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Impact of Lifestyle Interventions Targeting Healthy Diet, Physical Activity and Weight Loss on Asthma in Adults: What is the evidence?

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Abstract

Unhealthy lifestyle factors such as poor diet quality, sedentary lifestyle, and obesity are associated with negative health consequences in asthma including poor asthma control, impaired quality of life, and greater health care utilization. Lifestyle modification is the cornerstone of behavioral treatments and has been effective in chronic diseases such as atherothrombotic vascular disease and diabetes. There is a critical need for lifestyle interventions in asthma care that address obesity and its intimately linked risk behaviors in terms of poor diet and physical inactivity. We present in this commentary the promising lifestyle interventions emerging in asthma care that target poor diet, physical inactivity and weight loss, the proposed mechanisms of these lifestyle interventions, and the critical need for guideline-concordant lifestyle interventions in asthma care.

Keywords

Asthma; physical activity; obesity; diet; weight loss

Introduction

Asthma prevalence has risen markedly worldwide, affecting an estimated 300 million people currently and projected to increase by 100 million by 2025 [1]. While factors such as genetics and environmental exposures are important contributors to asthma, they cannot account solely for this rapid increase in asthma prevalence. Studies have shown this increase is significantly associated with environmental changes (e.g., urbanization) and unhealthy lifestyle behaviors (e.g., poor diet quality, sedentary lifestyle, and obesity) [2–6].

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Calorie-excess, nutrient-deficient diets and physical inactivity are associated with poor asthma control, impaired quality of life, and greater health care utilization [7–13]. Obesity, often a result of poor diet and sedentary lifestyle, is not only a risk factor for incident asthma but a disease modifier in pre-existing asthma. Asthma in obese individuals, or “obese asthma,” is a multiphenotypical disease complex whose exact mechanisms remain elusive, albeit likely multifactorial [2, 4, 14]. Compared with asthma in normal weight people, asthma in obese individuals is associated with poorer asthma-related quality of life, greater health care utilization, and is more difficult to control partly due to blunted response to standard drug therapy [7–12]. Both epidemiological and *in vitro* cellular studies show that increased body mass index (BMI ≥ 25 kg/m²) can negatively influence the response to corticosteroids [15, 16].

To address obesity in asthma, interventions targeting obese adults with asthma have been conducted and show improvements in asthma control and asthma-related quality of life [17]. Most of these studies focused on stringent caloric restriction, supervised exercise or bariatric surgery to attain these results. While short-term efficacy in asthma outcomes were shown, very low calorie diets and supervised exercise are difficult to sustain, and fewer than 2% of individuals eligible for bariatric surgery actually receive it [18, 19]. Behavioral medicine has been used to address unhealthy lifestyle behaviors such as poor diet and physical inactivity in other chronic diseases such as hypertension and diabetes [20, 21]. These interventions are not only effective in eliciting the desired behavior change but have also shown sustained clinical benefits [22, 23]. The need for integrating behavioral medicine in asthma care to specifically address poor diet quality, sedentary lifestyle, and obesity -- 3 major lifestyle risk factors for asthma morbidity -- is imperative, yet minimally met.

Evidence has begun to accrue over the last 2 decades on behavioral interventions promoting dietary change, physical activity and/or weight loss and their putative mechanisms, in patients with asthma. The scope of this clinical commentary does not entail an exhaustive review of the available literature on lifestyle interventions in asthma, which has been the topic of several recent systematic reviews [17, 24–26]. Instead, this commentary will review the most relevant studies of diet and exercise interventions in adult patients with asthma and focus on the need for guideline-concordant lifestyle interventions in pulmonary medicine, specifically asthma. We will emphasize that while lifestyle medicine in pulmonary disease is in its’ infancy, evidence-based practice and lessons learned from lifestyle interventions in other chronic diseases, such as diabetes and atherothrombotic vascular disease, should impart critical insights for lifestyle interventions in asthma. The overall goal of this commentary is to call for more rigorous research on scalable and sustainable lifestyle interventions specifically addressing unhealthy diet, physical inactivity and obesity that can effectively improve asthma care, and their underlying physiological mechanisms.

What do we know about lifestyle interventions in asthma?

Dietary Pattern Changes in Asthma

Healthy dietary patterns rather than specific foods or nutrients have received growing attention in nutrition research and practice guidelines for chronic disease prevention and control, such as in cardiovascular disease where there is robust evidence for dietary pattern

interventions [27]. Yet, this is only a nascent field in asthma [28]. Three pilot RCTs to date have investigated the effect of dietary patterns in adult asthma (Table 1). Wood et al. compared a high- versus low-antioxidant (AO) diet for 14 days in adults with stable asthma then participants went on to receive placebo or tomato extract for 14 weeks [29]. Despite its shortcomings (e.g. short duration and high attrition at 42%), it was the first study to provide evidence that a low AO diet could lead to a reduction in forced expiratory volume in 1 second (FEV₁; $p=0.01$) and forced vital capacity (FVC; $p=0.02$) and a 2.26 greater risk of having an asthma exacerbation. The author's concluded that a whole-food approach, rich in fruit and vegetables, could be more important than an isolated antioxidant supplementation in the management of asthma. Sexton and colleagues examined 2 interventions promoting Mediterranean diet with dietitian counseling over 3 months compared with an end-of-trial offering of a single dietitian counseling session, recipes and free food in 38 adults with symptomatic asthma. The trial showed the feasibility of improving Mediterranean diet scores (6.62 vs. 0.44; $p<0.001$) and clinically significant changes (MCID 0.5) in several subdomains of Asthma Quality of Life Questionnaire (symptoms, emotional and environmental) yet this did not reach statistical significance for either intervention [30]. Ma et al. conducted a pilot RCT of a 6-month behavioral intervention specifically promoting the Dietary Approaches to Stop Hypertension (DASH) diet in patients with uncontrolled persistent asthma. This study was designed for weight maintenance and produced greater improvements in diet quality (net increase in DASH score=0.8), asthma control (net decrease in ACQ=-0.2), and asthma-related quality of life (net increase in AQLQ overall=0.4) compared to usual care control [31]. These findings suggest that improved diet quality following a healthy dietary pattern intervention may have therapeutic benefits for adult patients with uncontrolled asthma.

