Ther Adv Respir Dis
2020, Vol. 14: 1–13
DOI: 10.1177/1753466620906323

Optimizing lifestyle interventions in adult patients with comorbid asthma and obesity

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***Abstract*:** The prevalence of obesity and asthma are both increasing at alarming rates. The link between obesity and asthma suggests that obesity contributes to both risk of new onset asthma and increased asthma severity. The emerging evidence demonstrating the role of obesity and other lifestyle factors, such as diet and physical activity, on asthma outcomes warrants lifestyle interventions that can address these components of asthma care. This review examines the current literature on the pathophysiology of obesity's role in asthma, as well as the role of diet and physical activity in weight loss and in asthma outcomes. We discuss recent studies that employ lifestyle interventions to target improved asthma outcomes. Finally, we discuss the future direction of research in this area.

The reviews of this paper are available via the supplemental material section.

Keywords: adult, asthma, lifestyle interventions, obesity

Received: 18 September 2019; revised manuscript accepted: 21 January 2020.

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Introduction

The World Health Organization reports that the worldwide prevalence of obesity almost tripled between 1975 and 2016.[1] One third of adults in the USA are obese,[2] and more than half of the US adult population has been obese at some point in their lifetime.[3] Obesity is associated with an increased incidence of asthma, as well as greater asthma severity.[4–6] To address obesity in asthma, interventions that target obesity have been developed and tested in order to gain control of both conditions.[7–9] These interventions included very low calorie diets or bariatric surgery and found significant weight reduction and improved asthma outcomes. Despite these outcomes, these interventions are not sustainable or have not been adequately accessed by the target population.[7,9–11]

Obesity is affected by multiple components of our lifestyle, including exercise, diet, and stress. Thus lifestyle interventions have been developed which address exercise, diet, and typically, at least one other component such as counseling and stress management.[12] These changes are meant to be sustainable and accessible, and have shown to be effective in reducing the risk of diabetes and cardiovascular disease.[13–15] Despite their effectiveness in these diseases, the use of lifestyle interventions to address obesity and asthma has been limited, yet is key to developing interventions that are pragmatic and sustainable for patients.

This review examines the current literature on the pathophysiology of obesity's role in asthma, as well as how diet, physical activity, and weight loss impact asthma outcomes. Further, we discuss recent studies that employ lifestyle interventions to target improved asthma outcomes and the future directions for research in this area.

Comorbid asthma and obesity

Obesity has been linked to both increased incidence of asthma and increased severity. Prospective studies have demonstrated an increase in incident asthma in both obese men and women, and have shown a dose–response relationship between body mass index (BMI) and new asthma diagnoses.[16–18] A meta-analysis including 7 studies with over 300,000 unique

