Effect of aerobic exercise training on asthma in adults: a systematic review and meta-analysis

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In this meta-analysis, aerobic exercise training improves asthma control and lung function in adults with asthma. The results provide valuable information for healthcare professionals when providing advice regarding exercise training for asthma patients. https://bit.ly/2VrsQMv

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ABSTRACT
Objective: To evaluate the effect of aerobic exercise training on asthma control, lung function and airway inflammation in adults with asthma.
Design: Systematic review and meta-analysis.
Methods: Randomised controlled trials investigating the effect of ⩾8 weeks of aerobic exercise training on outcomes for asthma control, lung function and airway inflammation in adults with asthma were eligible for study. MEDLINE, Embase, CINAHL, PEDro and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to April 3, 2019. Risk of bias was assessed using the Cochrane Risk of Bias Tool.
Results: We included 11 studies with a total of 543 adults with asthma. Participants' mean (range) age was 36.5 (22–54) years; 74.8% of participants were female and the mean (range) body mass index was 27.6 (23.2–38.1) $kg \cdot m^{-2}$. Interventions had a median (range) duration of 12 (8–12) weeks and included walking, jogging, spinning, treadmill running and other unspecified exercise training programmes. Exercise training improved asthma control with a standard mean difference (SMD) of −0.48 (−0.81–−0.16). Lung function slightly increased with an SMD of −0.36 (−0.72–0.00) in favour of exercise training. Exercise training had no apparent effect on markers of airway inflammation (SMD −0.03 (−0.41–0.36)).
Conclusions: In adults with asthma, aerobic exercise training has potential to improve asthma control and lung function, but not airway inflammation.

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This study is registered with PROSPERO ID CRD42019130156. All data relevant to the study are included in the article or uploaded as supplementary information. Data will be available immediately after publication to anyone who wishes to access the data with any purpose, with no end date.

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Introduction

Asthma is one of the most commonly encountered chronic conditions in today's society. Although inhaled anti-asthma medication is effective in most patients, the drugs used in asthma are associated with side-effects [1]. Furthermore, not all adults with asthma take their anti-asthma medication as prescribed. This is due to several reasons ranging from forgetfulness and nonadherence to fear of side-effects and costs [2]. This highlights the need for nonmedical treatment strategies in asthma. Emerging evidence suggests that regular exercise can replace or complement medical treatment for asthma [3]. A meta-analysis performed by Carson *et al.* [4] concluded that exercise training was well tolerated in asthma patients. However, whether regular exercise training is effective as a treatment for symptoms of chronic asthma remains to be verified. Current international treatment guidelines from the Global Initiative for Asthma advise physicians to encourage patients to engage in regular exercise because of its well-known health benefits, but they do not contain information on regular exercise training in the treatment of asthma symptoms *per se* [5]. Previous systematic reviews and meta-analyses investigating the effect of exercise training on asthma-related outcomes included children, adolescents and adults, giving three groups with different phenotypes and potentially different responses to exercise training [4, 6, 7]. Accordingly, since the last meta-analysis in 2013, several randomised controlled trials investigating the effect of regular exercise training on asthma in adults have been performed, calling for an updated review.

Methods

Protocol and registration

The protocol was registered in the international prospective register of systematic reviews (PROSPERO; ID: CRD42019130156). Study selection, assessment of eligibility criteria, data extraction, and statistical analyses were performed based on this predefined protocol according to the Cochrane Collaboration guidelines (www.cochrane-handbook.org): the Methodological Expectations of Cochrane Intervention Reviews (MECIR) project. This article follows Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.

Eligibility criteria

Types of studies

We included randomised controlled trials that compared aerobic exercise training interventions with no intervention. Additionally, studies were considered eligible if the aerobic exercise was the only part of the intervention separating the two groups. In the case of several interventions (multi-arm trials), only data from the aerobic exercise training group *versus* the control group were extracted. Studies using sham and placebo control conditions were considered eligible.

Types of participants

Participants in the studies were adults (aged >18 years) diagnosed with asthma. Eligible studies included participants with "physician-diagnosed asthma" without documentation of a positive bronchial provocation test or reversibility to β_2-agonists.

Types of interventions

We included studies with an aerobic exercise training intervention in adults with asthma. Acceptable exercise training included aerobic exercise performed at least twice a week for ⩾8 weeks, as defined by the American College of Sports Medicine guidelines [8]. All types of aerobic exercise were accepted, including walking, jogging, cycling, rowing, stair-stepping and swimming, and both supervised and nonsupervised interventions were allowed.

Types of outcomes

At least one of the three main outcomes (asthma control, lung function and airway inflammation) had to be reported to be included. Specific outcome measures were determined *a priori* and are presented in appendix B.

