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Original article

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Effect of aerobic exercise training on asthma in adults

A systematic review and meta-analysis

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Summary

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.

Keywords

Asthma, Aerobic exercise training, Adults, Asthma control, Lung function, Airway inflammation

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 (PROSPERO-ID: CRD42019130156)

Methods:

Eligibility criteria: Randomised controlled trials investigating the effect of at least 8 weeks of aerobic exercise training on outcomes for asthma control, lung function and airway inflammation in adults with asthma.

Information sources: Medline, EMBase, CINAHL, PEDro, Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to 3 April 2019.

Risk of bias: Risk of bias was assessed by the "Cochrane Risk of Bias Tool".

Results:

Included studies: We included 11 studies with a total of 543 adults with asthma. Participants' mean age was 36.5 years (range: 22 to 54 years); 74.8% of participants were women and the mean body mass index (BMI) was 27.6 kg/m^2 (range: 23.2 to 38.1 kg/m^2). Interventions had a median duration of 12 weeks (range: 8 to 12 weeks) and included walking, jogging, spinning, treadmill running and other unspecified exercise training programmes.

Synthesis of results: Exercise training improved asthma control with a standard mean difference (SMD) of -0.48 (-0.81 to -0.16). Lung function slightly increased with an SMD of -0.36 (-0.72 to 0.00) in favour of exercise training. Exercise training had no apparent effect on markers of airway inflammation [SMD: -0.03 (-0.41 to 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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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). Further, not all adults with asthma take their anti-asthma medication as prescribed. This is due to several reasons ranging from forgetfulness and non-adherence to fear of side effects and costs(2). This highlights the need for non-medical 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. (2013) concluded that exercise training was well tolerated in asthma patients(4). However, whether regular exercise training is effective as treatment for symptoms of chronic asthma remains to be verified. Current international treatment guidelines from the Global Initiative for Asthma (GINA) 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 (http://www.cochrane–handbook.org): the '*Methodological Expectations of Cochrane Intervention Reviews*' (MECIR) project. The manuscript is reported following the guidelines from the PRISMA statement.

Eligibility criteria

Types of studies

We included randomised controlled trials comparing 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 vs. the control group were extracted. Studies using sham and placebo control conditions were also considered eligible.

Types of participants

Participants in the studies were adults (>18 years of age) diagnosed with asthma. Studies were eligible that included participants with "physician-diagnosed asthma" without documentation of a positive bronchial provocation test or reversibility to $beta_2$-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 at least 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 non-supervised 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. (4) and included the following databases: Medline, EMBase, CINAHL, PEDro, Cochrane Central Register of Controlled Trials (CENTRAL). Databases were searched from 1 August 2012 to 3 April 2019. Studies prior to this date were identified through the previous Cochrane review and meta-analysis by Carson. (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 last 5 years were scrutinized. 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 above.

Study selection

Two authors (ESH and APF) independently assessed studies for potential eligibility. In the case of disagreement, a third party (MH) 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, 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 (ESH and APF) 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 (SD) from each study. If the SD was not reported, it was estimated from the reported standard error (SE), the 95% confidence interval (95% CI), inter-quartile-range (IQR), or P-value related to the pertinent number of participants(10). If necessary, we approximated mean score and SD 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 1988 as follows: 0.2–0.5 small effect, 0.5–0.8 moderate effect and > 0.8 large effect(11).

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 will be interpreted as variation due to heterogeneity rather than sampling error.

Analysis was performed using Review Manager (Version 5 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2008).

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 done by Carson et al.(4). Therefore, databases were searched from their last search date with a 6-month overlap to ensure 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 from Carson et al., we found 1107 unique records (CENTRAL and PEDRO 1086 and Carson et al. 21). From 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.

Figure 1: Flowchart of study selection process

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 of the 11 studies reported the sex of the participants, showing that 74.8% were women (range: 56 to 98%). Further, 10 reported age and the weighted mean age of the participants was 36.5 years (range: 22 to 54 years). The weighted mean BMI across 9 of the 11 studies was 27.6 kg/m^2 (range: 23.2 to 38.1 kg/m^2).

Asthma severity among participants was characterised as mild to moderate, persistent in 2 studies, moderate to severe, persistent in 6 studies and not reported in 3 studies. Furthermore, average dose of inhaled corticosteroids among participants was reported in 7 of the 11 studies, ranging from 700 to 1118 mcg/day.

Exercise training and control interventions had a median length of 12 weeks (range: 8 to 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 % of maximal oxygen consumption (VO_2max) or maximal heart rate (HRmax) in seven studies with a median intensity of 70% (range: 60 to 75%). One study (18) reported high-intensity interval training (HIIT) with peak HRmax over 90% in 10 second periods, and two studies (12,20) did not report exercise intensity (Table 1).