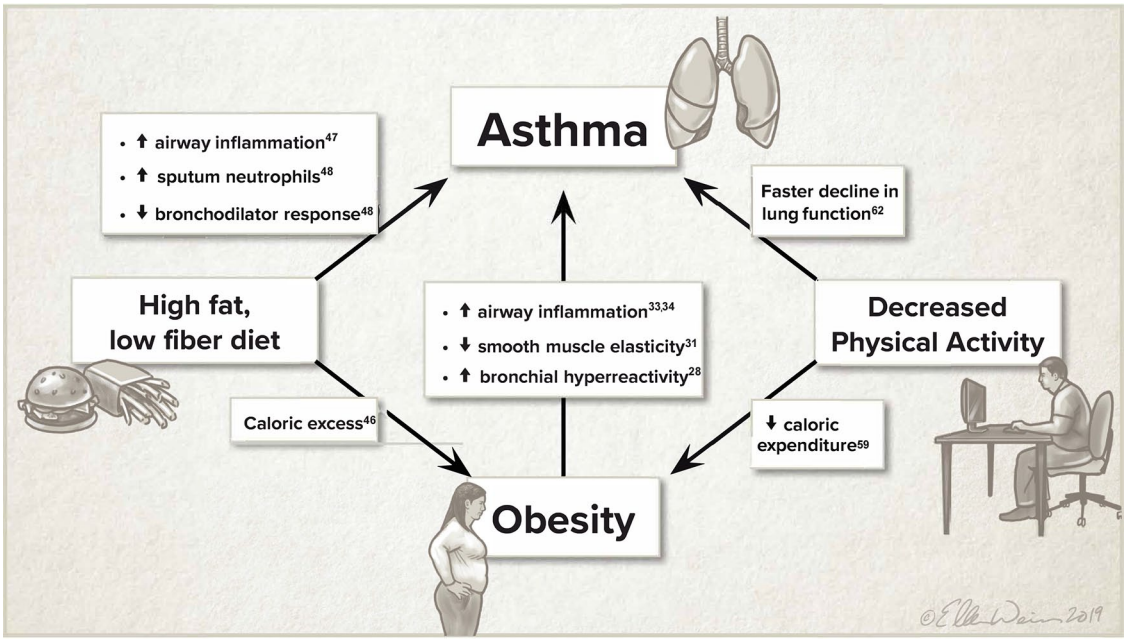

Figure 1. The role of diet and physical activity on obesity and asthma.
There are multiple proposed mechanisms for the effect of dietary changes and physical activity on both obesity and asthma. In addition, obesity itself plays a role in asthma development and severity.

subjects reinforced these findings, and found the odds of incident asthma were increased by 50% in overweight and obese individuals.[4] This study also found increasing odds of incident asthma with increasing BMI, with an odds ratio of 1.38 (95% confidence interval [CI] 1.17–1.62) in overweight *versus* normal-weight individuals and OR of 1.92 (95% CI 1.43–2.59) in obese *versus* normal-weight individuals. This trend has also been demonstrated in children.[19,20] Weinmayr *et al.* evaluated over 10,000 children and found an association between BMI and airway obstruction. This had a dose-dependent effect, with increased risk of airway obstruction in obese children *versus* overweight children. Furthermore, studies have shown an association between maternal obesity and increase in likelihood of asthma in offspring.[21,22]

In addition to an increased incidence of asthma, studies have demonstrated poorer asthma control in obese or overweight individuals, compared with normal-weight patients. A cross-sectional study in Lebanon demonstrated a significantly higher BMI in those who reported poor asthma control.[23] Obesity has been linked to an increased risk of asthma-related emergency room visits, greater length of stay in the emergency department, and higher hospitalization rates.[5,24] In addition, obesity has been linked to other comorbidities that have been shown to worsen asthma. Studies have demonstrated increased rates of gastroesophageal reflux and obstructive sleep apnea in obese individuals, both of which contribute to poor asthma control.[25–27]

The role of obesity in asthma is primarily thought of in two distinct phenotypes, i.e. early onset, allergic asthma that is complicated by obesity, and later onset, nonallergic asthma, in which obesity is implicated.[28,29] The increased incidence of asthma in obese individuals suggests that obesity contributes to the onset of asthma; however, the mechanisms are not clear (Figure 1). Obese individuals with asthma breathe at lower lung volumes due to excess weight on the chest wall, as well as increased abdominal obesity that impairs the diaphragm.[28] The lower lung volumes result in smooth muscle remodeling and airway hyperreactivity.[28] Obese individuals also have a reduced functional residual capacity (FRC).[30] Some postulate that this reduction in FRC leads to a reduction in airway smooth muscle tension, which results in an increased smooth muscle stiffness and airflow obstruction.[31]