Information sources and search

The search strategy used in this study was based on a previous search developed in the most recent Cochrane review in the area by Carson *et al.* [4] and included the following databases: MEDLINE, Embase, CINAHL, PEDro and the Cochrane Central Register of Controlled Trials (CENTRAL). Databases were searched from August 1, 2012 to April 3, 2019. Studies prior to this date were identified through the previous Cochrane review and meta-analysis by Carson *et al.* [4]. A systematic search was used with the terms: "work capacity" OR physical* OR train* OR rehabilitat* OR fitness* or exercis* or aerobic*. Reference lists from retrieved publications were reviewed and reference lists from systematic reviews from the past 5 years were scrutinised. This search could not specifically detect aerobic exercise training; however, it detected a broad variety of exercise studies. Studies were included based on the eligibility criteria as stated earlier.

Study selection

Two authors (E.S.H. Hansen and A. Pitzner-Fabricius) independently assessed studies for potential eligibility. In the case of disagreement, a third party (M. Henriksen) determined whether a study met the inclusion criteria.

Data collection process and data items

We collected data on author, year of publication, number of participants allocated to intervention and control, age, body mass index (BMI), sex, outcome measure, study duration and effect estimates on asthma control, lung function and airway inflammation with standard deviations or confidence limits.

Risk of bias in individual studies

Two reviewers (E.S.H. Hansen and A. Pitzner-Fabricius) independently assessed each included study using the Cochrane risk of bias tool [9]. Risk of bias was stated as high, low or unclear.

Synthesis of results

Effect sizes for main outcomes were expressed as standardised mean differences (SMDs) estimated from the mean follow-up scores and standard deviation from each study. If the standard deviation was not reported, it was estimated from the reported standard error, the 95% confidence interval, interquartile range or p-value related to the pertinent number of participants [10]. If necessary, we approximated mean score and standard deviation from figures in the individual study reports.

Using generic inverse variance analysis, we compared the pooled effect sizes for exercise training and control using a random-effects model allowing for anticipated differences in treatment effects from study to study. For sensitivity purposes, we repeated the analysis using a fixed-effects model to test the robustness of our findings. To facilitate interpretation of SMDs, we used "rule of thumb" cut-offs as proposed by Cohen [11] as follows: 0.2–0.5 (small effect), 0.5–0.8 (moderate effect) and >0.8 (large effect).

We computed homogeneity statistics to evaluate under the null hypothesis that there was no difference in interventions among studies with $k-1$ degrees of freedom where k is the number of studies in the meta-analysis. Inconsistency among studies was evaluated by the inconsistency index (I^2), which is interpreted as variation due to heterogeneity rather than sampling error.

Analysis was performed using Review Manager (version 5 https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman).

Deviations from protocol

Our inclusion criteria were narrower concerning exercise training interventions and study participants compared with the inclusion criteria used in the previous meta-analysis performed by Carson *et al.* [4]. Therefore, databases were searched from their last search date with a 6-month overlap to ensure that all publications were found and studies prior to our search were identified through the previous meta-analysis by Carson *et al.* [4].

Results

Study selection

When combining our search with the search by Carson *et al.* [4], we found 1107 unique records (CENTRAL and PEDro n=1086 and Carson *et al.* n=21 [4]). Of those, 1014 were excluded based on title and abstract, 108 articles were assessed in full and 11 articles were included in the final review and meta-analysis [12–22] (figure 1). We included 11 comparisons in total. Some asthma-related outcomes were not reported in all the included studies. In these cases, the meta-analysis was based on fewer articles.

Study characteristics

At randomisation, the 11 studies included a total of 543 adults diagnosed with asthma, of whom 68 were lost to follow-up, leaving 475 for per-protocol analysis. From the included studies, 10 out of the 11 studies reported the sex of the participants, showing that 74.8% were female (range 56–98%). Furthermore, 10 studies reported age, and the weighted mean (range) age of the participants was 36.5 (22–54) years. The weighted mean (range) BMI across nine of the 11 studies was 27.6 (23.2–38.1) $kg \cdot m^{-2}$.

