Weight loss and asthma: a systematic review

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ABSTRACT

Epidemiological studies first demonstrated the association between obesity and asthma and they have begun to provide additional evidence to support causality: a dose-effect relationship, consistency across studies (especially among women) and the correct temporal order (i.e., obesity before asthma). To date, relatively few studies have addressed reversibility, an important but less frequently demonstrated epidemiological criterion of causality. Reversibility suggests that if excessive weight is a risk factor for asthma, then reducing body weight should decrease the prevalence of asthma, or at least decrease asthma related symptoms or health care utilisation. We performed a systematic review on weight loss and asthma, based on searches between January 1966 and January 2007 of both PubMed and the Cochrane Clinical Trial Database. Of the 15 relevant studies, asthma was the primary outcome in only five. Only one study was conducted in children. Regardless of the type of intervention (surgical vs medical), all 15 studies noted an improvement in at least one asthma outcome after weight loss. The improvement was noted across studies that differed in sample age, gender or country of origin. The heterogeneity of the interventions and outcomes precluded quantitative synthesis. We briefly review the role of specific factors (e.g., gastro-oesophageal reflux) in the weight loss-asthma association, and potential directions for future research.

Rising obesity prevalence rates are a concern worldwide. Between 1980 and 2000, obesity rates in the USA increased by 50% for adults and threefold for children and adolescents.1 2 Over a similar timeframe, asthma prevalence rose by 75%.3 4 Although the upward trends transcend age, sex, race/ethnicity and geographic location, they disproportionately affect minority groups, the socioeconomically disadvantaged and inner city populations.

The simultaneous rise in the frequency of both conditions may not be coincidental. The 1999 reports of a strong positive association between body mass index (BMI) and risk of adult onset asthma in both the Nurses’ Health Study5 and the 1970 British Cohort Study6 prompted widespread interest in the obesity–asthma hypothesis. Increased BMI has also been associated with increased severity of asthma symptoms and use of health services.7 Although several groups around the world have confirmed a positive association between obesity and both prevalent and incident asthma,8 9 other researchers have shown the increase in asthma prevalence to be independent of rising obesity rates.10 11 In a British study,11 the odds ratio per year for asthma between 1982 and 1994 remained unchanged when adjusted for BMI, suggesting the obesity–asthma link may not be causal but rather reflect the effect of recent lifestyle changes. Whether a causal relationship truly exists, the potential for reverse causality (i.e., asthma causes obesity), and the biological mechanisms for the association, remain active topics of discussion.3 12 13 14

Cohort studies provide the strongest epidemiological evidence that obesity is a risk factor for asthma by demonstrating not only a significant relationship with incident asthma but also the correct temporal order.6 11 13 14 In our initial prospective study of 85 911 female registered nurses, weight gain greater than 25 kg after the age of 18 years was associated with an almost fivefold likelihood (odds ratio (OR) 4.7, 95% confidence interval (CI) 3.1 to 7.0) of reporting a doctor diagnosis of adult onset asthma.5 Proposed mechanisms for the obesity–asthma link include gastro-oesophageal reflux (GOR), genetic factors, dietary intake, inflammatory mediators (e.g., interleukins), abnormal chest wall mechanics and physical activity, but the evidence has not been consistent across studies.15

Some studies have investigated the obesity–asthma link from a different perspective, hypothesising that if excessive weight is the risk factor, then reducing body weight should decrease the prevalence of asthma, or at least reduce asthma related symptoms or health care utilisation. If true, this would provide evidence of reversibility, an important epidemiological criterion of causality.17 Unfortunately, most of these studies are small, underpowered and rarely focus on asthma as the only outcome. In light of these limitations, a systematic review on weight loss and asthma would be timely, and the results, taken together, might contribute important insights to current discussion about the obesity–asthma association. A systematic review would also enable us to generate hypotheses for future research on the factors (e.g., GOR) that are most likely to mediate or modify the obesity–asthma link. Accordingly, this systematic review will conduct an indepth evaluation of the extant literature on weight loss and asthma and examine potential directions for future research.