Other mechanisms proposed in the effect of obesity on asthma include an increase in systemic inflammatory mediators associated with obesity. Leptin is a hormone secreted by adipocytes, and its

level is proportional to the amount of adipose tissue in an individual.[32] Obese individuals have elevated leptin levels, which has been associated with increased airway inflammation.[33,34] A study comparing obese women, with and without asthma, found a significantly higher level of leptin in the visceral adipose tissue of women with asthma. Leptin was also associated with increased airway reactivity on methacholine challenge testing.[35] Obese patients have increased interleukin (IL)-6 expression, which in turn promotes T helper 17 differentiation. T helper 17 cells are associated with neutrophilic inflammation in asthma, as well as increased sputum IL-17 and IL-8.[36,37] In addition, CCL17, IL-4, and IL-13 have been identified as mediators in the effect of obesity on asthma.[38]

The role of innate lymphoid cells (ILCs) in obesity and asthma has been a growing area of research. ILCs contribute to immune function by producing cytokines as a response to stress signals. They are divided into three groups, primarily based on their cytokine production profiles.[39] ILC2 is associated with the metabolic homeostasis of healthy adipose tissue, whereas a lack of ILC2 has been linked to increased adiposity.[40,41] Alternatively, increased ILC2 levels peripherally, as well as in sputum, have been associated with asthma. It has been proposed that in obesity there is a redistribution of ILC2 cells from adipose tissue to the lungs, thus contributing to the increased incidence and severity of asthma.[40,41] This finding warrants further investigation to better elucidate the role of ILCs in obesity and asthma.

Genetic factors have also been linked to both obesity and asthma, and may play a role in the co-occurrence of these two diseases. One study formed a genetic risk score based on 26 BMI-associated single nucleotide polymorphisms (SNPs). This study found a significant association of an increased genetic risk score with asthma (OR = 1.09; 95% CI 1.004, 1.013) as well as lower forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).[42] Another study identified seven SNPs that were associated with increased BMI only in individuals with asthma. This association held true for two independent cohorts of patients.[43] More research is needed to better define the role of genetics in obesity and asthma development.

The interaction between asthma and obesity is complex and multifactorial. Many of the factors discussed above, such as inflammatory markers or impaired lung physiology, are affected by lifestyle factors, such as diet and level of physical activity. Lifestyle interventions work to target both obesity and asthma, independently and as comorbid conditions.

Mechanisms of lifestyle on improved asthma control

Lifestyle interventions were defined by a prior review as including both dietary and exercise components, as well as at least one other component, such as counseling, stress reduction, or behavior modification.[12] A lifestyle intervention by definition is multicomponent, which has been shown to be more effective than a single component intervention, especially over long durations.[44] While efficacious, the multiple components of the intervention can make it difficult to assess the exact mechanisms that lead to outcome improvements. We will review here the evidence surrounding the proposed roles each component of the lifestyle intervention has on asthma.

Diet

Poor diet has been associated with both increased risk of obesity and poor asthma symptom control in obese and nonobese patients.[45] A high-fat and low-fiber diet is associated with a significantly higher risk of obesity.[46] Furthermore, there is evidence that suggests a high-fat and low-fiber diet itself plays a role in asthma. High-fat intake is associated with increased airway inflammation.[47] Even one high-fat meal, particularly high in trans-fats, has been associated with increased sputum neutrophils and decreased response to bronchodilators.[48] Decreased saturated fat intake has been associated with a reduction in neutrophilic airway inflammation in patients with asthma.[49] Alternatively, a diet rich in fruits and vegetables can decrease airway inflammation. For example, tomato juice supplementation was associated with reduced airway neutrophil influx and sputum neutrophil elastase activity.[50] Fruit and vegetable intake have both been linked to improved asthma outcomes.[51]

The mechanism of decreased fat intake and increased fiber intake is under study. Changing to a diet with lower fat content can affect metabolomic pathways and physiological responses to mediations that are pertinent to obesity and asthma.[52]

