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Medical Group

Journal of Novel Physiotherapy and Physical Rehabilitation

ISSN: 2455-5487 DOI

Elissa M McDonald[1] and Felix S F Ram[2]*

[1]School of Nursing, Faculty of Medical and Health Sciences, University of Auckland, Private Bag 92019, Auckland, 1142, New Zealand
[2]College of Health, Massey University-Auckland, Private Bag 102 904, North Shore Mail Centre, Auckland, New Zealand

Dates: Received: 15 December, 2016; **Accepted:** 06 January, 2017; **Published:** 07 January, 2017

***Corresponding author:** Dr Felix S F Ram, College of Health, Massey University-Auckland, Private Bag 102 904, North Shore Mail Centre, Auckland, New Zealand, E-mail: fsfram@yahoo.co.uk

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Review Article

Pulmonary Rehabilitation Using Regular Physical Exercise for the Management of Patients with Asthma

Abstract

Background: Regular physical activity increases physical fitness and lowers ventilation during mild and moderate exercise thereby reducing the likelihood of provoking exercise-induced asthma. Regular exercise may also reduce the perception of breathlessness through a number of mechanisms including strengthening respiratory muscles. Subjectively, many asthmatics report that they are symptomatically better when fit, but results from trials have varied and have been difficult to compare because of different designs and training protocols.

Objectives: To assess evidence for the efficacy and effectiveness of regular physical training in patients with asthma. We searched the Cochrane database, Medline, Sportdiscus and Science citation index. Randomised trials in asthmatic patients undertaking regular physical training aged 7 years and older were considered for inclusion. Regular physical training had to involve at least 20 minutes, 2 to 3 times a week, over a minimum of four weeks.

Results: Eight studies could be included in this review. Physical exercise had no effect on resting lung function or the number of days of wheeze. Physical exercise improved cardiopulmonary fitness as measured by an increase in maximum oxygen uptake of 4.9 ml/kg/min (95% confidence interval 3.9 to 5.8). Regular exercise did not decrease any lung function measures. There were no data concerning quality of life measurements.

Conclusion: In patients with asthma, pulmonary rehabilitation using regular exercise improves cardiopulmonary fitness without changing lung function. There is no reason to withhold regular physical exercise in patients with asthma for the fear of deteriorating lung function. It is not known whether improved fitness is translated into improved quality of life.

Introduction

The diagnosis of asthma in majority of cases is based on patient symptoms of intermittent wheeze, chest tightness and response to bronchodilator medication. However, it is not as simple to define asthma, mainly due to our poor understanding of its causes. Asthma is defined by three characteristics: bronchial hyper-responsiveness, reversible airway obstruction and inflammation. Early definitions of asthma included the presence of airways obstruction that could reverse spontaneously or with treatment, and also the increased narrowing of the airways to stimuli (e.g. histamine, cold air, exercise, viral upper respiratory infection, cigarette smoke or respiratory allergens) causing bronchial hyper-responsiveness. Management of asthma has been enhanced by the recognition that the airways sub-mucosa of patients with asthma are chronically inflamed with a typical inflammatory infiltrate, and that inflammatory processes are important in causing the main characteristics of asthma of airways obstruction and bronchial hyper-responsiveness. As a result of inflammation the airways are hyper-responsive and they narrow easily in response to a wide range of stimuli. This may result in coughing, wheezing, chest tightness and shortness of breath with symptoms often worse at night. Narrowing of the airways is usually reversible with appropriate pharmacological intervention, but in patients with chronic inflammatory condition it leads to irreversible airflow obstruction [1-3]. Characteristic pathology of asthmatic airways displays lung hyperinflation, smooth muscle hypertrophy, mucosal edema, lamina thickening, epithelial cell sloughing, cilia disruption and mucus hyper-secretion. Its pathology is further characterized by the presence of increased numbers of eosinophils, neutrophils, lymphocytes, and plasma cells in the bronchial tissues, bronchial secretions, and mucus.

