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Early View

Review

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Increasing physical activity in severe asthma: a systematic review and meta-analysis

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Take home summary:

The evidence regarding the effectiveness of interventions in improving physical activity, exercise capacity, asthma control and quality of life in adults with moderate-to-severe asthma is promising, however further research in this area is needed.

Introduction/Aim: Physical inactivity is common in asthma and is recognised as an important modifiable risk for poor clinical outcomes such as impaired asthma control and health-related quality of life (HRQoL). Despite evidence supporting the role of physical activity (PA) in reducing the risk of these outcomes, little is known about optimal interventions for increasing PA in those with severe disease. This systematic review and meta-analysis evaluates the effectiveness of interventions in increasing PA in severe asthma.

Methods: Medline, CINAHL, EMBASE, PubMed, Informit, SPORTDiscus and Cochrane databases were searched up to September 2021 for PA-based intervention studies that assessed PA outcomes (e.g., steps/day, time spent undertaking PA) in adults with severe asthma. Data on asthma-related (e.g., asthma control) and health-related outcomes (e.g., HRQoL) were assessed as secondary outcomes. The Revised Cochrane ROB tool was used to assess risk of bias. Random-effects meta-analyses synthesised data where possible. PROSPERO ID: CRD42021210968

Results: Four RCTs (all 12-weeks in duration) including 176 adults with moderate-to-severe asthma were included. An increase in PA was reported with a moderate-vigorous intensity aerobic and resistance training intervention (steps/day and time spent undertaking PA), and an unsupervised pedometer-based intervention (steps/day). Meta-analyses showed that PA interventions had an overall positive effect on steps/day (MD=1588, 95% CI:399, 2778; p=0.009, I^2=23), asthma control (MD=-0.65, 95% CI: -0.95, -0.35; $p<0.0001$, I^2=0%), and HRQoL (MD=0.56, 95% CI:0.10,1.01; p=0.02, I^2=16%) compared to control.

Conclusion: While there is some evidence supporting the effectiveness of interventions in improving PA in adults with severe asthma, higher-quality, large-scale studies of longer duration are needed to determine the optimal intervention.

INTRODUCTION

Asthma is a complex heterogenous disease in which individual variability in clinical presentation, disease severity and therapeutic response is common[1,2]. To add to this complexity, behaviours/risk-factors and extrapulmonary comorbidities, also referred to as "Treatable Traits", that are associated with adverse clinical outcomes are common in asthma[3-5]. Physical inactivity is one proposed Treatable Trait that is recognised as an important modifiable risk-factor for impaired respiratory functioning, asthma control, quality of life (QoL) and mental health, increased disease severity and exacerbation risk, and ultimately increased healthcare use[6]. Compared to the general population, people with asthma spend significantly less time undertaking moderate to vigorous physical activity (MVPA) and achieve fewer steps per day[7,8]. Physical inactivity is particularly evident in those with severe asthma[8,9], which despite constituting only 3-8% of the overall asthma population, are responsible for much of the economic, mortality and morbidity-related burden associated with this disease[10,11]. Observational studies suggest that a fear of provoking asthma symptoms by participating in physical activity (PA) may in part explain these findings[12,13], as individuals with increased disease severity are more likely to believe that exercise should be avoided[14]. Interestingly, however, it has also been demonstrated that patients with severe asthma rate PA as one of the most important outcomes they want to achieve following any asthma treatment[15].

Previous reviews have not only demonstrated the safety of PA interventions in adults with asthma[16], but have also highlighted the promising role of PA as a non-pharmacological strategy to complement existing asthma management approaches[9,16-18], these reviews have focused on the general asthma population. Furthermore, while current asthma management guidelines recommend that people with asthma undertake PA[19], there are currently no clearly defined PA prescription guidelines for asthma, and particularly so for people with severe disease. In fact, the Global Initiative for Asthma (GINA) specifically state that there 'is insufficient evidence to recommend one form of physical activity over another[19].

Tyson et al. published a systematic review examining the effects of interventions on PA, sedentary behaviour and health outcomes in people with asthma[20]. However, as the intervention components were similar across all studies regardless of their effectiveness, a definitive conclusion regarding the optimal intervention for this population was unable to be drawn. Tyson et al.[20] also excluded pulmonary rehabilitation (PR) interventions, which have been shown to improve PA levels in other chronic respiratory diseases[21], and included all asthma severities, which makes it difficult to determine if the findings are applicable to a severe asthma cohort who experience more disease burden. To our knowledge, the effectiveness of interventions in increasing PA in people with severe asthma explicitly has not yet been systematically reviewed. This systematic review and meta-analysis therefore aimed to evaluate the effectiveness of interventions aiming to increase PA in adults with severe asthma on PA outcomes, and to explore the optimal type, intensity, duration and frequency needed to improve PA, as well as health- and asthma-related outcomes in severe asthma.

METHODS

Protocol and registration

This review was guided by the Cochrane handbook for Systematic Reviews of Interventions[22] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. PROSPERO ID: CRD42021210968.

Data sources and search strategy

Medline, CINAHL, EMBASE, PubMed (non-Medline), Informit (Health Collection), Cochrane Library and SPORTDiscus databases were searched from inception to 10 September 2021 for relevant English-language publications. The search strategy covered all relevant terms relating to "physical activity", "exercise" and "asthma", and was adapted for each database (Supplementary Figures 1-6). We also performed hand-searching of reference lists and cited reference searches of the included articles.

Eligibility and exclusion criteria

Studies were included if they met the following *a priori* defined inclusion criteria:

1). Participants: adults ≥18yrs with physician-diagnosed severe asthma defined according to the GINA criteria; asthma that remains uncontrolled despite adherence with maximised optimised therapy and the management of contributory factors, or that worsens when high-dose therapy is decreased[19]. Studies involving patients with moderate-to-severe asthma were also included.

2). Interventions: PA interventions of ≥2 weeks in duration including: walking, running, cycling, swimming or other aerobic and low-intensity exercise (i.e., yoga), weight-bearing exercise, PR, interval training; interventions with a PA component aimed at increasing activity in daily life (including multi-arm trials where one arm is PA-based); interventions utilising wearable technology (i.e., pedometers) to track or support/encourage PA; and movement-based interventions (supervised or unsupervised) with PA counselling.

3). Comparator/control: usual care or sham intervention (i.e., stretching or breathing exercises).

4). Outcomes: to be eligible, studies had to report on ≥1 PA outcome (i.e., time spent undertaking PA, steps/day) or sedentary time.

5). Study design: randomised controlled trials (RCTs), quasi-experimental RCTs, cohort, longitudinal, case-control, pilot or observational cross-sectional studies.

Exclusion criteria: Studies involving patients with no asthma diagnosis, mild asthma, or moderate asthma only, non-English language publications, no control/comparison arm, review articles, notes, editorials, scientific congress abstracts and qualitative studies.

Study selection

Two independent reviewers (RFM, VLC) performed the screening process against the *a priori* inclusion criteria using the web-based tool Covidence[23]. Discrepancies were resolved by consensus, with persistent disagreements resolved by a third reviewer (VMcD).

Data extraction

Data extraction was performed by two independent reviewers (RFM, PDU) using customised data extraction templates in Covidence[23]. Missing data were requested from study authors via email. To describe the profile of the included articles, the following data were extracted: authors, journal, year of publication, setting (country), study design, sample size, participant characteristics (i.e., age, sex, asthma severity), intervention details (i.e., the type of PA,

mode of delivery, frequency, intensity and duration of sessions), control conditions, study duration and follow-up time points.

To examine the effect of the intervention on PA (primary outcome), values of the following outcome variables (i.e., mean, standard deviation (SD), and sample size in each group) observed at baseline, the end of the intervention period, and any post-intervention follow-ups were extracted: time spent undertaking PA (total and by PA intensity), steps/day and sedentary time.

Also extracted were data on asthma-related outcomes (i.e., health-related quality of life (HRQoL), asthma control, lung function, exacerbation rates, asthma symptom-free days, biomarkers of airway [i.e., sputum eosinophils/neutrophils, fractional exhaled nitric oxide; FeNO] and systemic [i.e., serum c-reactive protein] inflammation), and health-related outcomes (i.e., body mass index (BMI), body composition, anxiety and depression scores, exercise capacity, and skeletal muscle strength).

Assessment of risk of bias in included studies

Two reviewers (RFM, PDU) independently assessed risk of bias (ROB) using the Revised Cochrane ROB tool for RCTs (RoB2; 22 August 2019 version)[24], with discrepancies resolved through discussion. ROB2 is a result-based tool which is structured into five domains: randomisation process, deviations from intended interventions, missing outcome data, outcome measurement and selection of the reported result. Each domain was judged as *low, some concerns,* or *high risk*, resulting in an overall bias judgement for the specific result being assessed. Given the number of outcomes of interest in this review, we conducted ROB assessments (effect of assignment to the intervention) for results included in the meta-analyses only. The Cochrane robvis web-application was used to create ROB plots[25].