Table 1: Characteristics of included studies

Study	Participants (Intervention)	Participants (Control)	Asthma diagnosis (inclusion criteria)	Asthma status at inclusion	Intervention (aerobic exercise training)	Control intervention	Outcome (Asthma control)	Outcome (Lung function)	Outcome (Airway inflammation)
Cochrane 1990	N= 18 Age: 27 % Female: 61 BMI: 24.7 Drop-out: -	N= 18 Age: 28 % Female: 61 BMI: 23.8 Drop-out: -	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 HRmax*	No intervention	Not reported	FEV_1	Not reported
Farid 2005	N= 18 Age: 27 % Female: 56 BMI: - Drop-out: -	N= 18 Age: 29 % Female: 56 BMI: - Drop-out: -	Airway symptoms, positive reversibility to $beta_2$-agonist and decrease in lung function after a 6-minute walk test.	Severity: *N/A* Control: *N/A* Average ICS-dose: *N/A*	Unspecified aerobic exercise training *8 weeks* *3 times per week* *Supervision: Unknown* *Intensity: Unknown*	No intervention	Not reported	FEV_1	Not reported
Goncalves 2008	N= 10 Age: 34.6 % Female: 70 BMI: 25.8 Drop-out: 1/10	N= 10 Age: 34.6 % Female: 60 BMI: 23.2 Drop-out: 2/10	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the GINA-report from 2006.	Severity: *Moderate to severe, persistent asthma* Control: *Clinically stable* Average ICS-dose: *700 mcg/day*	Treadmill training, education and breathing exercises *Duration: 12 weeks* *Frequency: 2 times per week* *Supervision: Yes* *Intensity: 60-70% of HRmax*	Education and breathing exercises	HRQoL	Not reported	FeNO
Mendes 2010	N= 50 Age: 39 % Female: 89 BMI: 25.2 Drop-out: 6/50	N= 51 Age: 40 % Female: 78 BMI: 24.5 Drop-out: 6/51	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the GINA-report from 2006.	Severity: *Moderate to severe, persistent asthma* Control: *Clinically stable* Average ICS-dose: *800 mcg/day*	Unspecified aerobic exercise training, breathing exercises and educational programme *Duration: 3 months* *Frequency: 2 times per week* *Supervision: Yes* *Intensity: 60-70% of HRmax*	Breathing exercises and educational programme	HRQoL	FEV_1	Not reported
Shaw 2011	N= 22 Age: 22 % Female: - BMI: - Drop-out: -	N= 22 Age: 22 % Female: - BMI: - Drop-out: -	Airway symptoms and peak flow-variability > 30%.	Severity: *Moderate to severe, persistent asthma* Control: *Clinically stable* Average ICS-dose:	Jogging/Walking *Duration: 8 weeks* *Frequency: 3 times per week* *Supervision: Yes* *Intensity: 60-65% of*	No intervention	Not reported	FEV_1	Not reported

				800 mcg/day	*HRmax*				
Mendes 2011	N= 34 Age: 38 % Female: 89 BMI: 24.5 Drop-out: 7/34	N= 34 Age: 36 % Female: 75 BMI: 25.8 Drop-out: 10/34	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the GINA-report from 2006.	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 HRmax*	Education and breathing exercises	Not reported	FEV_1	FeNO
Boyd 2012	N= 10 Age: 53 % Female: 88 BMI: 30.6 Drop-out: 2/10	N= 9 Age: 54 % Female: 100 BMI: 32.5 Drop-out: 1/9	Airway symptoms and positive reversibility to $beta_2$-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 HRmax*	No intervention	ACQ	FEV_1	Not reported
Scott 2013	N= 14 Age: 33.9 % Female: 53 BMI: 32.7 Drop-out: 1/14	N= 18 Age: 44.7 % Female: 53 BMI: 34.7 Drop-out: 3/18	Doctor's diagnosis of asthma and documentation of airway hyper-responsiveness.	Severity: *N/A* Control: *N/A* Average ICS-dose: *1000 mcg/day*	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
Franca-Pinto 2014	N= 30 Age: 40 % Female: 77 BMI: 26.5 Drop-out: 8/30	N= 28 Age: 44 % Female: 81 BMI: 26.4 Drop-out: 7/28	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the GINA-report from 2006.	Severity: *Moderate-severe persistent asthma* Control: *Clinically stable* Average ICS-dose: *857 mcg/day*	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	FeNO

Tønnesen 2017	N= 36 Age: 39.4 % female: 45 Bmi: 24.9 Drop-out: 7/36	N= 38 Age: 38.2 % female: 76 Bmi: 25.5 Drop-out: 4/38	Airway symptoms and reversibility to beta$_2$-agonist or airway hyperresponsiveness.	Severity: *N/A* Control: *ACQ ≥ 1.0* Average ICS-dose: *692 mcg/day*	Indoor cycling *Duration: 8 weeks* *Frequency: 3 times per week* *Supervision: yes* *intensity: high-intensity interval training up to 90% of maximal intensity.*	No intervention	Acq-5	Fev$_1$	Feno
Freitas 2017	N= 28 Age: 46 % Female: 96 BMI: 38.1 Drop-out: 2/28	N= 27 Age: 49 % Female: 100 BMI: 37.2 Drop-out: 2/27	Airway symptoms and prophylactic treatment with ICS. Diagnosis based on the GINA-report from 2006.	Severity: *Moderate to severe persistent asthma* Control: *Clinically stable* Average ICS-dose: *1118 mcg/day*	Unspecified aerobic exercise training and hypocaloric diet *Duration: 3 months* *Frequency: 2 times per week* *Supervision: Yes* *Intensity: 50-75% of peak VO$_2$*	Sham exercise and hypocaloric diet	ACQ	FEV$_1$	FeNO

Table 1: Description of the included studies. Doses of inhaled corticosteroids (ICS-dose) are reported as budesonide-equivalent in micrograms/day. N, number of participants; BMI, body mass index; ICS, Inhaled corticosteroids; HRQoL, Health-Related Quality of Life; FEV$_1$, forced expiratory volume in one second; HRmax, maximal heart rate; FeNO, fraction of exhaled nitric oxide; VO2, oxygen consumption; GINA, Global Initiative for Asthma; NAEPP, National institute for health expert panel report.

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 pre-specified protocols registered at www.clinicaltrials.gov or other similar registers (14,18–21).

Figure 2: Graphical summary of the risk of bias in the included studies

Asthma control

From the included studies, seven reported one of the predefined outcomes regarding asthma control (13,14,17–21). 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 to -0.16); P = 0.004; Figure 3). The heterogeneity across studies was considerable (I^2 = 45%). The sensitivity analyses (fixed effects) showed similar results (Appendix F).