Citation: McDonald EM, Ram FSF (2017) Pulmonary Rehabilitation Using Regular Physical Exercise for the Management of Patients with Asthma. J Nov Physiother Phys Rehabil 4(1): 001-008. DOI: http://doi.org/10.17352/2455-5487.000038

Prevalence and severity of asthma is increasing and no one doubts that the cause of this increase is due to multitude of factors. However, there is a growing body of evidence that implicates lifestyle changes, specifically decreased physical activity as the single most important contributor to the increase in asthma prevalence and severity, seen globally. There has been a steady decrease in the levels of physical activity of adults and children over the years and this decrease corresponds in time course to the increased prevalence of asthma [4-6]. Furthermore, most studies have shown that asthmatic subjects have a lower aerobic fitness level than their non-asthmatic peers and that this limited fitness level in asthmatic subjects seems not to be related to their degree of airway obstruction but rather to their decreased levels of habitual activity [7]. Exercise has long been recognized as a possible method of improving subjective and objective asthma indices even though there is the potential for exercise-induced asthma (EIA) while undertaking physical activity. However, it has been well documented that the incidence of EIA after proper medical (and pharmacological) prophylaxis is extremely low [8] and the benefits and safety of exercise in asthmatic subjects have been well demonstrated [7-9].

People with asthma have a unique response to exercise. In some, exercise can provoke an increase in airways resistance leading to EIA but regular exercise is also considered to be useful in the management of asthma, especially in children and adolescents [10]. However, the fear of inducing an episode of breathlessness inhibits many people from taking part in exercise. A low level of regular exercise leads to a low level of physical fitness, so it is not surprising that a number of studies [7-11] have found that patients with asthma have lower cardiorespiratory fitness than their peers although not every study has reported this finding [12].

Exercise programs have been designed for people with asthma with the aim of improving physical fitness, neuromuscular co-ordination and self-confidence. Anecdotally, many patients report that they are symptomatically better when fit, but the physiological basis of this perceived benefit has not been consistently shown in studies published to date. A possible mechanism is that an increase in regular exercise of sufficient intensity to increase aerobic fitness will raise the ventilatory threshold thereby lowering the minute ventilation during mild and moderate exercise. Consequently, breathlessness and the likelihood of provoking EIA will both be reduced. Exercise training may also reduce the perception of breathlessness through other mechanisms including strengthening of the respiratory muscles.

A systematic review was undertaken to gain a better understanding of the effects of regular exercise on the health of people with asthma. The systematic review focused on the effects of exercise on resting pulmonary function, aerobic fitness, clinical status and quality of life in people with asthma. With this systematic review explicit criteria were used to elect studies for inclusion and to assess their quality. Various electronic medical databases were searched for studies from their date of inception till November 2016. The reference lists of all studies obtained were reviewed to identify trials not captured by electronic and manual searches. In addition, authors of included studies were contacted when required for additional information or clarification and for any ongoing studies. This systematic review was originally published electronically [13] in 2000 on the Cochrane Library and has since been updated to encompass literature search up to and including November 2016.

Objectives

This systematic review was undertaken to gain a better understanding of the effects of regular exercise on the health of patients with asthma. The objective was to assess evidence from high quality randomized controlled clinical trials (RCTs) of the effects of regular exercise in the management of asthma.

Methods

Types of studies and participants

Only studies that involved subjects with asthma who were randomized to regular exercise (intervention group) or no exercise (control group) were selected. Subjects had to be aged 7 years and older and their asthma had to be diagnosed by a physician or by the use of objective criteria – for example bronchodilator reversibility. Subjects with any degree of asthma severity were included. To qualify for inclusion regular exercise had to include whole body aerobic exercise for at least 20 minutes, two or more times a week, for a minimum of four weeks.

Literature search and study identification

The following terms were used to search for studies: asthma* AND (work capacity OR physical activity OR training OR rehabilitation OR physical fitness). The Cochrane Trials Database, CENTRAL, (November 2016) was searched for studies. Additional searches were carried out on Medline (1966–2016), Embase (1980–2016), SPORTDiscus (1949–2016), Current contents index (1995–2016) and Science Citation Index (1995–2016). The reference lists of all the papers that were obtained were reviewed to identify trials not captured by electronic and manual searches. Abstracts were reviewed without language restriction. When more data were required for the systematic review, authors of the study were contacted requesting additional information or clarification.