Method of analysis

Results of individual studies were tabulated (Supplementary Tables S1-S3). Meta-analysis was performed using Review Manager (RevMan, version 5.3). Effect sizes were expressed as mean differences (MD) with 95% confidence intervals (CIs) estimated from the mean (SD) post-intervention (or change) scores from each study. In the case of different scales for the same outcome measure (e.g., exercise capacity), the effect size was expressed as the standardised mean difference (SMD), with the magnitude classified as small (≤0.2), moderate (0.5) or large (≥0.8)[26]. When the SD for an outcome was not reported, it was estimated from the 95% CI related to the pertinent number of participants. Using generic inverse-variance analysis, we compared the pooled effect sizes for PA interventions versus control using random-effects models which allows for anticipated differences in treatment effects between studies. Analyses were repeated using a fixed-effects model to test the robustness of our findings (Supplementary Table-S4)

Heterogeneity was examined using the χ^2 test ($P < 0.1$ indicative of significant heterogeneity) and the I_2 parameter (heterogeneity interpretation - low: 0-40%; moderate: 30–60%; substantial: 50–90%; considerable: 75–100%). Data that could not be assessed by meta-analyses were qualitatively summarised.

RESULTS

A total of 12,042 articles were identified, of which 3973 were duplicates (Figure 1). Of the remaining 8069 articles, 7499 were excluded based on title and a further 454 based on abstract. 116 full-text articles were retrieved and assessed for eligibility, of which five met the *a priori* defined criteria for inclusion in the review. The main reason for full text exclusion was incorrect patient population (i.e., participants with mild asthma, or asthma severity not specified), followed by incorrect article type.

Study and participant characteristics
Four RCTs which gave rise to five publications were identified[27-31]. Characteristics of the included RCTs are summarised in Table 1. Three studies were 2-arm parallel group RCTs, and one was a 3-arm parallel group RCT comparing two interventions (high-intensity PR only or high-intensity PR with an e-health self-management support programme (PR +SMS)) to a single control group. All RCTs were 12-weeks in duration, with post-intervention follow-ups conducted in all but one study[28]. Coelho et al. reported outcomes at 24- to 28-weeks post-randomisation[27], while Turk et al. conducted assessments every 3-months for a year. Freitas et al., conducted follow-up assessments of body weight only at 6- and 12-months post-randomisation[29,30]. Three studies were conducted in Brazil[27-30], and one in the Netherlands[31]. All studies were published in the last five years.

Overall, the four RCTs involved 176 physically inactive adults with moderate-to-severe asthma (sample size ranged from 37-54). No studies included participants with severe asthma only. Most participants were female (82%) and had comorbid overweight/obesity (BMI > 25kg·m^{-2}, mean BMI ranged from 27.1 to 38.1kg·m^{-2}). Mean age of participants ranged from 41.6 to 50.6 years.

Intervention characteristics
Interventions varied methodologically in terms of the mode of delivery, frequency, intensity, duration and type of PA, as summarised in Table 1. Freitas et al. used a supervised training program comprised of aerobic and resistance exercises and PA recommendations [28-30], Evaristo et al. studied the effect of supervised aerobic exercise only[29,30], and both intervention arms of the RCT by Turk et al. incorporated supervised high-intensity interval training (HITT) into a PR program. Coelho et al. was the only study to examine the effect of an unsupervised intervention on PA[27]. This study used a pedometer-based PA programme, whereby participants were prescribed individualised daily step targets calculated biweekly and were encouraged to walk at moderate intensity for 30-minutes at least 5 days/week.

Frequency of PA sessions ranged from 2-5 per week and were 30-60 minutes in duration. The intensity of the prescribed PA ranged from MVPA (based on 50-75% of peak VO_2[29,30]) to high-intensity PA (based on 90% of VO_2 max or a score of ≥ 7 on the 10-grade Borg scale)[31].

In addition to the PA component, all studies included some form of nutritional[29-31], educational[27-30] and/or behavioural change programme[29-31]. In Freitas et al., all participants, regardless of their group allocation, received a weight-loss programme (individualised hypocaloric diet supported by nutrition counselling and behaviour change techniques (BCT)) and 6hrs of education focusing on asthma management, the benefits of PA and the current PA recommendations[29,30]. Coelho et al. also provided all participants with a 1hr education session on asthma management and the benefits of exercise/PA[27], while Evaristo et al. implemented a 4hr educational programme on asthma management only[28]. Nutritional intervention and psychological sessions focusing on behavioural change and motivation strategies were provided to participants in both intervention arms (PR only and PR+SMS) in the study by Turk et al[31]. The PR+SMS group also received the e-health self-management programme “PatientCoach”, which facilitated goal setting and provided participants with tailored information, self-management education modules, and e-consults with healthcare professionals[31].

Comparator characteristics
Comparator/control groups varied across studies. Freitas et al. used a sham intervention comprised of stretching and breathing exercises[29,30], the control group in Evaristo et al., received a breathing exercise programme[28], while control participants in both Turk et al.[31] and Coelho et al.[27], were provided with general advice/encouragement to exercise, which is consistent with usual care.

Risk of bias assessment

ROB assessments were conducted for results in the following outcome categories; PA (steps/day), HRQoL (AQLQ), asthma control (ACQ score and asthma symptom-free days), and exercise capacity (VO_2). A summary of the ROB assessments for each outcome is presented alongside the respective meta-analysis forest plot (Figures 2 and 3). There was either *some concern* or *high* overall ROB for all outcome measures. This was largely driven by concerns of bias arising from the measurements of the outcomes (*some concerns* in 69% of outcomes), as the nature of the interventions precluded the blinding of participants which has the potential to impact patient-reported outcomes. This was of particular concern in the study by Coelho et al. as participants were required to record their daily step counts measured using pedometers[27]. There were also *some concerns* of bias arising due to missing data (56% of outcomes) and due to deviations from intended interventions (63% of outcomes) as limited information was provided as to whether deviations arose due to trial context.

Physical activity outcomes

PA outcomes were objectively measured using a device in all studies; three of which used accelerometers[28-31] and one used pedometers[27]. Outcomes included steps/day, which was measured in all studies[27-29,31], PA level (PAL)[31], and time spent performing light-intensity PA and MVPA[30] (Table 2). Only one study measured PA as the primary outcome[27].

Of the four included studies, two reported a significant beneficial effect on at least one PA outcome in favour of the intervention[27,29,30]. Freitas et al., reported a greater increase in steps/day ($p<0.0001$)[29], and time spent performing MVPA ($p<0.001$) and light-intensity PA ($p=0.03$) from baseline to post-intervention in the intervention group compared to control[30], with a higher percentage of participants in the intervention group achieving the recommendation of 10,000 steps/day (41.7% vs 4.3%, $p=0.019$). Coelho et al. reported an increase in PA (steps/day) from baseline to post-intervention in participants who received a pedometer-based programme, with a difference of 2488 steps (average adjusted difference, $p=0.005$) reported between groups post-intervention. This increase in PA, however, was not sustained after the intervention had ended, with the difference in steps/day between groups no longer significant 3- to 4-months post-intervention.

Turk et al., reported no significant between-group differences in PA (steps/day) post-intervention. There was, however, a significant within-group improvement in PA (steps/day and PAL) in the PR+SMS group from baseline to post-intervention[31]. Additionally, 9-months after the intervention had ended, the PR only group were reported to be undertaking significantly more steps/day than the control group[31]. Evaristo et al. also reported no significant between-group difference in steps/day post-intervention, with both groups increasing their step count by approximately 2000 steps/day, reaching the recommendation of 10,000 steps/day[28].

Random-effects meta-analysis (n=3)[27,28,30] showed an overall significant ($Z=2.63$, *$p=0.009$, $I^2=23$;* n=142*)* mean difference of 1588 (95% CI 399 to 2778) steps/day post-intervention between groups in favour of PA interventions (Figure 2). The magnitude of effect, however, differed by intervention type, ranging from small (SMD=0.1, 95% CI -0.43 to 0.64) in Evaristo et al[28], to large (SMD=0.91, 95% CI 0.23 to 1.59) in Coelho et al.[27] (Supplementary Figure S7). Turk et al. reported only change-from-baseline data, and therefore could not be included in the meta-analyses[31].

Asthma-related outcomes

The effect of PA on asthma-related outcomes was reported in the included studies (Table 2).

Health-related quality of life

Asthma-related QoL was measured in all four studies using the Asthma Quality of Life Questionnaire (AQLQ). While only one study reported a significant improvement following PA compared to control, random-effects meta-analysis (n=3)[27-29] demonstrated an overall positive effect of PA on asthma-related QoL post-intervention (MD=0.56, 95% CI 0.10 to

1.01; n=142, p=0.02, I^2=16%) (Figure 3a). The proportion of participants that had a clinically significant improvement in AQLQ score (≥0.5 units), however, did not significantly differ between the intervention and control group in any of the included studies.

Asthma control

A variety of asthma control outcome measures were reported; n=4 studies used the asthma control questionnaire (ACQ)[27-29,31], n=2 reported the number of asthma symptom-free days[28,30] and n=2 reported exacerbation rates[29,31]. Of the included studies, only Freitas et al. observed a significant improvement in asthma control measures (ACQ score, asthma-symptom free days and exacerbation rates) with PA compared to control. In addition, a higher percentage of participants in the intervention group (69%) achieved a clinically significant improvement in ACQ score (defined as a change or decrease in ACQ score of >0.5 points) post-intervention compared to control (36%, p=0.03)[29], with the percentage of participants who experienced no exacerbations during follow-up higher in the intervention group (53% vs 20%, p=0.03)[30]. Significant positive within-group changes in ACQ score were reported by Evaristo et al.[28] and Turk et al.[31] (in both intervention arms); between-groups differences were not significant in either study.

Random-effects meta-analysis (n=2)[27,29] showed a significant positive treatment effect on ACQ score post-intervention in favour of PA (MD=-0.65, 95% CI -0.95 to -0.35; n=88, *p<0.0001*, I^2=0%) (Figure 3b), with an overall non-significant (Z=1.27, *p=0.20, I^2=83%*) mean difference of 5.14 (95% CI -2.80, 13.08) asthma symptom-free days in favour of PA (Figure 3c).

