EUROPEAN RESPIRATORY journal

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

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

Cherry A. Thompson, Shaun R. Eslick, Bronwyn S. Berthon, Lisa G. Wood

Please cite this article as: Thompson CA, Eslick SR, Berthon BS, *et al*. Asthma medication use in obese and healthy weight asthma: systematic review/meta-analysis. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.00612-2020).

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

Cherry A. Thompson, BBSc[1]
Shaun R. Eslick, BNutrDiet[1]
Bronwyn S. Berthon, PhD[1]
Lisa G. Wood, PhD[1]

[1]Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, School of Biomedical Sciences and Pharmacy, Faculty of Health and Medicine, University of Newcastle, Callaghan, NSW 2308, Australia; cherry.thompson@uon.edu.au (C.A.T); shaun.eslick@uon.edu.au (S.R.E); bronwyn.berthon@newcastle.edu.au (B.S.B); lisa.wood@newcastle.edu.au (L.G.W)

Corresponding author/author to be contacted regarding manuscript after publication:
Lisa Wood, Centre for Healthy Lungs, Level 2, West Wing, HMRI Building, Kookaburra Crt, New Lambton Heights, NSW, Australia, 2305. Ph (61) 240420147, email: lisa.wood@newcastle.edu.au

Declarations of interest: None

Funding: None

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

Abstract

Background: Obesity is a common co-morbidity 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 (BMI≥30kg/m^2) versus healthy weight (BMI<25kg/m^2) subjects with asthma.

Design: Databases including CINAHL, Cochrane, EMBASE, and MEDLINE were searched for English language studies up to July 2019 that recorded medication use or dose in obese and healthy weight adults with asthma. A critical appraisal checklist was utilised for scrutinising methodologic quality of eligible studies. Meta-analysis was performed and heterogeneity was examined with the use of the χ^2 test. This review was conducted based on a published protocol (PROSPERO: CRD42020148671).

Results: Meta-analysis showed that obese subjects are more likely to use asthma medications including; short-acting β_2-agonists [odds ratio (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 dose (µg/day) was significantly higher in obese subjects (mean difference=208.14; 95% CI:107.01, 309.27; p<0.001, I^2=74%). 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/FVC% 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.

Keywords: asthma, obesity, asthma treatment, asthma-medication, asthma pharmacotherapy, asthma therapy

1. Introduction

Asthma is a chronic condition predominantly affecting the lower respiratory tract, characterised by airway hyperresponsiveness (AHR), 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 within the literature [3]. Obesity is associated with both increased asthma incidence and prevalence (particularly in adult women), shown in a meta-analysis conducted in over 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 also 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, non-atopic asthma (LONA), each with different etiologies and clinical implications. The first, EOA, manifests traditional features of allergic asthma [T-helper cell type 2 (Th)2 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, over $300 million per annum is spent on asthma pharmaceuticals, attributed mainly to inhaled corticosteroids (ICS) [15]. Increased obese asthma-related health care costs are largely a result of increased prescription medication expenses [16]. Mainstay clinical asthma management typically focuses on pharmacologic treatment, though 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, though 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, 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 it's paramount role in controlling disease, reducing severity and treating life-threatening exacerbations. Pharmacotherapies, in particular β_2-agonists, also 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.

2. Methods

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

2.1. 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 (MeSH) 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.

2.2. 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 (≥18 years) with asthma, including all genders and ethnicity's. The exposure of interest was obesity [body mass index (BMI)≥30kg/m^2], which was compared to healthy weight (BMI<25kg/m^2). The study outcome measures were asthma medication use (any use %), asthma medication dose (µg/day), and lung function using forced expiratory volume in 1 second (FEV_1)% predicted values, and forced expiratory volume in 1 second/forced vital capacity (FEV_1/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 2 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.

2.3. Study Quality

Following full-text appraisal, eligible articles were reviewed for methodologic quality using the standardised critical appraisal checklist designed by the American Dietetic Association [22]. This tool combines 4 relevance questions that address the translation of study findings to practice and 10 validity questions that address scientific rigor. All articles

were rated as positive, negative, or neutral quality. Studies of negative quality ("no" response to ≥6 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 (NHMRC) of Australia levels of evidence hierarchy [23].

2.4. 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 (LABA, anticholinergic) bronchodilator use, inhaled preventer use (ICS, ICS+LABA), oral preventer use [maintenance oral corticosteroid (OCS), rescue OCS, leukotriene receptor antagonists (LTRA)]}, ICS dose (μg/day) [reported as beclomethasone dipropionate (BDP) in hydrofluoroalkane (HFA) equivalents], and lung function measures (reported as FEV_1% predicted and FEV_1/FVC%).

2.5. Statistical Methods

Meta-analysis was performed using Review Manager (RevMan, version 5.3, Nordic Cochrane Centre) to analyse the difference between asthma medication use (any use %), asthma medication dose (μg/day), and lung function in obese and healthy weight subjects with asthma. Heterogeneity in meta-analysis models was examined with the use of the χ^2 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 (OR) [odds ratio effect size] and corresponding 95% CIs 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 (IV) statistical method was used for evaluating differences in ICS dose (μg/day), and lung function (FEV_1% predicted, FEV_1/FVC%) by weight status, and the mean difference [effect size] and corresponding 95% CIs were calculated. In assessment of ICS dose, fluticasone propionate (FP) equivalents (μg/day) were reported as approximately equivalent to BDP-HFA equivalents (μg/day) [25].

3. Results

The search strategy identified 8,941 articles of which 2,603 duplicates were discarded (see supplementary material for PRISMA flowchart). Next 6,338 article titles were evaluated based on the review inclusion and exclusion criteria of which 2,380 remained for abstract

appraisal. Then 491 articles were excluded after abstract review, with 1,889 retrieved for full text review. Based on full text, 1,854 articles were excluded based on exposure (n=1,177), outcomes (n=656) or study design (n=21). Finally, thirty-five articles were included in the review.

3.1. Description of Included Studies

Of the 35 included studies (Table 1), cross-sectional design [12, 15, 26-42] was most commonly used (n=19), followed by 6 retrospective cohort studies [43-48], 6 prospective cohort studies [49-54], 3 case-control studies [55-57], and one time series study [58]. 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, 9,180 from prospective cohort studies, 7,373 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. Prevalence of comorbidities are recorded in Table 1 when reported. Such comorbidities include diabetes, obstructive sleep apnea (OSA), gastro-esophageal reflux disorder (GERD), hypertension, depression, and rhinitis. The methodological quality of 28 of the studies included in this review was positive (80%). These studies were methodologically strengthened by their selection of study subjects, comparability of study groups, and clearly defining 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. Nil 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, whilst 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 use (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]. Then 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 SABA use in 17% of studies (n=6) [15, 26, 28, 32, 33, 57], ICS + LABA use (n=6) [28, 35, 41, 47, 48, 57], and 11% reported anticholinergic use (n=4) [15, 32, 40, 56]. From the 35 studies, 29% reported ICS dose (µg/day) (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.

3.2. 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) 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) (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), 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 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.

<u>Meta-Analysis – Inhaled short- and long-acting bronchodilator asthma medication use</u>

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 6 studies including a total of 3,478 subjects. The pooled OR 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%). Ten studies (including 4,372 subjects) reported data on LABA use by weight status. The pooled OR 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 2,327 subjects) reported on anticholinergic medication use by weight status. The pooled OR 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 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 6 studies (including 2,561 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 9 studies including a total of 1,321 subjects. The pooled results showed obese subjects with asthma use approximately 208µg 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) and 2 [33, 34] reported ICS dose in the form of FP equivalents (µg/day), which were equated to BDP-HFA equivalents before analysis.

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). Sixteen 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 3,643 subjects. The pooled OR 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 6 studies including a total of 10,865 subjects. The pooled OR 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 6,510 subjects) provided data on LTRA use by weight status. The pooled OR 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 6,521 subjects. The pooled mean difference showed a significant inverse association between obesity and FEV_1% predicted; obese subjects with asthma had approximately 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 5,584 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.

4. 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 indicates 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 [19, 61-64] 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≥40kg/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 1500µg 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, 64]. According to the post-hoc analysis of 1,052 persistent asthma patients by Sutherland et al. [64], 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 $\geq$30kg/m^2). In addition, Camargo et al. [61] investigated the relationship between BMI and response to treatment with ICS+LABA (inhaled FP + salmeterol 100/50µg) versus montelukast (10 mg) in a retrospective analysis of 4 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 200µg 4 puffs bidaily) or montelukast (oral 10mg once daily) in 3,073 patients with moderate asthma. In this study, overweight/obese subjects showed a reduced response to ICS, with less 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 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 [65]. 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 2,894 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, though 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, 66]. 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 non-eosinophilic, neutrophilic inflammatory phenotype, [59, 67, 68], demonstrated by low reduced fractional exhaled nitric oxide levels and high sputum neutrophils [45, 69-72]. This is consistent with the findings from the cluster analysis by Haldar et al. [73], which identified a clinical asthma phenotype defined by obesity, non-eosinophilic 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 [74]. 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. IL-1β and IL-6) and tumour necrosis factor alpha (TNF-α)] that can leak into the circulation and have effects on end organs such as the lungs [75]. Many of these cytokines and mediators increased in

obesity-induced systemic inflammation have also been linked to the development of corticosteroid insensitivity [76].

