanied by tissue remodelling, which promotes cell death and a build-up of pro-inflammatory mediators (*e.g.* leptin, C-reactive protein, interleukins (*e.g.* interleukin (IL)-1β and IL-6) and tumour necrosis factor (TNF)-α) which can leak into the circulation and have effects on end organs such as the lungs [74]. Many of these cytokines and mediators increased in obesity-induced systemic inflammation have also been linked to the development of corticosteroid insensitivity [75].

In addition, chronic lipogenesis inhibits adipocytes from being able to appropriately store excess lipids, thus remaining free fatty acids spill over into the bloodstream and switch on inflammatory responses. Evidence suggests that excess saturated fatty acids in the post-prandial phase lead to impaired responses to the SABA albuterol in asthma [76]. This highlights dyslipidaemia in obese asthmatics as another factor that potentially reduces the efficacy of pharmacotherapy in obese asthma.

Obesity fundamentally changes lung mechanics due to the mass loading of adipose tissue on the chest wall and visceral adipose tissue on the diaphragm. This restriction causes obese subjects to breathe (on average) at lower resting lung volumes compared to lean subjects, resulting in lower lung function values such as FEV_1 and FVC, with potentially preserved FEV_1/FVC ratios [77]. This relationship between obesity and chest wall restriction has been observed in our meta-analyses, with lower FEV_1 % predicted in obese subjects in the presence of preserved FEV_1/FVC %. FEV_1 % may be reduced in the presence of obesity, but not related to asthma severity, and therefore increases in prescribed medications may not ameliorate this deficit. Furthermore, the mechanical effects of obesity have been suggested as an explanation for reduced inhaled therapy efficacy, as delivery of inhaled therapies to the smaller airways may be compromised. However, this is unlikely to be a major contributing factor, as inhaled therapies function mainly in larger to medium-size airways [6] and obese patients still experience worse asthma control following oral treatment compared to nonobese patients [78].

Another important consideration is the possibility that a significant proportion of symptoms in the obese asthma population might be incorrectly attributed to asthma by the patient and/or physician. Obesity comorbidities (*e.g.* GORD and OSA) manifest clinically in symptoms of breathlessness, making it difficult to distinguish and classify the cause of these symptoms [79]. Misinterpretation of symptoms caused by

comorbidities as "asthma" may lead to increases in treatment, which neglects the underlying cause. This will probably result in persistent symptoms despite higher asthma medication use. This is a complex issue for physicians to overcome. To address the influence of obese comorbidities in the presence of asthma, physicians should perform multidimensional assessments [80] when treating patients to accurately identify the root cause of symptoms and treat appropriately. This also highlights the importance of adhering to the Global Initiative for Asthma guidelines [1] and using objective tests to confirm asthma diagnosis, to avoid falsely diagnosing obese patients as having asthma due to symptoms related to obesity comorbidities. The literature suggests that the misdiagnosis of asthma is common, although no convincing evidence shows that misdiagnosis is more common in obese than nonobese patients. Aaron *et al.* [81] performed a prospective study of 540 patients with physician-diagnosed asthma, and following extensive assessment with bronchial reversibility, methacholine challenge and withdrawal of asthma medication, they found that 31.8% of obese and 28.7% of nonobese patients given a prior diagnosis of asthma were misdiagnosed. This finding suggests that the increased prevalence of asthma in association with obesity is a true phenomenon and not simply due to diagnostic mislabelling. Other plausible explanations for increased medication use in the obese population include suboptimal inhaler technique, poor medication compliance, and psychosocial disturbances, leading to poorly controlled asthma. However, there is limited evidence suggesting that these factors are more prevalent in obese compared to healthy-weight asthmatics [82, 83]. In summary, obesity has pleiotropic effects on lung mechanics, immune function and inflammatory mediators, which may alter asthma therapy responsiveness. Current treatment recommendations do not differ according to BMI; however, our review clearly demonstrates that medication use is higher in obese subjects. Optimal pharmacological treatment strategies for obese patients remains to be determined and future trials focusing on the development and optimisation of treatments specifically for obese patients are indicated.

The strengths of this review include the comprehensive literature search, well-defined inclusion criteria, systematic approach to data collection, in-depth data extraction, and meta-analyses. Moreover, all studies were assessed for quality and validity. Limitations associated with this review include the lack of detail regarding the duration of asthma medication use, the dose used by subjects and assessment of medication compliance. Included studies were also heterogeneous in terms of study population age, sample size, comorbidities and level of asthma control and severity. It is important to note that many of the studies included in the review were conducted using subjects participating in clinical trials, which may not be representative of the general population. Some of the meta-analyses include a large number of studies, which helps explain the increased heterogeneity. Another limitation worth noting is that BMI is not the gold-standard method to assess body composition; however, it does correlate with total body fat content and has been the most widely used measure to assess obesity and to monitor changes in body weight. Future research should consider more in depth anthropometric measures (*e.g.* waist circumference, skinfold thickness or bioelectrical impedance analysis) that assess total body mass distribution and body fat mass.

In conclusion, this systematic review of the literature found that obese asthmatics have a higher likelihood of using all classes of asthma medications and higher ICS dose, despite lower FEV_1 and similar FEV_1/FVC %, in obese *versus* healthy-weight asthmatics. Future research is needed to explore the causes underlying these observations. Results yielded from this review emphasise the need to optimise treatment in obese asthma. In addition, we need to better understand the mechanisms underlying obese asthma to develop tailored pharmacological treatments which improve outcomes in this phenotype of asthma.

Conflict of interest: None declared.

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