Weight Management Interventions in Adult and Pediatric Asthma Populations: A Systematic Review

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Abstract

Background: Ample evidence suggests a dose-response relationship between increasing weight and level of asthma risk or reduced asthma control. To establish reversibility, several randomized controlled trials (RCTs) have recently been published to investigate the impact of weight management on asthma. This systematic review synthesizes evidence from these RCTs on the effects of weight management (weight loss, weight maintenance, maintenance of lost weight, or weight gain prevention) interventions on asthma outcomes in both adult and pediatric populations.

Methods: We searched Medline, CINAHL, PsychINFO, and Cochrane for studies published between 1950 and November 2014. Two researchers independently rated the included studies using the quality assessment tool for RCTs as outlined in the 2013 Obesity Treatment Guideline. Discrepancies were resolved by consensus after discussion between the raters and, if needed, with the senior author.

Results: Four RCTs in adults and 3 in children and adolescents were included. The adult studies seem to consistently support the benefit of substantial weight loss, but a threshold effect may exist such that only weight loss beyond a minimal amount will likely lead to clinically important improvement in asthma outcomes. Three of them suggest that the threshold may lie between 5-10% of weight loss. RCTs in youth suggest that modest calorie reductions alone or combined with increased physical activity, or even a healthy normocaloric diet, may lead to improved asthma outcomes. However, most RCTs reviewed were limited by small sample size, short intervention durations, and short follow-up periods.

Conclusion: Trial evidence shows the promise of weight loss interventions for asthma control in adults and youth. More adequately-powered, long-term RCTs are needed to elucidate the role of weight loss and other weight management interventions in asthma control and prevention. Definitive data are needed to guide clinical and public health practice to effectively address the dual epidemic of obesity and asthma.

Keywords: Randomized controlled trial; Weight; Asthma; Adults; Children; Adolescents

Introduction

Obesity and asthma are two major epidemics and their prevalence has increased concurrently in recent decades in the US [1-3]. Since a possible association between obesity and asthma was first reported in the 1980s [4], many cross-sectional and prospective observational studies in adults, children, and adolescents from diverse populations have been published, and a number of reviews have summarized the evidence [5-9].

Comorbid obesity and asthma are now recognized as a distinct phenotype; in some cases obesity may cause incident asthma whereas in other cases obesity alters pre-existing asthma to be more difficult to control and complicates its management, partly because of blunted effectiveness of inhaled corticosteroids. Evidence also suggests a dose-response relationship between increasing body mass index (BMI) and risk of incident asthma [10-12] and degree of reduced control in prevalent asthma [13]. It is hypothesized that multifactorial mechanisms involving mechanical, inflammatory, immunologic, hormonal, and genetic factors may link obesity and asthma [11,14]. To establish causality between obesity and asthma, adequate evidence is needed to address whether interventions to prevent or treat obesity lower the risk of asthma onset in high-risk individuals and/or improve disease outcomes in people already with asthma. Observational and quasi-experimental studies dominate the literature on weight loss in asthma [15,16], although several randomized controlled trials (RCTs) have recently been published.

We conducted a systematic review to provide an up-to-date evaluation of the published RCTs on the effects of weight management (defined as weight loss, weight maintenance, maintenance of lost weight, or weight gain prevention) interventions on asthma outcomes in both adult and pediatric populations.

Methods

An electronic literature search extending back to 1950 was conducted using Medline (PubMed), CINAHL, PsychINFO, and Cochrane in November 2014. The terms used to search titles and abstracts were (overweight or obese or obesity) and (asthma or wheeze or wheezing) and (weight or BMI or body mass index or waist or fat). Table 1 details the search strategy. Cross-referencing from the articles found was used to complete the search. Inclusion in the systematic review required that a study be original research with human subjects published in English, be an RCT of any type of weight management intervention, and specify a priori at least one asthma outcome as the primary outcome. Table 2 shows the complete inclusion and exclusion criteria for selection of publications.

Two researchers (NL and LX) independently rated all the RCTs...
### Search Strategy

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
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<tbody>
<tr>
<td>Population</td>
<td>Overweight and/or obese participants of any age with diagnosed or self-reported asthma or wheezing</td>
</tr>
<tr>
<td>Intervention</td>
<td>Behavioral, pharmacological, or surgical interventions for weight loss, maintenance of lost weight, weight maintenance, or weight gain prevention.</td>
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<tr>
<td>Comparator</td>
<td>Usual care</td>
</tr>
<tr>
<td>Outcome</td>
<td>One or more of the following asthma related outcomes as primary outcome(s):</td>
</tr>
<tr>
<td>Study Design</td>
<td>RCTs</td>
</tr>
<tr>
<td>Publication Type</td>
<td>Published original research studies</td>
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### Table 1: Search strategy.