Chronic lipogenesis also 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 postprandial phase lead to impaired responses to the short acting β_2-agonist, albuterol, in asthma [77]. This highlights dyslipidemia 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 [78]. 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 [79].

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. GERD and OSA) clinically manifest in symptoms of breathlessness, making it difficult to distinguish and classify the cause of these symptoms [80]. Misinterpretation of symptoms caused by comorbidities as ‘asthma’ may lead to increases in treatment, which neglects the underlying cause. This will likely 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 [81] 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 [82] 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. [83] 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 [84, 85]. 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, co-morbidities, 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.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. *Available from,: wwwginasthmaorg* 2019.

2. 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): 661-666.

3. Peters U, Dixon AE, Forno E. Obesity and asthma. *Journal of Allergy and Clinical Immunology* 2018: 141(4): 1169-1179.

4. Brigham EP, Steffen LM, London SJ, Boyce D, Diette GB, Hansel NN, Rice J, McCormack MC. Diet pattern and respiratory morbidity in the atherosclerosis risk in communities study. *Ann Am Thorac Soc* 2018: 15(6): 675-682.

5. Hallstrand TS, Fischer ME, Wurfel MM, Afari N, Buchwald D, Goldberg J. Genetic pleiotropy between asthma and obesity in a community-based sample of twins. *J Allergy Clin Immunol* 2005: 116(6): 1235-1241.

6. Dixon AE, Peters U. The effect of obesity on lung function. *Expert review of respiratory medicine* 2018: 12(9): 755-767.

7. Al-Alwan A, Bates JHT, Chapman DG, Kaminsky DA, DeSarno MJ, Irvin CG, Dixon AE. The nonallergic asthma of obesity. A matter of distal lung compliance. *Am J Respir Crit Care Med* 2014: 189(12): 1494-1502.

8. Dixon AE, Pratley RE, Forgione PM, Kaminsky DA, Whittaker-Leclair LA, Griffes LA, Garudathri J, Raymond D, Poynter ME, Bunn JY, Irvin CG. Effects of obesity and bariatric surgery on airway hyperresponsiveness, asthma control, and inflammation. *J Allergy Clin Immunol* 2011: 128(3): 508-515.e501-502.

9. Chapman DG, Irvin CG, Kaminsky DA, Forgione PM, Bates JHT, Dixon AE. Influence of distinct asthma phenotypes on lung function following weight loss in the obese. *Respirology* 2014: 19(8): 1170-1177.

10. Peters-Golden M, Swern A, Bird S, Hustad C, Grant E, Edelman J. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006: 27(3): 495-503.

11. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nature medicine* 2012: 18(5): 716-725.

12. Holguin F, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Erzurum SC, Fitzpatrick AM, Gaston B, Israel E, Jarjour NN, Moore WC, Peters SP, Yonas M, Teague WG, Wenzel SE. Obesity and asthma: an association modified by age of asthma onset. *J Allergy Clin Immunol* 2011: 127(6): 1486-1493.e1482.

13. Sutherland ER, Goleva E, King TS, Lehman E, Stevens AD, Jackson LP, Stream AR, Fahy JV, Leung DYM, Asthma Clinical Research N. Cluster analysis of obesity and asthma phenotypes. *PLoS ONE* 2012: 7(5): e36631.

14. Pradeepan S, Garrison G, Dixon AE. Obesity in Asthma: Approaches to Treatment. *Curr Allergy Asthma Rep* 2013: 13(5): 434-442.

15. Taylor B, Mannino D, Brown C, Crocker D, Twum-Baah N, Holguin F. Body mass index and asthma severity in the National Asthma Survey. *Thorax* 2008: 63(1): 14-20.

16. Raebel MA, Malone DC, Conner DA, Xu S, Porter JA, Lanty FA. Health services use and health care costs of obese and nonobese individuals. *Arch Intern Med* 2004: 164(19): 2135-2140.

17. Stoodley I, Williams L, Thompson C, Scott H, Wood L. Evidence for lifestyle interventions in asthma. *Breathe* 2019: 15(2): e50-e61.

18. Raissy HH, Kelly HW, Harkins M, Szefler SJ. Inhaled corticosteroids in lung diseases. *American journal of respiratory and critical care medicine* 2013: 187(8): 798-803.

19. Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DY, Sutherland ER, Goleva E, Strand M, Beuther DA, Leung DYM. Body mass and glucocorticoid response in asthma. *Am J Respir Crit Care Med* 2008: 178(7): 682-687.

20. Boulet L-P, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. *Respir Med* 2007: 101(11): 2240-2247.

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009: 151(4): 264-269.

22. Nutrition Ao, Dietetics. Evidence analysis manual: steps in the academy evidence analysis process. Academy of Nutrition and Dietetics Chicago, IL, 2012.

23. Health N, Council MR. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. *NHMRC* 2009.

24. Higgins JP CR, Chandler J, Cumpston MS, editor(s). Cochrane Handbook for Systematic Reviews of Interventions version 5.2.0 (updated June 2017). *The Cochrane Collaboration,* 2017: Available from www.training.cochrane.org/handbook.

25. Inhaled corticosteroid doses for NICE's asthma guideline. *National Institute for Health and Care Excellence,* 2018.

26. Clerisme-Beaty EM, Karam S, Rand C, Patino CM, Bilderback A, Riekert KA, Okelo SO, Diette GB. Does higher body mass index contribute to worse asthma control in an urban population? *J Allergy Clin Immunol* 2009: 124(2): 207-212.

27. Mosen DM, Schatz M, Magid DJ, Camargo CA, Jr. The relationship between obesity and asthma severity and control in adults. *J Allergy Clin Immunol* 2008: 122(3): 507-511.e506.

28. Rastogi D, Jung M, Strizich G, Shaw PA, Davis SM, Klein OL, Penedo FJ, Ries AL, Daviglus ML, Moreiras JJ, Salathe MA, Celedon JC, Isasi CR, Kaplan RC. Association of systemic inflammation, adiposity, and metabolic dysregulation with asthma burden among Hispanic adults. *Respir Med* 2017: 125: 72-81.

29. Bruno A, Pace E, Cibella F, Chanez P. Body mass index and comorbidities in adult severe asthmatics. *Biomed Res Int* 2014: 2014: 607192.

30. Desai D, Newby C, Symon FA, Haldar P, Shah S, Gupta S, Bafadhel M, Singapuri A, Siddiqui S, Woods J, Herath A, Anderson IK, Bradding P, Green R, Kulkarni N, Pavord I, Marshall RP, Sousa AR, May RD, Wardlaw AJ, Brightling CE. Elevated sputum interleukin-5 and submucosal eosinophilia in obese individuals with severe asthma. *Am J Respir Crit Care Med* 2013: 188(6): 657-663.

31. Nathell L, Jensen I, Larsson K. High prevalence of obesity in asthmatic patients on sick leave. *Respir Med* 2002: 96(8): 642-650.

32. Deesomchok A, Fisher T, Webb KA, Ora J, Lam Y-M, Lougheed MD, O'Donnell DE. Effects of obesity on perceptual and mechanical responses to bronchoconstriction in asthma. *Am J Respir Crit Care Med* 2010: 181(2): 125-133.

33. Lavoie KL, Bacon SL, Labrecque M, Cartier A, Ditto B. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med* 2006: 100(4): 648-657.

34. Wright A, Lavoie KL, Jacob A, Rizk A, Bacon SL. Effect of body mass index on self-reported exercise-triggered asthma. *Phys Sportsmed* 2010: 38(4): 61-66.

35. de Lima Azambuja R, da Costa Santos Azambuja LSE, Costa C, Rufino R. Adiponectin in Asthma and Obesity: Protective Agent or Risk Factor for More Severe Disease? *Lung* 2015: 193(5): 749-755.

36. Jesus JPVd, Lima-Matos AS, Almeida PCA, Lima VB, Mello LMd, Souza-Machado A, Ponte EV, Cruz ÁA. Obesity and asthma: clinical and laboratory characterization of a common combination. *Jornal Brasileiro de Pneumologia* 2018: 44(3): 207-212.

37. Maalej S, Yaacoub Z, Fakhfekh R, Yaalaoui S, Kheder AB, Drira I. Association of obesity with asthma severity, control and quality of life. *Tanaffos* 2012: 11(1): 38-43.

38. Sutherland TJT, Cowan JO, Young S, Goulding A, Grant AM, Williamson A, Brassett K, Herbison GP, Taylor DR. The association between obesity and asthma: interactions between systemic and airway inflammation. *Am J Respir Crit Care Med* 2008: 178(5): 469-475.

39. Adeyeye OO, Ogunleye OO, Onadeko BO, Bamisile RT, Brodie-Mends A, Ekrikpo U. Body mass index and asthma severity in a population of Nigerian asthmatics. *Afr J Med Med Sci* 2013: 42(1): 33-38.

40. Chen JH, Qin L, Shi YY, Feng JT, Zheng YL, Wan YF, Xu CQ, Yang XM, Hu CP. IL-17 protein levels in both induced sputum and plasma are increased in stable but not acute asthma individuals with obesity. *Respir Med* 2016: 121: 48-58.

41. Kwon J-W, Kim S-H, Kim T-B, Kim S-H, Park H-W, Chang Y-S, Jang A-S, Cho YS, Nahm D-H, Park J-W, Yoon HJ, Cho Y-J, Choi BW, Moon H-B, Cho S-H. Airway hyperresponsiveness is negatively associated with obesity or overweight status in patients with asthma. *Int Arch Allergy Immunol* 2012: 159(2): 187-193.