Lung function

Two studies examined the effect of PA on lung function[29,31]. Turk et al.[31] reported an improvement in FRC% and EVR following PR only compared to control, while Freitas et al.[29] reported significant improvements in FEV_1, FVC and ERV in the intervention group only. Meta-analyses were unable to be conducted.

Systemic and airway inflammation

Airway inflammation was examined in three studies[28,29,31], one of which reported a group-by-time interaction effect, with a decrease in FeNO observed in the intervention group only[29]. No significant within- or between-group differences in airway inflammation (FeNO, sputum neutrophils and eosinophils) were reported in the other two studies[28,31]. Two studies reported a significant reduction in systemic inflammation in the intervention group compared to control[29,31].

Health-related outcomes

A summary of health-related outcomes reported in the included studies are presented in Table 2.

Anthropometrics and body composition

Two studies examined the effect of PA on anthropometric measures and body composition, both of which had a focus on weight loss in addition to improving PA[29,31]. Both studies reported greater reductions in body weight, BMI and fat mass in participants who received the intervention compared to control[29,31]. Freitas et al. also reported a reduction in waist circumference, while preserving lean muscle mass[29].

Skeletal muscle strength

Freitas et al., reported significant improvements in skeletal muscle strength in participants who received a combined aerobic and resistance training programme compared to control[29].

Exercise capacity

Various methods were used to measure exercise capacity (i.e., 6-minute walk test[27,31], incremental shuttle walk test (ISWT)[28], work rate[29] and the cardiopulmonary exercise test (CPET)[29]). Freitas et al.[29], Coelho et al.[27], and Turk et al.[31], reported a significant

improvement in exercise capacity in the intervention group compared to control, while no significant group effect was reported by Evaristo et al[28]. The random-effects model (n=2)[29,31] showed a large positive effect of PA intervention on exercise capacity (VO_2 max) (SMD = 1.35, 95% CI 0.81 to 1.82; n=75, *p<0.00001, I^2=0)* (Figure 3d).

Anxiety and depression

Three studies examined the effect of PA on anxiety and depression measured using the hospital anxiety and depression scale (HADS)[27,28,30]; one of which reported the proportion of participants in each group with symptoms of anxiety (HADS-A score > 9) or depression (HADS-D score > 9)[30], with the other two reporting anxiety and depression scores[27,28]. In the study by Freitas et al., while there was a significant increase in the proportion of participants without symptoms of depression in the intervention group compared to control post-intervention, there was no significant difference in the proportion of participants with symptoms of anxiety between groups[30]. No within- or between-group changes in anxiety or depression scores were reported in the studies by Coelho et al.[27] and Evaristo et al.[28], and the random-effects meta-analyses (n=2)[27,28] showed no significant mean differences in anxiety (MD=-0.24, 95% CI -2.35 to 1.87; n=91, *p=0.82, I^2=18)* (Figure 3e) or depression scores (MD= -1.13, 95% CI -3.04 to 0.78; n=91, *p=0.25, I^2=0)* between groups post-intervention (Figure 3f).

DISCUSSION

This review identified four unique studies examining the effectiveness of PA interventions in increasing PA outcomes in people with moderate-to-severe asthma[27-31]. While this systematic review and meta-analysis provides promising evidence regarding the potential of PA interventions to increase PA and improve asthma control, HRQoL and exercise capacity in those with moderate-to-severe disease, there is insufficient evidence to draw a definitive conclusion regarding the optimal PA prescription. This paucity of evidence highlights an important research gap that needs to be addressed in order to inform the development of asthma-specific PA guidelines.

Of the identified studies only two reported a significant positive effect on PA in favour of the intervention compared to control [27,29,30]; one of which used an unsupervised pedometer-based programme, while the other used a supervised aerobic and resistance training programme. Given the methodological heterogeneity between these studies regarding the PA type, mode of delivery, frequency, intensity, duration of sessions, and study outcome type reported (i.e., post-intervention versus change-from-baseline data), direct comparison of the effectiveness of these interventions is difficult. However, the effect size of the interventions was different, suggesting PA prescription may be a crucial factor. Nonetheless these studies provide preliminary evidence regarding the types of interventions that may be most effective in increasing PA in this population.

Having a step goal has been identified as an important predictor of increased PA[32], with pedometer-based interventions effective in achieving both short- and long-term PA increases in the general population[33]. In Coelho et al., individuals with moderate-to-severe asthma who received a 12-week unsupervised pedometer-based programme significantly increased their daily step count compared to those who were encouraged to take daily 30-minute walks only[27]. While this provides evidence regarding the short-term benefits of a step-based intervention in this population, between-group differences in PA were no longer significant 12- to 16-weeks post-intervention, indicating that the intervention did not lead to a sustained improvement in PA behaviour. These findings mirror the evidence for the short-[34] versus long-term effectiveness[35] of pedometer-based interventions in increasing PA in the chronic obstructive pulmonary disease (COPD) population. In COPD, it has been suggested that multidimensional and possibly repeated intervention targeting not only PA but also exercise

capacity and HRQoL may be needed to achieve sustained improvements in PA[35]. Whether a similar approach is required in the severe asthma population warrants further investigation.

Freitas et al., on the other hand, demonstrated the short-term effectiveness of supervised exercise training (two 60-minute sessions of moderate-vigorous intensity aerobic and resistance exercises per week)[29,30] combined with a weight-loss programme, in increasing PA (steps/day and time spent undertaking MVPA and light-intensity PA) in obese adults with moderate-severe asthma compared to a weight-loss programme alone. This is consistent with the findings of the recent review by Tyson et al[36]. In this review, effective PA interventions in the general asthma population typically comprised of aerobic exercise and/or resistance/strength training of 30-60minutes in duration, 2-3 times a week[9]. Although not significant compared to control, Evaristo et al. also demonstrated that aerobic training alone can increase PA in individuals with moderate-severe asthma. In this study, both the intervention and the control group, who received breathing exercises, increased their step count by approximately 2000 steps/day, reaching the recommendation of 10,000 steps/day[28]. There is evidence that breathing exercises improve both symptom management and ventilatory control[37], which may subsequently increase an individual's confidence in undertaking PA. Indeed, in a study by Hiles et al., individuals with severe asthma reported increased confidence and motivation to be active after receiving a yoga and mindfulness intervention which focused on controlling breathing, increasing movement and meditation[38]. No increases in PA were reported following this intervention however, which the authors suggest may have been due to the participants prioritising relaxation activities or displacing more active exercise with the low-intensity yoga[38]. Further studies are needed to explore the benefits of aerobic training for increasing PA in this population, with breathing exercises a potentially important intervention component to include.

The final study identified by this review examined the effects of a PR programme using HIIT with and without an e-health self-management programme (PR+SMS versus PR only), compared to usual care. Compared to lower intensity exercise that requires longer duration sessions, HIIT is less time consuming and has been suggested to be more effective in eliciting a physiologic training response[39]. However, few studies using HIIT have been conducted in the asthma population due to concerns of provoking exercised induced bronchoconstriction[40]. While Turk et al. demonstrated the feasibility of HIIT in individuals with moderate-severe asthma, no significant between-group changes in PA were observed after 12-weeks. There was however a within-group improvement in daily steps and PAL in the PR+SMS group post-intervention, which was sustained post-intervention; providing some evidence for the use of HIIT to increase PA in this population. It is also interesting to note that at the 12-months post-randomisation visit which was conducted 9 months after the intervention had ended, daily steps were significantly higher in the PR only group compared to control[31]. It is unclear whether this increase in PA post-intervention was related to the PR intervention, however, it could be related to the weight loss achieved in the intervention period, leading to an increase in physical activity participation post-intervention. Further research exploring the long-term benefits of HIIT is warranted.

The second aim of this review was to examine the effect of PA interventions on asthma- and health-related outcomes. The findings of our meta-analyses demonstrated an overall positive effect of PA interventions on exercise capacity, asthma control and HRQoL in individuals with moderate-to-severe asthma, which complements previous reviews[16,17,36]. Interestingly however, of the two studies we identified that reported significant improvements in PA in favour of the intervention, only Freitas et al. reported a significant improvement in clinical outcomes[29,30]. Coelho et al., on the other hand, reported no improvements in any of the clinical outcomes measured (asthma control, HRQoL or psychological parameters) following

an unsupervised pedometer-based programme[27], despite achieving a greater mean difference in daily steps compared to control (MD=2605 vs MD=1506 in Freitas et al.).

A possible explanation is that the intensity of the PA performed in the study by Coelho et al. may not have been sufficient to induce a training effect. In COPD, it is suggested that a minimum intensity of 60% of the peak exercise capacity (moderate intensity) is needed to elicit a physiologic training effect[41]. Although participants in the study by Coelho et al. were advised to walk at moderate intensity, as this was unsupervised and exercise intensity was not assessed, it is unclear whether participants were adherent[27]. Furthermore, the improvement in exercise capacity observed in Coelho et al. (14.2m improvement in 6MWT distance)[27] while statistically significant, did not reach clinical significance (MCID=26m[42]). Improving cardiorespiratory fitness is one mechanism by which regular PA has been proposed to improve clinical outcomes in asthma[43-45]. Indeed, Freitas et al., reported an association between improvements in asthma control and QoL and an improvement in cardiorespiratory fitness[29]. It is also important to note however, that the intervention group in Freitas et al., also received a weight-loss programme and achieved a significant reduction in weight compared to control[29], which likely contributed to these clinical improvements[46,47]. Indeed, in a COPD population, targeting obesity using resistance training and caloric restriction has been shown to not only improve body weight and composition, but also clinical outcomes including health status, strength, dyspnoea and exercise and functional capacity[48]. Nonetheless, the findings from Coelho et al.[27] suggest that to achieve improvements in clinical asthma outcomes, it is important to consider not only the amount of PA but the intensity at which it is undertaken.