<table>
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<tr>
<td>CINAHL</td>
<td>(TI (overweight OR obese OR obesity)) OR (AB (overweight OR obese OR obesity))) AND ((TI (asthma OR wheeze OR wheezing)) OR (AB (asthma OR wheeze OR wheezing))) AND ((TI (weight OR BMI OR body mass index OR waist OR fat)) OR (AB (weight OR BMI OR body mass index OR waist OR fat))) Limit to English Language, Randomized Controlled Trial, Human</td>
</tr>
<tr>
<td>PsychInfo</td>
<td>(TI(overweight OR obese OR obesity)) OR (AB(overweight OR obese OR obesity))) AND ((TI(asthma OR wheeze OR wheezing)) OR (AB(asthma OR wheeze OR wheezing))) AND ((TI(weight OR BMI OR body mass index OR waist OR fat)) OR (AB(weight OR BMI OR body mass index OR waist OR fat))) Limit to Human, English; Exclude interview, Retrospective Study, Literature Review, Focus Group, Mathematical Model</td>
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### Table 2: Criteria for selection of publications.

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Exclusions</th>
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<tbody>
<tr>
<td>Population</td>
<td>Population not overweight or obese at baseline</td>
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<tr>
<td>Intervention</td>
<td>With the following characteristics:</td>
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<tr>
<td></td>
<td>Duration: short term (≤6 mos), intermediate (&gt;6 mos and ≤12 mos), long term (&gt;12 mos)</td>
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<td></td>
<td>Delivery: group and/or individual</td>
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<td></td>
<td>Frequency of contact: any</td>
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<tr>
<td>Comparator</td>
<td>No or minimal intervention</td>
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<tr>
<td></td>
<td>Attention control intervention</td>
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<td></td>
<td>Alternative active intervention</td>
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<tr>
<td>Outcome</td>
<td>One or more of the following asthma related outcomes as primary outcome(s):</td>
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<tr>
<td></td>
<td>Asthma or wheezing symptoms</td>
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<td></td>
<td>Lung function</td>
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<td>Asthma medication use</td>
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<td>Asthma-specific quality of life</td>
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<td></td>
<td>Asthma-specific health care utilization</td>
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<td>One or more of the following weight related outcomes:</td>
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<tr>
<td></td>
<td>Weight (kg, lbs, %)</td>
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<td></td>
<td>Body fat measures (BMI, BMI z-score, waist circumference, waist-hip ratio, % body fat)</td>
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<td></td>
<td>Weight loss maintenance</td>
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<td></td>
<td>Percent reduction of excess weight</td>
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<tr>
<td>Timing</td>
<td>Follow-up period: any length</td>
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<tr>
<td>Setting</td>
<td>Any clinical or research setting</td>
</tr>
<tr>
<td>Study Design</td>
<td>RCTs but with results not compared according to randomized treatment assignments.</td>
</tr>
<tr>
<td>Publication Type</td>
<td>Studies with &lt;10 subjects per treatment arm</td>
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<tr>
<td>Language</td>
<td>Full-text articles must be available in English</td>
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**Table 1**

<table>
<thead>
<tr>
<th>Search Strategy</th>
<th>Number of references</th>
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<tr>
<td>Pubmed</td>
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<tr>
<td>CINAHL</td>
<td>2</td>
</tr>
<tr>
<td>PsychInfo</td>
<td>81</td>
</tr>
<tr>
<td>Cochrane</td>
<td>47</td>
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Results

Of 179 references identified, 172 were excluded based on the review of titles (n=90), abstracts (n=75), and full text (n=7) (Figure 1). Seven RCTs were included, 4 in adults and 3 in children/adolescents (Tables 3 and 4). Five of the 7 RCTs were rated good quality, 1 rated fair quality, and 1 rated poor quality.