42. Liu Y, Zheng J, Zhang HP, Zhang X, Wang L, Wood L, Wang G. Obesity-Associated Metabolic Signatures Correlate to Clinical and Inflammatory Profiles of Asthma: A Pilot Study. *Allergy, asthma & immunology research* 2018: 10(6): 628-647.

43. Dixon AE, Shade DM, Cohen RI, Skloot GS, Holbrook JT, Smith LJ, Lima JJ, Allayee H, Irvin CG, Wise RA, American Lung Association-Asthma Clinical Research C. Effect of obesity on clinical presentation and response to treatment in asthma. *J Asthma* 2006: 43(7): 553-558.

44. Hasegawa K, Tsugawa Y, Lopez BL, Smithline HA, Sullivan AF, Camargo CA, Jr. Body mass index and risk of hospitalization among adults presenting with asthma exacerbation to the emergency department. *Ann Am Thorac Soc* 2014: 11(9): 1439-1444.

45. Lugogo N, Green CL, Agada N, Zhang S, Meghdadpour S, Zhou R, Yang S, Anstrom KJ, Israel E, Martin R. Obesity's effect on asthma extends to diagnostic criteria. *Journal of Allergy and Clinical Immunology* 2018: 141(3): 1096-1104.

46. Schatz M, Zeiger RS, Zhang F, Chen W, Yang S-J, Camargo CA, Jr. Overweight/obesity and risk of seasonal asthma exacerbations. *J Allergy Clin Immunol Pract* 2013: 1(6): 618-622.

47. Tang M, Henderson RJ, Holbrook JT, Que LG, Mathews AM, Wise RA, Dixon AE, Peters SP, Rogers L, Smith LJ. Does Obesity Increase Respiratory Tract Infections in Patients with Asthma? *The Journal of Allergy and Clinical Immunology: In Practice* 2019: 7(3): 954-961. e956.

48. Vermette A, Boulay ME, Boulet LP. Discrepancies between asthma control criteria in asthmatic patients with and without obesity. *Obesity (Silver Spring)* 2016: 24(9): 1854-1860.

49. Schatz M, Zeiger RS, Yang SJ, Chen W, Sajjan S, Allen-Ramey F, Camargo CA. Prospective study on the relationship of obesity to asthma impairment and risk. *Journal of Allergy and Clinical Immunology: In Practice* 2015: 3(4): 560.

50. Thomson CC, Clark S, Camargo CA, Jr., Investigators M. Body mass index and asthma severity among adults presenting to the emergency department. *Chest* 2003: 124(3): 795-802.

51. Gibeon D, Batuwita K, Osmond M, Heaney LG, Brightling CE, Niven R, Mansur A, Chaudhuri R, Bucknall CE, Rowe A, Guo Y, Bhavsar PK, Chung KF, Menzies-Gow A. Obesity-associated severe asthma represents a distinct clinical phenotype: analysis of the British Thoracic Society Difficult Asthma Registry Patient cohort according to BMI. *Chest* 2013: 143(2): 406-414.

52. Giouleka P, Papatheodorou G, Lyberopoulos P, Karakatsani A, Alchanatis M, Roussos C, Papiris S, Loukides S. Body mass index is associated with leukotriene inflammation in asthmatics. *Eur J Clin Invest* 2011: 41(1): 30-38.

53. Murphy VE, Jensen ME, Powell H, Gibson PG. Influence of maternal body mass index and macrophage activation on asthma exacerbations in pregnancy. *The Journal of Allergy and Clinical Immunology: In Practice* 2017: 5(4): 981-987. e981.

54. Camargo Jr CA, Weiss ST, Zhang S, Willett WC, Speizer FE. Prospective study of body mass index, weight change, and risk of adult- onset asthma in women. *Arch Intern Med* 1999: 159(21): 2582-2588.

55. Cohen RI, Ye X, Ramdeo R, Liu SF. The number and function of T regulatory cells in obese atopic female asthmatics. *J Asthma* 2019: 56(3): 303-310.

56. Holguin F, Cribbs S, Fitzpatrick AM, Ingram RH, Jr., Jackson AC. A deep breath bronchoconstricts obese asthmatics. *J Asthma* 2010: 47(1): 55-60.

57. Cortes-Telles A, Torre-Bouscoulet L, Silva-Ceron M, Mejia-Alfaro R, Syed N, Zavorsky GS, Guenette JA. Combined effects of mild-to-moderate obesity and asthma on physiological and sensory responses to exercise. *Respir Med* 2015: 109(11): 1397-1403.

58. Farah CS, Kermode JA, Downie SR, Brown NJ, Hardaker KM, Berend N, King GG, Salome CM. Obesity is a determinant of asthma control independent of inflammation and lung mechanics. *Chest* 2011: 140(3): 659-666.

59. Telenga ED, Tideman SW, Kerstjens HAM, Hacken NHTT, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. *Allergy* 2012: 67(8): 1060-1068.

60. Camargo Jr CA, Sutherland ER, Bailey W, Castro M, Yancey SW, Emmett AH, Stempel DA, Camargo CA, Jr. Effect of increased body mass index on asthma risk, impairment and response to asthma controller therapy in African Americans. *Curr Med Res Opin* 2010: 26(7): 1629-1635.

61. Camargo CA, Jr., Boulet L-P, Sutherland ER, Busse WW, Yancey SW, Emmett AH, Ortega HG, Ferro TJ. Body mass index and response to asthma therapy: fluticasone propionate/salmeterol versus montelukast. *J Asthma* 2010: 47(1): 76-82.

62. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J* 2006: 27(3): 495-503.

63. Anderson WJ, Lipworth BJ. Does body mass index influence responsiveness to inhaled corticosteroids in persistent asthma? *Ann Allergy Asthma Immunol* 2012: 108(4): 237-242.

64. Sutherland ER, Camargo Jr CA, Busse WW, Meltzer EO, Ortega HG, Yancey SW, Emmett AH, Stempel DA. Comparative effect of body mass index on response to asthma controller therapy. *Allergy and Asthma Proceedings* 2010: 31(1): 20-25.

65. Carpaij OA, van den Berge M. The asthma–obesity relationship: underlying mechanisms and treatment implications. *Curr Opin Pulm Med* 2018: 24(1): 42-49.

66. Gibson PG. Obesity and asthma. *Annals of the American Thoracic Society* 2013: 10(Supplement): S138-S142.

67. Scott HA, Gibson PG, Garg ML, Wood LG. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J* 2011: 38(3): 594-602.

68. van Veen IH, Ten Brinke A, Sterk PJ, Rabe KF, Bel EH. Airway inflammation in obese and nonobese patients with difficult-to-treat asthma. *Allergy* 2008: 63(5): 570-574.

69. Holguin F, Comhair SA, Hazen SL, Powers RW, Khatri SS, Bleecker ER, Busse WW, Calhoun WJ, Castro M, Fitzpatrick AM. An association between L-arginine/asymmetric dimethyl arginine balance, obesity, and the age of asthma onset phenotype. *American journal of respiratory and critical care medicine* 2013: 187(2): 153-159.

70. Komakula S, Khatri S, Mermis J, Savill S, Haque S, Rojas M, Brown L, Teague GW, Holguin F. Body mass index is associated with reduced exhaled nitric oxide and higher exhaled 8-isoprostanes in asthmatics. *Respir Res* 2007: 8: 32.

71. Berg CM, Thelle DS, Rosengren A, Lissner L, Torén K, Olin A-C. Decreased fraction of exhaled nitric oxide in obese subjects with asthma symptoms: data from the population study INTERGENE/ADONIX. *Chest* 2011: 139(5): 1109-1116.

72. Barros R, Moreira A, Fonseca J, Moreira P, Fernandes L, de Oliveira JF, Delgado L, Castel-Branco MG. Obesity and airway inflammation in asthma. *Journal of allergy and clinical immunology* 2006: 117(6): 1501.

73. Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH, Haldar P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, Wardlaw AJ, Green RH. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008: 178(3): 218-224.

74. Mancuso P. The role of adipokines in chronic inflammation. *ImmunoTargets and therapy* 2016: 5: 47.

75. Webster JC, Oakley RH, Jewell CM, Cidlowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative β isoform: a mechanism for the generation of glucocorticoid resistance. *Proceedings of the National Academy of Sciences* 2001: 98(12): 6865-6870.

76. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Archives of medical science: AMS* 2017: 13(4): 851.

77. Wood LG, Garg ML, Gibson PG. A high-fat challenge increases airway inflammation and impairs bronchodilator recovery in asthma. *J Allergy Clin Immunol* 2011: 127(5): 1133-1140.

78. Caspersen NF, Søyseth V, Berge T, Tveit A, Røsjø H, Einvik G. Symptoms of obstructive pulmonary disease in obese adults with normal FEV1/FVC ratio: Data from the ACE 1950 study. Eur Respiratory Soc, 2017.

79. Boulet LP. Asthma and obesity. *Clin Exp Allergy* 2013: 43(1): 8-21.

80. Dixon AE, Clerisme-Beaty EM, Sugar EA, Cohen RI, Lang JE, Brown ED, Richter JE, Irvin CG, Mastronarde JG. Effects of obstructive sleep apnea and gastroesophageal reflux disease on asthma control in obesity. *J Asthma* 2011: 48(7): 707-713.

81. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet* 2010: 376(9743): 803-813.

82. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. *Available from: wwwginasthmaorg* 2020.