Diet quality may affect asthma control through improved physiological responses to medications and metabolomic effects. A high fat meal reduces bronchodilator responsiveness in patients with asthma [32]. The underlying mechanisms behind this are unknown, though may be related to increased airway inflammation after a high fat meal [32]. Regardless of the cellular mechanism, this prior work suggests that improving diet quality (lower fat content) may enhance the responsiveness to β -agonist medication. The metabolomic effects of diet quality relate to circulating short chain fatty acids (SCFA). SCFAs promote dendritic cell hematopoiesis and impair the ability to promote Th2 effector cells, thus inhibiting allergic inflammation in a mouse model of asthma [33]. Further, SCFAs decrease allergic effector T cell responses, promote formation of T regulatory cells [34] [35] and reduce NF κ B activation in macrophages [36]. These studies link diet quality to SCFAs and altered innate and adaptive immune responses. This may suggest an important link between diet quality and asthma.

Physical Activity and Asthma

Several population-based studies show individuals with asthma engage in less physical activity and are more sedentary than their counterparts without asthma [7, 37–39]. A worsening of asthma symptoms during exercise or a restriction of physical activity leading to deconditioning have been identified as reasons for these low levels of physical activity among adults with asthma [40–42]. Low levels of physical activity have been associated

with negative health consequences including greater asthma symptoms, poorer asthma control and asthma-related quality of life.

Physical activity interventions in adults with asthma have focused primarily on improving physical fitness, lung function, asthma control, and airway inflammation through aerobic exercise training. The results of these studies have varied and are difficult to compare due to differences in study design and study protocols. The study protocols include various types of aerobic exercise such as, walking, running, jogging, weight training, or a combination of these [7]. Seven RCTs published to date have examined the effects of physical activity alone in adults with asthma (Table 2) [43–49]. These studies consistently found improvements in asthma-related quality of life, asthma symptoms, and exercise capacity (see Table 2 for effect size). While these studies are promising, they have included small groups of patients attending structured training sessions at a gym in academic centers or led by physiotherapists, which are poorly generalizable to a real-world setting.

How physical activity can impact asthma is poorly understood. Changes in airway inflammation have been assessed in 4 of these interventions, and all but one found significant decreases in fractionated exhaled nitric oxide [43, 45, 48, 49]. Three of these studies examined sputum cell counts; two found a decrease in total cells and eosinophils in individuals with asthma post-exercise training, while the other study found no changes in sputum cell differentials [43, 48, 49]. Murine models support these findings of reduced eosinophilic airway inflammation post-exercise. OVA-sensitized mice have a significant reduction in eosinophils in bronchoalveolar lavage after 45 minutes of exercise on a treadmill at a moderate intensity [50]. This appears to be mediated through an increase in the expression of the anti-inflammatory cytokine IL-10 and a reduction in Th2 cytokines, IL-5 and IL-4 [50, 51]. Changes in bronchial hyperresponsiveness (BHR) with physical activity have also been reported but with conflicting results. Two studies reported no change in BHR with exercise yet a recent study by Franca-Pinto showed improvements in BHR by 1 doubling dose (dd) (95% CI 0.3 to 1.7 dd) [44, 48, 52]. Physical activity may impact inflammation through metabolomic pathways including an increased production of butyrate, a SCFA, found in people with high cardiorespiratory fitness, independent of diet [53], and a reversal of the effects of a high fat diet on gut microbiome in animal models [54–56]. Physical activity can enhance the effects of T regulatory cell responses in individuals with asthma with an increase in IL-10 production and T regulatory cell count [57].

At this time, few studies have examined the effect on asthma of interventions promoting an active lifestyle, adhering to national guidelines for Americans, in routine settings (as opposed to highly structured aerobic training in exercise facilities and/or by specialists) [58, 59]. Also, evidence is limited on the mechanisms of physical activity in adults with asthma, though there is some evidence to suggest that it could be mediated by physiologic, metabolomic and immune pathways. Well-designed studies to specifically address these questions are urgently needed as increased daily physical activity via low-cost means (e.g., walking) may be an affordable and accessible intervention for asthma, if proven effective, in addition to its known cardiometabolic and other health benefits.

Combined Diet and Physical Activity Interventions in Obese and Non-Obese Adults with Asthma

Obesity increases the risk of asthma and compromises asthma control [14, 60]. Thus, several RCTs have focused on examining the impact of weight loss in asthma. The preponderance of evidence from these studies shows that obese adults with asthma who lose weight achieve better asthma control, lung function and asthma-related quality of life [17, 61]. However, the asthma benefits seem variable depending on the degree of weight loss [14, 25], and the minimal clinically important difference (MCID) appears to be within 5–10% weight loss based on prior work by Ma and colleagues [62] and others [63, 64]. First-generation RCTs of behavioral weight loss treatment in asthma were meant for proof of concept, and most used stringent low-calorie diets (<1,200 kcal/d), which are not sustainable long term or recommended in obesity treatment guidelines [65–69]. Also, few have included a physical activity component.