RCTs of weight loss interventions in adults

Table 3 summarizes the main characteristics and results of the 4 RCTs in adults, all of which focused on weight loss. The first weight loss trial in asthma was conducted in Finland by Stenius-Aarniala et al. who randomly assigned 38 obese adults with objectively confirmed asthma to a 14-week intervention or a control group [18]. The intervention group received a very low calorie dietary preparation, which contained 1760 kJ (420 kcal) of energy and daily allowances of all essential nutrients, for 8 weeks, and attended 12 group sessions for weight reduction and asthma/allergy education. The control group attended 12 group sessions for asthma/allergy education only. All participants were followed for one year. Intervention participants had a mean of 14.2 (range, 7.7-22.1) kg or 14.5% (variance estimate not reported) loss of baseline weight vs. 0.3 (range not reported) kg or 0.3% weight loss among controls at the end of the weight reduction program, and 11.1 (1.1-22.5) kg or 11.3% weight loss vs. 2.3 kg or 2.2% weight gain at month 12. Significant improvements were observed in forced expiratory volume in one second (FEV1: between-group mean difference, 7.6% predicted; 95% confidence interval [CI], 1.5% to 13.8%; P=0.02) and forced vital capacity (FVC: 7.6% predicted; 3.5% to 11.8%; P=0.01) at 12 months, but not in PEF (6.2% predicted; -1.4% to 13.7%; P=0.11). Also significant were the improvements in dyspnea severity (median change based on a visual analogue scale, intervention, -13 mm [variance estimate not reported]; control, -1 mm; P=0.02) and in rescue medication daily doses (intervention, -1.2; control, -0.1; P=0.03) at the end of the intervention, but not at 12 months. Significant improvements were also observed in the health status symptom domain (distress caused by specific respiratory symptoms: -12; -22 to -1; P=0.04) and total scores (-10; -18 to -1; P=0.02) as measured by the St George’s respiratory questionnaire at 12 months. Serum concentrations of sodium, potassium, calcium, and magnesium did not significantly differ between groups over the 12-month study period.
<table>
<thead>
<tr>
<th>Study Cited, Design, Primary Outcome, Setting, Quality Rating</th>
<th>Inclusion Criteria, Group Size, Baseline Characteristics, Retention at Primary Assessment Time Point</th>
<th>Intervention Groups, Component Details</th>
<th>Treatment Duration, Total Intervention Contacts, Intervention Adherence</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Stenius-Aarniala et al., 2000 [18] RCT, ITT (interpreted by reviewer) PEF was a primary outcome (interpreted by reviewer) Finland, Medical center</td>
<td>Inclusion criteria: ages 18-60 yrs, BMI ≥ 30 ≤ BMI ≤ 42, with asthma diagnosed with a spontaneous diurnal variation or a bronchodilator response of 15% or more, non-smoker or having stopped smoking for ≤ 2 yrs before age 50. N=38</td>
<td>G1: Intervention Diet during first 8 weeks: a very low calorie dietary preparation (1760 kJ/day [420 kcal/day] containing daily allowances of all essential nutrients) Medical: received normal medical care throughout the study Behavior: received education about asthma and allergy via group sessions (details unknown); measured daily morning and evening pre- and post-bronchodilator PEF during the dieting period and thereafter during the 2 weeks before each group meeting. G2: Control Diet: no intervention Medical: same as G1 Behavior: same as G1</td>
<td>Intervention: 14 weeks Contacts: G1: 12 group sessions on same education about asthma and allergy as G2 G2: 12 0.5-hour group sessions at the same intervals as G1, during which time themes about asthma and allergy chosen by the group were discussed freely.</td>
<td>At the end of the 14-week weight loss intervention Weight change, %, mean G1: -14.5 G2: -0.3 (calculated by reviewer) P NR Weight change, kg, mean (range) G1: -14.2 (-22.1, -7.7) G2: -0.3 (NR) P&lt;0.05 PEF (% of predicted) change, mean (95% CI) G1: 4.5 (-0.9, 9.8) G2: 0.3 (-4.6, 4.1) P=0.16 FEV1 (% of predicted) change, mean (95% CI) G1: 5.3 (2.2, 8.4) G2: 1.5 (-5.1, 2.2) P=0.006 FVC (% of predicted) change, mean (95% CI) G1: 1.9 (-0.7, 4.4) G2: 5.6 (-8.6, 1.5) P=0.002 Dyspnea symptom, median change on a 100 mm VAS G1: -13 (variance NR) G2: -1 (variance NR) P=0.02 Daily dose of an inhaled bronchodilator, median change G1: -1.2 (variance NR) G2: -0.1 (variance NR) P=0.03 At 1 year (whether primary time point NR) Weight change, %, mean G1: -11.3 G2: 2.2 P NR Weight change, kg, mean (range) G1: -11.1 (-22.5, -1.1) G2: 2.3 (NR) P NR PEF (% of predicted) change, mean (95% CI) G1: 5.6 (-0.2, 11.4) G2: -0.6 (-5.8, 4.7) P=0.11 FEV1 (% of predicted) change, mean (95% CI) G1: 4.9 (-0.5, 10.3) G2: -2.7 (-5.9, 0.5) P=0.02 FVC (% of predicted) change, mean (95% CI) G1: 2.0 (-1.4, 5.4) G2: 5.6 (-8.2, -3.1) P=0.001 Dyspnea symptom, median change on a 100 mm VAS G1: NR G2: NR P=0.12 Daily dose of an inhaled bronchodilator, median change G1: NR G2: NR P=0.08</td>
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Scott et al., 2013 [19]  
RCT, per protocol  
Completer analysis  
Primary outcome is not indicated.  
Australia, Medical center  
Duration: 10 weeks  
Quality: Fair  

