Defining a role for exercise training in the management of asthma

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Asthma remains prevalent and many patients are symptomatic despite optimised treatment regimes. This review explores the role of exercise as an immunomodulatory treatment in asthma, and the barriers to this. http://bit.ly/2sE6IE8

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ABSTRACT The prevalence of asthma remains high worldwide, with increasing awareness of the morbidity and mortality from asthma in low-income countries. In the UK, despite the development of biological treatments, many patients remain suboptimally controlled, and mortality rates have been static for decades. Therefore, new approaches are needed to treat asthma that are scalable at minimal cost. Exercise immunology is an expanding field, and there is growing evidence that exercise can modulate inflammatory and immune processes in asthma. Whilst exercise is encouraged in current treatment guidelines, there are no specific recommendations as to the intensity, frequency or duration of exercise exposure. Despite national and international guidance to increase exercise, patients with asthma are less likely to engage in physical activity. This review explores the disease modifying benefit of exercise in asthma. We also review the domains in which exercise exerts positive clinical effects in asthma, including the effects of exercise on symptom scores, quality of life, psychosocial health, and in the obese asthma phenotype. Finally, we review the barriers to exercise in asthma, given the benefits it confers. A better understanding of the mechanisms through which exercise exerts its positive effects in asthma may provide more accurate prescription of exercise training programmes as part of broader asthma management, with the potential of identification of new drug targets.

Introduction

The burden of respiratory disease is increasing, with asthma affecting over 300 million people worldwide. In children, asthma is the most common chronic disease [1], and amongst the highest global ranking for disability-adjusted life-years [2]. Historically, the prevalence of asthma in low-income countries was thought to be minimal, but phase three of the International Study of Asthma and Allergies in Childhood suggests otherwise, with the prevalence of asthma, rhinoconjunctivitis and eczema demonstrated to be high in nonaffluent areas with low socioeconomic conditions [3]. Similar trends for prevalence have been noted in adults, with a recent review concluding that further increases worldwide are likely. Despite development of biological treatments, many adult asthma patients remain suboptimally controlled, with frequent exacerbations, increased symptom burden and associated healthcare costs [4], with low-income countries demonstrating higher levels of poor control amongst both children and adults [5]. Biological treatments for children are increasingly available but current understanding of which children are likely to benefit from these is limited, as the majority of trial data exists in adults [6]. It is probable that, as with adults, there will

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be groups of patients for whom there is no suitable biological target or response to biological treatment is limited. Therefore, new approaches are needed to treat asthma that are scalable at minimal cost. Whilst exercise is encouraged in current national and international treatment guidelines for both children and adults, there are no specific recommendations as to the intensity, frequency or duration of exercise exposure [7]. Despite guidance to increase levels of exercise, patients with asthma are less likely to engage in physical activity [8]. Exercise, as pulmonary rehabilitation, has an established role in treatment of respiratory disease, but is not routinely employed in the management of complex asthma [9]. Part of this may be that the majority of asthma patients are less functionally disabled than the patients with COPD who engage with pulmonary rehabilitation, and therefore both clinicians and patients fail to see the benefit. There may also be the concern of exercise precipitating an exacerbation in patients with suboptimal control. There is, however, suggestion that the worse the asthma control, the greater improvement is demonstrated with pulmonary rehabilitation [10], refuting this concern. Emerging data suggest that exercise as a therapeutic intervention may modulate the immune and inflammatory basis for respiratory disease, and offer clinical benefit beyond functional capacity improvement through disease modification [11, 12], suggesting a potential cost-effective benefit to a wide range of suboptimally controlled asthma patients.

Exercise immunology is an expanding field, and recently, studies have demonstrated the effects of exercise on inflammation and immunity [13]. Whilst the immunosuppressive effects of extreme exercise in athletes has been well described, a recent review suggests the interaction between exercise and immune function may be more complex than traditionally thought [14]. Within athletes with asthma, there is the further consideration of potential worsening of symptoms due to exercise-induced bronchoconstriction and exposure to environmental factors such as cold air, chloramines in pool environments and allergens as exacerbators of disease, and this needs to be considered in the context of an exercise intervention as a nonpharmacological treatment for asthma. However, here, we focus instead on the role of more moderate exercise interventions in previously untrained populations. The use of exercise intervention as an anti-inflammatory treatment in chronic diseases is a more recently emerging research area and, within asthma, human mechanistic studies are lacking.

The Global Initiative for Asthma defines asthma as "a heterogenous disease, usually characterised by airway inflammation" with symptoms of "wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory flow limitation" [15]. It is thought that this chronic inflammatory state drives the symptom burden of asthma, with oxidative stress implicated in its pathogenesis [16]. There is growing evidence that exercise modulates this redox balance [17], as well as the inflammatory and immune processes in asthma [11, 12]. Beyond this generalised description, it is increasingly recognised that asthma encompasses several phenotypes and endotypes [18], with significant differences in disease patterns and treatment responsiveness between patients. Haldar *et al.* [18] identified four key clusters in their secondary care cohort; 1) early-onset atopic asthma; 2) female-predominant obese noneosinophilic asthma; 3) early-onset symptom-predominant asthma with minimal eosinophilic disease; and 4) male-predominant later-onset eosinophilic disease with fewer symptoms. Unlike targeted biological therapies, exercise as an intervention has the potential to improve control across a broad range of disease endotypes, and exercise intervention studies to date tend not to have investigated specific phenotypes or endotypes in isolation. Whilst biological therapies are emerging as a key treatment for asthma, many patients do not demonstrate the appropriate biological marker, or remain suboptimally controlled in spite of biological treatment [19, 20], hence new treatment targets are required. Understanding the mechanisms through which exercise improves asthma control and inflammation will help establish exercise as a therapeutic intervention and identify patient endotypes most likely to benefit. Better mechanistic understanding may also offer the potential to identify new therapeutic targets for medication.