One pathway is through the effects on short-chain fatty acid (SCFA) levels in the circulation. SCFAs are products of bacterial fermentation of dietary fiber in the gut, which enter the circulation. The quantity of SCFAs produced in the gut is significantly affected by dietary composition through the effects of specific diets on the gut microbiome.[53] For example, diets high in soluble fiber produce high levels of SCFA acetate, propionate, and butyrate. Dietary manipulation can alter the gut microbiome in an obese allergic animal model of asthma. Trompette *et al.* showed that a high-fiber diet increased circulating proprionate levels (through effects on the composition of the gut microbiome).[54] Propionate, signaling through G protein-coupled receptor 41 (also called free fatty acid receptor 3), promoted hematopoiesis of dendritic cells with a high phagocytic capacity, but with an impaired ability to promote T helper 2 effector cells, inhibiting allergic inflammation in a mouse model of asthma.[54] A second allergic mouse model demonstrated increases in the anti-inflammatory cytokine IL-10 in association with changes in the microbiome that increased circulating propionate.[55] SCFAs are known to promote the formation of regulatory T cells and reduce nuclear factor kappa B (NFκB) activation in macrophages.[56,57] Additional studies in this area are needed to better understand the mechanistic role of SCFAs in asthma.

Dietary quality may also affect asthma control through improved responses to medications. Wood *et al.* have shown that ingestion of a high-fat meal reduces bronchodilator responsiveness in patients with asthma.[48] The mechanisms explaining this change in response of airway smooth muscle to bronchodilator are not known. Recent work showed that human airway smooth muscle has receptors for free fatty acids, which when stimulated increase intracellular calcium, and can also prevent response to the bronchodilatory effects of isoproterenol.[58] These findings suggest that improved dietary quality could significantly improve response to β-agonist rescue medication.

Physical activity

Decreased physical activity is also associated with obesity and worsened asthma outcomes. Physical inactivity has been shown to contribute to the development of obesity.[59] Even in non-obese individuals, physical inactivity has been associated with increased asthma prevalence and worsened asthma outcomes. Individuals with a current or past diagnosis of asthma spent significantly less time engaging in physical activity.[60] A study evaluating asthma patients at primary care settings across the USA found that one third of women reported no days of even 15 min of physical activity in the previous week.[61] These low levels of physical activity were associated with poorer asthma control. Low levels of physical activity has also been associated with a more rapid decline in lung function.[62]

Over the past 20 years, physical activity research in asthma has grown immensely and found improvements in asthma control, quality of life, and reductions in exacerbations with regular physical activity.[52] The mechanisms underlying these improved asthma outcomes are not well elucidated but improvements in the cellular airway composition and airway hyperresponsiveness (AHR) have been shown.[63]

Airway inflammation is an important contributor to mechanisms of asthma and is strongly associated with disease severity.[64] Three physical activity interventions in adults with asthma have found reductions in airway inflammation as measured by fractionated exhaled nitric oxide, a measure of eosinophilic airway inflammation. Two studies have shown a decrease in sputum total cells and eosinophils after exercise.[65–67] Similar findings have been reported in the airways of ovalbumin-sensitized mice after 45 min of exercise.[68] The reduction in airway eosinophils in mice is mediated through an increased expression of IL-10, an anti-inflammatory cytokine, and a reduction of T helper 2 cytokines, IL-5, and IL-4.[68,69] Similarly in adults with asthma, T regulatory cell responses are enhanced with physical activity with an increase in IL-10 production and T regulatory cell count.[70] Physical activity can also modulate pulmonary allergic inflammation by increasing M2 recruitment and plasma dendritic cell activation, which leads to an increase in anti-inflammatory cytokines and a decrease in pro-inflammatory cells and mediators.[71] Similar to dietary changes, physical activity can impact metabolomic pathways that also leads to a reduction in inflammation. Butyrate, a SCFA, is found in higher levels among people with high cardiorespiratory fitness, independent of their diet.[72] Butyrate has also been shown to reverse the effects of a high-fat diet on gut microbiome in animal models.[73–75]