| Inclusion criteria: adults, overweight and obese (28 ≤ BMI ≤ 40), with asthma defined by doctor’s diagnosis and documented history of airway hyperresponsiveness, non-smoking  
N=48  
Female %: 54.3  
Group n’s: G1: 18  
G2: 14  
G3: 14  
Age, yrs, mean (SD): G1: 44.7 (14.7)  
G2: 42.2 (11.5)  
G3: 33.9 (11.5)  
White %: NR  
BMI, kg/m², mean (SD): G1: 34.7 (4.0)  
G2: 32.8 (2.5)  
G3: 32.7 (3.4)  
ACQ score, mean (SD): G1: 1.24 (0.57)  
G2: 1.00 (0.71)  
G3: 1.36 (0.63)  
AQLQ score, median (IQR): G1: 5.8 (5.4, 6.1)  
G2: 6.1 (5.0, 6.3)  
G3: 5.8 (4.8, 6.1)  
All groups had a similar baseline age, sex, body composition, asthma status, and sputum inflammatory profile.  
Retention %: G1: 83  
G2: 71  
G3: 93  
G1: Dietary intervention  
Diet: an intake of 3700–4900 kJ/day (885–1170 kcal/day), including two meal replacements provided free of charge  
Behavior: behavior modification and motivational strategies. Participants maintained a daily food diary during the intervention.  
G2: Exercise intervention  
Physical activity: a goal of increasing daily steps by 10% each week to a target of 10,000 steps per day. A 12-week gym membership and weekly 1-hour group personal training (both aerobic activities and resistance training) sessions. Participants attended gym ≥3 times/week.  
Behavior: participants set goal with dietitian, wore a pedometer daily, and completed a daily physical activity diary during the intervention.  
G3: Combined dietary and exercise intervention  
Diet: same as G1  
Physical activity: same as G2  
Behavior: same as G1 + G2  

| Intervention: 10 weeks  
Contacts: G1: weekly counselling with a dietitian: 7 1-hour clinic visits and 4 10-min phone consultations  
G2: weekly 1-hour group training sessions  
G3: same as G1 + G2  

| Intervention adherence:  
Diet: energy change, kJ, median (IQR): G1: -4261 (-5896, -2632)  
G2: -232 (-3254, -464)  
G3: -5584 (-7384, -4624)  
ACQ score, mean (SD): G1: 2.48 (0.12)  
G2: 2.98 (0.12)  
G3: 3.39 (0.12)  

At 10 weeks  
Weight change, %, mean (SD): G1: -5.5 (4.2)  
G2: -1.8 (2.6)  
G3: -3.3 (4.9)  
Weight change, kg, mean (SD): G1: -4.4 (4.4)  
G2: -1.0 (2.7)  
G3: -2.2 (5.1)  
G1 and G3 significantly different from G2 (P<0.001)  
ACQ change, mean (SD): G1: -0.6 (0.5)  
G2: -0.3 (0.5)  
G3: -0.5 (0.7)  
G1 and G3 significantly improved ACQ score; however, between group comparison is NS (P=0.343)  
AQLQ change, median (IQR): G1: 0.9 (0.4, 1.3)  
G2: 0.49 (0.03, 0.78)  
G3: 0.5 (0.1, 1.0)  
G1, G2, and G3 significantly improved AQLQ score; however, between group comparison is NS (P=0.212)  
TLC change, L, median (IQR): G1: -0.03 (-0.33, 0.14)  
G2: 0.13 (0.02, 0.28)  
G3: 0.06 (-0.06, 0.33)  
G2 and G3 significantly improved TLC compared with G1 (P=0.037 for overall group difference)  
A 5-10% weight loss resulted in clinically significant improvements to ACQ in 58% and AQLQ in 83% of participants.  
Women had a significantly greater reduction in sputum percentage neutrophils compared with men (P < 0.05); however, men and women experienced a similar degree of improvement to ACQ and AQLQ.  