While our meta-analysis demonstrated an overall positive effect of PA interventions on exercise capacity (VO_2), it is important to note that both studies included in this analysis used an intervention focused on weight loss in addition to improving PA [29,31]. This may in part explain the effect observed as the outcome is often dependent on weight. In Turk et al., however, while the PR only group showed an improvement in exercise capacity (VO2max), as well as a reduction in weight and BMI, change in BMI was not significantly associated with an improvement in VO_2max[31]. This may indicate that an improvement in exercise capacity was achieved irrespective of the amount of weight loss. Furthermore, in the study by Freitas et al., while both groups significantly reduced their weight, only the exercise group showed a significant improvement in VO_2, reported in both mlO_2.Kg.min and mlO_2.min[29]. This suggests that improved exercise capacity was not dependent on weight, and that the exercise intervention was effective in improving exercise capacity.

People with severe asthma are less likely to partake in PA compared to healthy controls[8]. The reasons for physical inactivity in severe asthma are likely to be heterogenous and complex. However, due to the adverse clinical implications of physical inactivity in severe asthma[6] and the observed benefits of targeting physical inactivity[16,17,36], there is an urgent need to develop interventions aimed at addressing this behaviour. Furthermore, in people with severe asthma, physical inactivity has been shown to cluster with obesity, increased sedentary time, and increased symptoms of anxiety and/or depression[49]. Given the clustering of these characteristics, and the additive deleterious clinical impacts observed when they co-exist in this population[49], the bundling of interventions which specifically target these characteristics has the potential to have a significant clinical impact. Further research exploring the benefits of multi-component interventions targeting these other interrelated characteristics is warranted.

Strengths and limitations

Key strengths of this review include the use of a structured protocol, a robust search strategy, and the involvement of two reviewers to independently conduct each step of the systematic review process. However, there are several potential limitations that warrant consideration. For instance, we included only English-language publications and therefore studies may have been missed, with publication bias also an important factor to consider. Another potential limitation is that we focused solely on PA-based interventions. Recent data indicates that comprehensive behaviour change intervention is also effective in increasing PA (steps/day and time spent undertaking MVPA) and improving asthma control, anxiety symptoms and sleep quality in adults with moderate-to-severe asthma[50]. This raises the possibility that behaviour change counselling alone may be sufficient in increasing PA in this population. Further research into the use of behaviour change counselling as either an alternative or complementary approach to PA-based interventions for increasing PA is warranted.

When interpreting the findings of this review, it is also important to consider the limitations of the included studies. Most studies were conducted in Brazil and involved primarily females with comorbid overweight or obesity, thus potentially limiting the generalisability of the findings. However, this high proportion of females is representative of the severe asthma population[51], with obesity also prevalent in this population[52]. Furthermore, although we acknowledge the inherent difficulty in blinding participants to PA interventions, ROB arising from deviations from intended interventions and from the measurement of patient-reported outcomes was identified to be of particular concern. Other common methodological limitations relate to the use of small sample sizes and short intervention periods, with no studies examining the maintenance of PA for longer than 12 months. Nonetheless, these studies demonstrate the feasibility and short-term effectiveness of different PA interventions in this population and may help to inform larger scale and longer duration trials. Finally, confounding is an important issue to consider, as other intervention components (i.e., education/BCT) and factors (i.e., weight reduction), may have contributed to the improvements in PA observed. It is, however, difficult to ascertain whether weight reduction preceded the improvements in PA observed in the included studies. For instance, in Freitas et al., while there was both a significant increase in PA outcomes (i.e., steps/day and time spent undertaking PA) and a reduction in body weight from baseline to post-intervention in the intervention group compared to control[29], it is difficult to determine which occurred first from the data provided. Conversely, in Turk et al., while there was a significant decrease in body weight from baseline to post-intervention in the PR only group compared to control, a significant difference in PA outcomes (steps/day) between groups was not observed until 9-months after the intervention had ended[31]. Nonetheless, as severe asthma is a complex heterogenous disease, it is possible that individualised, multi-component interventions which combine PA prescription with interventions such as PA counselling, goal setting and self-monitoring[53,54], and that address underlying barriers to PA such as obesity, are needed.

Conclusion:

This review provides promising evidence regarding the feasibility and effectiveness of interventions in improving PA, exercise capacity, asthma control and HRQoL in adults with moderate-to-severe asthma. While we are unable to draw a definitive conclusion or offer specific recommendations regarding the optimal PA intervention for the severe asthma population specifically, interventions identified by this review showed short-term improvements in PA outcomes regardless of the PA prescription used. This suggests that future studies should focus on the continued maintenance of PA for example via physical activity goals, such as step counts, or bundling other enabling interventions, such as behaviour change counselling.

Physical inactivity has a significant negative impact on people with asthma, particularly those with severe disease. There is therefore a critical need to develop, test and implement interventions that lead to sustained improvements in PA in this population, using high-quality, larger scale studies.

Author contributions: R.F McLoughlin contributed to the protocol design, data review and analysis and manuscript preparation; V.L Clark contributed to the protocol design, data review and analysis and manuscript preparation; P.D Urroz contributed to the protocol design, data review and analysis and manuscript preparation; P.G Gibson contributed to the protocol design, data review and manuscript preparation; V.M McDonald conceived the research question, contributed to the protocol design, data review and manuscript preparation. All authors approved the final manuscript before submitting for publication.

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Data availability: Data underlying the findings described in this manuscript are available from the authors upon request.

Table 1: Characteristics of included studies

Study (duration, design, country)	Intervention participants	Control participants	Intervention characteristics*	Control conditions
Freitas, 2017/18* (12 week, 2-arm P-RCT, Brazil)	N=26 moderate-severe asthma; age: 45.9±7.7; % female: 96; BMI: 38.1±2.8	N=25 moderate-severe asthma; age: 48.5±9.6; % female: 100; BMI: 37.2±2.1	**F:** 2 sessions/week **I:** 50-75% of peak VO_2 **T:** 60min/session **T:** Aerobic and resistance training **M:** Supervised, individual sessions	Sham exercise (stretching and breathing)
Coelho, 2018 (12 week, 2-arm P-RCT, Brazil)	N=20 moderate-severe asthma; age: 45.0±19.0; % female: 90; BMI: 27.1±6.5	N=17 moderate-severe asthma; age: 47.0±14.0; % female: 82; BMI: 30.3±7.4	**F:** 5 session/week (minimum) **I:** Moderate **T:** 30min/session (minimum) **T:** Pedometer-based programme (daily step targets calculated bi-weekly; (average daily steps over the previous week plus 1000 steps) **M:** Unsupervised, individualised step-based PA prescription, encouraged to walk at moderate intensity ≥5 days/week for ≥30min/day	Participants encouraged to walk at moderate intensity ≥5 days/week for at least 30minutes/day.
Evaristo, 2020 (12 week, 2-arm P-RCT, Brazil)	N=29 moderate-severe asthma; age: 49.8±9.7; % female: 76; BMI: 28.4±3.2	N=25 moderate-severe asthma; age: 50.6±9.2; % female: 68; BMI: 27.5±4.7	**F:** 2 sessions/week **I:** 60-80% HR recovery **T:** 49min/session **T:** Aerobic training **M:** Supervised, group sessions of 4-7 participants.	Breathing exercise program (based on pranayama yoga breathing technique)
Turk, 2020 (12 week, 3-arm P-RCT, Netherlands)	*PR only:* N=14 moderate-severe asthma; age: 41.6±9.7; % female: 71; BMI: 36.7±4.8 *PR + SMS:* N=7 moderate-severe asthma; age: 41.6±12.5; % female: 57; BMI: 36.8±5.0	N=10 moderate-severe asthma; age: 41.9±8.6; % female: 90; BMI: 35.2±3.9	**F:**3 sessions/week **I:** 90% of VO2 max **T:** 40-60min/session **T:** HIIT (body weight exercises) **M:** Supervised, individual sessions	Participants were encouraged to lose weight and exercise

P-RCT, parallel-group randomised controlled trial; BMI, body mass index; PR, pulmonary rehabilitation; PR+SMS, pulmonary rehabilitation with an internet-based self-management programme. *Physical activity/exercise components of the interventions are summarised according to the mode of delivery of the physical activity/exercise intervention (M) and the FITT principles: F, frequency of sessions; I, intensity of sessions; T, duration of each session; T, type of physical activity/exercise prescribed.