AHR is also a key feature of asthma, and physical activity has been shown to improve AHR. A meta-analysis of 17 studies found significant improvements in AHR with exercise training.[63] The improvements in AHR were associated with improvements in quality-of-life measures and exercise capacity. More recently, Franca-Pinto *et al.* conducted a 12-week physical activity intervention in patients with moderate to severe persistent asthma. They found improvements in AHR by 1 doubling dose (dd) (95% CI 0.3–1.7 dd) after 12 weeks of aerobic training.[66]

Weight loss

Obesity may directly cause or worsen asthma through its effects on: (a) airway mechanics such as reduced lung volumes, reduced peripheral airway diameters, and resultant alterations in airway smooth muscle function and AHR; (b) immune response modulation *via* adipocytokines such as leptin and tumor necrosis factor α (TNF-α); (c) female sex hormones such as estrogen in particular.[76] Of the randomized controlled lifestyle interventions in asthma, few have been mechanistically focused. Of those that have assessed potential mechanisms, conflicting results exist. Dias-Júnior *et al.* found no change in AHR or airway inflammation in a calorie-restricted, weight-loss intervention.[77] Interventions that incorporated physical activity training,[49,78] found reductions in airway and systemic (IL-6, TNF-α) inflammation, AHR,[49] and an increase in IL-10, an anti-inflammatory cytokine.[78] The effect of physical activity on airway inflammation appears to occur independently of weight loss as physical activity interventions have reported similar findings without weight loss.[66] This suggests that physical activity may play a role in the mechanisms of improved asthma control in lifestyle intervention studies.

Behavioral mechanisms

Behavioral and cognitive processes have been shown to be important in asthma self-management, physical activity, and dietary change.[79–81] More specifically, knowledge, self-efficacy, and negative attitudes toward asthma are some of the processes that have been identified. These processes are associated with poor self-management and negative perspectives about physical activity and diet in asthma.[80–82] Targeting these processes can mediate the transition from acquiring self-management skills to the performance of these skills but in nonlifestyle-focused interventions.[80] Lycett *et al.* performed a systematic review of theory-based digital interventions to enhance asthma self-management. Constructs addressed in these interventions included illness perceptions and self-efficacy beliefs that assessed how confident patients felt in taking medicines as prescribed. The digital interventions that were most effective in improving asthma control, quality of life, and reducing asthma exacerbations were those that were theory based and applied theoretical constructs.[83–85] While lifestyle interventions in asthma is in its' infancy, the use of theory and theoretical constructs has been used and is discussed below.

All three lifestyle interventions in asthma presented in this review target behavior modification and motivational strategies. Only two studies though specifically state the targets of behavior modification.[78,86] The intervention by Ma *et al.* was grounded in social cognitive theory.[86] Proven behavior change strategies (e.g. self-monitoring, action planning, and problem solving) were used to help participants achieve and maintain realistic, clinically meaningful weight loss and physical activity goals.[79,87] Freitas *et al.* used the transtheoretical model and behavior change strategies of goal setting, skill development, and self-control.[78,88] The use of theoretical frameworks and behavior change models is important in designing behavioral lifestyle interventions, but it is also important to link these constructs with outcomes measures so mechanisms of these behavioral lifestyle interventions can be better understood. To date, none of the lifestyle interventions in obese patients with asthma have reported findings on the mediating effects of these behavioral targets on outcomes. A better understanding of the mechanism of lifestyle behavioral interventions will help us optimize these interventions.

Lifestyle interventions

As described above, physical inactivity and poor diet are associated with greater morbidity from asthma, as well as increased risk for obesity. In attempts to address these lifestyle behaviors, there has been a range of studies which examined the effect of weight loss, physical activity, and dietary change on asthma outcomes. Most of the initial studies in asthma focused on stringent calorie restriction, meal replacement systems, or bariatric surgery.[7,9,10] While these studies demonstrated improvements in weight loss and

asthma control, they did not reflect a true lifestyle intervention as they were not sustainable or readily accessible.[89,90]