Three RCTs of weight loss in obese adults with asthma have tested behavior interventions including both diet and physical activity components (Table 3). Scott and colleagues compared a dietary intervention (stringent low-calorie diet 885–1170 kcal/day+ weekly dietitian counseling), an exercise program (gym membership and group training sessions) and a combined intervention over 10 weeks in 46 overweight or obese adults with asthma. Improvements in asthma control and asthma quality of life were found in the dietary restriction and the combined (dietary restriction + exercise) group [63]. A subgroup analysis found that participants with 5–10% weight loss achieved significant improvements in FVC (0.25 ± 0.36), AQLQ (0.83 IQR: 0.60, 1.36) and ACQ (-0.64 ± 0.49), with 83% and 58% achieving MCID (> 0.5) for AQLQ and ACQ, respectively (Table 3). Freitas and colleagues recently reported significant improvements in median asthma control (-0.7 ; 25–75%: -1.3 to -0.3), aerobic capacity (3.0 mL O₂/kg/min; 25–75%: 2.4 to 4.0) and FEV₁ (0.05 L; 25–75%: -0.1 to 0.3) in asthma patients that received both exercise training (3 months of aerobic and resistance exercise) and weight loss counseling (12 individual sessions conducted by a nutritionist and psychologist focused on lowering caloric intake through self-change behavioral techniques) compared to patients that received sham exercises (2 sessions of stretching and breathing per week for 3 months) and weight loss counseling [70]. Ma et al. completed the largest and longest behavioral weight loss RCT to date, with 330 obese adults with uncontrolled asthma for 12 months. Further, it is the only study that adapted a multicomponent lifestyle intervention from the evidence-based Diabetes Prevention Program, which consisted of diet, physical activity, and behavior therapy, as recommended in obesity guidelines [20, 65, 71]. The intervention targeted weight losses of 7–10% and recommended moderate calorie reductions of 500–1000 kcal/day and moderate-intensity physical activity for at least 150 minutes a week [62]. While the intervention promoted healthy eating, it did not focus on a specific dietary pattern. The intervention was well accepted but only had a modest effect on weight loss and no net benefit for asthma control. However, participants who lost 5–<10% and $> 10\%$ of their body weight had mean ACQ change -0.33 (Cohen $d=0.36$) and -0.53 (Cohen $d=0.76$), respectively, and 2–4 times the odds of achieving better asthma control of clinical significance (ACQ < 0.5) than those with stable weight. The intervention also had a sustained effect on energy expenditure and leisure

time physical activity at 12 months ($p=0.05$). But this study was not designed to examine the added benefits of physical activity in weight loss interventions.

While these combined behavioral interventions of dietary change and physical activity show promising results in obese adults with asthma, little is known about their effects in non-obese adults with asthma. Observational studies suggest an association between dietary composition, physical activity and asthma control independent of obesity [72, 73]. Toennesen and colleagues recently completed the first RCT to date to assess the effect of dietary change and physical activity on asthma control in 125 non-obese ($BMI < 30$) patients with asthma [74]. This RCT included 3 intervention groups (diet, physical activity, diet + physical activity) and a control group (usual care). The dietary change intervention targeted a high protein (25–28% of energy), low glycemic index (< 55) and anti-inflammatory diet (rich in vegetables, fruit, nuts, lean meat, fish and seafood). The caloric needs of each individual were set for weight stabilization though subjects in the intervention groups had significant weight loss (Table 3). The physical activity intervention consisted of 8 weeks of high-intensity interval training on indoor spinning bikes, 3 times a week, in a hospital setting. The combined intervention of dietary change and physical activity compared to usual care group improved asthma control (ACQ -0.9 vs. -0.3 , $p < 0.05$) and asthma-related quality of life (AQLQ 1.0 vs. 0.5, $p < 0.01$). These findings that non-obese individuals with asthma benefit from a combination of diet and high-intensity interval training are promising.

Summary of the State of Science (Table 4)

As we have reviewed, evidence is emerging but still weak for guideline concordant behavioral treatments to specifically tackle obesity and obesity-related lifestyle behaviors, poor diet and physical inactivity, among asthma patients. Most of the lifestyle interventions discussed showed improvements in at least one asthma outcome, yet diverging results between studies were found (Tables 1–3). Many of the studies used different asthma outcomes varying from observational to patient-reported outcomes. Further, many of these outcomes were not the primary study outcome. The behavioral treatments in the different interventions may be inter-related (ie. physical activity and weight loss), but also independent factors exist such as the type, location and intensity of physical activity. The divergence found between the studies supports this and while this does not negate the potential benefits of diet and physical activity, it indicates that we need a better understanding of the complex mechanisms that result in these improved outcomes.

The physiologic mechanisms underlying the changes in asthma found with dietary change, physical activity and weight loss interventions are not well understood. Dietary quality, physical activity and weight loss may affect both metabolomic and immune pathways pertinent to asthma and obesity. Studies are needed that investigate the mechanistic pathways by which behavioral interventions that promote diet quality, weight loss and physical activity may affect asthma in obese and non-obese populations.