This review explores anti-inflammatory effects of exercise in asthma, and the potential mechanisms behind this. We review the clinical domains in which exercise exerts positive effects on symptoms. Finally, we explore. the barriers to exercise in asthma.

Effects of exercise on inflammation and immunity in asthma

Whilst exercise should benefit asthma patients in terms of their symptom burden regardless of phenotype, it is in allergic and eosinophilic disease that there is most interest in exercise as a disease modifier. Allergic and eosinophilic asthma involves chronic inflammation and airway remodelling [21], with T-helper cells (Th)2 dominating the T-cell response [22], resulting in an increase of airway eosinophils, $CD4^+$ T-cells and mast cells [21]. Th2 cytokines interleukin (IL)-4, IL-5 and IL-13 initiate and propagate inflammation, with eventual airway remodelling, hyperresponsiveness and obstruction.

Animal studies

Much of the mechanistic work in this context has been undertaken in mice, using ovalbumin (OVA)-sensitised mice as a model for allergic asthma (table 1). This model demonstrated decreased

TABLE 1 Summary of findings from animal studies

First author [ref.]	Mouse model	Intervention	Significant outcomes
Pastva [23]	6–9 female BALB/cJ mice; sedentary and nonsensitised, sedentary and OVA-sensitised, exercised and nonsensitised, and exercised and OVA-sensitised	Thrice weekly 45-min sessions for 4 weeks of aerobic exercise at 50% V'_{O_2peak}	Reduced BAL IL-4, IL-5 and OVA-specific IgE Reduced chemokine production Reduced lung cellular infiltrate, mucus production and epithelial hypertrophy decreased both the phosphorylation of IκB-α and translocation of the NF-κB subunit p65
Pastva [24]	Female BALB/cJ mice split into six groups; sedentary and nonsensitised; sedentary and OVA-sensitised with placebo; sedentary and OVA-sensitised with RU486 treatment; exercised and nonsensitised; exercised and OVA-sensitised with placebo; and exercised and OVA-sensitised with RU486 treatment	Thrice weekly 45-min sessions for 4 weeks of aerobic exercise at 50% V'_{O_2peak}	RU486 blocked the exercise-induced reductions in cellular infiltration of the airways KC and soluble VCAM-1 protein levels in the BAL fluid and NF-κB translocation and DNA binding within the lung to levels similar to those observed in sedentary OVA-sensitised mice
Vieira [25]	8 per group OVA-sensitised male BALB/c mice *versus* sensitised and nonsensitised controls	Low-intensity training at 50% maximal speed and moderate intensity at 75% maximal speed for 60 min 5×week for 28 days	Reduced airway wall and BAL eosinophils in both exercised groups Decreased peri-bronchial density of cells positive for IL-4 and IL-5, and increased IL-10 Reduced airway wall collagen and elastin fibres in airways Normalisation of bronchoconstriction index
Hewitt [26]	Female BALB/cJ mice	Single 45-min bout of aerobic exercise at 50–75% V'_{O_2peak}	Decreased leukocyte infiltration, including eosinophils Decreased phosphorylation of the NF-κB p65 subunit Decreased IL-5, IL-3 and PGE_2
Silva [21]	7 male BALB/c mice in four groups; control; AT; OVA; and OVA+AT	5×60-min sessions for 4 weeks at 50% V'_{O_2peak}	Increase of IgE and IgG Reduction of eosinophils, $CD3^+$, $CD4^+$, IL-4, IL-5, IL-13, NF-κB, airway remodelling, mucus synthesis, smooth muscle thickness and tissue resistance and elastance Increase in IL-10 and IL-1ra independently of Foxp3
Lowder [27]	Female C.Cg-Foxp3tm2Tch/J reporter ($Foxp3^+$ reporter) mice bred on a BALB/cJ background	45 mins 3×week for 4 weeks at 50–75% maximum O_2 consumption	Reduced BAL macrophages, eosinophils and lymphocytes Enhanced the suppression function of $CD4^+CD25^+Foxp3^+$ T-reg cells
Vieira [28]	8 per group ovalbumin sensitised male BALB/c mice *versus* sensitised and nonsensitised controls	Low-intensity training 60 min 5×week for 28 days	Reduced total cells and eosinophils in BAL fluid Reduced percentage of goblet cells in airway walls Reduced epithelial expression of IL-4,5, IL-13 and increased IL-10 Reduced inducible nitric oxide synthase, and other markers of oxidative and nitrosative stress Reduced NF-κB and P2X7 receptor
Silva [29]	8 male BALB/c mice in four groups; control (nontrained and nonsensitised); AC (aerobic conditioning and nonsensitised); OVA (nontrained and OVA-sensitised); and OVA+AC (aerobic conditioning and OVA-sensitised)	60 min for 5 days per week for 8 weeks at 50% V'_{O_2peak} prior to and during OVA sensitisation	Inhibition of OVA-induced migration of eosinophils and lymphocytes to the airways Reduced IgE and IgG1 titres Inhibition of Th2 cytokines