Data extraction, analysis and study quality assessment

Following outcome measures were searched for:

- bronchodilator usage, episodes of wheeze
- symptoms (recorded in daily diary cards)
- exercise endurance
- work capacity
- walking distance
- quality of life

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- physiological measurements which included the following:
  - PEFR: peak expiratory flow rate, FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, VO_{2max}: maximum oxygen consumption or uptake, VEmax: maximum exercise ventilation, HR_{max}: maximum heart rate, MVV: maximum voluntary ventilation.

Two reviewers (EMM and FSFR) assessed the trials for inclusion by only looking at the methods section of each paper without reading the results of the study or conclusions [14]. Each reviewer independently applied written inclusion/exclusion criteria to the methods section of each study. Disagreement about inclusion of a study was resolved whenever possible by consensus and an independent person was consulted if disagreement persisted. All trials that appeared potentially relevant were assessed, and if appropriate were included in the review.

The methodological quality of the included trials was assessed with particular emphasis on treatment allocation concealment, which was ranked using the following Cochrane Collaboration approach:

- Grade A: Adequate concealment
- Grade B: Uncertain
- Grade C: Clearly inadequate concealment
- Grade D: Not used (no attempt at concealment).

Two reviewers independently extracted data from the trials. The trials were combined for meta-analysis using Review Manager 5.3.5 [15]. Fixed effect model was used for statistical analysis. The outcomes of interest in this review were continuous data. Data from each of the continuous outcomes were analyzed as weighted mean difference (WMD) with 95 per cent confidence intervals (95%CI).

Results

The electronic search yielded 1,964 potential studies: 184 references were found in Embase, 708 in Medline/PubMed, 86 in SPORT Discus and 843 from the Cochrane Trials Database. An additional 143 references were added from bibliographic searching of relevant articles. Of a total of 1,964 abstracts, only 126 dealt with physical training in asthma. The full text of each of the 126 papers was obtained and translated where necessary (one each from French and German). Sixty-eight studies were excluded as they were not relevant to the topic being reviewed, leaving 58 studies for potential inclusion in the review. Upon closer examination of the study methodology a further 34 studies were excluded (mostly due to not being an RCT) and the remaining 24 were included in this systematic review [16-38].

Corresponding authors of included studies were contacted to clarify areas of uncertainty. Most of the trials did not describe the method of randomisation and did not make any references to allocation concealment (blinding). All trials mentioned that subject allocation was carried out randomly. Using the Cochrane approach for allocation concealment, the trials reporting method of allocation (using coded random numbers and drawing lots) were graded 'A' and all other trials included in this review were allocated a grade 'B' indicating that there was uncertainty as to the method of treatment allocation used by the authors in their trials. All outcomes were graded according to the quality of evidence obtained. This was based on the number and size of trial(s) contributing data towards any particular outcome. Table 1 lists details for each outcome measure.

"A" grade level of evidence (randomized controlled trials only) has been shown in this review which has been graded as shown below. Arbitrarily, the following cut-off points for study size have been used; large study ≥60 patients per study; moderate study >40 patients per study; small study <40 patients in each study.

* A1: evidence from two or more large sized RCTs

A2: evidence from at least one large sized RCT

A3: evidence from two or more moderate sized RCTs

A4: evidence from at least one moderate sized RCT

A5: evidence from two or more small sized RCTs

A6: evidence from at least one small sized RCT

Figure 1 shows the effect of regular physical exercise on VO_2max. The output from the statistical software used (RevMan 5.3.5) shows the mean and standard deviation for the exercise/training group and the control group (no exercise) for each of the nine studies where VO_2max was measured. On the right hand side of Figure 1 the weighted mean difference (WMD) is shown. This is the difference between the exercise and control groups, weighted according to the precision of the study in estimating the effect (precision is calculated as the inverse of the variance). This method assumes that all of the trials have measured the outcome on the same scale and that for each study the baseline VO_2max was not significantly different between control and experimental groups. Where the WMD lies to the right of the line of zero effect, it favours regular exercise. If the 95 per cent confidence interval (represented by horizontal black lines) does not cross the line of zero effect, the result is

Table 1: Summarising the evidence.