While the efficacy and effectiveness of weight loss interventions in other chronic diseases have been well established, little is known about the effect of behavioral weight loss interventions in chronic pulmonary diseases such as asthma. As obesity is related to

increased asthma prevalence, poor asthma control and a diminished response to asthma treatment, behavioral weight loss interventions that specifically assess the efficacy of weight loss on asthma-specific outcomes are needed [2, 9, 76]. According to a Cochrane meta-analysis [77], the majority of behavioral weight loss RCTs in asthma had serious design flaws, including high or unclear risk of selection and detection biases, small sample sizes, and short durations (<6 months). Currently, the available evidence in asthma is limited to inform recommendations for the integration of lifestyle interventions in asthma treatment guidelines. Future research in lifestyle interventions should also include identifying subpopulations that benefit most from these dietary and physical activity interventions and best practices on the implementation of these lifestyle interventions in various environments such as the community, health system, and workplace.

In the vast majority of the studies presented here, the patients included represent a wide range of asthma severity from mild to severe persistent and the patient's asthma symptoms at baseline were partly or completely uncontrolled. None of the studies to date have published their results based on baseline asthma severity or control so it is not known which patients would benefit most from these interventions. One promising finding is that physical activity and combined diet and physical activity interventions that have included patients with uncontrolled severe persistent asthma have been well-tolerated. Future lifestyle behavioral interventions should not automatically exclude patients with severe and/or uncontrolled asthma and when possible analyze their findings within these asthma sub-populations. Other specific sub-populations of asthma to consider when conducting lifestyle interventions are those with specific asthma phenotypes. Three physical activity interventions have shown reductions in eosinophilic airway markers (FeNO, sputum eosinophils) and this may be an indicator of which patients may respond to these interventions[45, 48, 49]. Cluster analyses have also identified an asthma phenotype of mostly older obese women with late-onset non-atopic asthma and difficult to control symptoms[75]. As this phenotype is related with obesity, it would be of interest mechanistically and clinically to assess the response of a combined diet and physical activity intervention in this population. The recent study by Toennesen and colleagues, demonstrated that the effects of diet and physical activity may be beneficial for non-obese patients with asthma. Lifestyle studies that target both diet and physical activity should include both obese and non-obese patients with asthma and be powered to analyze both sub-populations. Obese asthma patients are more likely to have additional obesity-related co-morbid illnesses such as hyperlipidemia, obstructive sleep apnea and diabetes. There is a specific need to examine the effect of lifestyle interventions in those with asthma and other co-morbidities to assess if the benefits are greater in this subpopulation.

While lifestyle medicine in pulmonary disease is in its' infancy, we can learn from other lifestyle interventions in other chronic diseases (cardiovascular disease and diabetes). Their experiences may impart critical insights on how to integrate lifestyle interventions into evidence-based practice guidelines for asthma, identify subpopulations of responders and implementation considerations [78]. For example, previous lifestyle interventions that have used only training facilities at an academic center or physiotherapist led training sessions have shown short-term effects and limited sustainability[79]. Different delivery modalities such as healthcare, worksite or community settings have been studied and show promising

results. These different delivery modalities should be considered when designing future lifestyle interventions in asthma. Further, the maintenance of the lifestyle behavior change is critical but has been largely ignored in pulmonary medicine. Incorporating and assessing a maintenance intervention should be included in the design of future asthma behavior change interventions. Early physical activity research did not include behavior change theory but in the last 2 decades the importance of theory has been focused[80]. It is crucial that when designing behavioral lifestyle intervention that the researchers identify and test specific hypotheses about theoretical factors that will be changed in the intervention[79]. Integrating these key lessons learned when designing future pulmonary lifestyle interventions are necessary to move the field forward.

Practice Implications

On a population basis, the high prevalence of obesity among patients with asthma suggests an important opportunity to improve the lives of many such patients. While the clinical treatment of asthma should continue to emphasize implementation of proven pharmacological and patient self-management strategies [81], the available evidence is already sufficient to warrant the recommendation of weight loss in obese individuals with asthma. Weight loss strategies, such as very low-calorie diets and bariatric surgery show improvements in asthma control and asthma-related quality of life in the short-term [17, 26, 82]. Very low calorie diets are difficult to sustain long term though which has led to poor uptake and fewer than 2% of obese people eligible for bariatric surgery actually receive it [18, 19]. Lifestyle interventions such as weight loss strategies that promote dietary change AND physical activity have been shown to be sustainable options in other chronic diseases (cardiovascular and diabetes). The field of lifestyle interventions in pulmonary diseases is lagging compared to other chronic diseases and the efficacy of a comprehensive, evidence-based, lifestyle approach to weight loss in improving asthma outcomes needs to be investigated for patients with co-morbid asthma and obesity. In order to grow the field of lifestyle medicine in pulmonary disease more rapidly, researchers should consider adapting proven interventions in other chronic diseases and assessing their efficacy on asthma specific outcomes. Adapting and understanding how existing lifestyle interventions work in asthma should be the primary research focus until we begin to close our knowledge gap in pulmonary lifestyle medicine.

Based on evidence-based guidelines and reimbursement policies for lifestyle counseling in other chronic diseases (ie. cardiovascular disease and diabetes), lifestyle interventions in asthma should carefully consider potential for implementation so as to optimize the value of information for informing clinical practice. Further, using intervention delivery methods that use formats and intensity levels recommended by US health guidelines and are already reimbursable in Medicare and commercial health plans for other related conditions, (e.g., obesity management in primary care and diabetes prevention in clinical and community settings) will enhance dissemination and implementation of lifestyle interventions in asthma. Similarly, attention to sociocultural and physical environments (eg. Lack of physically active role-models, access to healthy foods and safe places to be physically active) of the target population, may be needed to address barriers and facilitators to intervention

implementation. Intervention optimization is an incremental and iterative process, aimed at optimal levels of safety, efficacy, efficiency, economy, and scalability.