Asthma severity among participants was characterised as mild to moderate, persistent in two studies, moderate to severe, persistent in six studies and not reported in three studies. Furthermore, average dose

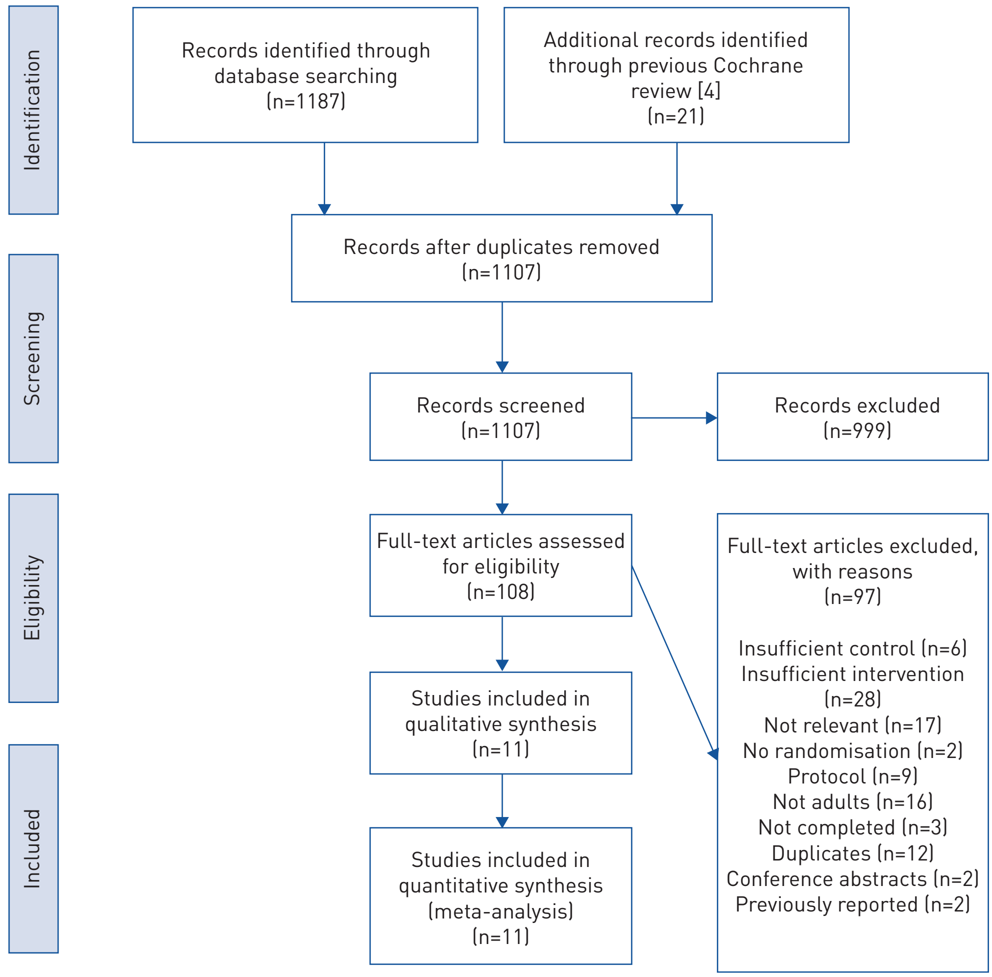

FIGURE 1 Flowchart of study selection process.

of inhaled corticosteroids among participants was reported in seven of the 11 studies, ranging from 700 to 1118 $\mu g \cdot day^{-1}$.

Exercise training and control interventions had a median (range) length of 12 (8–12) weeks. Interventions included both supervised [13–16, 18–22] and unsupervised [12, 17] exercise training. Modes of training included indoor cycling [18], treadmill running [13, 15, 21], walking [17, 22], mixed aerobic exercise [16] and unspecified aerobic exercise [12, 14, 19]. Exercise intensity was reported as percentage of maximal oxygen consumption or maximal heart rate (HR_{max}) in seven studies with a median (range) intensity of 70% (60–75%). One study [18] reported high-intensity interval training (HIIT) with peak HR_{max} >90% in 10-s periods, and two studies [12, 20] did not report exercise intensity (table 1).

Methodological characteristics

The methodological characteristics of the comparisons found that all 11 studies included random allocation of participants (figure 2). Adequate allocation concealment was reported in five (45%) studies [17–21]. No studies had adequate blinding procedures because participants could not be blinded from the exercise training intervention. In six (54%) studies, risk of attrition bias was considered low [12–14, 16, 19, 20]. From the included studies, five (45%) had prespecified protocols registered at www.clinicaltrials.gov or other similar registers [14, 18–21].