Table 2: Summary of physical activity, asthma-related and health-related outcomes reported in the intervention group compared to control in the included studies

	Freitas, 2017/18	Coelho, 2018	Evaristo, 2020	Turk, 2020
Physical activity outcomes				
Daily step count (steps/day)	↑	↑	↔	↔^
Light-intensity PA (minutes/day)	↑			
MVPA (minutes/day)	↑			
Sedentary time (minutes/day)	↔			
Physical activity level (PAL)				↔
Asthma-related outcomes				
HRQoL (AQLQ)	↑	↔	↔	↔
Asthma control questionnaire (ACQ) score	↓	↔	↔	↔^
Lung function	↑			↑
Exacerbations (rates)	↓			↔^
Airway inflammation	↓		↔	↔
Systemic inflammation	↓			↓
Asthma symptom-free days	↑		↔	
Health-related outcomes				
Weight	↓			↓
Body mass index	↓			↓^
Waist circumference	↓			↔
Skeletal muscle strength	↑			
Exercise capacity	↑	↑	↔	↑^
Anxiety/depression scores	↓*	↔	↔	

↑: Significant increase in the intervention group compared to control. ↔ no significant difference between the intervention group and the control group. ↓ Significant decrease in the intervention group compared to control.
^statistically significant positive effect in variable between intervention (PR only group) and control at 12-months follow-up. *significant increase in the proportion of participants without symptoms of depression in the intervention group compared to control. Blank cell indicates the outcome was not measured.

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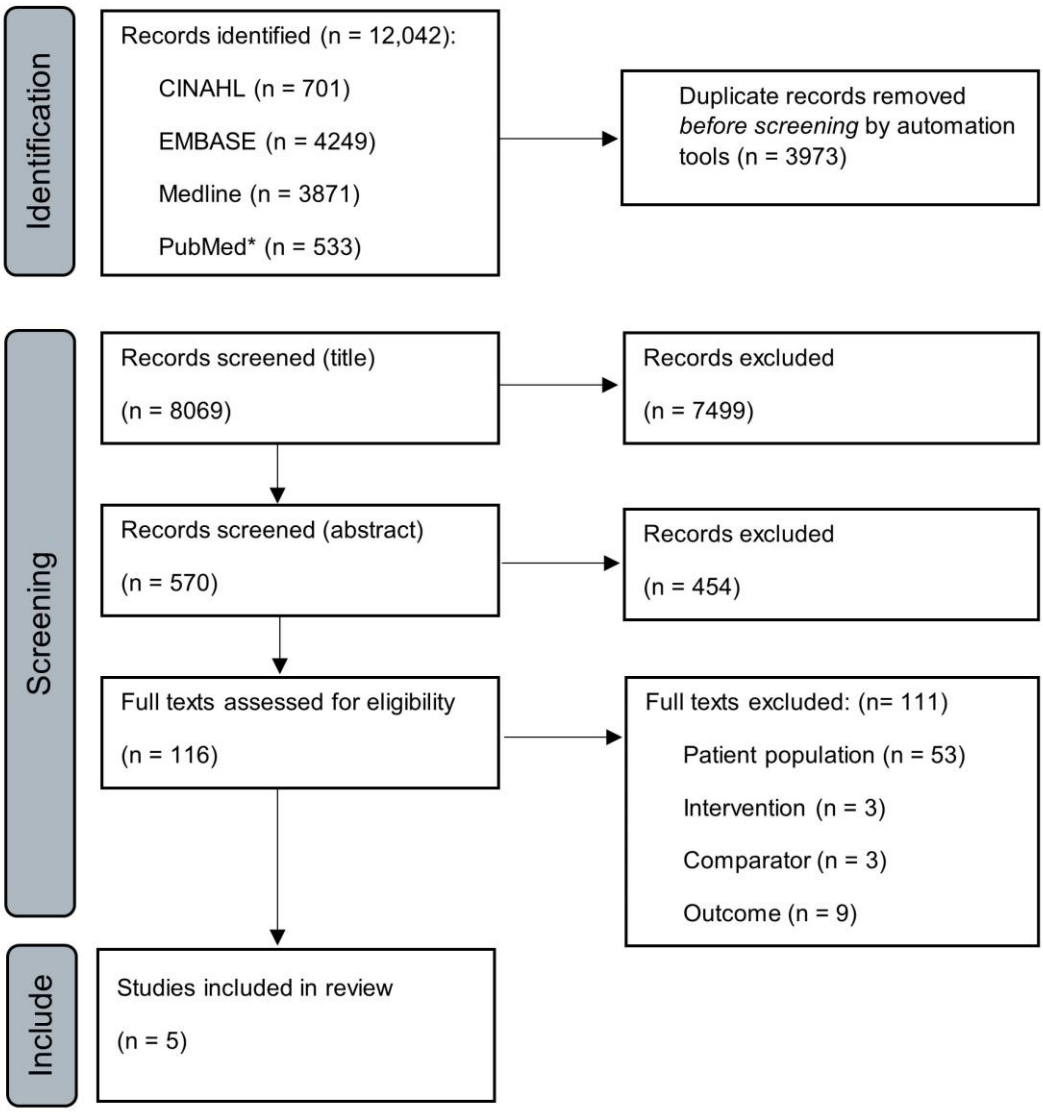

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of articles for inclusion. *non-Medline search

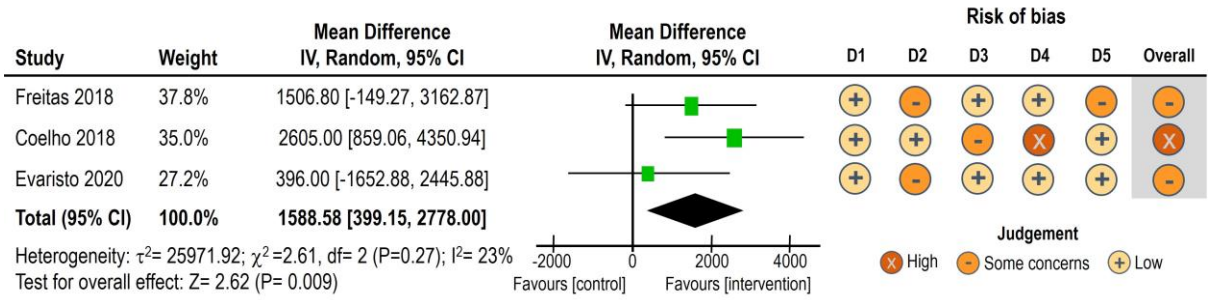

Figure 2: Meta-analysis of randomised controlled trials examining the effect of physical activity interventions versus control on steps per day (post-intervention). D1: Bias arising from the randomisation process; D2: Bias due to deviations from the intended intervention; D3: Bias due to missing outcome data; D4: Bias in measurement of the outcome; D5: Bias in the selection of the reported result.