Dias-Junior et al., 2014 [20]  
RCT, ITT and per protocol population analysis (patients who lost >10% of body weight)  
ACQ was a primary outcome  
Brazil, Medical center  
Duration: 6 months  
Quality: Good  

| Inclusion criteria: ages 18-65 yrs, BMI ≥ 30, with severe asthma according to GINA criteria after a 3-month run-in period, with a smoking history of less than 10 pack-years  
N=33  
Group n’s: G1: 22  
G2: 11  
Age, yrs, mean (SE): G1: 42 (15.75)  
G2: 44 (24)  
P=0.825  
Females %: G1: 90.9  
G2: 100  
P=0.542  
White %: NR  
BMI, kg/m², mean (SE): G1: 39.68 (1.31)  
G2: 37.29 (1.07)  
P=0.243  
ACQ score, mean (SE): G1: 3.02 (0.19)  
G2: 2.91 (0.25)  
P=0.718  
Retention %: G1: 100  
G2: 100  
G1: Intervention  
Diet: low caloric intake  
Medical: use of sibutramine (10 mg/day) and orlistat (≤120 mg/day) and orlistat (≤120 mg/day) and orlistat (≤120 mg/day)  
G2: Control  
No intervention  

| Intervention: 6 months  
Contacts: G1: bimonthly in-person consultations where participants saw the same investigator to have their use of inhaler checked, compliance with medication assessed, and receive education on asthma.  
G2: NR  

| Intervention adherence: G1: -8.3 (4.9)  
G2: -1.8 (2.6)  
G3: -3.3 (4.9)  
Weight change, kg, mean (SD): G1: -4.4 (4.4)  
G2: -1.0 (2.7)  
G3: -2.2 (5.1)  
G1 and G3 significantly different from G2 (P<0.001)  
ACQ change, mean (SD): G1: -0.6 (0.5)  
G2: -0.3 (0.5)  
G3: -0.5 (0.7)  
G1 and G3 significantly improved ACQ score; however, between group comparison is NS (P=0.343)  
AQLQ change, median (IQR): G1: 0.9 (0.4, 1.3)  
G2: 0.49 (0.03, 0.78)  
G3: 0.5 (0.1, 1.0)  
G1, G2, and G3 significantly improved AQLQ score; however, between group comparison is NS (P=0.212)  
TLC change, L, median (IQR): G1: -0.03 (-0.33, 0.14)  
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G3: 0.06 (-0.06, 0.33)  
G2 and G3 significantly improved TLC compared with G1 (P=0.037 for overall group difference)  
A 5-10% weight loss resulted in clinically significant improvements to ACQ in 58% and AQLQ in 83% of participants.  
Women had a significantly greater reduction in sputum percentage neutrophils compared with men (P < 0.05); however, men and women experienced a similar degree of improvement to ACQ and AQLQ.  

At 6 months (ITT analysis)  
BMI, kg/m², mean (SE): G1: 36.71 (1.37)  
G2: 36.85 (1.06)  
P < 0.001 for G1 and NS for G2 within groups  
P=0.015 for the comparisons between groups.  
ACQ score, mean (SE): G1: 2.25 (0.23)  
G2: 2.90 (0.16)  
P<0.001 for G1 and NS for G2 within groups  
P=0.044 for the comparisons between groups.  
FVC, L, mean (SE): G1: 2.98 (0.12)  
G2: 2.48 (0.12)  
P=0.004 for G1 and NS for G2 change within groups  
P=0.017 for the comparisons between groups.  
ITT analysis showed that the intervention group significantly lost weight (mean weight loss 7.88 kg; 7.5% of baseline weight), improved asthma control as measured by ACQ, and increased FVC.  
ACQ reached clinically significant improvements (>0.5) in 11 of the 12 intervention patients who lost >10% of their baseline weight.
Scott et al. compared a dietary restriction intervention, an exercise intervention, and a combined intervention over 10 weeks in 46 overweight or obese Australian adults with asthma (defined by physician diagnosis and documented history of airway hyperresponsiveness) [19]. The dietary intervention group was prescribed a daily calorie intake of 3700-4900 kJ (885-1170 kcal), including two meal replacements provided free of charge and one main meal and snacks provided by participants. Participants also completed weekly counselling with a dietitian. The exercise group received a membership to a gymnasium participants. Participants also completed weekly counselling with a dietitian. The exercise group received a membership to a gymnasium participants. Participants also completed weekly counselling with a dietitian. The exercise group received a membership to a gymnasium participants. Participants also completed weekly counselling with a dietitian. The exercise group received a membership to a gymnasium.

Table 3: Characteristics of RCTs for weight loss or maintenance interventions in adults with asthma.

ACQ: Asthma control questionnaire; ACT: Asthma control test; BMI: Body mass index; CI: Confidence interval; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; GINA, Global initiative for asthma; ITT, Intent-to-treat; IQR, Interquartile range; MET, Metabolic equivalent task; NR, Not reported; NS, Not significant; PEF, Peak expiratory flow; RCT, Randomized controlled trial; SD, Standard deviation; SE, Standard error; TLC, Total lung capacity; VAS, Visual analogue scale.