Asthma control

From the included studies, seven reported one of the predefined outcomes regarding asthma control [13, 14, 17–21]. The Asthma Control Questionnaire (ACQ) was reported in five studies [17–21] and asthma-related health-related quality of life (HRQoL) was reported in two studies [13, 14]. We observed a difference in asthma control in favour of exercise training (difference in SMD −0.48, 95% CI −0.81–−0.16;

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TABLE 1 Characteristics of included studies

First author, year	Participants: Intervention	Participants: Control	Asthma diagnosis (inclusion criteria)	Asthma status at inclusion	Intervention: Aerobic exercise training	Intervention: Control	Outcome: Asthma control	Outcome: Lung function	Outcome: Airway inflammation
Cochrane, 1990	n=18 Age 27 years Female 61% BMI 24.7 kg·m^{-2}	n=18 Age 28 years Female 61% BMI 23.8 kg·m^{-2}	Prophylactic treatment and positive bronchial challenge to histamine	Severity: mild to moderate, persistent asthma Control: N/A Average ICS dose: N/A	Cycling, jogging and "aerobics" Duration: 3 months Frequency: 3 times per week Supervision: some sessions Intensity: 75% of HR_{max}	No intervention	Not reported	FEV_1	Not reported
Farid, 2005	n=18 Age 27 years Female 56%	n=18 Age 29 years Female 56%	Airway symptoms, positive reversibility to β_2-agonist and decrease in lung function after 6-min walk test	Severity: N/A Control: N/A Average ICS dose: N/A	Unspecified aerobic exercise training Duration: 8 weeks Frequency: 3 times per week Supervision: unknown Intensity: unknown	No intervention	Not reported	FEV_1	Not reported
Gonçalves, 2008	n=10 Age 34.6 years Female 70% BMI 25.8 kg·m^{-2} Dropout 1/10	n=10 Age 34.6 years Female 60% BMI 23.2 kg·m^{-2} Dropout 2/10	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the 2006 GINA report	Severity: moderate to severe, persistent asthma Control: clinically stable Average ICS dose: 700 µg·day^{-1}	Treadmill training, education and breathing exercises Duration: 12 weeks Frequency: 2 times per week Supervision: yes Intensity: 60–70% of HR_{max}	Education and breathing exercises	HRQoL	Not reported	F_{ENO}
Mendes, 2010	n=50 Age 39 years Female 89% BMI 25.2 kg·m^{-2} Dropout 6/50	n=51 Age 40 years Female 78% BMI 24.5 kg·m^{-2} Dropout 6/51	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the 2006 GINA report	Severity: moderate to severe, persistent asthma Control: clinically stable Average ICS dose: 800 µg·day^{-1}	Unspecified aerobic exercise training, breathing exercises and educational programme Duration: 3 months Frequency: 2 times per week Supervision: yes Intensity: 60–70% of HR_{max}	Breathing exercises and educational programme	HRQoL	FEV_1	Not reported

Continued

TABLE 1 Continued

First author, year	Participants: Intervention	Participants: Control	Asthma diagnosis (inclusion criteria)	Asthma status at inclusion	Intervention: Aerobic exercise training	Intervention: Control	Outcome: Asthma control	Outcome: Lung function	Outcome: Airway inflammation
Shaw, 2011	n=22 Age 22 years	n=22 Age 22 years	Airway symptoms and peak flow variability >30%	Severity: moderate to severe, persistent asthma Control: clinically stable Average ICS dose: 800 $\mu g \cdot day^{-1}$	Jogging/walking Duration: 8 weeks Frequency: 3 times per week Supervision: yes Intensity: 60–65% of HR_{max}	No intervention	Not reported	FEV_1	Not reported
Mendes, 2011	n=34 Age 38 years Female 89% BMI 24.5 $kg \cdot m^{-2}$ Dropout 7/34	n=34 Age 36 years Female 75% BMI 25.8 $kg \cdot m^{-2}$ Dropout 10/34	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the 2006 GINA report	Severity: moderate, persistent asthma Control: uncontrolled (daily symptoms and nocturnal symptoms) Average ICS dose: N/A	Treadmill training, education and breathing exercises Duration: 12 weeks Frequency: 2 times per week Supervision: yes Intensity: 60–80% of HR_{max}	Education and breathing exercises	Not reported	FEV_1	F_{ENO}
Boyd, 2012	n=10 Age 53 years Female 88% BMI 30.6 $kg \cdot m^{-2}$ Dropout 2/10	n=9 Age 54 years Female 100% BMI 32.5 $kg \cdot m^{-2}$ Dropout 1/9	Airway symptoms and positive reversibility to β_2-agonist. Based on the 2002 NAEPP guidelines	Severity: mild to moderate, persistent asthma Control: N/A Average ICS dose: N/A	Walking Duration: 12 weeks Frequency: 3 times per week Supervision: no, monitored Intensity: 60–75% of HR_{max}	No intervention	ACQ	FEV_1	Not reported
Scott, 2013	n=14 Age 33.9 years Female 53% BMI 32.7 $kg \cdot m^{-2}$ Dropout 1/14	n=18 Age 44.7 years Female 53% BMI 34.7 $kg \cdot m^{-2}$ Dropout 3/18	Doctor's diagnosis of asthma and documentation of airway hyperresponsiveness	Severity: N/A Control: N/A Average ICS dose: 1000 $\mu g \cdot day^{-1}$	Gym membership and intermittent personal training sessions and a diet intervention Duration: 12 weeks Frequency: 3 times per week Supervision: once a week Intensity: unknown	Diet intervention	ACQ	FEV_1	Sputum eosinophils