83. Aaron SD, Vandemheen KL, Boulet L-P, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D, Canadian Respiratory Clinical Research C. Overdiagnosis of asthma in obese and nonobese adults.[Erratum appears in CMAJ. 2008 Dec 2;179(12):1301]. *Cmaj* 2008: 179(11): 1121-1131.

84. Janson SL, Earnest G, Wong KP, Blanc PD. Predictors of asthma medication nonadherence. *Heart & Lung: The Journal of Acute and Critical Care* 2008: 37(3): 211-218.

85. Dima AL, Hernandez G, Cunillera O, Ferrer M, de Bruin M. Asthma inhaler adherence determinants in adults: systematic review of observational data. *Eur Respir J* 2015: 45(4): 994-1018.

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

Author, (Reference) Year (Country)	**Study Population (n) (sex) (age) (BMI Healthy|Obese)**	**Design/evidence level[1]**	**Quality[2]**	**Method of Asthma Dx**	**Outcomes (Asthma medication class)**	**Comorbidities *excluded comorbidities**	**BMI<25 kg/m^2 (%)**	**BMI≥30 kg/m^2 (%)**
Adeyeye et al. [39], 2013 (Lagos)	118 M/F ≥18 y/o BMI<25|BMI≥30	Cross-sectional/IV	Ø	Dr-dx (NHLBI guidelines)	ICS LTRA mOCS FEV_1/FVC%	Not listed		
Bruno et al. [29], 2014 (Europe)	66 M/F ≥18 y/o 22.7±2.3|32.3±3.3	Cross-sectional/IV	+	Severe asthma outpatients (ATS criteria)	LABA rOCS FEV_1% predicted FEV_1/FVC%	T2D	0	38
						OSA	0	17
						GERD	33	53
						Systemic hypertension	12	33
						Left ventricle failure	5	13
						Osteoporosis	21	29
						Bronchiectasis	2	8
						Tuberculosis	5	4
						Psychologic factors	7	4
						*COPD excluded		
Camargo Jr et al. [54], 1999 (USA)	901 F ≥18 y/o BMI<22.5|BMI≥30	Prospective cohort/III-2	+	Dr-dx (guidelines not specified)	ICS FEV_1% predicted	Not listed		
Chen et al. [40], 2016 (China)	136 M/F ≥18 y/o 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/d FEV_1% predicted mOCS	OSA	10	20
						GERD	21	39
						Depression BDI Score ≥ 14	23	36
Clerisme-Beaty et al. [26], 2009 (USA)	227 M/F ≥17 y/o 18.5-24.9|BMI≥30	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	SABA FEV_1% predicted FEV_1/FVC%	GERD	42	54
						Rhinitis	69	53
						Sinusitis	39	59
						Chronic bronchitis	28	33
						*Comorbidities interfere with study excluded		
Cohen et al. [55], 2019 (USA)	32 F 18-50 y/o 22.8±11.6|35.9±24.7	Case control/III-2	+	Dr-dx childhood-onset asthma (<12 y/o) (guidelines not specified)	ICS FEV_1% predicted	*Comorbidities excluded: any comorbidity ↑ systemic inflammation, active infection, diabetes, OSA, hepatic disease, cardiac disease		

Author, (Reference) Year (Country)	Study Population (n) (sex) (age) (BMI Healthy|Obese)	Design/evidence level[1]	Quality[2]	Method of Asthma Dx	Outcomes (Asthma medication class)	Comorbidities *excluded comorbidities	BMI<25 kg/m^2 (%)	BMI≥30 kg/m^2 (%)
Cortes-Telles et al. [57], 2015 (Mexico)	28 M/F ≥18 y/o 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 co-morbidities interfere with exercise testing excluded		
Deesomchok et al. [32], 2010 (Canada)	96 M/F 20-60 y/o 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	3	19
						Heart disease	0	5
						Anxiety	14	17
						Depression	11	26
						Severe allergic rxn	9	5
de Lima Azambuj et al. [35], 2015 (Brazil)	50 M/F ≥18 y/o 18.5-24.9|BMI≥30	Cross-sectional/IV	+	Dr-dx (ATS/ERS criteria)	ICS ICS+LABA FEV_1% predicted	Hypertension	36	60
						T2D	4	16
						GERD	20	40
						Metabolic syndrome	28	52
Desai et al. [30], 2013 (England)	83 M/F ≥18 y/o 22.0±2.1|36.2±5.9	Cross-sectional/IV	+	Dr-dx (severe) (GINA step 4 or 5)	ICS (BDP equivalent) dose µg/d mOCS FEV_1% predicted FEV_1/FVC%	Not listed		
Dixon et al. [43], 2006 (USA)	361 M/F ≥18 y/o 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	71	69
						Sinusitis	41	50
						GERD	21	36
Farah et al. [58], 2011 (Australia)	35 M/F ≥18 y/o 18.5-24.9|BMI≥30	Time series/III-2	+	Dr-dx (guidelines not specified)	LABA ICS (BDP equivalent) dose µg/d FEV_1% predicted FEV_1/FVC%	*Comorbidities excluded; lung diseases other than asthma		
Gibeon et al. [51], 2013 (UK)	471 M/F ≥18 y/o 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	35	33
						Seasonal rhinitis	39	42
						Eczema	23	32
						Nasal polyps	18	11
						GERD	40	54
						Central bronchiectasis	18	7
						Other bronchiectasis	28	21
						Emphysema	6	5

Author, (Reference) Year (Country)	Study Population (n) (sex) (age) (BMI Healthy|Obese)	Design/evidence level[1]	Quality[2]	Method of Asthma Dx	Outcomes (Asthma medication class)	Comorbidities *excluded comorbidities	BMI<25 kg/m^2 (%)	BMI≥30 kg/m^2 (%)
Giouleka et al. [52], 2011 (Greece)	66 M/F ≥18 y/o 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%	*Comorbidities excluded; illnesses (e.g. OSA) that could interfere with proposed tests		
Hasegawa et al. [44], 2014 (USA)	904 M/F 18-54 y/o BMI<25|BMI≥30	Retrospective cohort/III-2	Ø	Dr-dx (guidelines not specified)	ICS LABA LTRA mOCS	*COPD excluded		
Holguin et al. [56], 2010 (USA)	68 M/F ≥18 y/o BMI≤25|BMI≥30	Case control/III-2	+	Dr-dx (guidelines not specified)	Anticholinergic ICS LABA LTRA FEV_1% predicted FEV_1/FVC%	Not listed		
Holguin et al. [12], 2011 (USA)	769 M/F ≥18 y/o 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 et al. [36], 2018 (Brazil)	605 M/F ≥18 y/o BMI<25|BMI≥30	Cross-sectional/IV	+	Dr-dx (mild-to-moderate or severe) (guidelines not specified)	rOCS	Hypertension/diabetes/ dyslipidaemia	21	57
						Rhinitis	91	93
						GERD	35	66
						Severe depression	4	9
						*Comorbidities excluded; any disease severe enough to make it difficult to assess asthma symptoms or any other disease that causes dyspnea		
Kwon et al. [41], 2012 (Korea)	619 M/F ≥18 y/o BMI<25|BMI≥30	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS+LABA FEV_1% predicted FEV_1/FVC%	Allergic rhinitis	77	75
Lavoie et al. [33], 2006 (Canada)	233 M/F ≥18 y/o	Cross-sectional/IV	Ø	Dr-dx (guidelines not specified)	ICS ICS (FP equivalent) dose µg/d	Hypertension	23	28
						Diabetes	3	8
						Hypercholesterolemia	19	22

Author, (Reference) Year (Country)	Study Population (n) (sex) (age) (BMI Healthy|Obese)	Design/evidence level[1]	Quality[2]	Method of Asthma Dx	Outcomes (Asthma medication class)	Comorbidities *excluded comorbidities	BMI<25 kg/m^2 (%)	BMI≥30 kg/m^2 (%)
	BMI<25|BMI≥30				LABA LTRA mOCS SABA FEV_1% predicted FEV_1/FVC%	*Comorbid diseases were excluded from study (disease types not specified)		
Liu et al. [42], 2018 (China)	33 M/F ≥18 y/o 22.2±1.8|31.7±1.9	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS ICS (BDP equivalent) dose µg/d LABA LTRA FEV_1% predicted FEV_1/FVC%	*Comorbidities excluded; chronic respiratory disease + severe systemic disease (lung cancer, bronchiectasis, heart disease, hypertension, diabetes or psychiatric disorders)		
Lugogo et al. [45], 2018 (USA)	454 M/F ≥18 y/o BMI≤24.9|BMI≥30	Retrospective cohort/IV	+	Dr-dx (guidelines not specified)	ICS FEV_1% predicted	*Comorbidities excluded; presence of other lung diseases		
Maalej et al. [37], 2012 (Tunisia)	137 M/F ≥18 y/o 18.5-24.9|BMI≥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/d FEV_1% predicted FEV_1/FVC%	Diabetes	4	17
						Hypertension	3	18
						Hypercholesterolemia	0	8
						GERD	1	10
						Rhinitis	59	8
						Sinusitis	13	3
						*Comorbidities excluded; any additional respiratory disease excluded		
Mosen et al. [27], 2008 (USA)	703 M/F 35+ y/o BMI<25|BMI≥30	Cross-sectional/IV	+	Health care use suggestive of active asthma (guidelines not specified)	ICS ICS (BDP equivalent) dose µg/d rOCS	GERD	34	43
Murphy et al. [53], 2017 (Australia)	111 Pregnant women ≥18 y/o 22.3±2.1|33.6±6.1	Prospective cohort/III-2	+	Dr-dx (guidelines not specified)	ICS ICS (BDP equivalent) dose µg/d FEV_1% predicted FEV_1/FVC%	* Comorbidities excluded; presence of a chronic medical disease (other than asthma)		
Nathell et al. [31], 2002 (Sweden)	160 M/F	Cross-sectional/IV	+	Questionnaire, phone interview + clinical	ICS rOCS	Not listed		