Figure 3: Forest plot of the meta-analysis of the effect of exercise training on asthma control

Lung function

From the included studies, 10 reported lung function (12,14–22). All 10 studies reported FEV_1 in litres or % of 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 2011 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).

Figure 4: Forest plot of the meta-analysis of the effect of exercise training on lung function

Airway inflammation

From the included studies, six reported one of the predefined surrogate markers for airway inflammation(13,15,18–21). From the six studies, all but one study reported fraction of exhaled nitric oxide (FeNO). The single study not reporting FeNO reported sputum eosinophils(20). There was no difference in SMD relating to airway inflammation (SMD: -0.03 (95%CI: -0.41 to 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).

Figure 5: Forest plot of the meta-analysis of the effect of exercise training on asthma control

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 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 HRQoL. 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 to 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.

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 describe adults with asthma and the late-onset phenotype with low inflammation, severe symptoms and poor medication response. Children with asthma, however, 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., who showed no effect of exercise on lung function(4) (SMDs: -0.36 vs -0.00). However, in our meta-analysis, one study by Farid et al. reported a considerable increase in lung function. This study was not included in the meta-analysis by Carson et al. and when excluding it 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 chronic obstructive pulmonary disease (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 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 high-intensity interval training was the only one who significantly improved asthma control compared with the control group (ACQ reduction from 1.9 to 1.0 vs 1.8 to 1.5). In addition, the participants in the exercise and diet group lost more weight than did 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 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 biologic treatments used in asthma(25).

We observed no effect of exercise training on airway inflammation, most frequently measured by FeNO (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 ICS throughout the complete 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 mcg/day, which suggests that aerobic exercise is a good adjuvant asthma therapy. Additionally, the patients in the included studies were 20–50-year-olds, overweight or obese and with a majority of women, but it is unknown whether these characteristics influence the effect of exercise. Further, 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. On 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

ESH, VB and MH developed the initial protocol. All authors made relevant changes to the protocol before submission to PROSPERO. ESH, APF and MH performed the literature search and initial data analysis. ESH was responsible for the initial manuscript. VB, APF, YH, MH, LT and HR contributed to the interpretation of data and manuscript writing. All authors approved the final manuscript before submitting for publication. ESH, VB and MH take full responsibility for the results.

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Transparency declaration

ESH, VB and MH 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.

Ethical approval

Ethical approval was not required for this study.

Competing interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organisation for the submitted work; Professor Henriksen reports personal fees from Thuasne; Dr. Backer reports grants, personal fees and other from GSK, grants, personal fees and other from Chiesi, grants, personal fees and

other from Novartis, grants, personal fees and other from AstraZeneca, grants, personal fees and other from Sanofi, grants, personal fees and other from MSD, grants, personal fees and other from TEVA outside the submitted work. Otherwise, there were no financial relationships over the previous three years with any organisations that might have an interest in the submitted work; and no other relationships or activities that could appear to have influenced the submitted work.

Data sharing

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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Appendix A: Search

Asthma search

1. exp Asthma/ 2. asthma$.mp. 3. (antiasthma$ or anti-asthma$).mp. 4. Respiratory Sounds/ 5. wheez$.mp. 6. Bronchial Spasm/ 7. bronchospas$.mp. 8. (bronch$ adj3 spasm$).mp. 9. bronchoconstrict$.mp. 10. exp Bronchoconstriction/ 11. (bronch$ adj3 constrict$).mp. 12. Bronchial Hyperreactivity/ 13. Respiratory Hypersensitivity/ 14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp. 15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp. 16. or/1-15

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Filter to identify RCTs

1. exp "clinical trial [publication type]"/ 2. (randomised or randomized).ab,ti. 3. placebo.ab,ti. 4. dt.fs. 5. randomly.ab,ti. 6. trial.ab,ti. 7. groups.ab,ti. 8. or/1-7 9. Animals/ 10. Humans/ 11. 9 not (9 and 10) 12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix B: Prioritised, predefined outcome-hierarchy

A prioritized list of outcome measures		
Asthma control	**Lung function**	**Local airway inflammation**
1. Asthma Control Questionnaire-5 2. Asthma Control Questionnaire-6 3. Asthma Control Questionnaire-7 4. Asthma Control Test 5. Asthma Quality of Life Questionnaire 6. Asthma specific HRQoL	1. Forced expiratory volume in 1 second 2. Forced vital capacity 3. Tiffaneu Index (FEV1/FVC)	1. FeNO 2. Sputum eosinophilia and neutrophilia

Appendix C: Table of outcomes from each included study on asthma control

Attached file

Appendix D: Table of outcomes from each included study on lung function

Attached file

Appendix E: Table of outcomes from each included study on airway inflammation

Attached file

Appendix F: Forest plot of the meta-analysis on the fixed effect of exercise training on asthma control