Continued

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TABLE 1 Continued

First author, year	Participants: Intervention	Participants: Control	Asthma diagnosis (inclusion criteria)	Asthma status at inclusion	Intervention: Aerobic exercise training	Intervention: Control	Outcome: Asthma control	Outcome: Lung function	Outcome: Airway inflammation
França-Pinto, 2014	n=30 Age 40 years Female 77% BMI 26.5 kg·m^{-2} Dropout 8/30	n=28 Age 44 years Female 81% BMI 26.4 kg·m^{-2} Dropout 7/28	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the 2006 GINA report	Severity: moderate to severe, persistent asthma Control: clinically stable Average ICS dose: 857 µg·day^{-1}	Treadmill training and breathing exercises Duration: 12 weeks Frequency: 2 times per week Supervision: yes Intensity: vigorous training based on anaerobic threshold	Breathing exercises	ACQ-6	FEV_1	F_{ENO}
Toennesen, 2017	n=36 Age 39.4 years Female 45% BMI 24.9 kg·m^{-2} Dropout 7/36	n=38 Age 38.2 years Female 76% BMI 25.5 kg·m^{-2} Dropout 4/38	Airway symptoms and reversibility to β_2-agonist or airway hyperresponsiveness	Severity: N/A Control: ACQ $\geqslant$1.0 Average ICS dose: 692 µg·day^{-1}	Indoor cycling Duration: 8 weeks Frequency: 3 times per week Supervision: yes Intensity: HIIT up to 90% of maximal intensity	No intervention	ACQ-5	FEV_1	F_{ENO}
Freitas, 2017	n=28 Age 46 years Female 96% BMI 38.1 kg·m^{-2} Dropout 2/28	n=27 Age 49 years Female 100% BMI 37.2 kg·m^{-2} Dropout 2/27	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the 2006 GINA report	Severity: moderate to severe persistent asthma Control: clinically stable Average ICS dose: 1118 µg·day^{-1}	Unspecified aerobic exercise training and hypocaloric diet Duration: 3 months Frequency: 2 times per week Supervision: yes Intensity: 50–75% of peak V'_{O_2max}	Sham exercise and hypocaloric diet	ACQ	FEV_1	F_{ENO}

Doses of inhaled corticosteroids (ICS) are reported as budesonide-equivalent in µ·day^{-1}. BMI: body mass index; N/A: not available; HR_{max}: maximal heart rate; FEV_1: forced expiratory volume in 1 s; GINA: Global Initiative for Asthma; HRQoL: health-related quality of life; F_{ENO}: fraction of exhaled nitric oxide; NAEPP: National Asthma Education and Prevention Program; ACQ: Asthma Control Questionnaire; HIIT: high-intensity interval training; V'_{O_2max}: maximal oxygen consumption.

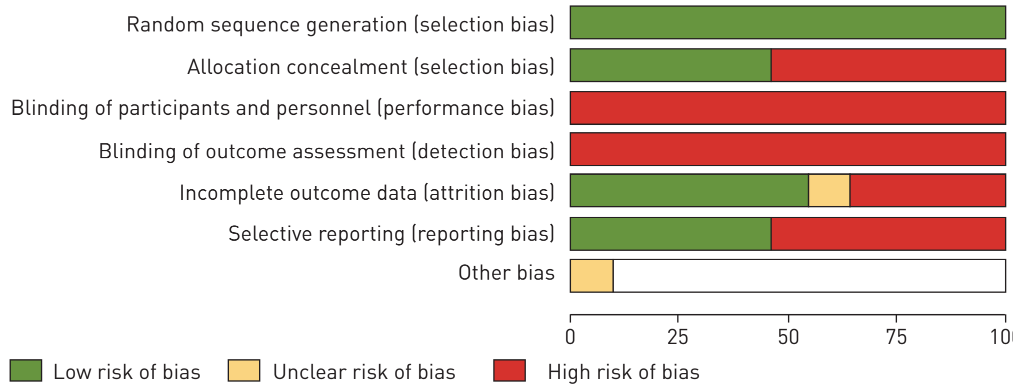

FIGURE 2 Graphical summary of the risk of bias in the included studies.

p=0.004) (figure 3). The heterogeneity across studies was considerable (I^2=45%). The sensitivity analyses (fixed effects) showed similar results (appendix F).