Continued

TABLE 1 Continued

First author [ref.]	Mouse model	Intervention	Significant outcomes
Dugger [30]	Female wild-type mice on a BALB/c split into four groups; sedentary OVA-sensitised; exercised OVA-sensitised; sedentary nonsensitised; and exercised nonsensitised	45 min thrice weekly for 4 weeks at 13.5 m per min	Surface expression levels of lung-homing chemokine receptors were comparable across groups Lung-derived Th cells from exercised OVA-sensitised mice exhibited decreased migratory function *versus* controls; Th cells from exercised mice are less responsive to lung-homing chemokines
Bruggemann [31]	8 male Swiss mice per group; control swimming OVA-sensitised and OVA-sensitised+swimming	30-min high-intensity swimming for 3 weeks	Decreased OVA-increased total IgE, IL-1, IL-4, IL-5 and IL-6 levels, total cells, lymphocytes and eosinophils in BAL fluid Increased IL-10 and glutathione levels Increased glutathione peroxidase and catalase in the swimming-only group
Alberca-Custodio [32]	16 per group; control, exercise, OVA and OVA+exercise groups	60 min 5× week for 4 weeks	Decreased eosinophils neutrophils lymphocytes and macrophages in BAL Decreased eosinophils lymphocytes and macrophages in airway walls Reduced collagen elastic fibres, mucus production, and smooth muscle thickness Reduced IL-5, IL-13, cysLT and LTB_4 in BAL Reduced 5-LO, LTA_{4H}, $cysLT_1$ receptor, $CysLT_2$ receptor, LTC+synthase and BLT2 expression by peri-bronchial leukocytes and airway epithelium Reduced AHR to methacholine
Fernandes [33]	10 BALB/c mice in four groups; control, exercise, OVA, and OVA exercise group	5 weeks exercise for 60 min 5×week at 50% V'_{O_2peak}	Increased IL-10 and TGF-β Increased recruitment of M2 in the lungs, influx and activation of Tregs and $CD4^+$ and $CD8^+$ lymphocytes Decreased proinflammatory common dendritic cells' expression of co-stimulatory molecules Increased anti-inflammatory ICOSL in plasmacytoid dendritic cells

OVA: ovalbumin; BAL: bronchoalveolar lavage; V'_{O_2peak}: peak oxygen uptake; IL: interleukin; Ig: immunoglobulin; NF-κB: nuclear factor-κB; VCAM: vascular cell adhesion molecule; PGE_2: prostaglandin E_2; AT: anaerobic threshold; Treg: regulatory T-cell; Th: T-helper; cysLT: cysteinyl leukotriene; LTB_4: leukotriene B_4; LTC: leukotriene synthase; LTA_{4H}: leukotriene A4 hydrolase; AHR: airway hyperresponsiveness; TGF-β: transforming growth factor β; ICOSL: inducible T-cell co-stimulator ligand.

leukocyte infiltration, cytokine production (IL-4, IL-5, IL-13), adhesion molecule expression, and structural remodelling within the lungs following a 4-week period of moderate intensity exercise [21, 23, 25]. In addition, Vieira *et al.* [25] and Silva *et al.* [21] demonstrated a reduction in activation of the inflammatory transcription factor nuclear factor-κB (NF-κB) with aerobic training. Exercise reduced airway remodelling, mucus synthesis, smooth muscle thickness and tissue resistance and elastance, and increased IL-10 and IL-1ra. Silva *et al.* [21] found this change occurred independently of regulatory T-cell (Treg) cell activity (FoxP3), whereas Lowder *et al.* [27] found that exercise increased levels of $FoxP3^+$ cells in the lungs and mediastinal lymph nodes of OVA-sensitised mice.

A single bout of moderate intensity exercise in OVA-sensitised mice causes similar decreases in leukocyte infiltration, including eosinophils, within the lungs [26]. There was decreased phosphorylation of the NF-κB p65 subunit and reduced IL-5, IL-13 and prostaglandin E_2. There was attenuation of the chemokines KC, RANTES and monocyte chemoattractant protein (MCP)-1. However, a single bout of exercise had no effect on airway hyperresponsiveness, epithelial cell hypertrophy, mucus production, or airway wall thickening.

When aerobic conditioning was performed before and during OVA sensitisation of mice, rather than after, a similar reduction in inflammation was observed. Exercise reduced the OVA-induced migration of eosinophils and lymphocytes into the airways, and reduced expression of Th2 cytokines, as well as expression of intracellular adhesion molecule (ICAM)-1, vascular cellular adhesion protein (VCAM)-1, RANTES, transforming growth factor (TGF)-β and vascular endothelial growth factor (VEGF). Airway remodelling and production of allergen-specific immunoglobulin (Ig)E and IgG-1 were reduced [29], suggesting exercise may be protective to subsequent inflammatory insults.

The mechanisms of how exercise exerts its anti-inflammatory effects in this simplified mouse model of asthma remain unclear, although reduced NF-κB activation [23], increases in glucocorticoid receptor expression [24], FoxP3 increases [27], T-cell trafficking in response to an allergen challenge [30] with increased lung recruitment of Tregs and macrophages [33], and increased IL-10 and IL-1ra have been proposed [25, 21], with IL-10 increases recently directly linked with increases in M2 macrophages in the lung tissue [33].

Potential mechanisms to explain the anti-inflammatory effect of exercise in animal models

In search of a mechanistic link within this animal model, Alberca-Custodio *et al.* [32], looked specifically at whether moderate intensity exercise modulates the leukotriene pathway in OVA mice. They found that moderate aerobic exercise reduced eosinophils in bronchoalveolar lavage (BAL) and airway walls, and reduced IL-5 and IL-13 in BAL, which was associated with reduced total cysteinyl leukotrienes (cysLTs) in the BAL and airway epithelial cells of exercised OVA mice, as well as reduced airway hyperresponsiveness. It is known that cysLTs activate NF-κB. In OVA-sensitised mice treated with a cysLT receptor antagonist [34], corticosteroids were shown to inhibit cysLTs, which may contribute to the of the mechanism through which they exert their anti-inflammatory effects. As NF-κB is activated by cysLTs, this provides support for the role of NF-κB and cysLTs as a mechanism for reduced inflammation in exercise.