METHODS AND MATERIALS

We performed a computerised search of PubMed and the Cochrane Clinical Trial Database between January 1966 and January 2007 using the following combination of search terms: “weight loss/asthma, bariatric surgery/asthma, gastric bypass/asthma, physical activity or exercise/asthma, and diet/weight loss/asthma”. To broaden our coverage of the literature, we also reviewed bibliographies of textbooks, original research, symposia and commentaries for additional references. We used the
following a priori inclusion criteria: (a) asthma as an outcome measure and (b) studies on weight loss. Two authors (IUE and CAC) reviewed each abstract. We excluded case studies, reviews, and publications where the outcome was limited to only pulmonary function indices as these did not represent a diagnosis of asthma. We did not identify any relevant case studies. Fifteen of 21 papers met all of the inclusion criteria and were selected for critical review.

Next, two authors (IUE and TS) reviewed each paper, extracting information on study design, sample size, population, method of weight loss, identification of covariates, asthma diagnosis and outcomes. We categorised outcomes into number of asthma exacerbations, asthma symptoms, impact of asthma on daily function, use of asthma medications and asthma related health care utilisation (eg, emergency department visits, hospitalisations). Based on method of weight loss, studies were divided into two categories: surgical and medical weight loss interventions.

STUDIES ON WEIGHT LOSS AND ASTHMA

Of the 15 studies that addressed weight loss and asthma (table 1), asthma was the primary outcome in only five studies. More often, asthma related outcomes were included in a list of outcomes from different clinical conditions (eg, percentage weight loss, type 2 diabetes, sleep apnoea, hypertension, dyslipidaemia). The method of asthma diagnosis was usually not described. The median sample size for the asthma subpopulation in the included papers was 28 subjects (range 6-40), with median length of follow-up of 1 year (range 8 weeks to 14 years). All of the studies were conducted in adults (mostly women) and in white populations, which limits the generalisability of the findings to men and other racial/ethnic groups. There was a single paediatric study, with a single subject with asthma. Only four studies used low calorie diets or a medical weight loss programme. The most common surgical procedure was the vertical banded gastroplasty or Lap band procedure which was used in seven studies. The majority of the studies reported at least one of the following outcomes: use of asthma medication, severity of asthma symptoms and resolution of asthma symptoms (yes/no). The most frequently assessed outcome was resolution of asthma symptoms. None of the studies investigated healthcare costs related to office visits, urgent or emergent care, missed workdays or years of productive life lost. Despite similar outcome measures in most of the studies, the heterogeneity of the study populations, interventions and definition of outcomes precluded quantitative analysis. Improvement in asthma outcomes was seen across studies that differed in sample age, gender or country of origin.

One of the earlier studies to focus on asthma outcomes was conducted by Dixon et al in 1999. Asthma was assessed preoperatively and at least 12 months after surgery using a scaled asthma score based on severity, daily impact, medications needed, hospitalisation, sleep and exercise. Patients were categorised into mild, moderate or severe asthma based on the National Asthma Campaign criteria. Although 10 had a history of severe asthma at baseline, none had severe asthma at the 12 month follow-up. The impact of asthma on daily living activities improved by 50%. There was a 57% decline in the number of patients that needed daily medications from 14 to six after weight loss. The mean preoperative scaled asthma score of 44.5 (16) decreased to 14.5 (11) at follow-up (p<0.001). The investigators reported a correlation coefficient of 0.21 between per cent weight loss and improvement in asthma scores.