Lung function

Of the included studies, 10 reported lung function [12, 14–22]. All 10 studies reported forced expiratory volume in 1 s (FEV_1) in litres or percentage predicted. In the studies from Mendes *et al.* (2011 [15] and 2010 [14]), 26 participants overlapped with no specification of group allocation in the two studies. Thus, a correction was made by reducing the number of participants in Mendes *et al.* [15] equally in both the intervention group and the control group. No further corrections were made on other outcomes.

We observed a difference in favour of exercise training (SMD −0.36, 95% CI −0.72–0.00; p=0.05) with considerable heterogeneity I^2=69% (figure 4). The fixed effect analysis (sensitivity analysis) showed similar results (appendix G).

Airway inflammation

Of the included studies, six reported one of the predefined surrogate markers for airway inflammation [13, 15, 18–21]. Of the six studies, all but one study reported exhaled nitric oxide fraction (F_{ENO}). The single study not reporting F_{ENO} reported sputum eosinophils [20]. There was no difference in SMD relating to airway inflammation (SMD −0.03, 95% CI −0.41–0.36; p=0.89) with considerable heterogeneity I^2=56% across studies (figure 5). The sensitivity analysis (fixed effects) showed similar results (appendix H).

Discussion

Summary of key findings

This systematic review and meta-analysis points to beneficial effects of aerobic exercise training on asthma control and lung function, but no effect on markers of local airway inflammation. Thus, the results indicate that symptom control can be achieved through exercise training without a reduction in

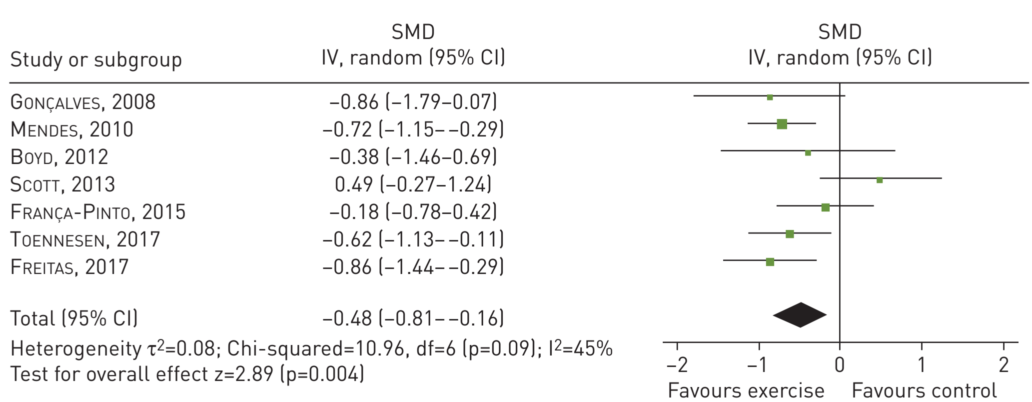

FIGURE 3 Forest plot of the meta-analysis of the effect of exercise training on asthma control. SMD: standard mean difference; IV: inverse variance.

Study or subgroup	SMD IV, random (95% CI)
Boyd, 2012	−0.52 (−1.61–0.56)
Cochrane, 1990	0.14 (−0.52–0.79)
Farid, 2005	−2.26 (−3.11–−1.40)
França-Pinto, 2015	−0.27 (−0.87–0.33)
Freitas, 2017	−0.58 (−1.14–−0.02)
Mendes, 2010	0.15 (−0.27–0.56)
Mendes, 2011	0.11 (−0.68–0.90)
Scott, 2013	−0.16 (−0.90–0.58)
Shaw, 2011	−0.46 (−1.06–0.14)
Toennesen, 2017	−0.22 (−0.72–0.28)
Total (95% CI)	−0.36 (−0.72–0.00)

Heterogeneity τ^2=0.22; Chi-squared=28.81, df=9 (p=0.0007); I^2=69%
Test for overall effect z=1.95 (p=0.05)

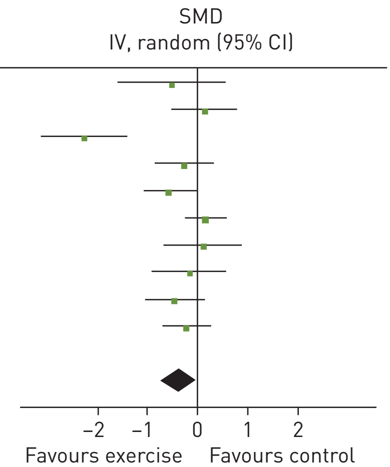

FIGURE 4 Forest plot of the meta-analysis of the effect of exercise training on lung function. SMD: standard mean difference; IV: inverse variance.

inflammation. However, the between-study heterogeneity, methodological limitations and the imprecision of the pooled SMDs make the interpretation of the evidence challenging.