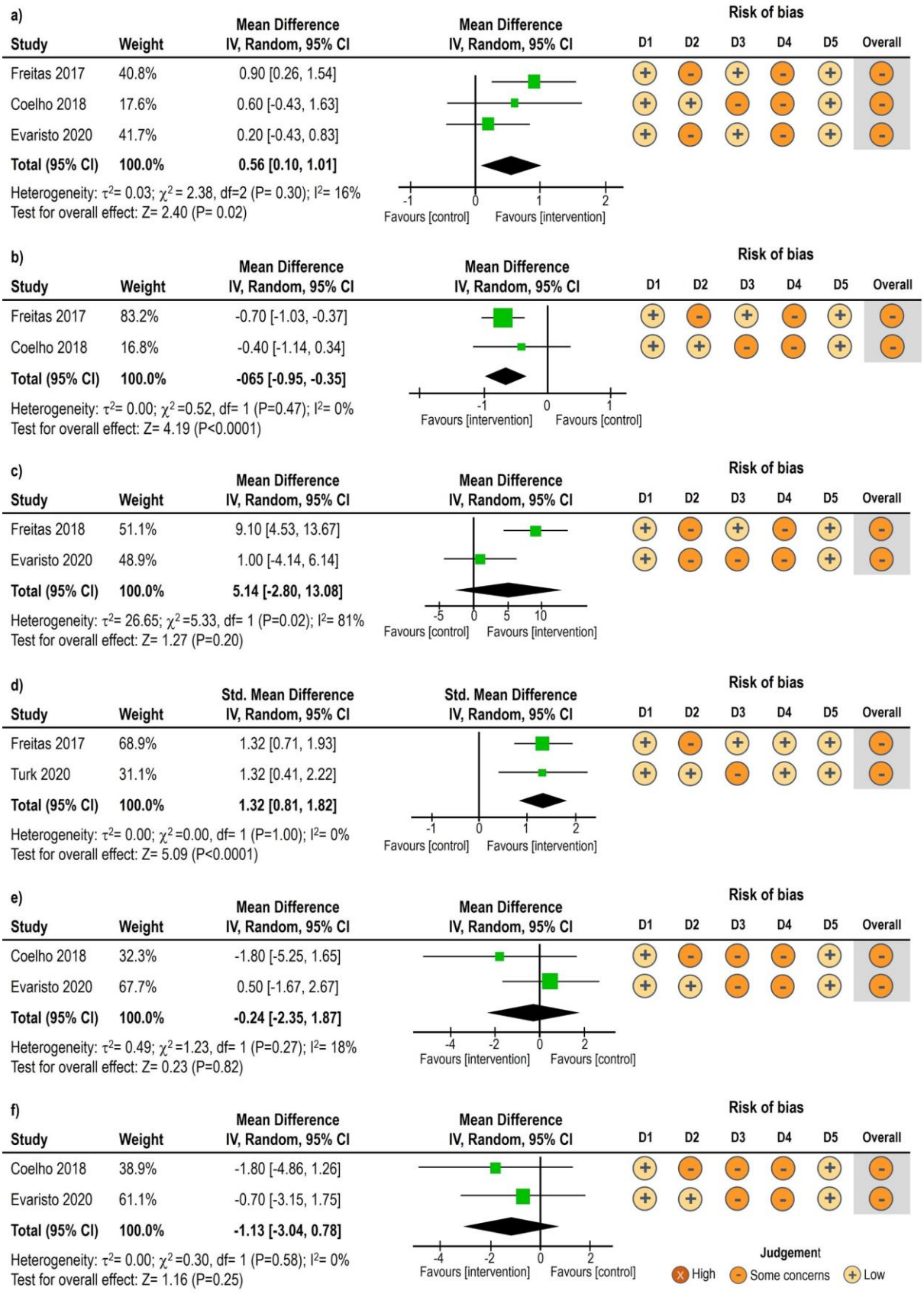
a)
Study
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Freitas 2017 40.8% 0.90 [0.26, 1.54]
Coelho 2018 17.6% 0.60 [-0.43, 1.63]
Evaristo 2020 41.7% 0.20 [-0.43, 0.83]
Total (95% CI) 100.0% 0.56 [0.10, 1.01]
Heterogeneity: τ²= 0.03; χ² = 2.38, df=2 (P= 0.30); I²= 16%
Test for overall effect: Z= 2.40 (P= 0.02)
-1 0 1 2
Favours [control] Favours [intervention]
b)
Study
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Freitas 2017 83.2% -0.70 [-1.03, -0.37]
Coelho 2018 16.8% -0.40 [-1.14, 0.34]
Total (95% CI) 100.0% -065 [-0.95, -0.35]
Heterogeneity: τ²= 0.00; χ² =0.52, df= 1 (P=0.47); I²= 0%
Test for overall effect: Z= 4.19 (P<0.0001)
-1 0 1
Favours [intervention] Favours [control]
c)
Study
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Freitas 2018 51.1% 9.10 [4.53, 13.67]
Evaristo 2020 48.9% 1.00 [-4.14, 6.14]
Total (95% CI) 100.0% 5.14 [-2.80, 13.08]
Heterogeneity: τ²= 26.65; χ² =5.33, df= 1 (P=0.02); I²= 81%
Test for overall effect: Z= 1.27 (P=0.20)
-5 0 5 10
Favours [control] Favours [intervention]
d)
Study
Weight
Std. Mean Difference IV, Random, 95% CI
Std. Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Freitas 2017 68.9% 1.32 [0.71, 1.93]
Turk 2020 31.1% 1.32 [0.41, 2.22]
Total (95% CI) 100.0% 1.32 [0.81, 1.82]
Heterogeneity: τ²= 0.00; χ² =0.00, df= 1 (P=1.00); I²= 0%
Test for overall effect: Z= 5.09 (P<0.0001)
-1 0 1 2
Favours [control] Favours [intervention]
e)
Study
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Coelho 2018 32.3% -1.80 [-5.25, 1.65]
Evaristo 2020 67.7% 0.50 [-1.67, 2.67]
Total (95% CI) 100.0% -0.24 [-2.35, 1.87]
Heterogeneity: τ²= 0.49; χ² =1.23, df= 1 (P=0.27); I²= 18%
Test for overall effect: Z= 0.23 (P=0.82)
-4 -2 0 2
Favours [intervention] Favours [control]
f)
Study
Weight
Mean Difference IV, Random, 95% CI
Mean Difference IV, Random, 95% CI
Risk of bias
D1 D2 D3 D4 D5 Overall
Coelho 2018 38.9% -1.80 [-4.86, 1.26]
Evaristo 2020 61.1% -0.70 [-3.15, 1.75]
Total (95% CI) 100.0% -1.13 [-3.04, 0.78]
Heterogeneity: τ²= 0.00; χ² =0.30, df= 1 (P=0.58); I²= 0%
Test for overall effect: Z= 1.16 (P=0.25)
-4 -2 0 2
Favours [intervention] Favours [control]
Judgement
High Some concerns Low

Figure 3: Meta-analysis of randomised controlled trials examining the effect of physical activity interventions versus control on secondary outcomes of interest: a) asthma-related quality of life (AQLQ) (post-intervention), b) asthma control (ACQ) (post-intervention) and c) asthma control (asthma symptom-free days) (post-intervention), d) exercise capacity (VO2) (change from baseline), e) anxiety scores (post-intervention) and f) depression scores (post-intervention). D1: Bias arising from the randomisation process; D2: Bias due to deviations from the intended intervention; D3: Bias due to missing outcome data; D4: Bias in measurement of the outcome; D5: Bias in the selection of the reported result.

ONLINE SUPPLEMENT

Figure S1: Medline search strategy

Database(s): **Medline** 1946 - present
Search Strategy:

#	Searches
1	"Activities of Daily Living"/
2	activities of daily living.tw.
3	physical activit*.mp.
4	exercise/ or exp running/ or swimming/ or walking/ or stair climbing/
5	(cycl* or walk* or runn* or interval train* or resistance train* or exercis* or intensity train* or weight bearing or hiit or aerobic train*).tw.
6	circuit-based exercise/ or endurance training/ or high-intensity interval training/ or plyometric exercise/ or resistance training/
7	1 or 2 or 3 or 4 or 5 or 6
8	Asthma/
9	asthma*.tw.
10	8 or 9
11	pilot stud*.mp.
12	clinical trial/
13	Randomized Controlled Trial/
14	(random* or trial or group or intervention* or observational or case-control or longitudinal or pre-post or crossover).tw.
15	11 or 12 or 13 or 14
16	7 and 10 and 15
17	animals/ not humans/
18	16 not 17

Figure S2: CINAHL search strategy

#	Query	Limiters/Expanders	Last Run Via	Results
S21	S19 NOT S18	Limiters - Human Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S20	S19 NOT S18	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S19	S8 AND S12 AND S17	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S18	(MH "Animal Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S17	S13 or S14 or S15 or S16	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S16	AB "pilot stud*" or "randomised controlled trial*" or "randomized controlled trial*" or group or intervention* or observational or longitudinal or pre-post or crossover	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S15	TI "pilot stud*" or "randomised controlled trial*" or "randomized controlled trial*" or group or intervention* or observational or longitudinal or pre-post or crossover	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S14	(MH "Pilot Studies") OR (MH "Cross Sectional Studies")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S13	(MH "Randomized Controlled Trials") OR (MH "Clinical Trials")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S12	S9 or S10 or S11	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S11	AB asthma" or "severe asthma" or "moderate-severe asthma" or "disease refractory asthma" or "treatment resistant asthma" or "difficult to treat asthma" or therapy-resistant asthma" or "steroid-dependent asthma" or "brittle asthma"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S10	TI asthma" or "severe asthma" or "moderate-severe asthma" or "disease refractory asthma" or "treatment resistant asthma" or "difficult to treat asthma" or therapy-resistant asthma" or "steroid-dependent asthma" or "brittle asthma"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S9	(MH "Asthma")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S8	S1 or s2 or s3 or s4 or s5 or s6 or s7	Expanders - Apply equivalent subjects	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	Display

		Search modes - Boolean/Phrase	Database - CINAHL Complete	
S7	AB "resistance train"* or "strength train"* or "weight train"* or "resistance exercis"* or "aerobic train"* or "intensity train"* or "endurance train"* or hiit or walk* or runn* or jog* or sprint* or exercis* or "activities of daily living" or "physical activit"*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S6	TI "resistance train"* or "strength train"* or "weight train"* or "resistance exercis"* or "aerobic train"* or "intensity train"* or "endurance train"* or hiit or walk* or runn* or jog* or sprint* or exercis* or "activities of daily living" or "physical activit"*	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S5	(MH "Walking")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S4	(MH "Jogging") OR (MH "Sprinting") OR (MH "Running") OR "running or jogging or run or jog"	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S3	(MH "Exercise") OR (MH "Resistance Training") OR (MH "Group Exercise")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S2	(MH "Physical Activity") OR (MH "Exercise")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display
S1	(MH "Activities of Daily Living")	Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	Display

Figure S3 – EMBASE search strategy

1	daily life activity/
2	"activities of daily living".mp.
3	"daily life activity".tw.
4	physical activity/ or "physical activity, capacity and performance"/ or climbing/ or cycling/ or jogging/ or jumping/ or lifting effort/ or running/ or swimming/ or walking/ or weight bearing/ or weight lifting/
5	(physical activit* or climb* or walk* or cycl* or jogg* or swimm* or weight bearing or weight lifting or interval train* or resistance train* or hiit or aerobic train* or endurance train*).tw.
6	high intensity interval training/ or exercise/
7	aerobic exercise/ or aquatic exercise/ or arm exercise/ or breathing exercise/ or circuit training/ or dynamic exercise/ or endurance training/ or high intensity interval training/ or isokinetic exercise/ or leg exercise/ or pilates/ or plyometrics/ or resistance training/ or static exercise/
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	asthma/ or severe persistent asthma/
10	asthma*.tw.
11	9 or 10
12	randomized controlled trial/
13	pilot study/
14	clinical trial/
15	case control study/
16	(random* or trial or intervention* or observational or case-control or longitudinal or pre-post or crossover).tw.
17	12 or 13 or 14 or 15 or 16
18	8 and 11 and 17
19	animals/ not humans/
20	18 not 19
21	limit 20 to english language