In another study of 24 patients with asthma who had laparoscopic adjustable gastric banding, use of asthma medication declined for 10 patients and was completely discontinued for four. None of the patients noted an increase in asthma symptoms or medication use, although there was no significant change in their reported asthma related quality of life pre- and postoperatively. Stenius-Aarniala et al conducted a randomised controlled trial using low calorie diets in Finland. Each participant completed a dyspnoea scale using a visual analogue scale from 0 to 100 mm. Health status related to asthma was measured using three domains: respiratory symptoms; limitation in physical activity; and social and psychological impact. Improved health status was defined as a decline in the total score percentage for all three domains. Following the intervention, there was a fall in reported dyspnoea scale by 12 units for the intervention group compared with 1 unit for controls (p = 0.05), while the health status scale decreased by 10 (95% CI −1 to −18). Although the authors reported a statistically significant difference in the use of rescue medication between the two groups (0.5 doses for the treatment group and no change for the control group), the difference probably would not have been meaningful in clinical practice. Only one study has indirectly examined asthma expenses before and after weight loss, using a population based study. At the 6 year follow-up, the 510 participants that underwent a surgical procedure had a 20% relative decrease in weight compared with the medical weight loss group (n = 455) that had lost less than 5%. Pharmaceutical costs for asthma in the surgical group decreased from 213 to 164 Swedish kroner while for the medical group the costs increased from 127 to 165 Swedish kroners. Macgregor and Greenberg in Australia described strong evidence of reversibility in their weight loss study. In a subset of five patients with asthma who had bariatric surgery, asthma symptoms improved following weight loss. The symptoms worsened after subjects regained some of their weight. Subsequently, the five patients underwent revisional surgery, lost weight again and the frequency of asthma symptoms decreased again. In the single patient in the study who did not lose weight despite surgery, the frequency of his asthma symptoms remained unchanged.

Two studies assessed for GOR, a condition which may mediate or confound an association between weight loss and change in asthma status. In the study by Macgregor and Greenberg, complete remission of asthma occurred in 48%, with an additional 12.5% free of asthma exacerbations. Mean excess weight loss following surgery was 68%. Improvement of asthma symptoms was marked among subjects who had severe attacks (ie, those with >10 exacerbations in 1 year). Of the 36 subjects whose asthma improved following weight loss and who reported acid reflux symptoms preoperatively, 50% had complete resolution of their reflux postoperatively. Although the authors reported a significant correlation between weight loss and asthma symptoms, they did not find a statistically significant association between change in GOR and change in asthma. Spivak and colleagues reported similar findings in 40 patients who had a diagnosis of GOR prior to surgery. In their study, the GOR of seven patients (15%) improved after weight loss (mean excess weight loss of 45%) while for 35 patients (75%) GOR resolved completely.

In summary, all studies, regardless of mode of intervention for weight loss, reported an improvement in some measure of asthma status. Although these studies are hardly definitive, the
### Table 1  Studies on weight loss and asthma