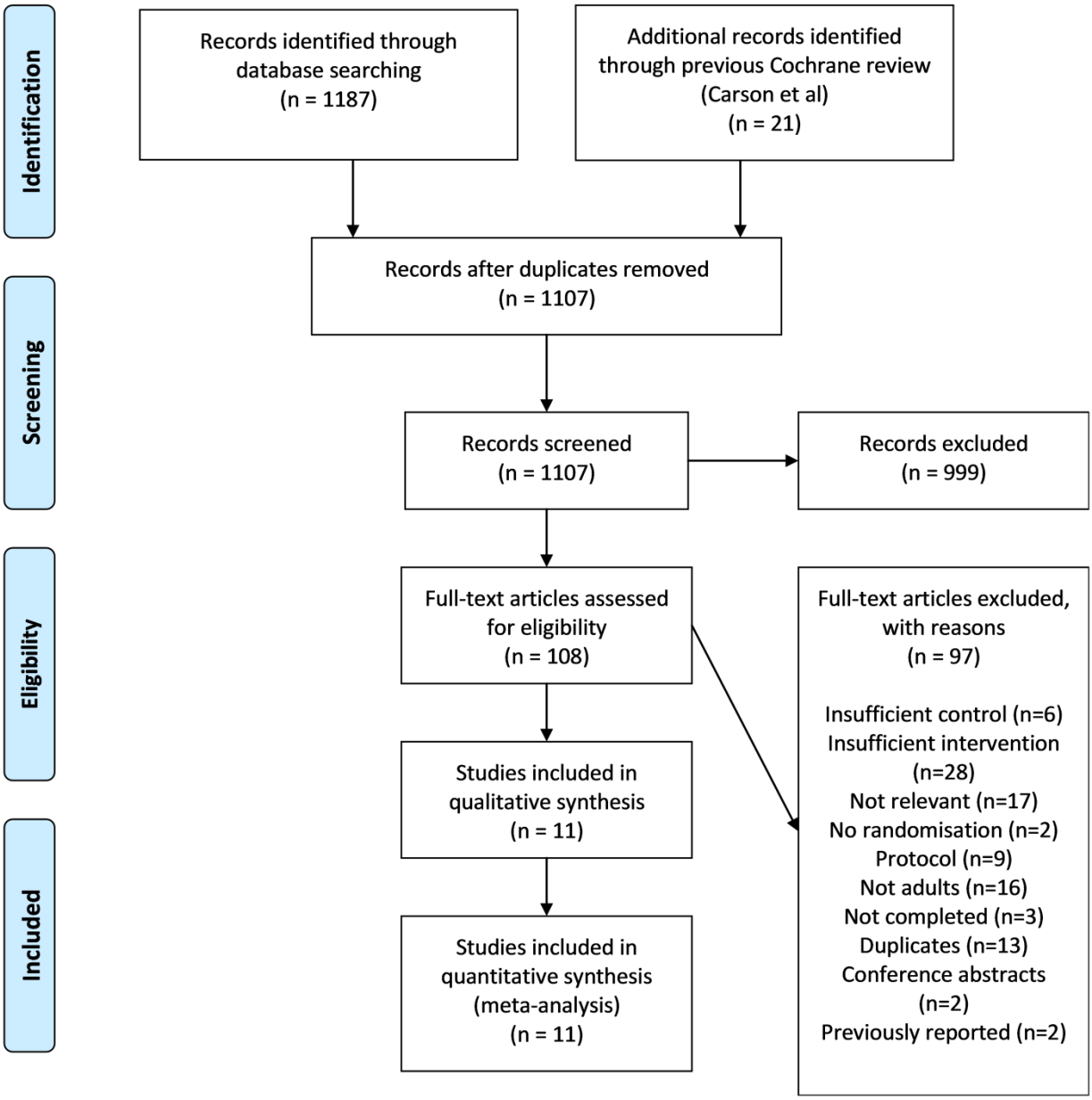
Attached file

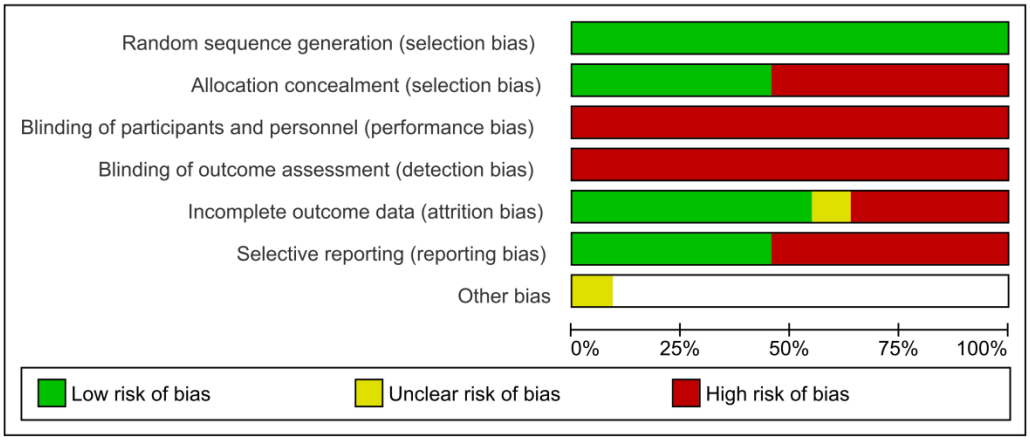
Appendix G: Forest plot of the meta-analysis on the fixed effect of exercise training on lung function