Strengths and limitations

A strength of this study is that we included patient-reported outcomes. To make research more patient-centred, it is critical that patient-reported outcomes are included when evaluating whether a treatment should be recommended. Some of the included patient-reported outcomes regarding asthma control in this study were asthma-related quality-of-life questionnaires such as QQL-EPM. Studies comparing the Asthma Quality of Life Questionnaire and the ACQ showed that there was a distinct correlation between quality of life and asthma control for both questionnaires (Pearson correlation coefficient 0.64–0.69) [23]. As a result, we assumed that the different quality-of-life questionnaires used in asthma cover the same underlying constructs as do the specific asthma control questionnaires. This may limit the interpretation of the results.

Although our results suggest that aerobic exercise training is beneficial for adults with asthma, our findings should be interpreted with caution. When systematically assessing the quality of the evidence, we found that the included studies had several methodological limitations. Additionally, the between-study heterogeneity, imprecision and inconsistency were considerable, and the overall risk of bias within each study was high because of the impossibility of blinding an exercise intervention. Together, these limitations lower the confidence in the results and, consequently, the quality of the evidence is low.

In our meta-analysis, we treated the exercise training interventions in the included studies as a single group. It should be noted that differences in type, duration and intensity of the exercise training regimens undertaken most likely explain part of the between study heterogeneity. Moreover, compliance with the exercise interventions was often not reported, making it difficult to evaluate any dose–response relationships.

Study or subgroup	SMD IV, random (95% CI)
Gonçalves, 2008	−0.74 (−0.17–1.66)
Mendes, 2011	−0.75 (−1.32–−0.18)
Scott, 2013	0.16 (−0.59–0.90)
França-Pinto, 2015	0.25 (−0.35–0.85)
Freitas, 2017	−0.32 (−0.87–0.23)
Toennesen, 2017	0.11 (−0.39–0.60)
Total (95% CI)	−0.03 (−0.41–0.36)

Heterogeneity τ^2=0.12; Chi-squared=11.26, df=5 (p=0.05); I^2=56%
Test for overall effect z=0.13 (p=0.89)

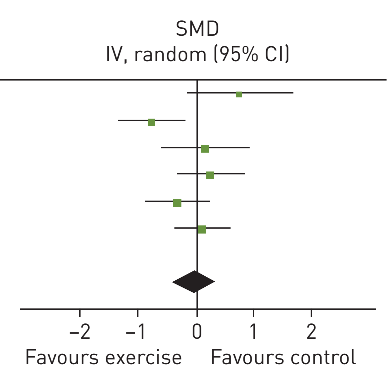

FIGURE 5 Forest plot of the meta-analysis of the effect of exercise training on airway inflammation. SMD: standard mean difference; IV: inverse variance.

Strengths and weaknesses in relation to other studies

In contrast to the previous review and meta-analysis performed by Carson *et al.* [4], we included only adults with asthma. We consider this important because asthma often differs between adults and children. This was illustrated in a phenotype cluster analysis by Haldar *et al.* [7], in which they described adults with asthma and the late-onset phenotype with low inflammation, severe symptoms and poor medication response. However, children with asthma often experienced early onset of symptoms, severe inflammation and excellent treatment effect of inhaled corticosteroids. Consequently, this meta-analysis, including only adults, provides pooled evidence for a more homogenous population. In support of this claim, we found a significant increase in lung function after an exercise intervention compared with Carson *et al.* [4], who showed no effect of exercise on lung function (SMDs −0.36 *versus* −0.00). However, in our meta-analysis, one study by Farid *et al.* [12] reported a considerable increase in lung function. This study was not included in the meta-analysis by Carson *et al.* [4] and when it was excluded from our analysis, results were more in line with those of Carson *et al.* (SMD −0.16 in favour of exercise training).

A potential limitation of our study is that we did not include resistance training. Recent data indicate that concurrent aerobic and resistance exercise training improves COPD outcomes, raising the possibility that a combination of these exercise regimes would be favourable in asthma as well [24]. However, despite being on the same disease spectrum, asthma and COPD have markedly different aetiology, pathology and histology, and this makes the comparison challenging.