In a Brazilian study by Dias-Junior et al. [20], 33 obese adults with severe uncontrolled asthma (defined by specialist diagnosis, documented history of airway hyperresponsiveness within the previous 5 years, ≥1 exacerbation requiring systemic corticosteroids in the last year, and use of high doses of inhaled corticosteroids) were randomly assigned in a 2:1 ratio to 6 months of treatment with a low-calorie diet (energy intake unspecified) and sibutramine (10 mg per day) and orlistat (maximum dose of 120 mg per day) or to a control group. Participants also attended bimonthly asthma education. At 6 months, intervention participants had significantly reduced BMI (mean [standard error]SE, 36.71 [1.37] vs. 39.68 [1.31] kg/m² at baseline) and improved ACQ scores (2.25 [0.28] vs. 3.02 [0.19]), with 11 of the 12 participants who had >10% weight loss achieving clinically important improvement in ACQ. BMI and ACQ changes were insignificant in the control group. The between-group difference was statistically significant for changes in both BMI (P=0.015) and ACQ (P=0.044), but not for changes in most spirometric results (except FVC), airway hyperresponsiveness, nitric oxide fraction in exhaled air (FeNO), and other airway and systemic inflammatory markers. The authors suggested that changes in airway inflammation might not explain the effect of weight loss on asthma outcomes in obese adults with severe asthma.

Our research group conducted the largest RCT of weight loss in asthma to date. We compared the Breathe Easier through Weight Loss Lifestyle (BE WELL) intervention with usual care in a major US ambulatory care system among 330 adults with objectively confirmed obesity and uncontrolled asthma [21,22]. Adapted from the efficacious Diabetes Prevention Program lifestyle intervention [23], the BE WELL intervention dually targeted modest (7-10%) weight loss and increased physical activity (daily minimum of 150 minutes of moderate-intensity physical activity). The 12-month program had 13 weekly group sessions.
over a 4-month period and 2 monthly individual sessions, followed by bimonthly or more frequent individual phone consultations depending on participant needs, preferences, and availability for the remainder 6 months. All intervention and control participants received usual care enhanced with a pedometor, a weight scale, information about existing weight management services at the participating clinics, and a standard asthma education DVD. Compared with controls, the intervention group achieved significantly greater weight loss at 12 months (mean [SE], -4.0 [0.8] kg or -4.1% [0.7%] vs. -2.1 [0.8] kg or -2.1% [0.7%]) and increased weekly leisure-time physical activity levels (metabolic equivalent task [MET] minutes: 418.2 [110.6] vs. 178.8 [109.1]). Both groups had modestly improved asthma control, but the between-group difference (ACQ changes: intervention, -0.3±0.1 vs. control, -0.2±0.1) was not significant. Subgroup analyses of all participants regardless of randomization showed that at least 10% weight loss was associated with a Cohen's d effect of 0.76 and with 3.78 (95% CI, 1.72-8.31) times the odds of achieving clinically important reductions on ACQ as stable weight (i.e., <3% loss or gain from baseline). Thus, weight loss of at least 10% may be required to produce clinically meaningful improvement in asthma control. The between-group difference was insignificant for other clinical asthma outcomes (e.g., MiniAQLQ, spirometric results, medication acquisition, and healthcare encounters). Furthermore, the intervention effects on ACQ change and weight loss at 12 months were comparable among men and women.
RCTs of weight management interventions in children and adolescents

Three RCTs of weight management interventions have been published in children and adolescents (Table 4); Jensen et al. compared a 10-week diet-induced weight loss intervention with a wait-list control group in 28 obese Australian youth aged 8-17 years with BMI z-scores ≥1.64 and physician diagnosed asthma [24]. The intervention targeted a 500 kcal/day reduction from the age- and gender-appropriate energy requirements. Intervention participants received dietary counseling in person and by phone during the 10 weeks. Parents were invited to attend the in-person sessions as well to help facilitate their child's dietary change and monitoring. Compared with controls, the intervention group had significantly reduced BMI z-scores (median [IQR] change, -0.2 [-0.4, -0.1] vs. 0 [-0.1, 0]; P=0.014), improved ACQ scores (-0.4 [-0.7 to 0] vs. 0.1 [0 to 0.6]; P=0.004), and decreased C-Reactive Protein (-0.4 [-0.5, 0.4] vs. 0.1 [-0.1, 1.9]; P=0.037) at 10 weeks. Changes in other airway and systemic inflammatory markers (e.g., FeNO, leptin, eosinophils, neutrophils) and spirometric results did not differ significantly by group.