Author, (Reference) Year (Country)	Study Population (n) (sex) (age) (BMI Healthy|Obese)	Design/evidence level[1]	Quality[2]	Method of Asthma Dx	Outcomes (Asthma medication class)	Comorbidities *excluded comorbidities	BMI<25 kg/m^2 (%)	BMI≥30 kg/m^2 (%)
	≥18 y/o 19.9±2.3|33.7±3.7			examination (guidelines not specified)	FEV_1% predicted FEV_1/FVC%			
Rastogi et al. [28], 2017 (USA)	792 M/F ≥18 y/o 18.5-24.9|BMI≥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	15	18
						Coronary heart disease	3	5
						Congestive heart failure	1	5
Schatz et al. [46], 2013 (USA)	12,137 M/F 18-65 y/o BMI<25|BMI≥30	Retrospective cohort/III-2	+	Persistent asthma (HEDIS criteria)	ICS	* Comorbidities excluded; COPD, emphysema, or chronic bronchitis		
Schatz et al. [49], 2015 (USA)	7,229 M/F 18-56 y/o BMI<25|BMI≥30	Prospective cohort/III-3	+	Persistent asthma (HEDIS criteria)	rOCS	Reported as total: Gastroesophageal reflux Depression	Total 28 28	
Sutherland et al. [38], 2008 (New Zealand)	39 F 18-50 y/o 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%	* Comorbidities excluded; any disease that could potentially ↑ systemic inflammation		
Tang et al. [47], 2019 (USA)	924 M/F ≥18 y/o BMI<25|BMI≥30	Retrospective cohort/IV	+	Dr-dx (guidelines not specified)	ICS ICS+LABA LTRA FEV_1% predicted FEV_1/FVC%	GERD	13	33
						OSA	2	14
						Diabetes	0	9
Taylor et al. [15], 2008 (USA)	2,102 M/F ≥18 y/o BMI<25|BMI≥30	Cross-sectional/IV	+	Self-reported Dr-dx (guidelines not specified)	Anticholinergic ICS LABA LTRA rOCS SABA	Not listed		
Thomson et al. [50], 2003 (USA/Canada)	402 M/F 18-54 y/o BMI<25|BMI≥30	Prospective cohort/III-2	+	Dr-dx (acute asthma) (guidelines not specified)	ICS	COPD	3	3

Author, (Reference) Year (Country)	Study Population (n) (sex) (age) (BMI Healthy|Obese)	Design/evidence level[1]	Quality[2]	Method of Asthma Dx	Outcomes (Asthma medication class)	Comorbidities *excluded comorbidities	BMI<25 kg/m^2 (%)	BMI≥30 kg/m^2 (%)
Vermette et al. [48], 2016 (Canada)	148 M/F ≥18 y/o 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/d ICS+LABA mOCS FEV_1% predicted FEV_1/FVC%	* Comorbidities excluded; associated comorbidities causing dyspnea		
Wright et al. [34], 2010 (Canada)	405 M/F 18-75 y/o 22.7±1.6|33.8±3.6	Cross-sectional/IV	+	Dr-dx (guidelines not specified)	ICS (FP equivalent) dose µg/d FEV_1% predicted	* Comorbidities excluded; conditions that conferred greater morbidity than asthma		
Total number of subjects	31,644							

Values are shown as mean±SD.

[1]Evidence levels are defined by the National Health and Medical Research Council [23]. [2]Methodologic study quality was determined with the use of the American Dietetic Association critical to appraisal checklist [22]. Abbreviation: ATS, American Thoracic Society; BDI, Beck Depression Inventory; BDP, Beclomethasone dipropionate; BMI, body mass index; COPD, chronic obstructive sleep disorder; Dx, Diagnosis; Dr, Doctor; ED, Emergency Department; ERS, European Respiratory Society; FEV_1, Forced Expiratory Volume in 1 second; FP, Fluticasone propionate; GERD, gastro-esophageal reflux disorder; GINA, Global Initiative for Asthma; HEDIS, Healthcare Effectiveness Data and Information Set; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonists; LTRA, leukotriene receptor antagonists; mOCS, maintenance oral corticosteroids; NHLBI, National Heart lung and blood institute; OSA; obstructive sleep apnea syndrome; Pred, predicted; rOCS, rescue oral corticosteroids; rxn, reaction; SABA, short-acting β_2-agonists; T2D, type II diabetes; Ø, neutral study quality; +, positive study quality.

Figure legends

Effect of obesity on inhaled short- and long- acting bronchodilator asthma medication use

Figure 1. Forest plots of studies showing the difference in inhaled short-acting [SABA (A)] and long-acting [LABA (B), ACH (C)] bronchodilator use, between obese (BMI≥30kg/m^2) and healthy weight (BMI<25kg/m^2) subjects with asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% CIs determined with the use of generic M-H random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. ACH, anticholinergic; BMI, body mass index; CI, confidence interval; df, degree of freedom; LABA, long-acting β_2-agonists; M-H, Mantel-Haenszel; SABA, short-acting β_2-agonists.

Effect of obesity on inhaled preventer asthma medication use and dose

Figure 2. Forest plots of studies showing the difference in ICS use (A), ICS+LABA use (B), and ICS (BDP-HFA) dose (µg/day) (C) between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/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% CIs determined with the use of generic M-H random-effects models. For graph (C), values are mean differences with 95%

CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BDP, beclomethasone dipropionate; BMI, body mass index; CI, confidence interval; df, degree of freedom; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IV, Inverse Variance; LABA, long-acting β_2-agonists; M-H, Mantel-Haenszel.

Effect of obesity on oral preventer asthma medication use

Figure 3. Forest plots of studies showing the difference in OCS use (A) subgrouped into maintenance OCS use and rescue OCS use, and LTRA use (B) between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/m^2) asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% CIs determined with the use of generic M-H random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BMI, body mass index; CI, confidence interval; df, degree of freedom; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids; M-H, Mantel-Haenszel.

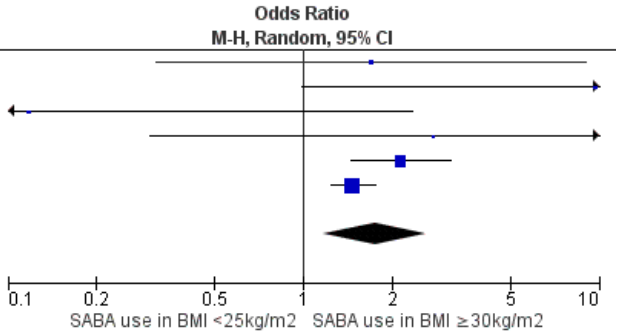
Effect of obesity on lung function

Figure 4. Forest plot of studies showing the difference in lung function [FEV_1% predicted (A) and FEV_1/FVC% (B)] between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/m^2) asthma. The pooled effect estimate (diamond) for each meta-analysis is shown. Values are mean differences with 95% CI determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BMI, body mass index; CI, confidence interval; df, degree of freedom; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; IV, Inverse Variance.

A

Study or Subgroup	Obese Events	Obese Total	Healthy weight Events	Healthy weight Total	Weight	Odds Ratio M-H, Random, 95% CI
Clerisme-Beaty 2009	178	183	42	44	5.1%	1.70 [0.32, 9.04]
Cortes-Telles 2015	13	14	8	14	2.9%	9.75 [0.98, 96.56]
Deesomchok 2010	42	45	51	51	1.7%	0.12 [0.01, 2.35]
Lavoie 2006	93	94	135	139	3.1%	2.76 [0.30, 25.05]
Rastogi 2017	303	648	42	144	36.4%	2.13 [1.44, 3.15]
Taylor 2008	573	1022	502	1080	50.8%	1.47 [1.24, 1.75]
Total (95% CI)		**2006**		**1472**	**100.0%**	**1.75 [1.17, 2.60]**
Total events	1202		780			

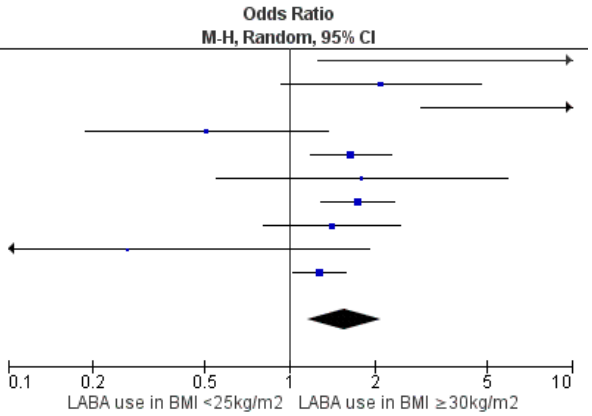
Heterogeneity: Tau² = 0.07; Chi² = 8.50, df = 5 (P = 0.13); I² = 41%
Test for overall effect: Z = 2.75 (P = 0.006)