<table>
<thead>
<tr>
<th>Study</th>
<th>Subject</th>
<th>Asthma diagnosis*</th>
<th>Intervention</th>
<th>Duration</th>
<th>Resolves at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical interventions</strong></td>
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<tr>
<td>Ahroni(^{12}) 2005 USA</td>
<td>Total = 179</td>
<td>History of asthma</td>
<td>LAGB</td>
<td>1 y</td>
<td>Mean BMI 32.3 (7.0) kg/m(^2) ( (\downarrow) 18.5); ↓ in use of asthma meds (30%); asthma much better (74%); no change in SF-36 (quality of life)</td>
</tr>
<tr>
<td>Dhabuwala(^{20}) 2000 New Zealand</td>
<td>Total = 157; 80% female</td>
<td>History of asthma</td>
<td>SRGBP</td>
<td>2.5 y (0–9.5)</td>
<td>BMI 28 kg/m(^2) (20–52); asthma resolved – 50%; improved—26%, unchanged—14%; reduced medication use (84%)</td>
</tr>
<tr>
<td>Dixon(^{19}) 1999 Australia</td>
<td>Total = 380; 88% female</td>
<td>Physician diagnosis</td>
<td>LAGB</td>
<td>12 mo</td>
<td>BMI 32.9 kg/m(^2); asthma score 14.3 ( (\downarrow) 30.2 points), asthma severity score 2.03 ( (\downarrow) 1.63 points); daily impact score 1.21 ( (\downarrow) .87 points); ↓ use of daily meds (84%), no hospitalisation, 34% resolved symptoms</td>
</tr>
<tr>
<td>Hall(^{10}) 1990 Australia</td>
<td>Total = 310; 93% female</td>
<td>History of asthma</td>
<td>VBGP</td>
<td>3 y</td>
<td>Wt (kg) median 76–93; discontinued asthma meds (50%)</td>
</tr>
<tr>
<td>Macgregor(^{26}) 1993 USA</td>
<td>Total = 40; 80% female</td>
<td>History of asthma</td>
<td>VBGP</td>
<td>2–11 ((\chi = 4)) y</td>
<td>BMI 30 at 4 y; 90% improved asthma symptoms; 46% remission, discontinued meds: moderate (42%); severe (36%)</td>
</tr>
<tr>
<td>Murr(^{29}) 1995 USA</td>
<td>Total = 62; 80% female</td>
<td>History of asthma</td>
<td>VBGP</td>
<td>1–3 y</td>
<td>BMI loss 44 (5%) at 1 y; wt loss 33 (6%) at 3 y; decreased use of asthma meds (100%)</td>
</tr>
<tr>
<td>Narbro(^{36}) 2002 Sweden</td>
<td>Total = 1294; 69% female</td>
<td>History of asthma</td>
<td>Gastric banding</td>
<td>6 y</td>
<td>↓ Weight 16%; no difference in cost of asthma meds between both the intervention group and reference group at follow-up</td>
</tr>
<tr>
<td>O’Brien(^{37}) 2002 Australia</td>
<td>Total = 709; 85% female</td>
<td>Asthma severity score</td>
<td>LAGB</td>
<td>1 y</td>
<td>Mean BMI 31 kg/m(^2); asthma resolved (30%); no hospitalisations; discontinued asthma meds (80%); no oral steroids needed</td>
</tr>
<tr>
<td>Simard(^{20}) 2004 Canada</td>
<td>Total = 398; 70% female</td>
<td>History of asthma</td>
<td>BPD-DS</td>
<td>2 y</td>
<td>Of the 139 at follow-up: BMI 30 kg/m(^2); improved severity of asthma (79%)</td>
</tr>
<tr>
<td>Spivak(^{38}) 2005 USA</td>
<td>Total = 163; 90% female</td>
<td>History of asthma</td>
<td>Lap band</td>
<td>3 y</td>
<td>Mean BMI 35 ( (\downarrow) 10 kg/m(^2)); 82% resolved asthma</td>
</tr>
<tr>
<td><strong>Medical interventions</strong></td>
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<td></td>
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<tr>
<td>Sugerman(^{30}) 2003 USA</td>
<td>Total = 33</td>
<td>History of asthma</td>
<td>Gastric bypass</td>
<td>Up to 14 y</td>
<td>Asthma resolved (100%)</td>
</tr>
<tr>
<td>Aaron(^{24}) 2004 Canada</td>
<td>Total = 58; 100% female</td>
<td>Physician diagnosis</td>
<td>Wt loss programme</td>
<td>6 mo</td>
<td>Mean wt ↓ 20 kg (19%); for 10% wt loss, FVC ↑ 92 ml; for 10% wt loss, FEV (_1) ↑ 73 ml; improvement in symptoms (p&lt;0.05); no hospitalisations or ER visits</td>
</tr>
<tr>
<td>Hakala(^{11}) 2000 Finland</td>
<td>Total = 14; 80% female</td>
<td>Physician diagnosis</td>
<td>Low cal diet</td>
<td>8 wk</td>
<td>BMI 32.1 kg/m(^2) ( (\downarrow) 5.1 kg/m(^2)); dyspnoea score 8.1 ( (\downarrow) 6.5); use of rescue meds 0.4 does/day ( (\downarrow) 0.2)</td>
</tr>
<tr>
<td>Johnson(^{27}) 2007 USA</td>
<td>Total = 10, 80% female</td>
<td>Physician diagnosis</td>
<td>Low cal diet</td>
<td>8 wk</td>
<td>Weight 96.4 kg ( (\downarrow) 8%); improved asthma control on ACG</td>
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</table>

Continued
consistency of the results is reassuring and they provide some evidence to support a causal relationship between obesity and asthma. The mechanism to explain these observations merits further investigation.