In El-Kader et al.'s study in Saudi Arabia, 80 obese youth with a mean (SD) age of 14 (3) years who had a BMI between 30-35 kg/m² and bronchial asthma (case definition not found in the article) were randomly assigned to an 8-week weight loss intervention including both diet and exercise regimens or a control group [25]. The intervention group was prescribed a low calorie diet, which provided an energy deficit of about 250 kcal per day and balanced macronutrients, and an 8-week training program with four sessions of aerobic exercise per week. Intervention participants had significantly reduced BMI (mean [SD], 27.15 [2.38] post intervention vs. 32.31 [2.46] kg/m² at baseline) and inflammation (leptin: 26.98 [4.50] vs. 31.43 [5.47] ng/ml; IL-6: 1.85 [0.76] vs. 2.19 ± [0.81] pg/ml; IL-8: 12.14 [3.72] vs. 15.66 [4.63] pg/ml). Changes in BMI and the inflammatory biomarkers were insignificant in the control group. However, the authors did not report the between-group differences in these outcomes or any clinical asthma outcomes.

Luna-Pech et al. randomly assigned 51 obese Mexican adolescents aged 12-16 years who had a BMI ≥95th percentile (per the Centers for Disease Control and Prevention BMI-for-age growth charts) and objectively confirmed asthma to a 28-week normocaloric diet intervention (n=26) or a control group (n=25) [26]. Both groups attended biweekly follow-up visits to review dietary recalls, perform PEF, assess asthma control, and develop an action plan in case of worsened asthma symptoms. In addition, the intervention group received advice from a certified nutritionist on normocaloric diet according to the adolescent's height and physical activity levels and on menu planning based on an equivalent exchange system. Compared with controls, intervention participants had significantly reduced BMI (mean [SD], -1.64 [-2.5 to -0.7] vs. 0.76 ± [0.9] kg/m² at 28 weeks: P<0.001) and nighttime awakenings (11 vs. 26, P<0.001). Compared with G2, G1 had significantly fewer acute asthma events requiring short-acting β-agonists (17 vs. 39, P<0.02) and nighttime awakenings (11 vs. 26, P<0.001).

Discussion

This systematic review focused on RCTs of weight management interventions in adults and youth with asthma. The 4 RCTs in adults with asthma support the benefit of substantial weight loss, but a
threshold effect may exist such that only weight loss beyond a minimal amount would lead to clinically important improvement in asthma outcomes. Secondary findings from 3 of the RCTs [19,20,22] suggest that the threshold may lie between 5-10% of weight loss, which needs to be confirmed in future study. The 3 RCTs in obese youth with asthma suggest that modest calorie reductions alone or combined with increased physical activity, or even a healthy normocaloric diet, may be beneficial on asthma outcomes in this population.

The trial results strengthen and extend the evidence from observational and quasi-experimental weight loss in asthma studies. A number of non-RCT studies in adults have shown that substantial weight reductions through bariatric surgery [27-33] or very low calorie diets [34,35] are associated with significantly improved asthma outcomes, including overall control, symptoms, lung function, medication use, quality of life, and health care utilization. Fewer non-RCT studies have been conducted in children or adolescents with asthma [36,37]. One single-arm study showed that an interdisciplinary intervention consisting of medical, nutritional, exercise, and psychological therapy led to significant weight loss as well as improved lung function, systemic inflammation, and asthma severity in obese adolescents with asthma [36]. Another study reported that a school-based program consisting of nutrition, weight management, and asthma education significantly improved participants’ self-efficacy (i.e., perceived ability to manage asthma), quality of life, and self-care related to asthma; however, no objective asthma outcomes were measured [37].

Most of the RCTs included in this review were limited by small sample sizes, short intervention durations, and short follow-up periods. Different from all the other weight loss RCTs in adults with asthma, the BE WELL intervention tested by Ma et al. lasted 12 months (vs. 10 weeks to 6 months) and used a comprehensive approach encompassing moderately calorie-restricted healthy eating, moderate-intensity physical activity, and evidence-based behavioral self-management strategies, as recommended in the latest (2013) Obesity Treatment Guideline [17]. As the largest RCT of weight loss in asthma, the BE WELL study showed that adults with uncontrolled asthma can safely participate in lifestyle interventions proven for cardiometabolic benefits but that modest improvements in weight and activity level are not likely to significantly change asthma outcomes consistently within the population treated [22]. Ma et al. posited that to achieve clinically important improvement in asthma among adults it may require at least 10% weight loss, which would be greater than the accepted modest amounts of 3-5% for diabetes prevention and cardiovascular risk factor control [22]. While somewhat encouraging, the trial evidence on weight loss in children and adolescents with asthma is even more limited than in adults. More adequately-powered, well-designed, and well-conducted RCTs are clearly needed. The gaps in knowledge identified through this review highlight several specific future research directions.