Pastva *et al.* [24] treated exercised OVA mice with the glucocorticoid receptor antagonist RU486, and with this, exercise-induced changes in airway infiltration and BAL levels of KC and VCAM-1 were reduced to levels of sedentary mice, as were NF-κB translocation and DNA binding within the lung, and exercise-induced increases in glucocorticoid receptor nuclear translocation. Silva *et al.* [35] looked at the timescales of these changes and found that the OVA-induced reduction in glucocorticoid receptor expression was attenuated at day 3 of exercise training. Exercise training reversed the OVA-induced increase in the expression of NF-κB at 7 days, with increased expression of IL-10 and IL-1ra, and no change in the expression of FoxP3. Eosinophil migration into the airways, and expression of ICAM-1 and VCAM-1 in the exercised OVA group reduced at this time-point, as did IL-4, IL-5, exotoxin and RANTES. OVA-induced levels of vascular endothelial growth factor and transforming growth factor-β also reduced at day 7. The timescales demonstrated in this study suggest that modifications in the status of the glucocorticoid receptor may initiate the anti-inflammatory changes induced by exercise.

Alterations in airway epithelium are important in inflammation and airway remodelling in asthma. Vieira *et al.* [33] investigated the effects of aerobic exercise on airway epithelial cells in OVA-sensitised mice and showed that low-intensity aerobic exercise reduced oxidative and nitrosative stress. There was reduced epithelial expression of NF-κB and P2X7R (a plasma membrane receptor involved in control of proinflammatory cytokine expression) and increased expression of epithelial IL-10. In a similar mouse model, high-intensity swimming resulting in increased glutathione with attenuation of pulmonary allergic inflammation, with the authors suggesting the effects of swimming were partly mediated through reduced oxidative stress and increased IL-10 production [31].

Effect of exercise on inflammation in children

Intervention studies of exercise as a disease-modulating treatment for children with asthma are small, scarce and tend to focus on clinical improvements as primary outcomes (table 2). Changes in markers of inflammation are recorded as a secondary outcome, but without mechanistic work to investigate how these changes are affected.

In atopic, asthmatic, school-aged children, a 12-week moderate intensity exercise programme reduced mite-specific IgE, with no change in exhaled nitric oxide fraction (F_{eNO}), blood eosinophil levels or serum C-reactive protein [37]. High-intensity interval training in children demonstrates an improvement in body mass index (BMI) and aerobic fitness but without improving inflammation as assessed by F_{eNO} [41]. The most mechanistic work to date was undertaken in adolescents, and demonstrated that exercise training reduced glucocorticoid receptor expression in leukocytes and monocytes [38]. The authors postulated that exercise training reduced the stress response overall, resulting in a reduction in glucocorticoid receptor expression in several lymphocyte subsets after an acute exercise challenge and sustained after an exercise training intervention. An 8-week exercise intervention improved lung function in children compared to

TABLE 2 Summary of findings from studies investigating exercise interventions in children with asthma

First author [ref.]	Patient demographics	Intervention	Significant outcomes
Counil [36]	9 *versus* 7 control Mean age 13 years Atopic with bronchodilator reversibility	3×weekly 45 min, 1-min sprint at work rate at AT followed by 4 min recovery cycling	Improved V'_{O_2peak} and AT
Moreira [37]	17 *versus* 17 control Children aged 12.7 ±3.5 years Atopic On maintenance OCS	50-min twice-weekly training session for 3 months 30–35 min submaximal training	Improved pAQLQ Reduced total IgE and mite-specific IgE
Onur [17]	15 with 15 asthmatic controls and 15 healthy controls	8-week exercise training intervention	Decreased oxidant stress markers Increased antioxidant enzyme activity Improved lung function
Willeboordse [34]	43 with 44 control Median age 12.3 years Median BMI 25; 53% of group obese	60 min 2×week at 60–75% maximal heart rate for 6 months	Improved asthma control and quality of life, reduced weight and improved FVC
Lu [38]	12 *versus* 14 healthy adolescents Mean BMI 22	Acute exercise challenge followed by 60 min thrice weekly for 8 weeks	Reduced glucocorticoid receptor expression in several lymphocyte subsets after an acute challenge and 8 weeks of training
Abdelbasset [39]	19 with 19 control Children aged 8–12 years with moderate persistent asthma	40 min thrice weekly training sessions at 50–70% maximum heart rate for 10 weeks	Improved FEV_1 and FVC Improved V'_{O_2peak} Improved 6MWT
Lucas [40]	86 asthma, 142 nonasthmatic obese Mean BMI percentile 98.14 Mean age 11.26 years	40 min physiologist-designed exercise weekly	Reduced weight and improved V'_{O_2peak}

AT: anaerobic threshold; V'_{O_2peak}: peak oxygen uptake; OCS: oral corticosteroids; pAQLQ: paediatric Asthma Quality of Life Questionnaire; Ig: immunoglobulin; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; 6MWT: 6-min walk test.

pharmacological management only, along with an improvement in levels of oxidative stress [17]. Otherwise, exercise intervention studies in children have tended to focus more on symptom control and quality of life as outcomes.

Effect of exercise on inflammation in adults

Exercise intervention studies in adults similarly focus on clinical outcome with inflammatory changes as secondary outcomes (table 3). An exercise intervention study in adults examined moderate-to-severe adult asthma patients who completed a twice-weekly exercise programme of 3months' duration, with a control group of matched patients undergoing a breathing training programme.