**POTENTIAL MECHANISMS FOR IMPROVED ASTHMA STATUS**

In this section, we briefly review variables that may mediate or confound the association between weight loss and improved asthma (box 1). Understanding or refuting each pathway requires a better understanding of the variables that may be involved in the weight loss–asthma link.

**Gastro-oesophageal reflux**

Weight loss improves both GOR and asthma symptoms, a situation that suggests that GOR may mediate or modify the obesity–asthma link.41–43 The relationship between GORD–asthma is thought to be bidirectional. Asthma increases intra-abdominal pressure while asthma medications such as xanthines increase intra-abdominal pressure, predisposing to GOR. GOR is an exacerbating factor in asthma. Proposed mechanisms include: (1) chest expansion with diaphragmatic flattening, which leads to air trapping and negative intrathoracic pressure, and thereby impairs the integrity of the lower gastro-oesophageal sphincter; and (2) gastric acid within the oesophagus initiates a vagal response causing a bronchospastic reflex within the airways. While some studies demonstrate an increased rate of GOR with obesity,42 others do not find this association.44 A meta-analysis found a dose effect, with increasing reflux associated with overweight (OR 1.57, 95% CI 1.36 to 1.80) and obesity (OR 2.15, 95% CI 1.89 to 2.45).42 One of the strongest pieces of evidence that BMI and GOR are connected stems from the improvement in GOR symptoms after weight loss.26–38 In a prospective follow-up study (19 months (range 7–32)) of 31 patients who had undergone gastric banding, patients reported a decrease in symptoms from 48% preoperatively to 16% postoperatively (p = 0.01) and the diagnosis of GOR on 24 h pH recordings decreased from 77% preoperatively to 16% postoperatively (p = 0.01).45 Both of the studies in our review that found a dose effect, with increasing reflux associated with overweight and obesity,42 43 others do not find this association.44 A well designed large prospective cohort study is needed to confirm or refute the hypothesis that GOR mediates or at least contributes to the association between BMI and asthma.

**Dietary intake**

The link between dietary content, obesity and asthma—should one exist—is undoubtedly complex. Cross sectional studies have suggested a deleterious role for linoleic acid and other fatty acids and asthma.46–51 Linoleic acid, an essential fatty acid, has been implicated in the production pathway of several prostanoids and leukotrienes active in bronchoconstriction and neutrophil chemotaxis.52 By contrast, omega-3 polyunsaturated fatty acids (n-3 PUFA) which uses linolenic acid as its building block competes with arachidonic acid to form less active metabolites, and may thereby reduce airway inflammation and bronchoconstriction.53 54 Oddy et al reported cross sectional data showing a positive association between dietary n-6:n-3 fatty acid ratio and asthma in children,55 while a long term double blind trial of n-3 PUFA supplementation in patients with asthma found a positive effect on respiratory function.56 But more recent research disputes the “fatty acid” theory of asthma.57 58 In a 2005 study, Nagel and Linseisen found no association between fat intake, saturated fatty acids, monosaturated fatty acids or n6/n3 PUFA ratio and asthma, or between BMI and asthma.59

**Inflammatory mediators**

Interleukin (IL) 6, expressed by adipocytes, has been associated with IL4, IL2 and tumour necrosis factor stimulation and other cytokines implicated in asthma. Leptin, a protein secreted by fat cells and found in greater amounts in obese individuals, has also been associated with higher interleukin levels in individuals with asthma.59 60 In a study of overweight 12 year olds, who had been born with a very low birthweight, leptin levels were considerably higher in those with current asthma compared with overweight children without asthma (median value 30.8 vs 14.3 ng/ml).60 Using data from the National Health and Nutrition Examination Survey, Sood and colleagues59 found higher leptin levels among participants with asthma compared with those who did not have asthma (geometric mean (SE) 9.2 (0.6) µg/l vs 7.6 (0.2) µg/l; p = 0.02). The association was stronger among females, especially premenopausal women. However, in a regression analysis, leptin levels did not explain the association between BMI and asthma noted in the study population.