The individual effects of diet and exercise on obesity and asthma have been shown to improve asthma outcomes; however, there are less data on comprehensive lifestyle interventions that incorporate multiple lifestyle behavior modifications. As mentioned above, a prior review defines a lifestyle intervention as including both dietary and exercise components, as well as at least one other component, such as counseling, stress reduction, behavior modification, etc.).[12] We conducted a literature search through PubMed with the terms 'asthma' and 'obesity' and ('lifestyle' or 'physical activity' or 'exercise' or 'diet' or 'weight loss' or 'behavior modification'), and set a limitation on clinical trials, randomized controlled trials (RCTs), and clinical studies. We identified randomized controlled studies that evaluated the effect of a lifestyle intervention on asthma outcomes in obese adult individuals. This search revealed three studies that met this inclusion criteria (Table 1).

Freitas *et al.* conducted a RCT evaluating the effect of a weight-loss program paired with an exercise intervention in patients with moderate to severe asthma with a BMI between 35 and 40.[78] Subjects initially completed an education program that consisted of two 90-min sessions outlining asthma basics, and two 90-min sessions describing physical activity recommendations and benefits. Both groups underwent a nutritionist- and psychologist-led weight-loss program, which consisted of diet and counseling sessions conducted twice weekly for 3 months. Subjects kept food diaries, and received feedback from the nutritionist. They also received targeted counseling which focused on behavior change in the context of weight loss. The intervention group additionally participated in two sessions per week for 3 months of aerobic and resistance training. Both groups achieved weight loss during the study, but only the exercise-intervention group demonstrated improvement in asthma control, as defined by an asthma-control questionnaire (ACQ). The exercise-intervention group had greater improvements in asthma-specific quality-of-life score, lung-function parameters, fractioned exhaled nitric oxide levels, and inflammatory biomarkers (reduced CCL2, IL-4, IL-6, TNF-α, and leptin, increased 25(OH)D, IL-10, and adiponectin; $p < 0.05$). This suggests that the changes are associated with a decrease in eosinophilic inflammation but additional work on discerning the mechanisms are needed.

The second lifestyle intervention in asthma enrolled overweight and obese subjects with asthma with a BMI between 28 and 40 and a physician's diagnosis of asthma.[49] Participants were randomized to a dietary intervention, exercise intervention, or a combined dietary and exercise intervention. The dietary intervention involved a hypocaloric diet, which involved two meal replacements per day. In addition, subjects participated in seven 1-h counseling sessions with a dietician, as well as four 10-min phone sessions on a weekly basis. Participants were instructed to keep a daily food diary. The exercise intervention involved a gymnasium membership and a 1-h per week personal training session. Participants went to the gym at least three times weekly, kept a daily physical activity diary, and wore a pedometer with the goal of increasing their daily steps to 10,000. All three groups demonstrated improvements in lung-function parameters, asthma-specific quality-of-life score, and ACQ score. Only the combined exercise and dietary group had a significant decrease in airway hyperreactivity.[49]

Ma *et al.* conducted a randomized controlled lifestyle intervention in obese subjects with asthma who had a BMI > 30 and a diagnosis of uncontrolled persistent asthma.[79] Both groups received a pedometer, a body-weight scale, information regarding weight-management services, and an asthma-education DVD. Patients in the intervention arm underwent a 12-month lifestyle intervention modeled from the Diabetes Prevention Program trial.[91] This included 13 weekly sessions over 4 months that covered a defined curriculum on behavior change to achieve weight loss and increase physical activity. After 4 months, subjects had two monthly in-person sessions, then bimonthly telephone sessions for the remainder of the year. The intervention included counseling on healthy eating with moderate calorie reduction, as well as increases in physical activity throughout their daily life. The intervention did have significantly greater weight loss and increased physical activity compared with the control group; however, this study found no difference between intervention and control groups in asthma control (measured by an ACQ), lung-function parameters, or asthma-specific quality of life questionnaire). Of note, participants who lost 10% or

Table 1. Lifestyle interventions in obese patients with asthma.