Here, induced sputum eosinophil counts fell in the training group after exercise, as did F_{eNO}, with greatest reductions seen with highest baseline levels [44]. Asthma symptoms also reduced in the training group [44]. Reduction in sputum eosinophils was also demonstrated in an exercise and dietary intervention in obese asthma patients [46]. Others have shown that aerobic training at moderate intensity reduces bronchial hyperreactivity, with reduced IL-6 and MCP-1 [12]. Quality of life, as measured by the Asthma Quality of Life Questionnaire (AQLQ) results and asthma exacerbation rates also improved. The effects of exercise and weight loss were explored in a randomised control trial of obese asthmatic adults; the combined programme demonstrated an improvement in clinical symptoms and aerobic capacity, accompanied by weight loss. There was also reduction in F_{eNO}, CCL2, IL-4, tumour necrosis factor-α and leptin, with increased levels of vitamin 25(OH)D, IL-10 and adiponectin [11]. However, the exercised group showed a significantly larger reduction in BMI, and therefore it is impossible to exclude confounding from reduced obesity-driven systemic inflammation. High-intensity intermittent exercise training without strength training has been looked at in adult asthmatic patients [49], and was shown to be beneficial in terms of symptom scores as assessed by Asthma Control Questionnaire (ACQ) and AQLQ. There were no significant changes in

TABLE 3 Summary of findings from studies investigating exercise interventions in adults with asthma

Study	Patient demographics	Intervention	Significant outcomes
Farid [42]	18 *versus* 18 controls Mean age 29 years Exercise-induced asthma Atopic	3×weekly 20 min aerobic exercise for 8 weeks	Improved FEV_1, FVC, PEF, $FEF_{25-75\%}$ and MVV
Mendes [43]	44 *versus* 45 controls Median age 39 years Median BMI 25.2 Moderate or severe persistent asthma	2×30-min training session on indoor treadmill for 3 months 60–80% V'_{O_2max}	Improved V'_{O_2max} Improved asthma-related QoL Reduced Beck Depression Inventory Reduced State-Trait Anxiety Inventory Scores
Mendes [44]	34 *versus* 34 controls Median age 34 years Median BMI 25.8 Moderate or severe persistent asthma	2×30-min training session on indoor treadmill for 3/12 60–80% V'_{O_2max}	Reduced F_{eNO} Reduced sputum total and eosinophil counts Increased number of symptom free days Improved V'_{O_2max}
Turner [45]	19 *versus* 15 controls Mean age 71 years Mean BMI 26.8 Moderate-to-severe asthma with fixed airflow obstruction	1×weekly 20 min walking at 80% of average walking speed on 6MWT circuit training based on Borg RPE scale	Improved AQLQ activity and symptom domains
Scott [46]	10 exercise *versus* 15 dietary intervention *versus* 13 diet and exercise Mean BMI 33.7	Personal training 60 min per week and visit gym 3×week for 12 weeks	Improved symptoms with diet and combined Improved QoL with all three interventions Reduced sputum eosinophils with exercise Reduced BMI
Franca-Pinto [12]	22 *versus* 21 controls Mean age 40 years Mean BMI 26.5 91% atopy Mean maintenance ICS 909 Moderate-severe asthma	2×weekly 35 min (25-min training, 5-min warm up/cool down) "vigorous" aerobic training programme on an indoor treadmill for 3 months	Improved bronchial hyperreactivity by 1 doubling dose Reduced serum IL-6 and MCP-1
Freitas [47]	28 *versus* 27 controls Mean age 45.9 years Mean BMI 38.1 Obese participants	2×weekly constant WR aerobic training 50–75% V'_{O_2peak} and resistance training 60% 1 RM	Greater proportion of patients with improved depression symptoms Lower risk of developing OSA Improved sleep quality
Turk [48]	44 *versus* 30 controls Obese mean BMI 44.75	Thrice weekly sessions of 40–60 min high-intensity interval training for 12 weeks	Improved asthma control at surgery Improved asthma-related QoL
Candemir [9]	35 patients Mean age 45 years	30-min sessions thrice weekly for 8 weeks at 85% V'_{O_2peak} plus quadriceps resistance training	Improved ACT Reduced BMI in obese participants Reduced emergency admissions and hospitalisations
Toennesen [49]	29 exercise; 29 diet and exercise, 33 diet, 34 control Mean age 38.2–43.7 years Mean BMI 24.9–26.1 72–85% atopy 59–76% ICS	2–5 repeats of 5-min interval training consisting of: 1) 30 s at 30 V'_{O_2max}; 2) 20 s at 60% V'_{O_2max}; 3) 10 s at 90% V'_{O_2max}	Improved ACQ
Freitas [11]	28 *versus* 27 controls Mean age 45.9 years Mean BMI 38.1 Obese participants	2×weekly constant WR aerobic training 50–75% V'_{O_2peak} and resistance training 60% 1 RM	Reduced F_{eNO} Improved FEV_1/FVC Improved ACQ score Decreased serum CCL2, IL-4, IL-6, TNF-α, leptin Increased vitamin D, adiponectin, IL-10

Continued

TABLE 3 Continued

Study	Patient demographics	Intervention	Significant outcomes
Prossegger [50]	18 exercise, 24 control Mean age 40.6 years HDM sensitisation	Four 3–5-h guided GPS-monitored hiking/snow-shoe tours with an average altitude difference of 411 m and 11 km in distance per day Four all-day skiing sessions with an average of 42 km in ski slopes in three different ski regions (2000–2500 m)	Improved F_{eNO} Reduced nasal eosinophil count Improvement in allergic symptoms
Saxer [51]	24 *versus* 24 controls Low altitude: mean age 47 years, BMI 24 High altitude: mean age 43 years, BMI 26	5×weekly 30–45-min guided walks, endurance training, strength training and education for maximum 5 h per day for 3 weeks at either 760 m above sea level or 3100 m above sea level	ACQ in both groups PEF variability in both groups
Jaakkola [52]	44 *versus* 45 controls Mean age 39.7 years Mean BMI 24.97	3×weekly 30-min aerobic exercise at 70–80% maximal HR for 24 weeks	Improved ACT score

FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC; MVV: maximum voluntary ventilation; BMI: body mass index; V'_{O_2max}: maximal oxygen uptake; QoL: quality of life; F_{eNO}: exhaled nitric oxide fraction; 6MWT: 6-min walk test; RPE: rate perceived exertion; AQLQ: Asthma Quality of Life Questionnaire; ICS: inhaled corticosteroid; IL: interleukin; MCP-1: monocyte chemoattractant protein 1; WR: work rate; V'_{O_2peak}: peak oxygen uptake; RM: repetition maximum; OSA: obstructive sleep apnoea; ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; TNF: tumour necrosis factor; HDM: house dust mite; HR: heart rate.

anti-inflammatory parameters, and the improvements in fitness and asthma control were not sustained at 1 year [53]. An outdoor walking exercise intervention, which may be more sustainable long term than a gym-based intervention, demonstrated reduction in F_{eNO} after a single hiking tour, sustained at 10 days. This recreational study demonstrated improvements in allergic symptoms but not in nasal eosinophil cell count at 60 days suggesting some persisting benefit [50]. In an observational context, Del Giacco *et al.* [54] monitored a professional football team across a season, and found that natural killer cell absolute count and percentage increased in both atopic and nonatopic athletes, and IL-2 and IL-4 production reduced. The most marked reduction in IL-4 was seen in atopic individuals, suggesting that the immunological mechanisms observed in the short term in murine models and humans are translatable to real-life, longer-term situations, although mechanistic data in asthmatic humans are lacking. Consistently with these early findings, a systematic review of the effect of physical training on airway inflammation in asthma [55] concluded that whilst some findings suggested physical training may reduce airway inflammation in asthma patients, more information was necessary.

Potential mechanisms to explain the anti-inflammatory effect of exercise in children and adults with asthma

Potential mechanisms include redox modifications of the glucocorticoid receptor, linking in with results from murine studies discussed above [35]. Higher levels of cysteine oxidation of the glucocorticoid receptor have been demonstrated in children with difficult-to-treat asthma, with levels correlating with disease severity and poor control [56]. Greater oxidation of the glucocorticoid receptor in humans promotes post-translational modification that may impair receptor function [56]. Redox regulation and oxidative stress have been implicated in the pathogenesis of asthma [16]. Higher levels of oxidant stress markers have been demonstrated in children with asthma, and a reduction in these markers together with an increase in antioxidant enzyme activity and an improvement in lung function have been shown following an 8-week exercise training intervention [17]. Changes in the interactions between reactive oxygen species in healthy humans undergoing exercise intervention have been demonstrated [57], but this is yet to be investigated in adults with asthma. Additionally, mechanistic involvement of the glucocorticoid receptor does not necessarily fit with the findings of Lu *et al.* [38] when investigating he effect of exercise on glucocorticoid receptor expression in adolescents.

Given the suggestion of a reduction in inflammation, along with the broader, well-known benefits of increased physical activity, completion of an exercise training intervention would not be an unreasonable

prerequisite to starting biological treatment and may increase the response rates of these expensive treatments.

Effects of exercise on symptom scores, quality of life and psychosocial morbidity in asthma in children

It seems exercise confers an anti-inflammatory benefit in patients with asthma, but patients are unlikely to adhere to exercise training interventions without demonstrable improvements in their symptoms. Symptom scores are a frequently assessed outcome in studies investigating the effects of an exercise intervention patients with asthma. Whilst any improvements demonstrated are likely to be multifactorial, a better understanding of the mechanism through which they occur is fundamental to the wider incorporation of exercise intervention into asthma management, both in children and adults.

A study of an exercise intervention in overweight and obese children with asthma demonstrated improvement in symptom scores [34]. However, this was associated with a reduction in weight, so it is difficult to tease apart whether this was a result of reduced asthma-driven inflammation or because of reduction in BMI.

Improvements in quality of life scores are one of the most widely studied areas in which exercise can exert a positive effect in asthma,

Exercise training programmes in children with asthma have shown significant improvements in quality of life [34, 37]. These were associated with improvements in BMI in obese children and asthma-related inflammation [37].

Exercise training has shown a beneficial effect on the symptoms of anxiety and depression in meta-analyses, with greatest effects on depression [58]. A Cochrane review of exercise training in asthma concluded that exercise training-related improvements in quality of life may result in improved psychosocial well-being [59] Anxiety and depression are prevalent in asthma, particularly within difficult and severe asthma [60], and depression is related to higher levels of hospital admission, corticosteroid use [61] and poorer quality of life [62].

Studies in children to date have not specifically investigated psychosocial morbidity but, as discussed above, there have been improvements in quality of life scores, which contain some questions relevant to psychosocial morbidity.

Effects of exercise on symptom scores, quality of life and psychosocial morbidity in adults with asthma

Studies in adults have demonstrated improvements in symptom scores with exercise interventions, as assessed by the ACQ or Asthma Control Test scores [11, 42, 49, 51, 52], with a recent Cochrane review suggesting that physical training improves asthma control [52].

The majority of studies investigating the role for exercise training in asthma report on quality of life as an outcome measure [11, 42, 63], with a variety of exercise training programmes including constant work rate and high-intensity interval training. Reviews support the positive effect of exercise on quality of life [8, 59, 64, 65].

Exercise training programmes in asthma patients have demonstrated significant improvements in anxiety and depression levels, with improvements in health-related quality of life and symptom scores [43 45, 47].

Potential mechanisms to explain the effect of exercise on symptom scores, quality of life and psychosocial morbidity in asthma

Whether symptom scores reduce through an improvement in disease related inflammation though a more generalised improvement in fitness has not been assessed, and this remains key to targeting of exercise interventions in asthma.

It may be impossible to tease out whether the improvements in quality of life are because of improved symptom control or other changes associated with exercise training. However, it seems that quality of life improvements are among the first [66] and sometimes only significant improvement demonstrated with exercise training [49].