**Chest mechanics and physical activity**

In a recent systematic review, Lucas and Flatts-Mills described five prospective studies in adults and children that reported a relationship between decreased physical activity and asthma,61 suggesting decreased physical activity precedes asthma.
Likewise, in the European Community Respiratory Health Survey II, participants who exercised for 4 h or more/day had a lower prevalence of bronchial hyperresponsiveness compared with those who exercised for less than 1 h (15.9% vs 10.7%).\textsuperscript{41} Dysfunctional chest wall mechanics, due to extrinsic chest wall and intra-abdominal adipose tissue, are hypothesised to prevent full downward excursion during deep inspiration with a resulting decrease in forced expiratory volume in 1 s, forced vital capacity and total lung capacity, and a set-up for development of the lath phase.\textsuperscript{13} This state is thought to lead to sustained airway obstruction with increased airway hyper-reactivity. During physical activity, deeper breaths are taken which increase end tidal volume, avoiding the lath phase. Another mechanism by which physical activity may exert its influence may be through an inflammatory pathway. Participation in physical activity has been linked to lower high sensitivity C reactive protein levels,\textsuperscript{62} although not consistently.\textsuperscript{63} This effect was stronger among individuals who engage in vigorous activity compared with moderate and light activity, suggesting a dose effect.

**DISCUSSION**

As with most systematic reviews, our findings are limited by the quality and quantity of information provided in the primary studies. The heterogeneity of the study outcomes and interventions precluded a quantitative synthesis. Nonetheless, there was a consistent improvement in asthma outcomes (symptoms, use of medications or hospitalisations) across all studies. Asthma was typically determined by self-report and use of asthma medications, which might not truly reflect a diagnosis of asthma. Symptoms such as cough or shortness of breath occur in a wide variety of conditions, which can be inadvertently misdiagnosed as asthma. Poor physical conditioning with activity seen in overweight individuals can also be misdiagnosed as asthma or an asthma exacerbation.

Subjects represented a large age range, from young adults to older adults in their 60s. There was, however, only one adolescent subject. The paucity of data on weight loss and childhood asthma is a limitation that requires attention. It will be important to demonstrate that weight loss improves asthma in children, especially as the natural history of asthma during childhood differs from that with adult onset.\textsuperscript{44} Assessing asthma severity according to established guidelines such as the National Asthma Campaign criteria\textsuperscript{45} or the National Institutes of Health asthma guidelines\textsuperscript{46} would provide a better baseline asthma status with which to compare subjects later in the course of the weight loss study. With most of the studies in our review, asthma was not the primary outcome, perhaps reducing the chance that the results were skewed in favour of a publication bias. However, publication bias still poses a real threat as studies reporting a positive association are more likely to be published.

**Conclusions**

Despite a relatively small extant literature, and several methodological limitations, our systematic review found a fairly consistent association between weight loss and improved asthma. The interventional nature of the reviewed studies suggest causality with obesity as the risk factor. Nevertheless, small sample sizes and inconsistent methods make aetiological interpretation challenging. Most of the studies were observational or quasi-experimental, making it difficult to account adequately for some factors that can confound or modify the association (eg, severity of asthma, presence or absence of gastro-oesophageal reflux). Randomised clinical trials with weight loss intervention in an established asthma cohort will allow us to better assess the effect of weight loss per se. The intervention can target nutrients that have been tested in both asthma and obesity trials (eg, polyunsaturated fatty acids).\textsuperscript{56}–\textsuperscript{66} As with any weight loss trial, the challenge is selecting an effective intervention, ensuring participant compliance and limiting attrition. Investigators will need to recognise that loss to follow-up may be differential, with patients with severe asthma dropping out if they feel they will be unable to comply with the certain aspects of the intervention (eg, physical activity).

We hope that this review will motivate further work on this important topic. Future randomised trials, with an emphasis on elucidating biological mechanisms, will further clarify the nature of the association between weight loss and asthma. Finally, identification of an effective weight loss strategy for obese patients with asthma would reduce the medical, social and economic burden of both health conditions for the individual and general population.

**Competing interests:** None.

**REFERENCES**

Asthma