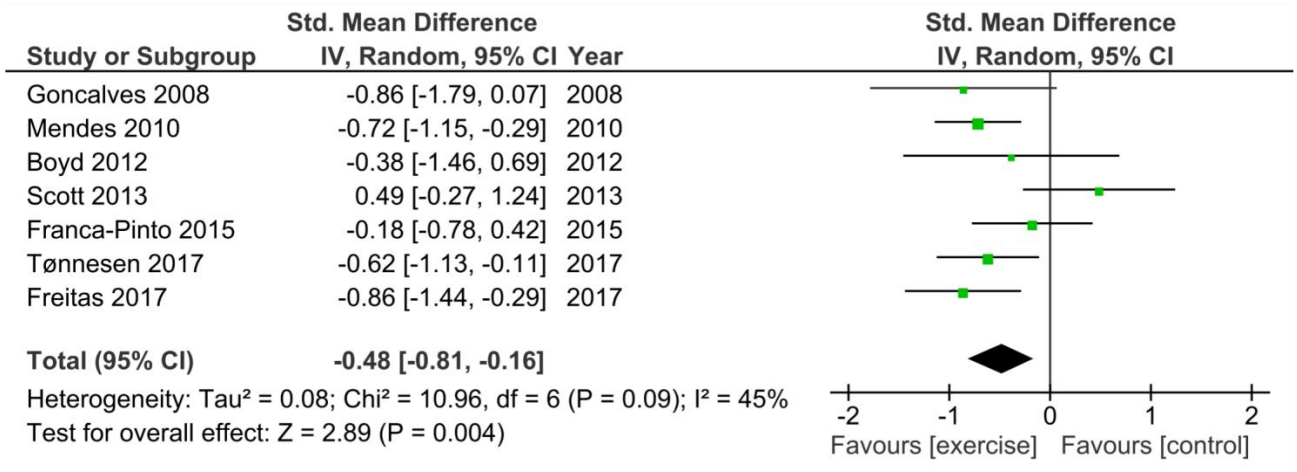
Attached file

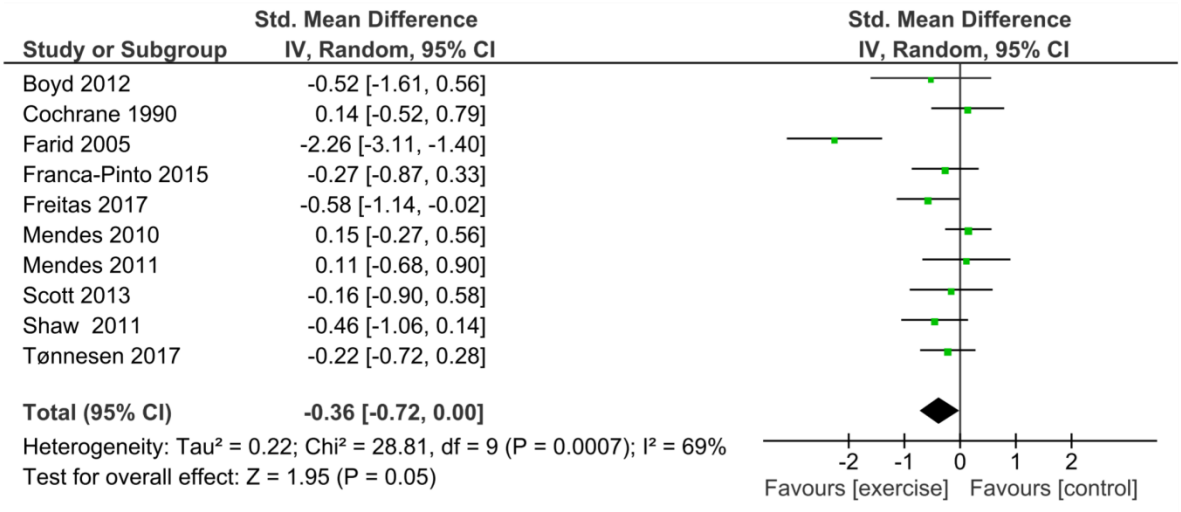
Appendix H: Forest plot of the meta-analysis on the fixed effect of exercise training on airway inflammation