Figure S4 – Pubmed (non-medline) search terms

((((((((((((((((((((((("activities of daily living"[All Fields]) OR ("physical activity"[All Fields])) OR ("exercise"[All Fields])) OR ("running"[All Fields])) OR ("jogging"[All Fields])) OR ("cycling"[All Fields])) OR ("climbing"[All Fields])) OR ("walking"[All Fields])) OR ("interval training"[All Fields])) OR ("resistance training"[All Fields])) OR ("high intensity training"[All Fields])) OR ("weight bearing exercise"[All Fields])) OR ("hiit"[All Fields])) OR ("aerobic training"[All Fields])) OR ("circuit training"[All Fields])) OR ("endurance training"[All Fields])) OR ("endurance exercise"[All Fields])) AND ("asthma"[All Fields])) OR ("severe asthma"[All Fields])) OR ("difficult asthma"[All Fields])) OR ("treatment resistant asthma"[All Fields])) OR ("brittle asthma"[All Fields])) AND ("randomized controlled trial"[All Fields])) OR ("clinical trial"[All Fields])) OR ("pre post trial"[All Fields])) OR ("observational study"[All Fields])

Figure S5 – Informit (health collection) search strategy

informit

Search History

Set	Search Terms	Limits
3	("activities of daily living" OR " physical activit*" OR exercis* OR runn* OR jogg* OR cycling OR climb* OR walk* OR "interval train*" OR "resistance train*" OR "intensity train*" OR "weight bearing" OR hiit OR "aerobic train*" OR "circuit-based exercise" OR "endurance train*" OR "high-intensity interval train*" OR "resistance train*") AND (asthma* OR "severe asthma" OR "disease refractory asthma" OR "treatment resistant asthma" OR "difficult to treat asthma" OR "therapy-resistant asthma" OR "steroid-dependent asthma" OR "brittle asthma")	
2	("activities of daily living" OR " physical activit*" OR exercis* OR runn* OR jogg* OR cycling OR climb* OR walk* OR "interval train*" OR "resistance train*" OR "intensity train*" OR "weight bearing" OR hiit OR "aerobic train*" OR "circuit-based exercise" OR "endurance train*" OR "high-intensity interval train*" OR "resistance train*") AND (asthma* OR "severe asthma" OR "disease refractory asthma" OR "treatment resistant asthma" OR "difficult to treat asthma" OR "therapy-resistant asthma" OR "steroid-dependent asthma" OR "brittle asthma") AND ("randomi?ed controlled trial" OR "pilot stud*" OR "clinical trial" OR "trial" OR intervention*)	
1	"exercis*" AND ("severe asthma")	

Figure S6 – SPORTDiscus search strategy

#	Query	Limiters/Expanders	Last Run Via
S1	("activities of daily living" OR " physical activit*" OR exercis* OR runn* OR jogg* OR cycling OR climb* OR walk* OR "interval train*" OR "resistance train*" OR "intensity train*" OR "weight bearing" OR hiit OR "aerobic train*" OR "circuit-based exercise" OR "endurance train*" OR "high-intensity interval train*" OR "resistance train*") AND (asthma* OR "severe asthma" OR "disease refractory asthma" OR "treatment resistant asthma" OR "difficult to treat asthma" OR "therapy-resistant asthma" OR "steroid-dependent asthma" OR "brittle asthma") AND ("randomi?ed controlled trial" OR random* OR group OR observational OR "pilot stud*" OR "clinical trial" OR "trial" OR intervention* OR crossover OR "pre-post" OR longitudinal)	Limiters - Published Date: 19790101-20200931; Language: English Expanders - Apply equivalent subjects Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - SPORTDiscus with Full Text

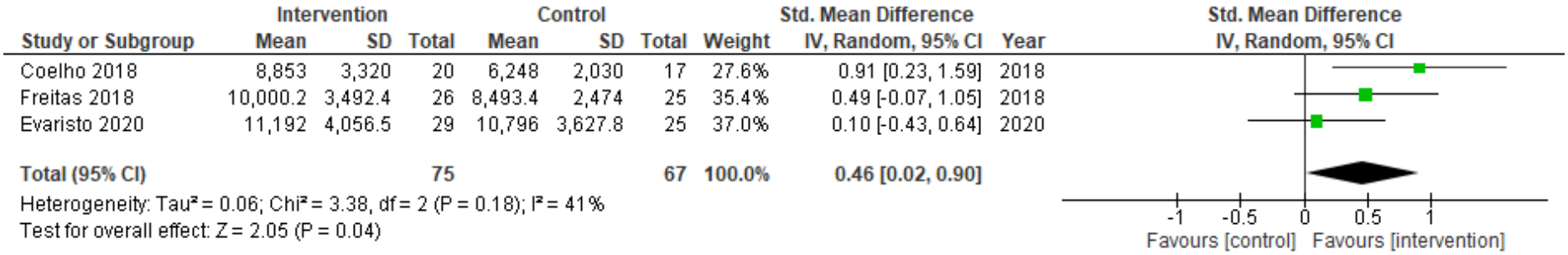

Figure S7. Random effects meta-analysis of randomised controlled trials examining the effect of physical activity interventions versus control on steps per day (post-intervention).

Table-S1: Summary of physical activity outcomes reported in included studies

Study		N	Baseline	Post-intervention	Change	Included in meta-analysis	ROB
Daily step count (steps/day)							
Freitas, 2017/18	IG: CG:	26 25	7306 ± 2304 7764 ± 2176	10000.2 ± 3492.4[a] 8493.4 ± 2474.0	3274 ± 2693[b] 729 ± 1145	Yes – Figure 2	Some concerns
Coelho, 2018	IG CG:	20 17	7295 ± 3241 6998 ± 3490	8853 ± 3320[c] 6248 ± 2030	-	Yes – Figure 2	High
Evaristo, 2020	IG: CG:	29 25	9186 (7926, 10446)* 8809 (7428, 10189)*	11 192 (9649, 12 735)* 10 976 (9298, 12 293)*	-	Yes – Figure 2	Some concerns
Turk, 2020	IG1: IG2: CG:	14 7 10	5997 (4024, 8048) 5616 (4306, 6080) 7413 (2962, 8155)	-	1008 (70, 2994) 3097 (1785, 4740) 1281 (-65, 4036)	No – post-intervention data not available	-
Light-intensity physical activity (minutes/day)							
Freitas, 2018	IG: CG:	26 25	340.9 ± 71.4 369.4 ± 63.7	395.7 ± 72.5[d] 366.6 ± 67.5	54.8 -2.8[e]	No – insufficient studies	-
Moderate to vigorous physical activity (minutes/day)							
Freitas, 2018	IG: CG:	26 25	25.3 ± 14.5 26.3 ± 16.9	43.5 ± 22.2[a] 34.2 ± 19.9[d]	18.2 ± 17.9[b] 7.9 ± 13.8	No – insufficient studies	-
Sedentary time (minutes/day)							
Freitas, 2018	IG: CG:	26 25	488.9 ± 84.2 489.5 ± 143.4	477.3 ± 86.1 497.0 ± 104.4	-11.6[e] 7.5[e]	No – insufficient studies	
Physical activity level (PAL)							
Turk, 2020	IG1: IG2: CG:	14 7 10	1.48 ± 0.16 1.43 ± 0.09 1.47 ± 0.14	-	0.00 ± 0.18 0.11 ± 0.08[d] 0.04 ± 0.08	No – insufficient studies	-

Data reported as mean ± SD or median (interquartile range; IQR), unless otherwise stated. *mean (95% confidence interval; CI),
[a]p<0.001 versus baseline, [b]p<0.001 versus control, [c]p<0.05 versus control post-intervention, [d]p<0.05 versus baseline. [e]mean change calculated from baseline

and post-intervention data, insufficient information to calculate SD of mean change.

Table-S2: Summary of asthma-related outcomes reported in included studies

Study		N	Baseline	Post-intervention	Change	Included in meta-analysis	ROB
Health-related quality of life (AQLQ)							
Freitas, 2017	IG: CG:	26 25	3.7 ± 1.1 3.6 ± 0.9	4.9 ± 1.3[a] 4.0 ± 1.0[b]	-	Yes – Figure 3a	Some concerns
Coelho, 2018	IG CG:	20 17	4.5 ± 1.4 4.2 ± 1.3	4.9 ± 1.6 4.3 ± 1.6	-	Yes – Figure 3a	Some concerns
Evaristo, 2020	IG: CG:	29 25	3.9 ± 1.1 4.2 ± 1.0	4.7 ± 1.0[d] 4.5 ± 1.3	-	Yes – Figure 3a	Some concerns
Turk, 2020	IG1: IG2: CG:	14 7 10	4.77 (4.33, 5.43) 4.40 (4.13, 5.33) 4.47 (3.47, 5.00)	-	0.2 (-0.33, 0.84) 1.47 (-0.4, 1.74) 0.12 (-0.26, 0.62)	No – post-intervention data not available	-
Asthma control (ACQ)							
Freitas, 2017 (ACQ-7)	IG: CG:	26 25	2.0 ± 0.9 2.0 ± 0.7	1.1 ± 0.7[a] 1.8 ± 0.5	-	Yes – Figure 3b	Some concerns
Coelho, 2018 (ACQ-7)	IG CG:	20 17	1.7 ± 1.4 1.8 ± 0.8	1.5 ± 1.2 1.9 ± 1.1	-	Yes – Figure 3b	Some concerns
Evaristo, 2020 (ACQ-6)	IG: CG:	29 25	2.0 (1.6-6.3)* 1.7 (1.2–2.0)*	1.3 (0.9-1.6)[a]* 1.5 (1.0-1.8)*	-	No – data non-parametric (median 95% CI)	-
Turk, 2020	IG1: IG2: CG:	14 7 10	2.17 (1.46, 2.50) 1.67 (1.17, 1.83) 2.09 (1.50, 2.68)	-	-0.67 (-1.42, 0.00) -0.66 (-0.17, -0.33) -0.25 (-0.66, 0.63)	No – post-intervention data not available	-