Interpretation and explanation of key findings

Asthma control was found to be improved (SMD −0.48) after a period of exercise training, which corresponds to a small effect size [11]. However, as judged by the precision of the estimated SMD (95% CI) the true effect size is uncertain as the lower 95% CI limit suggests no effect and the upper limit suggests a large effect size. One of the few studies that individually showed a clinically significant change in asthma control (ACQ reduction from 2.0 to 1.4) after a training intervention also included a weight loss programme for both the intervention group and the control group [19]. This presents the possibility that combined exercise and diet and/or weight-loss interventions may be more effective than exercise alone. This is further supported by the multi-arm study by Toennesen *et al.* [18], which showed that the group who received both diet and HIIT was the only one to significantly improve asthma control compared with the control group (ACQ reduction from 1.9 to 1.0 *versus* 1.8 to 1.5). In addition, the participants in the exercise and diet group lost more weight than those in the exercise group. Several factors influence the subjective experience of asthma control and thus the optimal solution probably includes a more general lifestyle change where patients move from a sedentary lifestyle to a lifestyle with healthy choices combined with increased levels of daily physical activity. Nevertheless, the results of this study indicate that aerobic exercise training alone (without concomitant diet or weight loss) may improve asthma control (ACQ reduction from 1.7 to 1.0).

Lung function improved after an exercise intervention (SMD −0.36 corresponding to a small effect size). However, as judged by the precision of the estimated SMD (95% CI), the true effect size is uncertain as the lower 95% CI limit suggests no effect and the upper limit suggests a large effect size. To our knowledge, this is the first meta-analysis to document a beneficial effect of exercise training on lung function in adults with asthma. It is possible that other factors, such as adherence to asthma medication and performance bias due to inadequate blinding, could be the cause of the improvement. However, between-group heterogeneity was not considered as a cause of the difference based on pre-intervention FEV_1 values, which showed no difference between the groups. The effect on lung function in the included studies was generally not clinically significant. However, the reported effect is similar to the effect of expensive biological treatments used in asthma [25].

We observed no effect of exercise training on airway inflammation, most frequently measured by F_{ENO} (SMD −0.03), despite an increase in asthma control and lung function, suggesting that other factors or mechanisms are involved. It is possible that other measures of airway inflammation (sputum eosinophils and neutrophils) are more sensitive to exercise interventions. Another explanation could be that all participants in the included studies were treated with inhaled corticosteroids throughout the study period.

Implications for clinicians and research

Despite the limitations of the studies included, this systematic review and meta-analysis provides an informative summary of the effectiveness of aerobic exercise training in adults with asthma, which may guide clinical discussions and decisions. It should be noted that asthma severity in the included studies was generally moderate to severe with an ICS dosage of 700–1118 $\mu g \cdot day^{-1}$, which suggests that aerobic exercise is a good adjuvant asthma therapy. Additionally, the patients in the included studies were aged 20–50 years, overweight or obese and predominantly female, but it is unknown whether these characteristics influence the effect of exercise. Furthermore, for patients to experience the reported effect of exercise on asthma as well as general health, patients should be encouraged to follow the American College of Sports Medicine guidelines for aerobic exercise, as they provide the main inclusion criteria for interventions in this study.

The effect size estimates are imprecise and further high-quality studies are needed to strengthen our confidence in the effect of exercise. Future studies should focus on determining the effectiveness of different types, intensities and frequencies of exercise, as well as the potential beneficial effect of combined resistance and aerobic training. Moreover, new high-quality studies with a translational perspective on exercise and asthma are warranted to increase confidence in exercise as medicine, and ultimately to forward understanding of the mechanisms behind the effects.

In conclusion, a lifestyle intervention with aerobic exercise training has potential to improve asthma control and lung function in adults with asthma. Against this background, healthcare professionals should inform adults with asthma about the potential benefits of regular exercise training. However, the quality of the evidence is low, and future well-designed, strictly controlled studies are warranted to determine the effects of exercise training on asthma as well as the underlying mechanisms.

Author contributions: E.S.H. Hansen, V. Backer and M. Henriksen developed the initial protocol. All authors made relevant changes to the protocol before submission to PROSPERO. E.S.H. Hansen, A. Pitzner-Fabricius and M. Henriksen performed the literature search and initial data analysis. E.S.H. Hansen was responsible for the initial manuscript. V. Backer, A. Pitzner-Fabricius, Y. Hellsten, M. Hostrup, L.L. Toennsen and H.K. Rasmusen contributed to the interpretation of data and manuscript writing. All authors approved the final manuscript before submitting for publication. E.S.H. Hansen, V. Backer and M. Henriksen take full responsibility for the results. E.S.H. Hansen, V. Backer and M. Henriksen affirm that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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