Conclusion/Future Research Directions

Asthma affects millions of people worldwide. Addressing lifestyle modifications to improve the lives of patients with asthma and obesity has been understudied and under recognized. Rigorous yet pragmatic studies are needed to evaluate the effects of a comprehensive weight loss intervention that combine dietary pattern change, physical activity, and behavioral modification -- on asthma symptoms, lung function, airway hyperresponsiveness and asthma exacerbations with adults who have co-morbid asthma and obesity. We also need to better understand the nature of the obesity-asthma relationship and understand the mechanisms that influence lifestyle interventions. Further, identification of effective behavioral approaches will add to the armamentarium of medical and environmental strategies for the management of asthma in adults, which, in turn, may lead to reduced morbidity and mortality associated with these prevalent chronic diseases.

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Abbreviations

AO	Antioxidant
BHR	Bronchial Hyperresponsiveness
CI	Confidence Interval
DASH	Dietary Approaches to Stop Hypertension
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
IL	Interleukin
MCID	Minimal Clinically Important Difference
NFκB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
RCT	Randomized Controlled Trial
SCFA	Short Chain Fatty Acids
Th2	T helper cell type 2

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Table 1
Existing Randomized Controlled Trials of Dietary Pattern Change in Adults with Asthma

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result *
Wood 2012 [29]	137 adults with stable asthma	High-antioxidant (AO) diet or a low-antioxidant (AO) diet for 14 d; then high-AO diet group received placebo and low-AO diet group receive placebo or tomato extract for another 12 weeks or until exacerbation	Low-AO diet vs. high-AO diet; Placebo vs. tomato extract	1°: % Sputum neutrophils 2°: Time to first exacerbation, FEV ₁ %, C-Reactive Protein (CRP), Airway and systemic inflammation, Asthma control Questionnaire (ACQ)	Intervention: 14 weeks Outcomes measured: 14 weeks	Not stated	Asthma-related -Change in time to first exacerbation between High AO and Low AO diet (p<0.05) -Change in asthma exacerbations 19.6% in High AO diet vs. 27.5% in low AO diet; low AO diet 2.26 more likely to have exacerbation at any time than high AO diet -Change in ACQ in high AO diet (-0.1) compared to low AO diet (0.00) Lifestyle-related NR Mechanism-related -No statistically significant change in % sputum neutrophils -Decline in FEV ₁ % predicted in low AO diet at 14 days vs. baseline (p<0.05) -No statistically significant difference in outcomes with tomato supplement
Sexton 2013 [30]	38 adults with symptomatic asthma	High Intervention (HI): Adopt Mediterranean Diet (MD), 5 dietitian sessions Low Intervention (LI): Adopt MD, and 1 dietitian session	Control: At end-of trial, offered 1 dietitian session, MD recipes and free food	1°: adherence to MD 2°: Spirometry, ACQ, Asthma Quality of Life Questionnaire (AQLQ), Food Frequency Questionnaire (FFQ)	Intervention: 12 weeks Outcomes measured: 6 weeks and 12 weeks	Not stated	Asthma-related Clinically significant (MCID 0.5) pre-post change in AQLQ symptom (0.55), emotional (0.69) and environmental (0.64) subdomains in HI group and environmental (0.71) subdomain in LI group. Lifestyle-related -Mean change in MD adherence is 6.62 (1.11) in HI group vs. 0.44 (1.11) in control group (p < 0.001). Mechanism-related -No statistically significant improvement in FEV ₁ or FVC
Ma 2016 [31]	90 adults with uncontrolled persistent asthma	DASH diet +8 group and 3 individual sessions	Usual Care	1°: change in ACQ 2°: change in DASH score and AQLQ	Intervention: 6 months Outcomes measured: 3 and 6 months	Not stated	Asthma-related -Change in mean ACQ in DASH group -0.2 (95% CI -0.5, 0.1) -Change in mean AQLQ in DASH group • Overall mean score 0.4 (95% CI 0, 0.8) • Mean score of individual domains: symptoms 0.5 (95% CI 0, 0.9), environmental 0.4(95% CI -0.1, 1.0), emotional 0.4 (95% CI -0.2, 0.9) and activities 0.3 (95% CI 0, 0.7) Lifestyle-related -Change in mean DASH score in DASH group 0.8 (95% CI 0.2, 1.5); -Change in mean weight -0.1 kg (95% CI -1.8, 1.5) Mechanism-related No statistically significant improvement in FEV ₁ or FVC

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ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; CI: Confidence Interval; DASH: Dietary Approaches to Stop Hypertension; FEV₁: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; NR: Not reported;

* Between group differences reported unless otherwise stated

Table 2
Existing Randomized Controlled Trials of Physical Activity in Adults with Asthma