First, the proposition that more than modest weight loss may be required for clinically meaningful improvement in asthma among adults is provocative and certainly warrants further investigation. Studies are needed to identify the minimum threshold of clinically significant weight loss in asthma and what factors may affect the threshold chosen (e.g., clinical and sociodemographic characteristics of the target population and the specific asthma outcomes of interest). In addition, if such threshold cannot be achieved by pragmatic lifestyle interventions alone (the BE WELL intervention, for example), then stepped-up obesity treatment regimens such as medically supervised very low calorie diet, weight loss drug therapy, or bariatric surgery should be evaluated.

Second, the underlying mechanisms of the influence of obesity and weight loss on asthma remain an enigma. Although many of the RCTs reviewed examined the impact of weight management interventions on asthma outcomes (e.g., spirometric results, airway and systemic inflammation) in addition to asthma control and asthma-related quality of life, the findings were exploratory and largely inconsistent. The postulated mechanisms for improved asthma status after weight loss include improvements in gastroesophageal reflux symptoms, airway and systemic inflammation, oxidative stress, and lung function [16,38,39]. These hypotheses need to be tested in well-designed mechanistic studies. Research to investigate the threshold effect as noted above should concurrently explore the role of varying degrees of weight loss in lung mechanics, airway physiology, immune response, and inflammation as well.

Third, subpopulation studies are needed to help elucidate the effect of weight loss in asthma and potential mechanisms. Emerging data suggest the possibility of at least two distinct asthma phenotypes in obese adults depending on the age of asthma onset and the presence of atopy [29,40]. The later-onset (>12 years of age), typically nonatopic asthma phenotype that is predominantly found in women has been previously shown to respond more favorably to weight loss [29]. In addition, some observational studies suggest a stronger relationship between obesity and certain asthma manifestations in females than in males [41-43]. However, the only two RCTs reviewed that reported intervention effects by gender found no differences [19,22]. Baseline obesity status (e.g., obese class I, II, and III) may be another factor that could modify the effects of weight management interventions among asthmatic patients, but none of the 7 RCTs examined this. Thus, future weight loss trials focused on subpopulations (e.g., females with nonatopic, later-onset asthma and people with different baseline obesity status) are needed.

Fourth, more research is needed to define the most suitable weight management approach for obese children and adolescents with asthma. An expert committee recommended that pubertal development should be evaluated in the prevention, assessment, and treatment of overweight and obesity in children and adolescents [44]. Luna-Pech et al. recommended that a healthy normocaloric dietary approach should be used in obese pubertal adolescents with asthma to ensure normal development [26]. Recent systematic reviews focusing on dietary patterns (not weight management) in asthma found good epidemiologic evidence supporting potentially protective effects of Mediterranean diet on child asthma and wheeze [45,46]. Thus, future RCTs need to rigorously test the efficacy of a Mediterranean diet or similarly healthy dietary pattern with or without weight management strategies in pediatric populations with asthma. This is particularly important because healthy eating habits formed at a young age have not only potential short-term benefits on asthma outcomes but also life-long benefits on general health.

Fifth, the potential independent and synergistic effects of a healthy diet and weight loss are equally worthy of investigating in adults with asthma. Evidence on the effect of healthy dietary patterns in this population is mixed [45], although at least one short-term RCT showed improved FEV1 and FVC values as well as time to asthma exacerbation following increased fruit and vegetable intake [47]. We recently completed the first RCT of the Dietary Approaches to Stop Hypertension (DASH) eating pattern in adults with uncontrolled asthma [48], with results forthcoming.

Last, research on weight management interventions other than weight loss and on the management as well as prevention of asthma is needed. Even though we purposely defined weight management to
broadly include weight loss, weight maintenance, maintenance of lost weight, and weight gain prevention in our search strategy, all but one of the included RCTs tested weight loss interventions only, whereas Luna-Pech et al. [26] evaluated a normocaloric diet intervention which nevertheless led to weight loss as opposed to weight gain in the controlgroup. Further, no RCTs have examined any type of weight management interventions for the prevention of asthma.

This systematic review was limited to studies published in English only. At least one RCT on the topic of interest but published in a foreign language was not included [49]. Also, the small number of studies and the heterogeneity of the interventions and outcomes precluded a meta-analysis. Despite these limitations, this is the most up to date synthesis of RCTs on weight management in asthma for all age groups. It reveals that overall the available trial evidence is weak but nevertheless supportive of the benefit of weight loss in adults and youth with asthma, although a minimum of 5-10% weight loss may be required to reach clinical significance at least in obese asthmatic adults. Future work in the several specifically recommended areas will be important to elucidate the role of weight management in asthma control and prevention, thereby guiding clinical and public health practice to effectively address the dual epidemic of obesity and asthma.

Declarat on of Interest

NL, LX, JM declare that they have no conflict of interest.

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