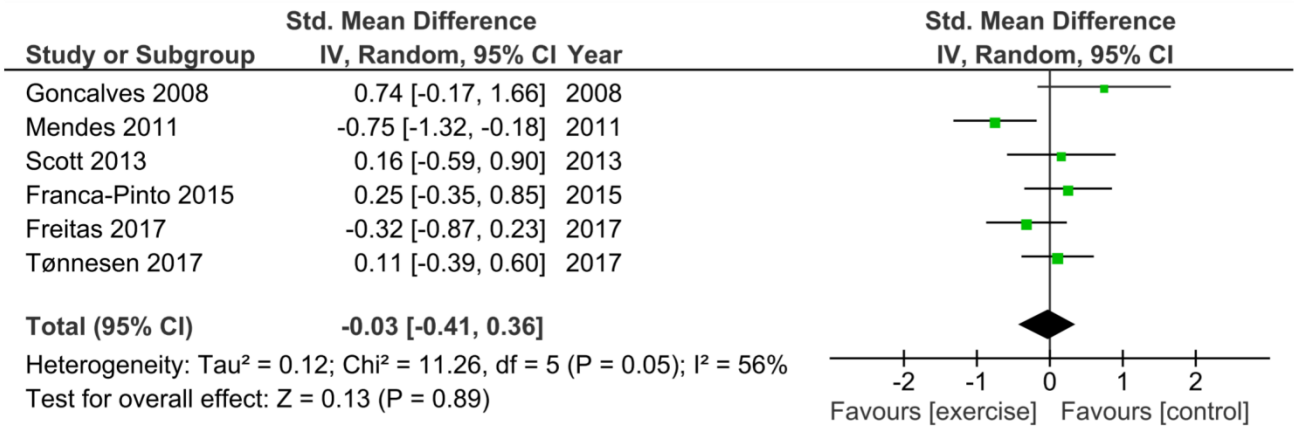
Attached file

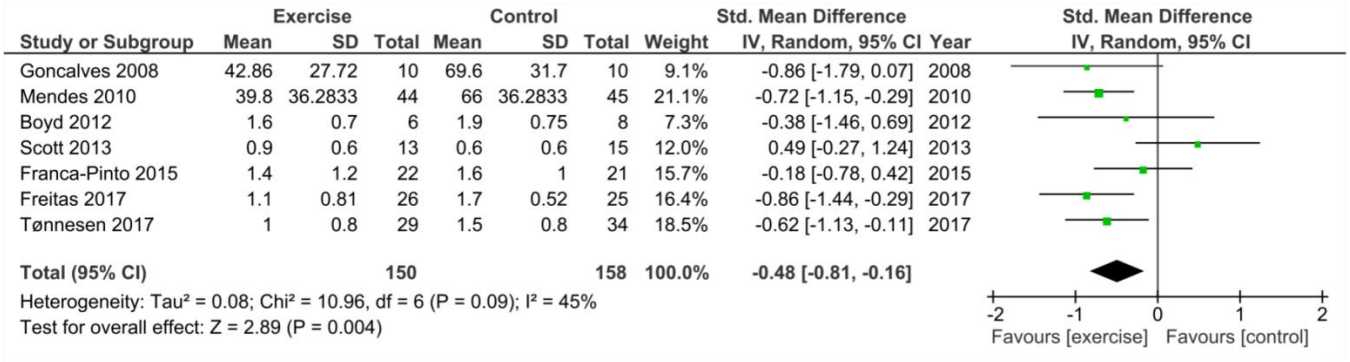

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 1187)
Additional records identified through previous Cochrane review (Carson et al) (n = 21)
Records after duplicates removed (n = 1107)
Records screened (n = 1107)
Records excluded (n = 999)
Full-text articles assessed for eligibility (n = 108)
Full-text articles excluded, with reasons (n = 97)
Insufficient control (n=6)
Insufficient intervention (n=28)
Not relevant (n=17)
No randomisation (n=2)
Protocol (n=9)
Not adults (n=16)
Not completed (n=3)
Duplicates (n=13)
Conference abstracts (n=2)
Previously reported (n=2)
Studies included in qualitative synthesis (n = 11)
Studies included in quantitative synthesis (meta-analysis) (n = 11)


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias


Std. Mean Difference
Study or Subgroup
IV, Random, 95% CI
Year
Std. Mean Difference
IV, Random, 95% CI
Goncalves 2008 -0.86 [-1.79, 0.07] 2008
Mendes 2010 -0.72 [-1.15, -0.29] 2010
Boyd 2012 -0.38 [-1.46, 0.69] 2012
Scott 2013 0.49 [-0.27, 1.24] 2013
Franca-Pinto 2015 -0.18 [-0.78, 0.42] 2015
Tønnesen 2017 -0.62 [-1.13, -0.11] 2017
Freitas 2017 -0.86 [-1.44, -0.29] 2017
Total (95% CI) -0.48 [-0.81, -0.16]
Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 2.89 (P = 0.004)
-2
-1
0
1
2
Favours [exercise]
Favours [control]


Std. Mean Difference
Study or Subgroup
IV, Random, 95% CI
Std. Mean Difference
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]
Franca-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]
Tønnesen 2017 -0.22 [-0.72, 0.28]
Total (95% CI) -0.36 [-0.72, 0.00]
Heterogeneity: Tau² = 0.22; Chi² = 28.81, df = 9 (P = 0.0007); I² = 69%
Test for overall effect: Z = 1.95 (P = 0.05)
-2
-1
0
1
2
Favours [exercise]
Favours [control]

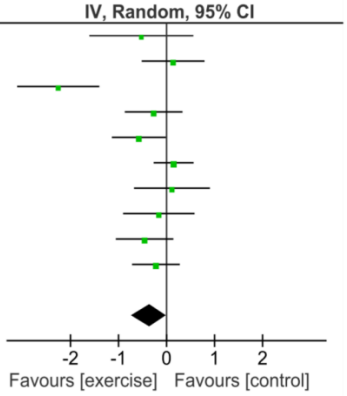

Std. Mean Difference
Study or Subgroup
IV, Random, 95% CI
Year
Goncalves 2008 0.74 [-0.17, 1.66] 2008
Mendes 2011 -0.75 [-1.32, -0.18] 2011
Scott 2013 0.16 [-0.59, 0.90] 2013
Franca-Pinto 2015 0.25 [-0.35, 0.85] 2015
Freitas 2017 -0.32 [-0.87, 0.23] 2017
Tønnesen 2017 0.11 [-0.39, 0.60] 2017
Total (95% CI) -0.03 [-0.41, 0.36]
Heterogeneity: Tau² = 0.12; Chi² = 11.26, df = 5 (P = 0.05); I² = 56%
Test for overall effect: Z = 0.13 (P = 0.89)
Std. Mean Difference
IV, Random, 95% CI
-2
-1
0
1
2
Favours [exercise]
Favours [control]


Exercise
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year
IV, Random, 95% CI
Goncalves 2008 42.86 27.72 10 69.6 31.7 10 9.1% -0.86 [-1.79, 0.07] 2008
Mendes 2010 39.8 36.2833 44 66 36.2833 45 21.1% -0.72 [-1.15, -0.29] 2010
Boyd 2012 1.6 0.7 6 1.9 0.75 8 7.3% -0.38 [-1.46, 0.69] 2012
Scott 2013 0.9 0.6 13 0.6 0.6 15 12.0% 0.49 [-0.27, 1.24] 2013
Franca-Pinto 2015 1.4 1.2 22 1.6 1 21 15.7% -0.18 [-0.78, 0.42] 2015
Freitas 2017 1.1 0.81 26 1.7 0.52 25 16.4% -0.86 [-1.44, -0.29] 2017
Tønnesen 2017 1 0.8 29 1.5 0.8 34 18.5% -0.62 [-1.13, -0.11] 2017
Total (95% CI) 150 158 100.0% -0.48 [-0.81, -0.16]
Heterogeneity: Tau² = 0.08; Chi² = 10.96, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 2.89 (P = 0.004)
-2
-1
0
1
2
Favours [exercise]
Favours [control]