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result*
Cochrane 1990 [44]	36 adults with mild-moderate asthma	30-minutes of aerobic exercise (aerobics, jogging, cycling) then light calisthenics and stretching 3 times a week	Educational sessions only	1°: not stated -FEV ₁ , max tidal volume -max oxygen consumption (VO ₂ max), max minute ventilation (VE max), max VE/VO ₂ , max heart rate, respiratory rate, max oxygen pulse	Intervention: 3 times a week for 3 months Outcomes measured: 3 months	Hospital	Asthma and Lifestyle-related: NR Mechanism-related -Change in mean VO ₂ max 5.4 mL/kg/min from baseline (p<0.001) -Change in mean anaerobic threshold: 0.27 L/min change from baseline(p<0.001) - No statistically significant improvement in FEV ₁
Goncalves 2008 [45]	23 adults with moderate or severe persistent asthma	Education program, respiratory exercise program and 3 month aerobic conditioning program (30 min aerobic training on a treadmill 2 times a week)	Control: Education program only	1°: not stated -Pulmonary function, max aerobic capacity -Quality of life -levels of anxiety and depression, asthma symptoms and exhaled nitric oxide levels	Intervention: 2 times a week for 12 weeks Outcomes measured: 30, 60 and 90 days	Not stated	Asthma-related -Change in median symptom-free days (9.1 days) at 90 days Lifestyle-related -Change in median health-related quality of life (-26.8%; p<0.05) at 90 days Mechanism-related -Change in median peak VO ₂ (5.2 mL/kg/min; p<0.05) at 90 days -Change in median exhaled nitric oxide (-18.8 ppb; p<0.05) at 90 days
Turner 2011 [47]	34 adults with moderate to severe asthma with fixed airway obstruction	80–90 min exercise sessions of walking and circuit training (cycle ergometry, step-ups, wall squats and upper limb endurance training supervised by physiotherapists 3 times a week)	Usual Care	1°: AQLQ and 6-minute walk (6MW) test 2°: Asthma control, health status (SF-36), anxiety, depression, peripheral muscle strength	Intervention: 3 times a week for 6 weeks Outcomes measured: 6 weeks and 3 mo post-intervention	Hospital	Asthma-related -At 6 weeks and 3 months, change in mean AQLQ in symptom domain (0.2; p<0.05 for both time points) and activity limitation domain (0.4 @ 6 weeks and 0.5 @ 3 mo; p<0.05 for both time points) Lifestyle-related -Change in mean SF-32 physical component score at 6 weeks (7.9; p<0.05) -Change in mean 6MW distance compared to

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result*
Mendes 2010 [46]	101 adults with moderate or severe persistent asthma	Education program on breathing exercise, 30 minutes of aerobic exercise training 2 times a week	Education program on breathing exercises	1°: Asthma specific HRQoL 2°: anxiety and depression, asthma symptoms (# of asthma symptom free days), FEV ₁ , FEVC, VO ₂ max	Intervention: 2 times a week for 12 weeks Outcomes measured: 12 weeks	Not stated	baseline (36 meters at 6 weeks and 33 meters at 3 mo; p<0.05 for both time points) Mechanism-related -No statistically significant improvement in resting lung function at 6 wks or 3 mo Asthma-related -Change in mean asthma symptom free days/month from baseline (10 days; p<0.001) Lifestyle-related -Change in median physical limitations, frequency of symptoms, and psychosocial domains and total scores of HRQoL from baseline (p<0.05) Mechanism-related -Change in VO ₂ max p<0.001)
Mendes 2011 [49]	68 adults with moderate or severe persistent asthma	Education program on asthma and breathing exercises, 30 minutes of aerobic exercise training (treadmill) 2 times a week	Education program on asthma and breathing exercises	1°: Induced sputum cellularity 2°: fractional exhaled nitric oxide (FeNO), pulmonary function tests, cardiopulmonary exercise testing, asthma symptom-free days, asthma exacerbations	Intervention: 2 times a week for 12 weeks Outcomes measured: 12 weeks	Not stated	Asthma-related -Change in asthma exacerbations (1 vs. 7 in control; p<0.01) -Change in mean asthma symptom-free days from baseline (10 days; p<0.001) Lifestyle-related NR Mechanism-related -Decrease in median sputum total cell count and eos (p<0.05), FeNO (p=0.009) -Change in median VO ₂ max % predicted (12.3; p<0.001)
Boyd 2012 [43]	19 adults with mild-moderate persistent asthma	-30 minutes of moderate intensity aerobic exercise (walking) 3 times a week, weekly phone calls	Standard patient education and weekly phone calls	1°: Serum Eosinophilic Cationic Protein 2°: ACQ, Inflammatory biomarkers in blood and nasal lavage, FEV ₁ , FEV _F /FVC, Fitness measures (VO ₂ peak, heart rate peak, respiratory exchange	Intervention: 3 times a week for 12 weeks Outcomes measured: 12 weeks	University Recreational Facility	Asthma-related - No statistically significant improvement in ACQ Lifestyle-related -Change in mean total treadmill time from baseline (1.39 min; p 0.04)

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result*
Franca-Pinto 2015 [48]	58 adults with moderate to severe persistent asthma	-Breathing exercise program supervised by physiotherapist -35 minute aerobic training (treadmill) 2 times a week	-Breathing exercise program twice weekly for 12 weeks	1°: bronchial hyperresponsiveness (PC ₂₀) 2°: serum cytokines, fractional exhaled nitric oxide (FeNO), sputum eosinophils, ACQ, asthma exacerbations, AQLQ	Intervention: 2 times a week for 12 weeks Outcomes measured: 12 weeks	Not stated	<p>Mechanism-related</p> <ul style="list-style-type: none"> -Change in mean VO₂ peak from baseline (2.64 mL/min/kg; p=0.04) - No statistically significant improvement in airway and systemic inflammatory biomarkers <p>Asthma-related</p> <ul style="list-style-type: none"> -Change in mean activity limitation domain(-1.1; p=0.009) and mean overall AQLQ score (-0.9; p=0.034) -Change in asthma exacerbations (0.6 vs 1.5 exacerbations/patient; p=0.021) <p>Lifestyle-related</p> <p>NR</p> <p>Mechanism-related</p> <ul style="list-style-type: none"> -Change in mean VO₂ max (-0.48 mL/kg/min; p=0.019) -Change in PC₂₀ by 1 doubling dose (p=0.031) -Change in mean serum IL-6 (207.1 p=0.042) and MCP-1 (-5.3 p=0.045)