Study	Participants	Intervention			Comparator	Outcome	Results
		Dietary	Physical activity	Other			
Freitas *et al.*[78]	51 moderate to severe patients with asthma aged 30–60 years with BMI 35–40	Nutritionist-led sessions focused on hypocaloric diet. Daily food diary.	Aerobic and resistance training exercises twice weekly. Physical activity diary.	Psychologist-led counseling sessions focused on behavior change. Education sessions for asthma and physical activity.	Nutritionist- and psychologist-led counseling sessions. Education sessions for asthma and physical activity.	ACQ AQLQ Airway inflammation (FeNO, IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, chemokines, serum leptin and adiponectin). Lung function.	ACQ improved from 2.0 to 1.1 ($p < 0.001$); AQLQ improvement in total score ($p > 0.03$). Significant improvement in FeNO, significant reduction in IL-4, IL-6, TNF-α, and leptin; FEV1, FVC, ERV significantly improved, no change in FEV1/FVC.
Ma *et al.*[79]	330 subjects with uncontrolled persistent asthma aged 18–70 years and a BMI $\geqslant$ 30	Counseling on healthy eating and moderate calorie reductions (500–1000 kcal/day).	Counseling on moderate intensity physical activity for at least 150 min/week.	Counseling on behavioral self-management skills.	A pedometer, a body-weight scale, a list of weight-management services, and a asthma educational DVD was distributed to all participants.	ACQ Mini-AQLQ Lung function.	No difference in ACQ score. No differences in mini-AQLQ. No difference in lung-function parameters.
Scott *et al.*[49]	46 patients with asthma with an average age of 33.9 years and BMI 28–40	Limited daily caloric intake (885–1170 kcal/day), including two meal replacements. Counseling sessions with a dietician. Daily food diary.	Gymnasium membership. 1-h group personal training session per week. Daily pedometer usage with a goal of 10,000 steps per day. Daily physical activity diary.	Counseling included behavior modification and motivational strategies.	Groups consisted of exercise-only intervention, dietary-only intervention, or both combined.	ACQ AQLQ Lung function. Sputum cell counts. Inflammatory markers.	ACQ improved in the dietary and combined interventions. AQLQ improved in all three groups. Total lung capacity improved in exercise and combined groups. ERV improved in dietary group. Airway hyperreactivity reduced in combined group. Sputum eosinophils reduced in exercise intervention. Reduction of serum leptin and IL-6 in combined intervention.

ACQ, asthma-control questionnaire; AQLQ, asthma quality-of-life questionnaire; BMI, body mass index; ERV, expiratory reserve volume; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL, interleukin; TNF-α, tumor necrosis factor α.

more of their body weight had 3.78 (95% CI 1.72–8.31) times the odds of significant improvement in the ACQ compared with those with a stable weight (3% or less change in body weight). Only one-quarter of participants achieved 10% or greater body-weight loss through the lifestyle intervention.[79]

There are limitations to these lifestyle intervention studies. The studies by Freitas *et al.* and Scott *et al.* both involved relatively small sample sizes (55 and 46 participants, respectively) and had a short intervention interval (3 months and 12 weeks, respectively).[49,78] Of note, Freitas *et al.* did report sustained weight loss at 6 months and 1 year after the intervention.[78] Ma *et al.* included a larger sample size of 330 participants, and their lifestyle intervention spanned 12 months, but this study found no statistically significant difference between intervention and control groups, apart from improvement in the ACQ in those participants that had a 10% or greater reduction in body weight.[79]

Two of the three lifestyle interventions above showed significant improvements in asthma outcomes in obese participants.[49,78] One study showed improvement in ACQ score only with 10% or more reduction in body weight, which suggests a threshold in weight loss necessary for lifestyle interventions to be effective.[79] Body-weight losses of 5–10% have been associated with improvements in hemoglobin a1c, cardiovascular risk factors, and decreases in medication use for diabetes, hypertension, and hyperlipidemia management.[92,93] Further research is needed to define a percentage body-weight loss goal in asthma management. In addition, research is needed to better determine how to implement lifestyle changes that target healthy eating and increased physical activity. Further investigation into the mechanisms of weight loss through lifestyle intervention changes could aid in developing more effective interventions.