	Exercise			Control				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Boyd 2012	-82	7.5	6	-76	12.5	8	6.4%	-0.52 [-1.61, 0.56]	
Cochrane 1990	-3.21	0.81	18	-3.32	0.76	18	10.2%	0.14 [-0.52, 0.79]	
Farid 2005	-84.89	11.38	18	-55.08	14.3	18	8.2%	-2.26 [-3.11, -1.40]	
Franca-Pinto 2015	-2.1	0.76	22	-1.9	0.7	21	10.7%	-0.27 [-0.87, 0.33]	
Freitas 2017	-2.15	0.59	26	-1.86	0.37	25	11.1%	-0.58 [-1.14, -0.02]	
Mendes 2010	-2.3	0.6726	44	-2.4	0.6726	45	12.7%	0.15 [-0.27, 0.56]	
Mendes 2011	-2.3	1.78	14	-2.5	1.63	11	8.8%	0.11 [-0.68, 0.90]	
Scott 2013	-3.03	0.81	13	-2.88	0.98	15	9.3%	-0.16 [-0.90, 0.58]	
Shaw 2011	-2.97	0.65	22	-2.7	0.5	22	10.7%	-0.46 [-1.06, 0.14]	
Tønnesen 2017	-84.5	13.1	29	-81.6	12.8	34	11.8%	-0.22 [-0.72, 0.28]	
Total (95% CI)			**212**			**217**	**100.0%**	**-0.36 [-0.72, 0.00]**	

Heterogeneity: Tau² = 0.22; Chi² = 28.81, df = 9 (P = 0.0007); I² = 69%

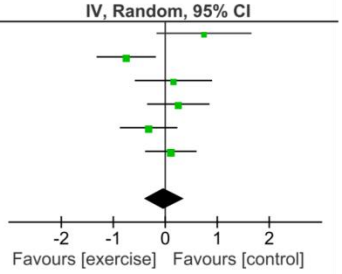
Test for overall effect: Z = 1.95 (P = 0.05)

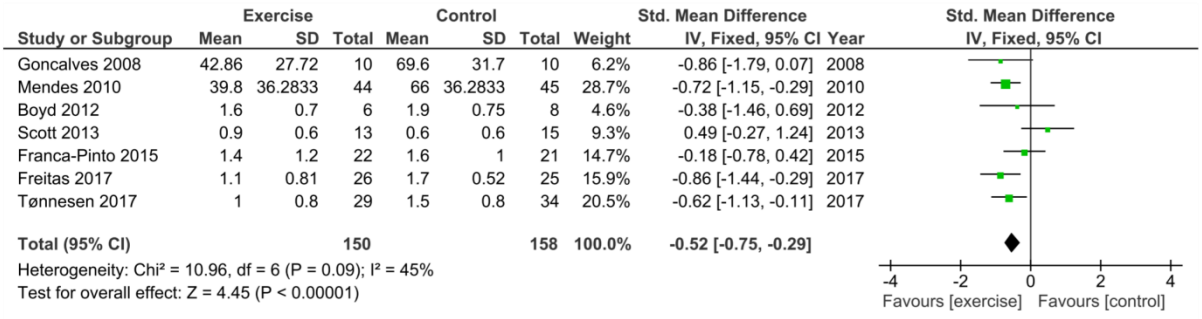


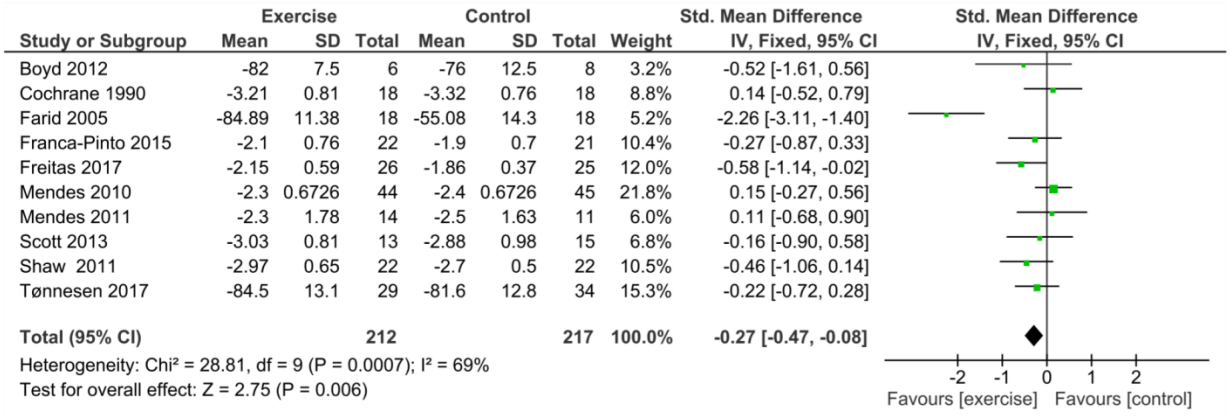
	Exercise			Control				Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year
Goncalves 2008	44.35	26.67	10	25.6	21.26	10	11.2%	0.74 [-0.17, 1.66]	2008
Mendes 2011	26.3	11.3999	27	35	11.3999	24	18.2%	-0.75 [-1.32, -0.18]	2011
Scott 2013	3.8	9.6	13	2.6	4.8	15	14.2%	0.16 [-0.59, 0.90]	2013
Franca-Pinto 2015	36.5	17.2257	22	32.1	17.2257	21	17.5%	0.25 [-0.35, 0.85]	2015
Freitas 2017	17.9	13.63	26	22.1	12.15	25	18.7%	-0.32 [-0.87, 0.23]	2017
Tønnesen 2017	23.5	36.3	29	20.3	22.3	34	20.2%	0.11 [-0.39, 0.60]	2017
Total (95% CI)			**127**			**129**	**100.0%**	**-0.03 [-0.41, 0.36]**	