B

Study or Subgroup	Obese Events	Obese Total	Healthy weight Events	Healthy weight Total	Weight	Odds Ratio M-H, Random, 95% CI
Bruno (Severe Asthma) 2014	23	24	29	42	1.9%	10.31 [1.25, 84.73]
Deesomchok 2010	25	45	19	51	8.7%	2.11 [0.93, 4.77]
Farah 2011	11	15	3	20	2.9%	15.58 [2.91, 83.46]
Giouleka 2011	13	37	15	29	6.7%	0.51 [0.19, 1.36]
Hasegawa 2014	184	607	62	297	18.6%	1.65 [1.19, 2.29]
Holguin 2010	31	54	6	14	5.1%	1.80 [0.55, 5.90]
Holguin 2011	315	446	187	323	19.3%	1.75 [1.29, 2.36]
Lavoie 2006	66	94	87	139	13.2%	1.41 [0.80, 2.47]
Liu 2018	8	11	20	22	2.2%	0.27 [0.04, 1.91]
Taylor 2008	224	1022	195	1080	21.3%	1.27 [1.03, 1.58]
Total (95% CI)		**2355**		**2017**	**100.0%**	**1.56 [1.15, 2.11]**
Total events	900		623			

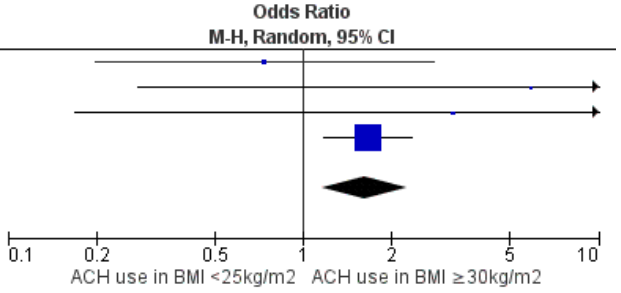
Heterogeneity: Tau² = 0.10; Chi² = 22.57, df = 9 (P = 0.007); I² = 60%
Test for overall effect: Z = 2.86 (P = 0.004)



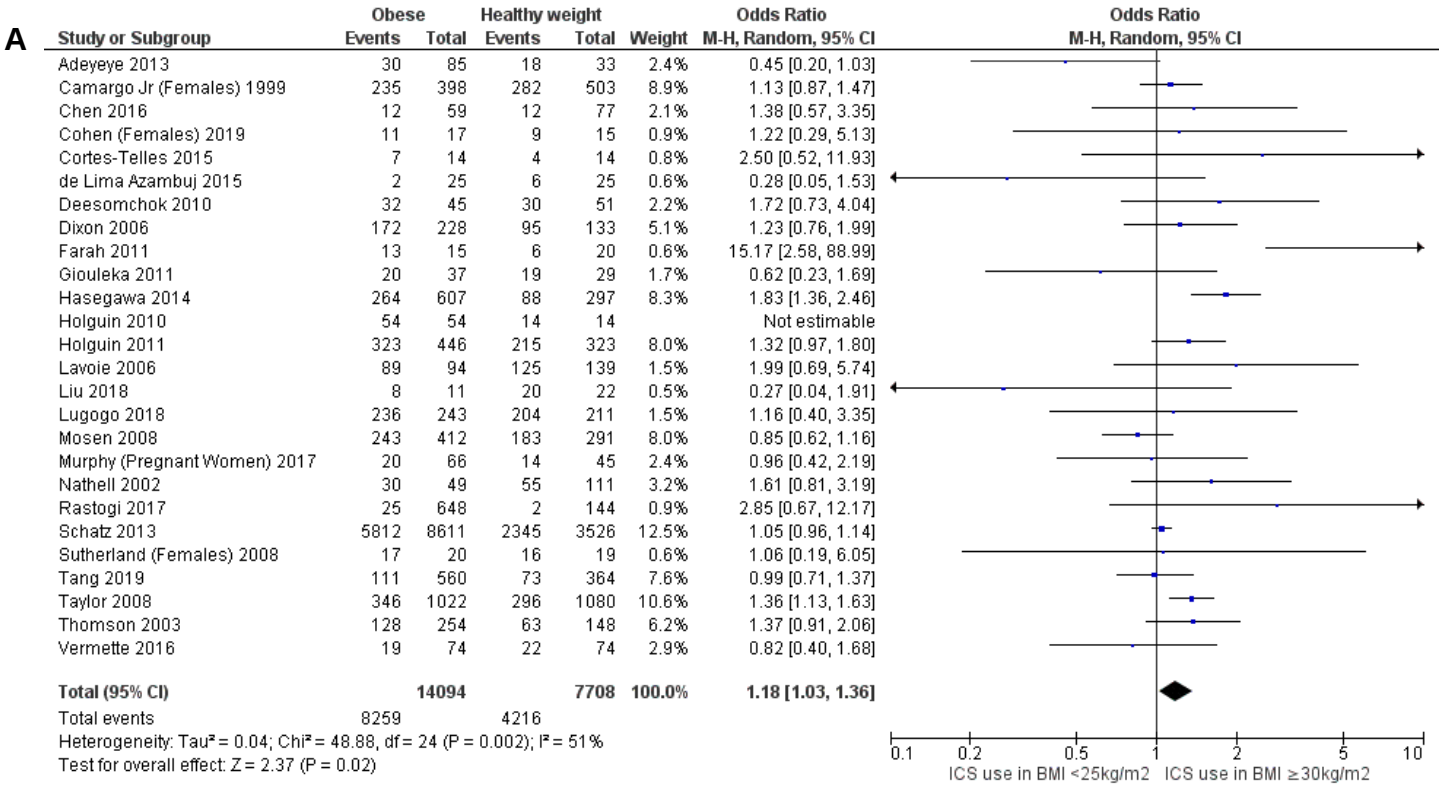
C

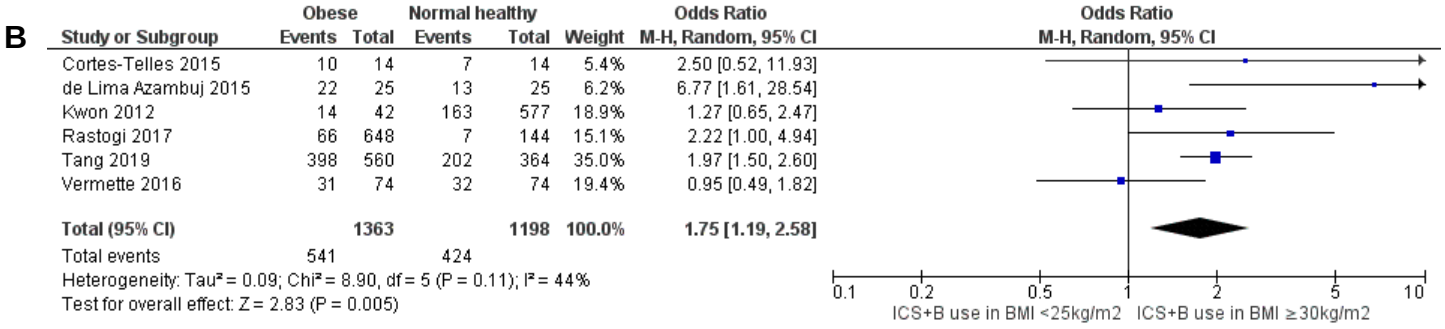
Study or Subgroup	Obese Events	Obese Total	Healthy weight Events	Healthy weight Total	Weight	Odds Ratio M-H, Random, 95% CI
Chen 2016	4	22	9	39	6.2%	0.74 [0.20, 2.76]
Deesomchok 2010	2	45	0	51	1.1%	5.92 [0.28, 126.64]
Holguin 2010	5	54	0	14	1.2%	3.22 [0.17, 61.79]
Taylor 2008	88	1022	58	1080	91.4%	1.66 [1.18, 2.34]
Total (95% CI)		**1143**		**1184**	**100.0%**	**1.62 [1.16, 2.24]**
Total events	99		67			

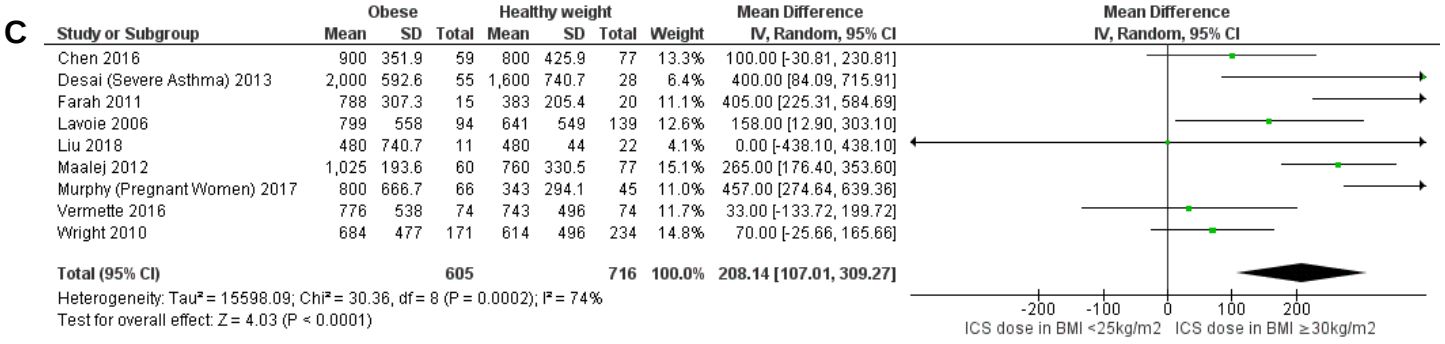
Heterogeneity: Tau² = 0.00; Chi² = 2.28, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)



Effect of obesity on inhaled short- and long- acting bronchodilator asthma medication use
Figure 1. Forest plots of studies showing the difference in inhaled short-acting [SABA (A)] and long-acting [LABA (B), ACH (C)] bronchodilator use, between obese (BMI≥30kg/m^2) and healthy weight (BMI<25kg/m^2) subjects with asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% CIs determined with the use of generic M-H random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. ACH, anticholinergic; BMI, body mass index; CI, confidence interval; df, degree of freedom; LABA, long-acting β_2-agonists; M-H, Mantel-Haenszel; SABA, short-acting β_2-agonists.