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; FEV₁: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; HRQoL: Health Related Quality of Life; MCP: Monocyte Chemoattractant Protein; NR: Not reported; SF-36: Short Form Health Survey; VO₂: oxygen consumption;

* Between group differences reported unless otherwise stated

Existing Randomized Controlled Trials Combining Diet and Physical Activity in Obese and Non-Obese Adults with Asthma

Table 3

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result*
Scott 2013 [63]	46 Overweight and Obese adult with mild-severe persistent asthma	Group 1: low calorie diet (885–1170 kcal/Day) Group 2: Aerobic and resistance exercises at gym at least 3 times a week, 1h- personal training session/ week, walking prescription with goal of 10,000 steps/day Group 3: Combined dietary and exercise intervention	Pre- and post intervention and compared to diet alone group	1-: not stated AQLQ ACQ Airway hyper-responsiveness (AHR) Airway inflammation Leptin IL-6	Intervention: At least 3 times a week for 10 weeks Outcomes measured: 10 weeks	Gym	Asthma related -ACQ (% with MCID of 0.5): 53% in Group 1 and 42% in Group 3 (P = 0.250) -AQLQ (% with MCID of 0.5): 73% in Group 1 and 50% in Group 2 and 3 (P = 0.365) Lifestyle related -Mean % weight loss: 8.5% (p 0.001) and 8.3% (p 0.001) in Group 1 and 3 respectively, 1.8% (p=ns) in Group 2 Mechanism related -Change in # of subjects that had AHR [measured as PD15 (mL)] in Group 3 (100% pre-intervention vs. 66.7% post-intervention respectively, p = 0.027) -Change in %Sputum eosinophils in Group 2 (-1.3; p 0.05). Between group comparison p=0.763
Ma 2015 [62]	330 obese adults with uncontrolled persistent asthma	12-month comprehensive behavior weight loss intervention adapted from the Group Lifestyle Balance program[73], which was based on the Diabetes Prevention Program[20]. The intervention promoted health eating with moderate calorie reductions (500–1000 kcal/d) and moderate intensity physical activity for at least 150 minutes a week.	Control: Enhanced usual care	1-: ACQ 2-: intervention adherence, Leisure-time physical activity, Weight change, AQLQ	Intervention: 12 months Outcomes measured: 6 and 12 months	Health system	Asthma related -ACQ: Pre-post mean ACQ change in Intervention group -0.36 vs. control group -0.26 (p= 0.92). Lifestyle related -Change in mean weight: -4.0 kg; p = 0.01. -Weight loss of 10% or greater was associated with a Cohen d effect of 0.76 and with 3.78 (95% CI, 1.72–8.31) times the odds of achieving clinically significant reductions (i.e., 0.5) on ACQ as stable weight (<3% loss or gain from baseline). Mechanism related No statistically significant improvement in FEV ₁ or FVC
Freitas 2017 [70]	55 obese moderate to severe persistent asthmatic	Weight loss + Exercise (WL + E) -6 hour educational program -Behavioral weight loss: 12 individual hypocaloric diet counseling sessions conducted by nutritionist and psychologist -Aerobic (based on 50–75% peak VO ₂) and resistance exercises for major muscle groups	Control: Weight loss + Sham (WL + S) Behavioral weight loss (hypocaloric diet counseling) + Sham exercise (Stretching and breathing exercise)	1-: ACQ 2-: AQLQ Lung function Body composition Aerobic capacity Muscle strength Inflammatory/anti-inflammatory biomarkers	Intervention: 2 times a week for 12 weeks Outcomes measured: 6 and 12 months	Not stated	Asthma related -Change in median ACQ scores of greater than 0.5 points, was found in WL + E group and 36% in WL + S group (P = 0.03) -Pre-post median ACQ is -0.7 in WL + E and -0.4 in WL + S (p=0.01) -Change in median AQLQ activity limitation domain score by 0.7 in WL + E (p<0.001) and 0.2 in WL + S. Between group comparison p=0.007 Lifestyle related -Change in median weight: -6.8% in WL + E and -3.1% in WL + S, (p<0.001)