The mechanisms behind improvements in psychosocial morbidity in both children and adults also remain unclear and are most likely multifactorial, with contributions from an increase in post-exercise dopamine expression and improved symptom control. At a mechanistic level, molecular and biochemical changes induced by exercise may underpin improvements in psychological status, with oxidative stress implicated in depression and increased levels of antioxidants seen following antidepressant treatment [67]. A mouse model of asthma has demonstrated that exercise training decreased OVA-induced depression and anxiety

behaviours demonstrated by the mice, as well as increasing antioxidant levels in the lung and hippocampus [68], with the authors suggesting a link between the two.

Exercise training and the obese asthma phenotype

The obese asthma phenotype is emerging as a distinct group of patients that demonstrate poorer asthma control, reduced treatment responsiveness, and increased asthma severity and exacerbation rates [69].

Exercise interventions in obese asthma in children

Exercise interventions in obese and overweight children with asthma have demonstrated a reduction in BMI and improvements in maximal fitness as assessed by maximal oxygen uptake [40], lung function and quality of life [34]. Given the associated weight loss, it is difficult to distinguish whether these improvements are weight related or asthma related. Inflammatory markers have not been assessed in conjunction with this.

Exercise interventions in obese asthma in adults

There are some small studies to support the role for exercise training in the adult obese asthma group, with pulmonary rehabilitation demonstrating a reduction in BMI in obese patients, and an improvement in fat-free mass index in both overweight and obese patients, with associated improvements in Asthma Control Test, dyspnoea perception and admission rates [9]. Similarly, a pilot of pulmonary rehabilitation, with exercise in the form of high-intensity intermittent training in obese asthma patients prior to bariatric surgery, demonstrated improved asthma control at surgery when compared to controls [48]. In another group, weight loss of >5% in combination with exercise demonstrated improved symptom scores and a reduction in dynamic hyperinflation [70]. A year-long interdisciplinary intervention that included exercise training in obese asthma patients showed a reduction in asthma severity, improved lung function and increased expression of anti-inflammatory adipokines when compared to controls, with adiponectin identified as an independent factor for the improvement of lung function in both groups [71]. A randomised controlled trial of exercise training in in obese adults with asthma, investigating weight loss *versus* weight loss and exercise intervention, demonstrated that the exercise group achieved increased improvement in symptom scores, weight loss, aerobic capacity, lung function and airway and systemic inflammation [11]. The same study reported improvements in daily step counts in the exercise group, and in sleep latency and efficiency, and a reduced risk of developing obstructive sleep apnoea [47]. Interestingly, a weight loss and exercise intervention demonstrated improvement in symptom scores in addition to a reduction in neutrophilic inflammation within the airways, that in women was related to a reduction in gynoid adipose tissue, whereas in males, reduced neutrophilic inflammation was associated with a reduction in dietary saturated fat [46]. In this study, there was also a reduction in eosinophilic airway inflammation which was only associated with exercise training [46], suggesting that modification of inflammation through exercise is complex and potentially driven through a number of mechanisms.

Potential mechanisms to explain the effect of exercise intervention in obese asthma

The mechanistic link between asthma and obesity remains to be clarified, and there is some question of "chicken and egg"; does the chronic inflammation known to be associated with obesity drive the development of asthma, or is the shortness of breath associated with asthma a driver for reduced levels of activity resulting in increased weight gain and obesity? It seems that within obese asthma there are, as within asthma as a whole, more than one endotype of disease. A recent review suggested that the obesity associated with Th2 high early-onset obese asthma was a consequence of the asthma whereas in Th2 low, later-onset disease, the asthma was more likely a consequence of obesity [72]. These interactions are summarised in figure 1. Either way, it seems that exercise training should be beneficial in this group of patients. Regardless of whether the improvement in inflammatory parameters demonstrated in these studies were a result of reduced BMI and therefore obesity associated inflammatory drive, or a reduction in asthma-driven systemic inflammation, there appears to be a disease-modifying role for exercise in the obese asthma group.

Barriers to exercise in asthma

The first step to design and implement an exercise training programme for asthma patients is to understand what prevents patients with asthma from exercising, despite recommendations in guidelines to do so. Intensity of physical activity has been shown to be associated with increased peak expiratory flow, although causation could not be determined in this cross-sectional study [73], yet even patients with relatively mild disease have been shown to avoid physical activity because they are concerned about triggering asthma symptoms [74]. Asthma severity as assessed by forced expiratory volume in 1 s and methacholine challenge were not predictive of maximal oxygen uptake as a marker of aerobic fitness [74], hence disease burden alone cannot explain reluctance to engage in physical activity.