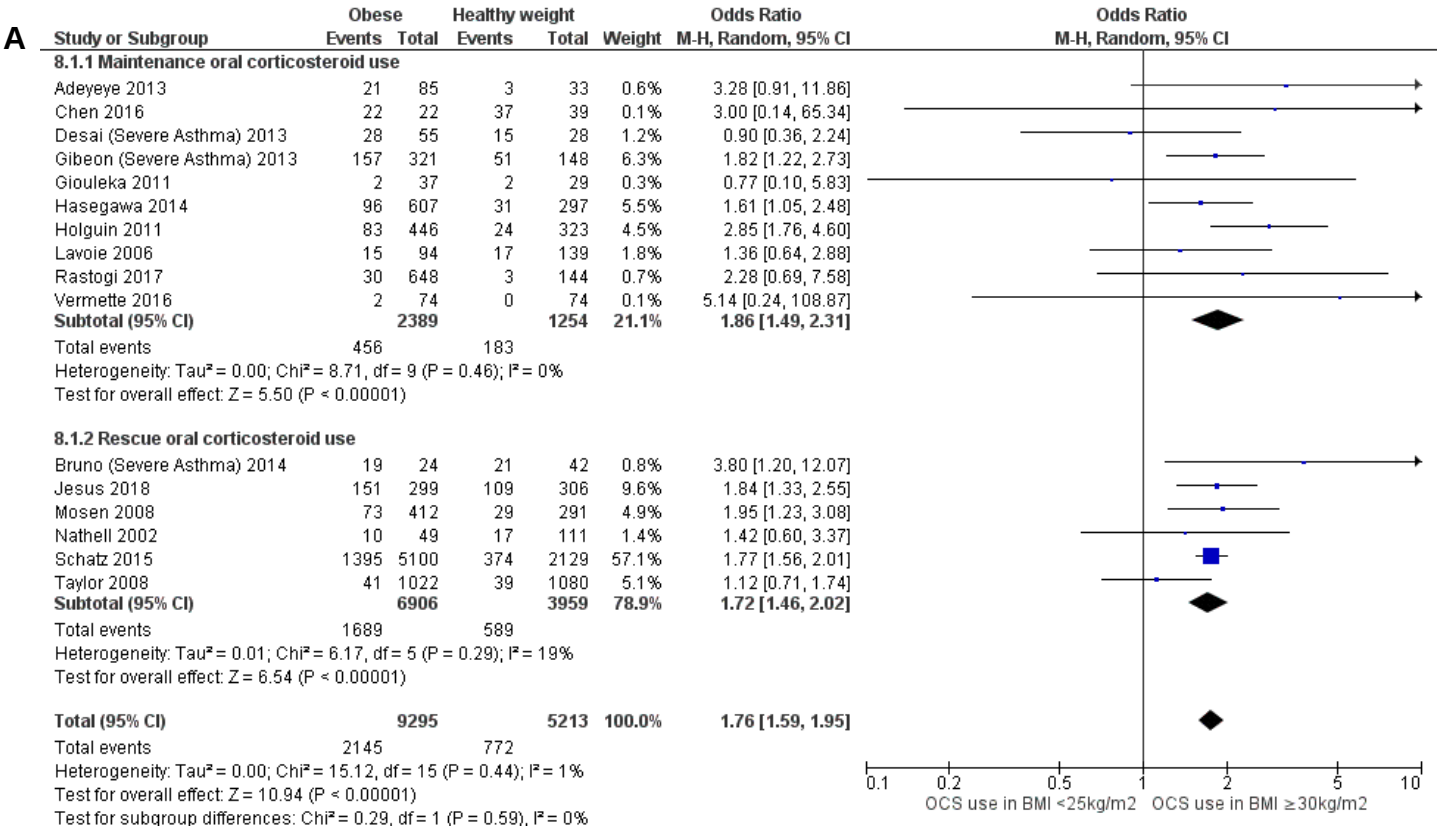


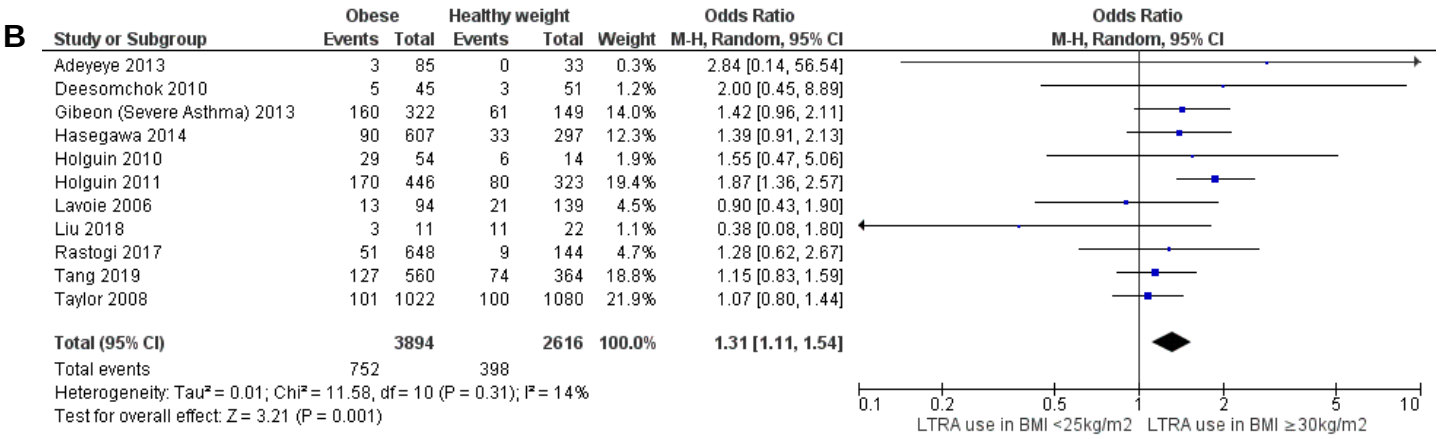




Effect of obesity on inhaled preventer asthma medication use and dose

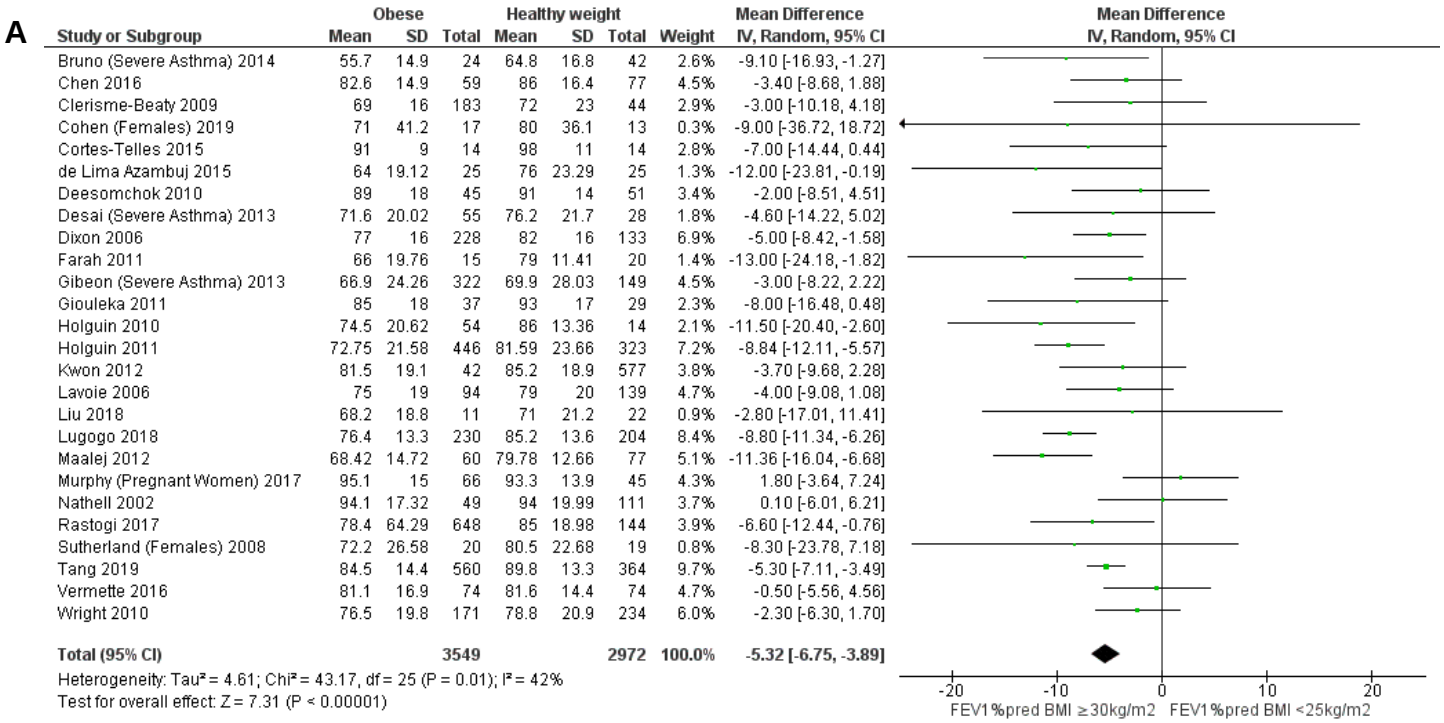
Figure 2. Forest plots of studies showing the difference in ICS use (A), ICS+LABA use (B), and ICS (BDP-HFA) dose (µg/day) (C) between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/m^2) asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. For graphs (A) and (B), values are odds ratios with 95% CIs determined with the use of generic M-H random-effects models. For graph (C), values are mean differences with 95% CIs determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BDP, beclomethasone dipropionate; BMI, body mass index; CI, confidence interval; df, degree of freedom; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids; IV, Inverse Variance; LABA, long-acting β_2-agonists; M-H, Mantel-Haenszel.