Study	Population	Intervention	Comparator	Outcome	Timing	Setting	Result*
Toennesen In press [74]	125 non-obese (BMI >20 and <30 kg/m ²) adults with asthma (ACQ 1 at baseline)	Group 1 (Exercise): high-intensity interval training concept on indoor spinning bikes. Sessions included a 10 minute warm-up followed by 2,3 or 4 5-min intervals. Each 5-min interval had 5 consecutive 1-min intervals divided into 30,20 and 10 seconds at an intensity corresponding to <30%, <60% and >90% of maximal intensity. Group 2 (Diet): 6 counselling sessions with dietician (5 group/1 individual) over 8 weeks; Diet: High protein content (25–28% of energy), low glycemic index (< 55), anti-inflammatory (vegetables, fruit, nuts, lean meat, fish and seafood); Caloric needs were based on weight stabilization. Group 3: Exercise and Diet	Control: Usual care and encouraged to maintain usual physical activity levels and diet	1-: ACQ 2-: Mini AQLQ VO ₂ max Dual-energy X-ray Absorptiometry scan Lung function Induced sputum FeNO Mannitol provocation test Blood eosinophil Serum IL-6, high sensitivity C-reactive protein Urine urea excretion Allergy skin prick tests	Intervention: 3 times a week for 8 weeks Outcomes measured: 8 weeks	Hospital	Result* -Change in median aerobic capacity: 3 mL O ₂ /kg/min in WL + E and 0.9 mL O ₂ /kg/min in WL + S (p<0.001) Mechanism related -Change in median FeNO: -6.8 ppb in WL + E and -0.2 ppb in WL + S (p<0.001). -No statistically significant improvement in FEV ₁ or FVC Asthma related -ACQ: Pre-post change in mean ACQ score -0.7 in Group 1 and 2 (p<0.001), -0.9 in Group 3 (p<0.001). -Difference in mean ACQ change between Group 3 and control -0.6 (p<0.05). Between group comparison p=0.05. -AQLQ: Pre-post change in mean AQLQ total score is 0.5 in Group 1 (p<0.001), 0.6 in Group 2 (p<0.001) and 1.0 in Group 3 (p<0.001); Difference in mean AQLQ change between Group 3 and control 0.5 (p<0.01). Between group comparison p=0.04 Lifestyle related -Weight loss: Pre-post change in mean weight(kg) compared to control -1.0 (p<0.01) in Group 1, -2.3 (p<0.001) in Group 2 and -3.1 (p<0.001) in Group 3. Between group comparison p<0.001 Mechanism related -VO ₂ max: Pre-post mean change compared to control 3.1 in Group 1 (<0.05), 0.8 in Group 2 (p=ns), 5.3 in Group 3 (p<0.001). Between group comparison p<0.0001

ACQ: Asthma Control Questionnaire; AHR: Airway Hyperresponsiveness; AQLQ: Asthma Quality of Life Questionnaire; CI: Confidence Interval; FeNO: Fractionated exhaled Nitric Oxide; MCID: Minimal Clinically Important Difference; NR: Not reported; VO₂: oxygen consumption;

* Between group differences reported unless otherwise stated

Summary of the State of Science and Future Research Considerations of Lifestyle Interventions in Adults with Asthma

Table 4

Summary of State of Science	Dietary change [28–30]	Physical Activity [45–51]	Combined Dietary Change and Physical Activity
	<ul style="list-style-type: none"> - Improved diet quality following a healthy dietary pattern intervention (high anti-oxidant, DASH diets) improved time to asthma exacerbation, asthma control and asthma related quality of life. -This may have therapeutic benefits for adult patients with stable and uncontrolled asthma. -Few mechanism-related outcomes have been evaluated to date. 	<ul style="list-style-type: none"> -Adults with a range of asthma severity (mild-to-severe persistent) can safely participate in physical activity interventions. -The physical activity interventions in asthma to date have shown improvements in asthma exacerbations, symptom free days and asthma-related quality of life but have been highly structured in exercise facilities or supervised by specialists. -Eosinophils may play a role in the underlying mechanisms as a reduction in sputum eos% and FeNO was found in two studies. 	<p>Obese Adults [64, 65, 72]:</p> <ul style="list-style-type: none"> • Lifestyle interventions targeting dietary change and physical activity result in weight loss and active living comparable to similar interventions in other chronic diseases. • Improvements in asthma control (ACQ) and asthma quality of life (AQLQ) are seen when at least 5–10% weight loss occurs. • Most randomized controlled trials of behavioral weight loss interventions in obese adults with asthma had serious methodological flaws and used stringent caloric restrictions, which are not recommended in obesity guidelines. <p>Non-Obese Adults [76]:</p> <ul style="list-style-type: none"> • Improved asthma control found in a short-term intervention of intense cycling and dietary change that resulted in weight loss.
Future Research Considerations	<ul style="list-style-type: none"> -Researchers should consider using asthma-related primary outcomes. -Adequately powered studies are needed to confirm the efficacy of dietary pattern changes in improving asthma outcomes in a range of asthma disease severity and elucidate the underlying mechanisms. 	<ul style="list-style-type: none"> -Interventions that focus on increasing physical activity in routine settings are needed for wide-spread dissemination and implementation. -Include patient-reported outcomes as a primary outcome measure. -The biological mechanisms of physical activity on asthma warrant further study and should include a closer evaluation of the role of eosinophils. -Identify asthma subpopulations that benefit most from physical activity interventions (ie. specific inflammatory phenotypes or disease severity) 	<ul style="list-style-type: none"> • Well-designed, well-conducted clinical studies of guideline concordant behavioral weight loss interventions using scalable, sustainable delivery approaches, are urgently needed to advance the knowledge of weight loss in asthma. • Basic science studies of the mechanisms of weight loss in adults are needed and should include subpopulations such as obese, non-obese, co-existing medical conditions, and different asthma phenotypes. • Long-term RCTs are needed that include both obese and non-obese adults with asthma to elucidate the role of dietary change and physical activity in asthma control.

ACQ: Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; DASH: Dietary Approaches to Stop Hypertension; FeNO: Fractionated exhaled nitric oxide; RCT: Randomized Controlled Trial