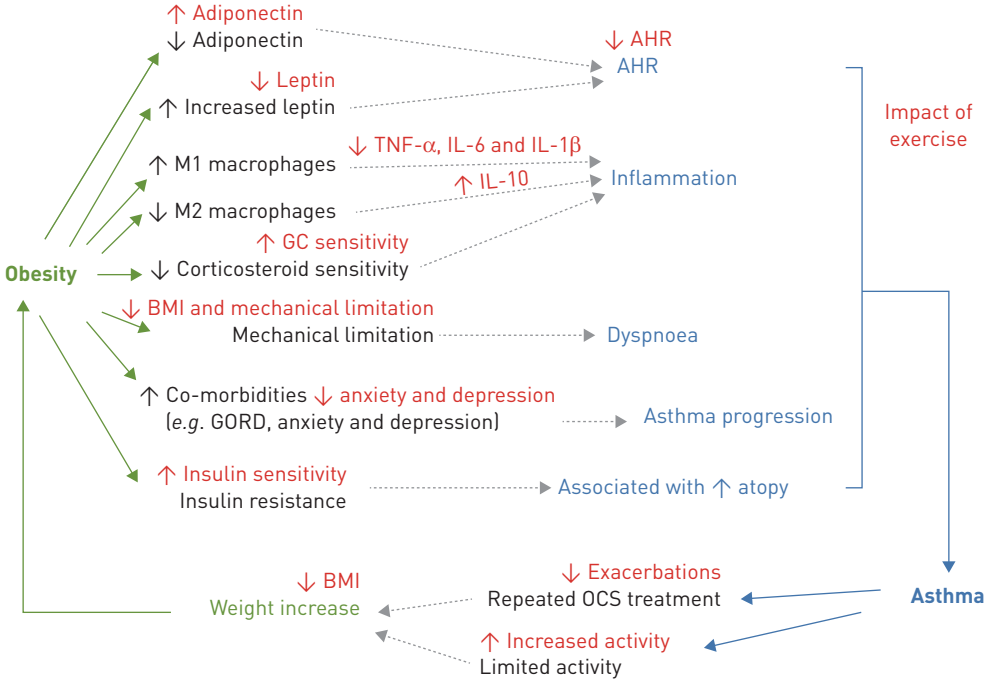

FIGURE 1 The interaction between asthma and obesity. AHR: airway hyperresponsiveness; OCS: oral corticosteroid; BMI: body mass index; GORD: gastro-oesophageal reflux disease; GC: glucocorticoid; TNF: tumour necrosis factor; IL: interleukin.

Barriers to exercise in children with asthma

Relatively few studies have investigated the barriers and facilitators to exercise and physical activity in asthma. The majority of these are in adolescents, partly because asthma tends to affect younger populations at a time when they should be establishing healthy lifestyles, and therefore it is a critical intervention point for encouraging long-term adoption of physical activity. Whilst a cross-sectional review suggests exercise is viewed by parents as beneficial in childhood asthma, with 97% of mothers agreeing, 37% of the same group admitted to imposing restrictions on physical activity with associations with mother's anxiety levels and severity of disease. Interestingly, the restrictive behaviour displayed by some of the mothers were not associated with lower levels of physical activity in their children [75]. Similarly, a study of elementary school teachers demonstrated few were aware that students with asthma need not avoid exercise [76]. Part of parental concern appears to be driven by worry regarding lack of symptom perception in children and lack of trust in school asthma management [77]. Other barriers have also been identified that prevent this group of patients in engaging with physical activity: fear of exacerbating symptoms, with patients with more severe disease more likely to view exercise as detrimental [78], and children's poor adherence to treatment also identified as barriers [77].

Barriers to exercise in adults with asthma

Adult studies similarly suggest that healthy participants and asthma patients think exercise is beneficial [79]. Fear of exacerbating symptom was also a common theme amongst adults [79]. Obesity and musculoskeletal problems, conditions that are common in asthma and exacerbated by oral steroid therapy, were also listed as a reason for not exercising, as were extreme weather conditions [79]. A lack of time is more likely to be reported as a barrier in younger patients [79]. Facilitators included the desire to be healthy and having encouragement from a motivated companion or physician, with lifestyle activities more acceptable to patients as a way to increase their physical activity levels [79]. In terms of intrinsic characteristics, patients with less asthma knowledge, lower self-efficacy and more negative attitudes towards asthma were more likely to view exercise negatively [79], also listed as a reason for not exercising, as were extreme weather conditions [79].

Summary

In summary, the evidence reviewed here supports the role of exercise in delivering wide-ranging health benefits in asthma, in terms of symptom perception, modification of mood, weight management and reduction in inflammation. Exercise could potentially play a key role as a therapeutic strategy in patients' care. Exercise training has the potential to effect improvements in many phenotypes and endotypes of

disease, and we suggest it may be of benefit as part of a repertoire of treatments offered by difficult asthma services, along with other allied healthcare. Engagement with exercise training could be part of the optimisation process prior to biological treatment, with the potential to augment responses to these expensive therapies. We would suggest expanding guideline recommendations regarding exercise to include completion of a prescribed exercise training programme as part of routine management of asthma, with exercise viewed across all severities and endotypes as a standard "treatment" in the way that pulmonary rehabilitation has been incorporated into routine COPD care. Before this can happen, further mechanistic work is required to better elucidate the mechanisms behind the anti-inflammatory effect of exercise in asthma, to allow clarification of the optimal disease-modulating training programme. With regards to the anti-inflammatory benefit, the mechanism through which this is affected needs greater clarification, with a focus on the role of redox regulation. The mechanism of impact on symptom control and quality of life is of most relevance in relation to the anti-inflammatory story: are patients feeling better due to a reduction in disease associated inflammation as opposed to the well-known positive effects of exercise in general? If the psychosocial benefit of exercise is also mediated through a reduction in inflammation, then this has the potential to identify new strategies and medication targets for treating anxiety and depression. In obese asthma, it would be useful to determine whether exercise impacts its effect on the chicken or the egg; on asthma-driven inflammation or inflammation driven by adipose tissue.

Furthermore, given the effects of exercise training interventions on symptom control and fitness appear not to be sustained [39], patients need to adopt exercise as a lifestyle measure rather than a short-term intervention, and this requires improved understanding of the barriers and facilitators to exercise in asthma. Better understanding of these barriers will allow development of patient-centred training programmes to maximise uptake. A definitive study is needed to confirm the benefit of a defined exercise intervention for symptom control and reduction of inflammation in patients with asthma, with mechanistic investigation embedded within this efficacy study. Greater mechanistic understanding may help tailor exercise-based treatments to disease phenotypes, with huge health economic benefits. In the longer term, improved understanding of the immunomodulatory role of exercise in asthma may offer new opportunity to identify future drug targets that lead to improvements in airway inflammation, linking for the first time the benefits of exercise to the development of new pharmacological therapies.

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