Data reported as mean ± SD or median (IQR), unless otherwise stated. *median (95% CI). [a]p<0.001 versus baseline, [b]p<0.05 versus baseline, [c]p<0.05 versus control post-intervention, [d]p<0.001 time effect

Table-S2 continued: Summary of asthma-related outcomes reported in included studies

Study		N	Baseline	Post-intervention	Change	Included in meta-analysis	ROB
Asthma control (asthma symptom-free days)							
Freitas, 2018	IG: CG:	26 25	6.5 ± 7.6 5.2 ± 5.3	21.3 ± 7.9 12.2 ± 8.7	14.5 ± 9.6 8.6 ± 11.4	Yes – Figure 3c	Some concerns
Evaristo, 2020	IG: CG:	29 25	6 (2.7, 9.7)* 8 (3.8, 11.7)*	12 (8.4, 15.6)* 11 (6.6, 14.6)*	-	Yes – Figure 3c	Some concerns
Airway inflammation							
Freitas, 2017 (FeNO)	IG: CG:	26 25	24.7 (15.3, 33.7) 22.3 (16.2, 32.6)	-	-6.8 (-14.6, 0.7)[a] -0.2 (3.9, 1.6)	No	-
Turk, 2020 (FeNO)	IG1: IG2: CG:	14 7 10	18.0 (10.5, 25.0) 17. (16.0, 25.0) 17.0 (8.5, 26.0)	-	-0.5 (-3.3, 3.3) 0.5 (-7.3, 6.5) -0.5 (-14.8, 4.0)	No	
Turk, 2020 (sputum neutrophils %)	IG1: IG2: CG:	14 7 10	37.2 (28.4, 51.0) 29.6 (23.4, 57.9) 49.4 (39.6, 57.2)	-	-3.6 (-33.5, 35.9) 15.1 (-9.8, 22.4) -7.2 (-49.1, -7.2)	No	-
Turk, 2020 (sputum eosinophil %)	IG1: IG2: CG:	14 7 10	0.65 (0.05, 4.30) 0.90 (0.23, 4.05) 0.65 (0.50, 2.90)	-	-0.15 (-2.40, 1.13) 0.00 (-0.83, 1.05) 1.20 (0.25, 3.05)	No	-

Data reported as mean ± SD or median (IQR), unless otherwise stated. *mean (95% CI). [a]p<0.001 versus baseline, [b]p<0.05 versus baseline, [c]p<0.05 versus control post-intervention, [d]p<0.001 time effect

Table-S3: Summary of health-related outcomes reported in included studies

Study		N	Baseline	Post-intervention	Change	Included in meta-analysis	ROB
Weight							
Freitas, 2017	IG: CG:	26 25	91.1 (86.3, 99.8) 88.6 (84.4, 94.4)	-	-6.1 (-7.4, -4.2)[a] -2.9 (-3.9, -1.4)[a]	No	-
Turk, 2020	IG1: IG2: CG:	14 7 10	103.3 ± 17.76 106.3 ± 10.87 100.7 ± 17.56	-	-4.9 ± 4.9[b] -10.9 ± 8.4[b] -0.1 ± 1.7	No	-
Body mass index							
Freitas, 2017	IG: CG:	26 25	37.7 (35.4, 40.1) 37.4 (35.2, 38.7)	-	-2.7 (-3.3, -1.8)[a] -1.1 (-1.8, -0.4)[a]	No	-
Turk, 2020	IG1: IG2: CG:	14 7 10	36.7 ± 4.8 36.8 ± 5.0 35.2 ± 3.9	-	-1.81 ± 1.79[b,d] -3.62 ± 2.73[b] 0.25 ± 0.65	No	-
Waist circumference							
Freitas, 2017	IG: CG:	26 25	111.0 (106.0, 118.0) 112.0 (106.1, 117.2)	-	-6.2 (-11.0, -3.0)[a] -4.0 (-6.0, -0.9)[a]	No	-
Turk, 2020	IG1: IG2: CG:	14 7 10	109.7 ± 13.7 114.3 ± 8.8 107.0 ± 10.5	-	-3.68 ± 7.23 -12.14 ± 9.84 4.67 ± 11.96	No	-
Fat mass %							
Turk, 2020	IG1: IG2: CG:	14 7 10	44.7 ± 5.9 39.6 ± 11.8 44.1 ± 4.5	-	-1.41 ± 1.36[b,d] -2.01 ± 3.86[b] -0.33 ± 1.75	No	-

Data reported as mean ± SD or median (IQR), unless otherwise stated. [a]p<0.001 versus baseline, [b]p<0.05 versus baseline, [c]p<0.01 versus baseline, [d]p<0.05 versus control post-intervention, [e]p<0.001 time effect, [f]p<0.05 group x time, [g]p<0.01 time effect

Table-S3 continued: Summary of health-related outcomes reported in included studies

Study		N	Baseline	Post-intervention	Change	Included in meta-analysis	- ROB
Exercise capacity							
Freitas, 2017 (VO2)	IG: CG:	26 25	1423 (1321, 1591) 1291 (1178, 1475)	-	156 (91.4, 229.3)[a] 8.4 (-95.4, 75.6)	Yes – Figure 3d	Some concerns
Freitas, 2017 (work rate)	IG: CG:	26 25	91.5 (83.0, 103.0) 85.0 (69.0, 98.7)	-	26.0 (22.0, 39.0)[a] 12.0 (-2.2, 20.5)[c]	No	-
Coelho, 2018 (6MWT- m)	IG CG:	20 17	535.5 ± 41.5 522.7 ± 76.4	549.7 ± 46.1[d] 515.5 ± 75.6	-	No	
Evaristo, 2020 (ISWT)	IG: CG:	29 25	342 (302-382)* 360 (not reported)	429 (389-470)[fg]* 412 (369-456)*	-	No	-
Turk, 2020 (VO2 max %)	IG1: IG2: CG:	14 7 10	51.1 ± 17.7 60.6 ± 11.3 56.5 ± 11.3	-	13.2 ± 9.2[h] 11.2 ± 13.5 -0.1 ± 10.5	Yes – Figure 3d	Some concerns
Turk, 2020 (6MWT - m)	IG1: IG2: CG:	14 7 10	578 ± 76 606 ± 56 587 ± 73	-	52 ± 40[h] 63 ± 40[b] -14 ± 51	No	-
Anxiety score							
Coelho, 2018	IG CG:	20 17	9.4 ± 5.6 11.1 ± 5.3	8.3 ± 5.9 10.1 ± 4.8	-	Yes – Figure 3e	Some concerns
Evaristo, 2020	IG: CG:	29 25	8.7 ± 3.9 8.6 ± 4.6	7.7 ± 3.6[e] 7.2 ± 4.4	-	Yes – Figure 3e	Some concerns
Depression score							
Coelho, 2018	IG CG:	20 17	7.2 ± 4.6 8.1 ± 4.2	5.8 ± 4.9 7.6 ± 4.6	-	Yes – Figure 3f	Some concerns
Evaristo, 2020	IG: CG:	29 25	7.2 ± 3.8 8.3 ± 4.4	5.7 ± 4.3[e] 6.2 ± 3.9	-	Yes – Figure 3f	Some concerns

Data reported as mean ± SD or median (IQR), unless otherwise stated. *mean (95% CI). [a]p<0.001 versus baseline, [b]p<0.05 versus baseline, [c]p<0.01 versus baseline, [d]p<0.05 versus control post-intervention, [e]p<0.001 time effect, [f]p<0.05 group x time, [g]p<0.01 time effect

Table S4: Sensitivity analysis

			Random-effects analysis		Fixed-effects analysis	
Outcome	**Studies (n)**	**Participants (n)**	**Effect estimate**	**I^2**	**Effect estimate**	**I^2**
Steps/day	3	IG: 75, CG: 67	MD [95% CI]: 1588.58 [399.15, 2778.00]	23%	MD [95% CI]: 1609.86 [573.28, 2646.45]	23%
AQLQ	3	IG: 75, CG: 67	MD [95% CI]: 0.56 [0.10, 1.01]	16%	MD [95% CI]: 0.55 [0.14, 0.96]	16%
ACQ	2	IG: 46, CG: 42	MD [95% CI]: -0.65 [-0.95, -0.35]	0%	MD [95% CI]: -0.65 [-0.95, -0.35]	0%
Asthma symptom-free days	2	IG: 55, CG: 50	MD [95% CI]: 5.14 [-2.80, 13.08]	81%	MD [95% CI]: 5.53 [2.11, 8.94]	81%
*Exercise capacity (VO2)**	2	IG: 40, CG: 35	SMD [95% CI]: 1.32 [0.81, 1.82]	0%	SMD [95% CI]: 1.32 [0.81, 1.82]	0%
Anxiety score (HADS-A)	2	IG: 49, CG: 42	MD [95% CI]: -0.24 [-2.35, 1.87]	18%	MD [95% CI]: -0.15 [-1.98, 1.68]	18%
Depression score (HADS-D)	2	IG: 49, CG: 42	MD [95% CI]: -1.13 [-3.04, 0.78]	0%	MD [95% CI]: -1.13 [-3.04, 0.78]	0%

AQLQ, asthma quality of life questionnaire; ACQ, asthma control questionnaire; VO2, maximum oxygen consumption; HADS-A, anxiety subscale of the hospital anxiety and depression scale; HADS-D, depression subscale of the hospital anxiety and depression scale; IG, intervention group; CG, control group; MD, mean difference; CI, confidence interval; SMD, standardised mean difference. *change from baseline data analysed.