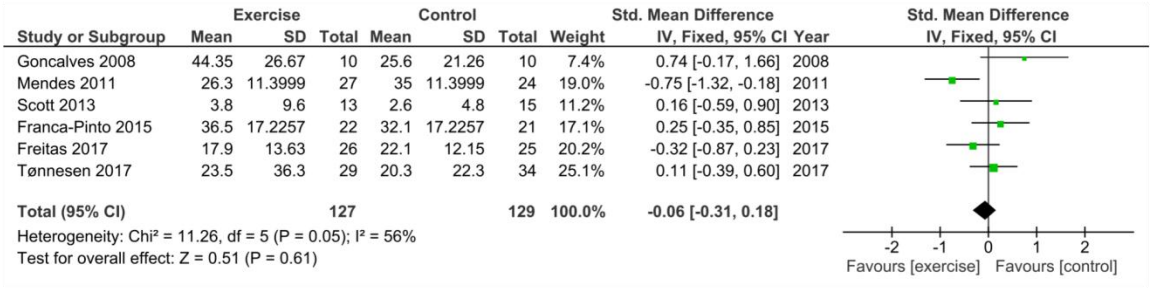
Heterogeneity: Tau² = 0.12; Chi² = 11.26, df = 5 (P = 0.05); I² = 56%

Test for overall effect: Z = 0.13 (P = 0.89)




Exercise
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Goncalves 2008 42.86 27.72 10 69.6 31.7 10 6.2% -0.86 [-1.79, 0.07] 2008
Mendes 2010 39.8 36.2833 44 66 36.2833 45 28.7% -0.72 [-1.15, -0.29] 2010
Boyd 2012 1.6 0.7 6 1.9 0.75 8 4.6% -0.38 [-1.46, 0.69] 2012
Scott 2013 0.9 0.6 13 0.6 0.6 15 9.3% 0.49 [-0.27, 1.24] 2013
Franca-Pinto 2015 1.4 1.2 22 1.6 1 21 14.7% -0.18 [-0.78, 0.42] 2015
Freitas 2017 1.1 0.81 26 1.7 0.52 25 15.9% -0.86 [-1.44, -0.29] 2017
Tønnesen 2017 1 0.8 29 1.5 0.8 34 20.5% -0.62 [-1.13, -0.11] 2017
Total (95% CI) 150 158 100.0% -0.52 [-0.75, -0.29]
Heterogeneity: Chi² = 10.96, df = 6 (P = 0.09); I² = 45%
Test for overall effect: Z = 4.45 (P < 0.00001)
-4
-2
0
2
4
Favours [exercise]
Favours [control]


Exercise
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
Boyd 2012 -82 7.5 6 -76 12.5 8 3.2% -0.52 [-1.61, 0.56]
Cochrane 1990 -3.21 0.81 18 -3.32 0.76 18 8.8% 0.14 [-0.52, 0.79]
Farid 2005 -84.89 11.38 18 -55.08 14.3 18 5.2% -2.26 [-3.11, -1.40]
Franca-Pinto 2015 -2.1 0.76 22 -1.9 0.7 21 10.4% -0.27 [-0.87, 0.33]
Freitas 2017 -2.15 0.59 26 -1.86 0.37 25 12.0% -0.58 [-1.14, -0.02]
Mendes 2010 -2.3 0.6726 44 -2.4 0.6726 45 21.8% 0.15 [-0.27, 0.56]
Mendes 2011 -2.3 1.78 14 -2.5 1.63 11 6.0% 0.11 [-0.68, 0.90]
Scott 2013 -3.03 0.81 13 -2.88 0.98 15 6.8% -0.16 [-0.90, 0.58]
Shaw 2011 -2.97 0.65 22 -2.7 0.5 22 10.5% -0.46 [-1.06, 0.14]
Tønnesen 2017 -84.5 13.1 29 -81.6 12.8 34 15.3% -0.22 [-0.72, 0.28]
Total (95% CI) 212 217 100.0% -0.27 [-0.47, -0.08]
Heterogeneity: Chi² = 28.81, df = 9 (P = 0.0007); I² = 69%
Test for overall effect: Z = 2.75 (P = 0.006)
-2 -1 0 1 2
Favours [exercise] Favours [control]


Exercise
Control
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI Year
IV, Fixed, 95% CI
Goncalves 2008 44.35 26.67 10 25.6 21.26 10 7.4% 0.74 [-0.17, 1.66] 2008
Mendes 2011 26.3 11.3999 27 35 11.3999 24 19.0% -0.75 [-1.32, -0.18] 2011
Scott 2013 3.8 9.6 13 2.6 4.8 15 11.2% 0.16 [-0.59, 0.90] 2013
Franca-Pinto 2015 36.5 17.2257 22 32.1 17.2257 21 17.1% 0.25 [-0.35, 0.85] 2015
Freitas 2017 17.9 13.63 26 22.1 12.15 25 20.2% -0.32 [-0.87, 0.23] 2017
Tønnesen 2017 23.5 36.3 29 20.3 22.3 34 25.1% 0.11 [-0.39, 0.60] 2017
Total (95% CI) 127 129 100.0% -0.06 [-0.31, 0.18]
Heterogeneity: Chi² = 11.26, df = 5 (P = 0.05); I² = 56%
Test for overall effect: Z = 0.51 (P = 0.61)
-2 -1 0 1 2
Favours [exercise] Favours [control]