Of note, our search revealed an explorative case-control study that investigated the effect of a 12-week pulmonary-rehabilitation program prior to bariatric surgery in obese patients with asthma. The 12-week program included exercise training three times a week observed by a physiotherapist, a 1500 kcal/day intake restriction with seven total consultations with a dietician, as well as psychological counseling focused on behavior modification and motivational strategies. The study was limited as it only included four cases and was not a RCT. However, it did find a greater improvement in ACQ; cases also had improved FEV1, which was not seen in the controls.[94] Although this study did not meet our search criteria, we feel this initial evidence points towards the importance of continued evaluation with a greater study population and a randomized controlled model.

Research gaps in lifestyle interventions in obese asthma

While the evidence for lifestyle interventions in obese patients with asthma is growing, this area is in its nascency. The existing lifestyle interventions also have their limitations. A Cochrane meta-analysis found the majority of behavioral weight-loss RCTs in asthma to have serious design flaws, including high or unclear risk of selection and detection biases, small sample sizes, and short durations ($<$ 6 months).[95]

While the evidence on lifestyle interventions in obese patients with asthma is not robust, the mechanisms that underlie the improvements in asthma morbidity seen to date remain poorly understood. Future studies in lifestyle interventions should include an evaluation of the potential inflammatory and metabolomic pathways that mediate obesity. In addition, as the lifestyle interventions do incorporate changes in diet and exercise, the role of the gut microbiome needs to be considered. One large gap we identified was an assessment of the behavioral mechanisms in lifestyle interventions. While the intervention included the use of a theoretical framework of behavior change model, it is also important to measure the theoretical factors that the intervention targets.

Another important gap in our knowledge is an assessment of maintenance of these lifestyle interventions. Only one of the lifestyle interventions lasted longer than 6 months.[79] Further, only one study examined weight maintenance after the intervention:[78] Freitas *et al.* found weight loss to be maintained at 6 months and at 12 months. In order to move this area of lifestyle interventions forward more rapidly in asthma, researchers should learn from other lifestyle interventions in other chronic diseases (e.g. cardiovascular disease and diabetes). Their experiences may impart

critical insights on best practices to assess and achieve weight-loss maintenance.

As we gain more knowledge on the efficacy and effectiveness of lifestyle interventions in obese patients with asthma, it is important that the next step, implementation of evidence to practice, is taken. Implementation is considered one of the last stages of the intervention research process that follows the results of effectiveness studies.[96] It explores the role of context, best approaches to prepare for evidence adoption and scale up, practical considerations of implementation, and the best ways to facilitate sustainability. Lifestyle interventions in other chronic diseases have found challenges when implemented in different patient populations and geographic locations.[97,98] Lessons learned from these studies should be applied in lifestyle interventions in asthma when applicable.

Conclusion

Asthma and obesity affect millions of people worldwide. Addressing obesity and asthma through lifestyle modifications is a relatively new approach and needs additional study. Rigorous studies are needed to evaluate the efficacy and effectiveness of lifestyle interventions that combine dietary pattern change, physical activity, and behavioral modification on asthma symptoms, lung function, AHR, and asthma exacerbations in obese adults with asthma. We also need to understand the biological and behavioral mechanisms that influence lifestyle interventions. Efficacy and effectiveness lifestyle interventions should also consider examining maintenance and implementation potential. This will allow us to prepare for the next stage of the intervention research process. Identification of effective lifestyle interventions will give clinicians another tool to manage asthma in obese adults, which, in turn, may lead to improved morbidity and mortality in this population.

Acknowledgement

We would like to thank Ellen Weiss for her assistance with the figure.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this work was supported by a National Institutes of Health (K01 HL 133370) award to SN.

Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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