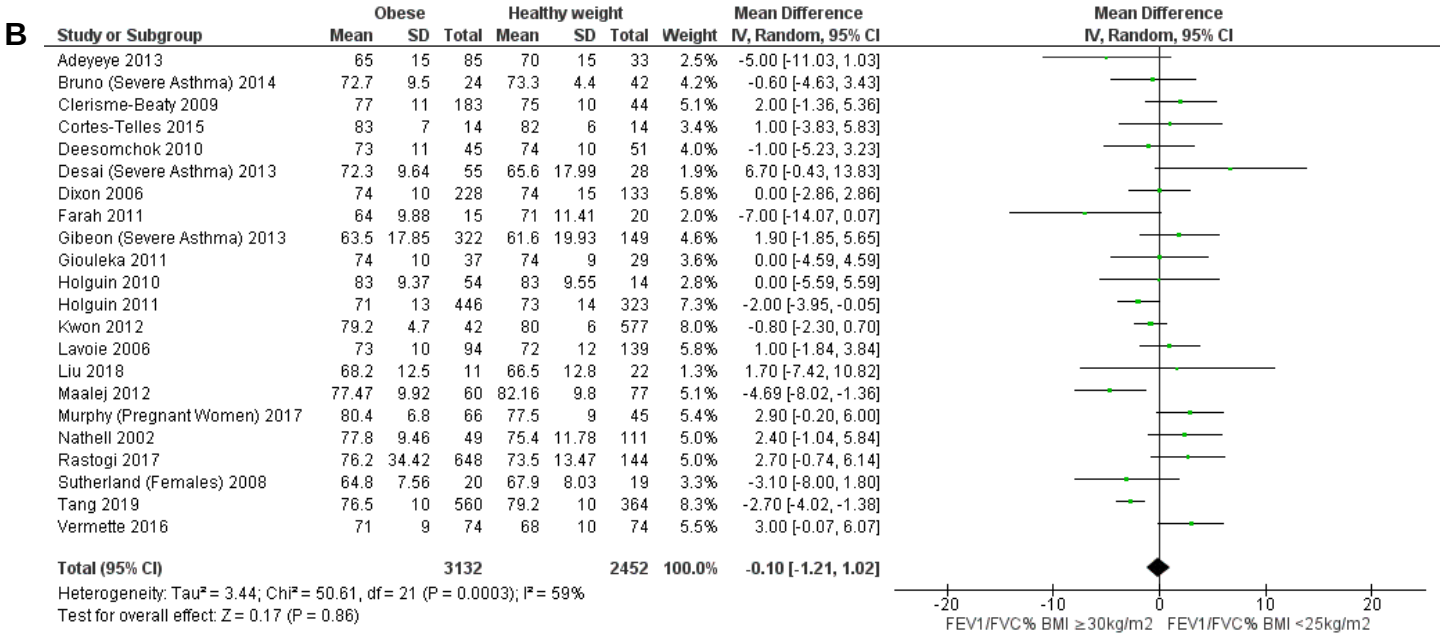




Effect of obesity on oral preventer asthma medication use

Figure 3. Forest plots of studies showing the difference in OCS use (A) subgrouped into maintenance OCS use and rescue OCS use, and LTRA use (B) between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/m^2) asthma. The pooled effect estimate (diamonds) for each meta-analysis is shown. Values are odds ratios with 95% CIs determined with the use of generic M-H random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BMI, body mass index; CI, confidence interval; df, degree of freedom; LTRA, leukotriene receptor antagonists; OCS, oral corticosteroids; M-H, Mantel-Haenszel.

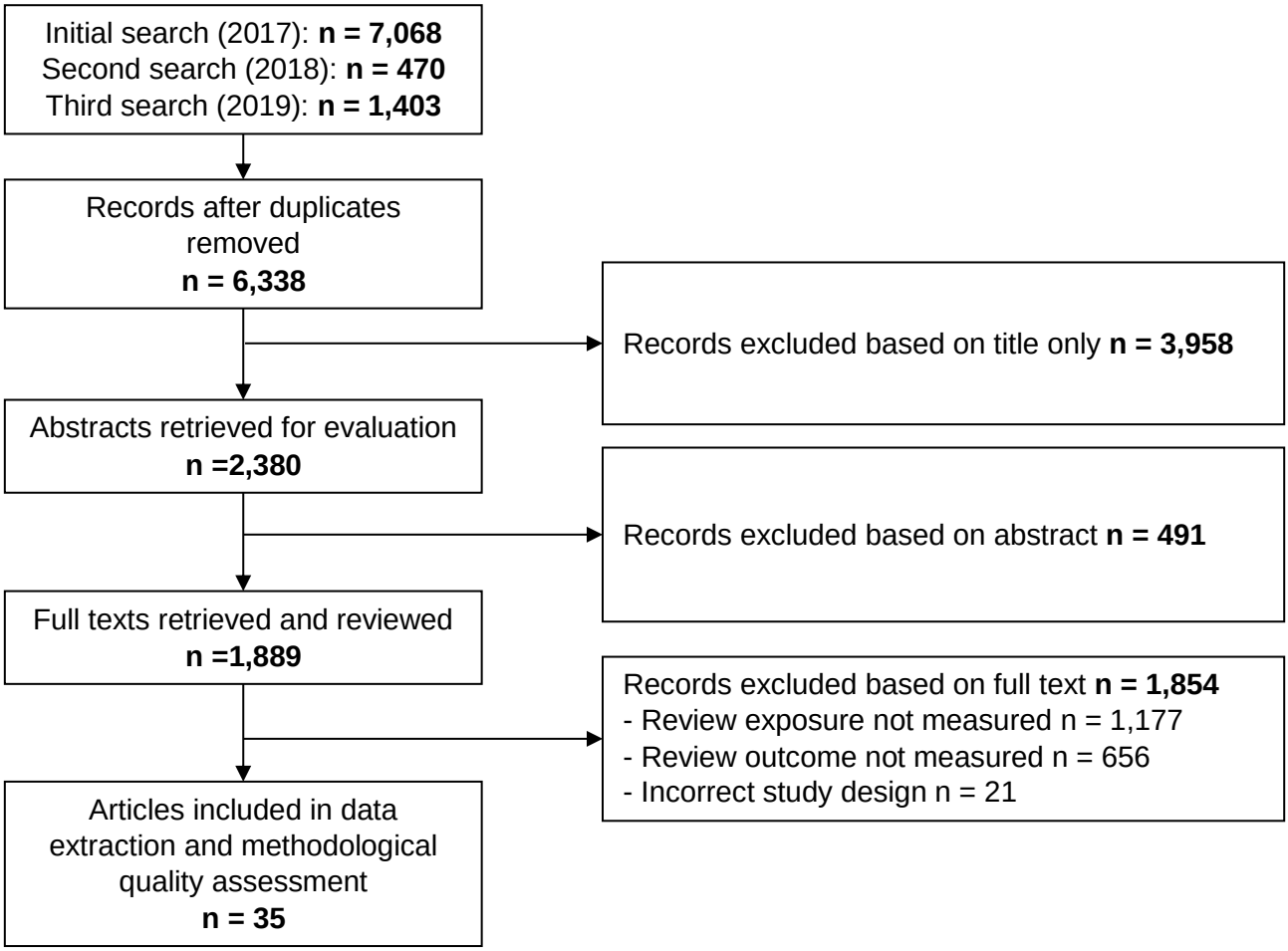




Effect of obesity on lung function

Figure 4. Forest plot of studies showing the difference in lung function [FEV_1% predicted (A) and FEV_1/FVC% (B)] between obese (BMI≥30kg/m^2) asthma and healthy weight (BMI<25kg/m^2) asthma. The pooled effect estimate (diamond) for each meta-analysis is shown. Values are mean differences with 95% CI determined with the use of generic IV random-effects models. Heterogeneity was quantified by I^2 at a significance of P<0.10. BMI, body mass index; CI, confidence interval; df, degree of freedom; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; IV, Inverse Variance.

Supplementary Material



Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of articles for inclusion in a systematic review of the effect weight status on asthma medication use in asthma.