Outcome measure	Results	Level of evidence
PEFR	5 RCTs, two moderate and three of small size	A3
FEV_1	11 RCTs, three of large size, six of moderate size and two of small size	A1
FVC	9 RCTs, , three of larg e size, two of moderate size and four of small size	A1
VE_{max}	5 RCTs, one of large size, two of moderate size and two of small size	A2
VO_{2max}	9 RCTs, one of large size, one of moderate size and seven of small size	A2
HR_{max}	2 RCTs two of small size	A5

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statistically significant. The overall weighted mean difference (95 per cent confidence interval) for the nine studies was 4.91 ml.kg⁻¹min⁻¹ (3.98 to 5.84), represented by the diamond at the bottom of the figure – i.e. regular exercise resulted in an increase in VO_2max of 4.91 ml.kg⁻¹min⁻¹.

The Chi^2 value (12.49) gives an indication of the heterogeneity of the studies. The test of heterogeneity shows whether or not the differences in the results of the nine studies are greater than would be expected by chance. In this instance the Chi^2 value has to be greater than 15.51 (critical value of chi^2 with 8 degrees of freedom and α = 0·05) before the studies would be considered heterogeneous. For the VO_2max outcome measure it is 12.49 and therefore it can be concluded that the RCTs contributing to this particular outcome were not heterogeneous. This is also denoted by the p value of 0.13 (i.e. heterogeneity being non-significant). The Z statistic (10.33) indicates the level of significance of the overall result (with $p < 0.00001$).

Table 2 provides a summary of the overall results. The overall WMD is shown for each outcome measure along with the 95 per cent confidence intervals.

Regular exercise led to a significant increase in VO_{2max} (9 studies) and showed a trend towards improving VE_{max} with five studies (Figure 2). Six minute walk distance was reported by one study [32] which improved significantly with regular exercise. However, regular exercise did not change FEV_1, FVC or PEFR (Figures 3-5). Heart rate showed slight increase (3.67 bpm) with regular exercise.

No usable data were available for the following outcome measures: maximum voluntary ventilation, bronchodilator use, symptom diary scores, exercise endurance, work capacity, quality of life or walking distance. There were insufficient studies to justify subgroup analysis by gender, age or exercise intensity.

Discussion

The clearest finding of this meta-analysis was that aerobic power (VO_{2max}) significantly increased with regular exercise. This shows that the response of subjects with asthma to regular exercise is similar to that of healthy people [39] and therefore presumably the benefits of an increase in cardiorespiratory fitness are also accessible to them. In addition, VE_{max} also showed an increase with regular exercise, although the overall result was not statistically significant it is consistent with the observation that VO_{2max} increased. Further studies would likely confirm the increase in VE_{max} seen with regular exercise.

This review also showed convincingly that resting lung function does not change with regular exercise. This is not surprising since there is no obvious reason why regular exercise should improve PEFR, FEV_1 or FVC. It seems that any benefits of regular exercise in patients with asthma are unrelated to effects on lung function. On the other hand, evidence from this review suggests that regular exercise does not have any detrimental effect on lung function. This is reassuring for the continued promotion of exercise prescription by health professionals [40].

One study [32] reported both 6MWD and quality of life, both of which improved significantly with regular exercise. However, as only one study to date has reported these outcomes further studies are required to confirm these findings, prior to any conclusions being drawn on the benefits of regular exercise on these outcome measures.

Typically physical training has no effect or slightly reduces the maximum heart rate whereas maximum stroke volume, and thus maximum cardiac output improves [41,42]. In the studies that were included in this review [16-35], HR_{max} increased after physical training. This suggests that cardiac factors did not limit maximum exercise capacity prior to training. Breathlessness

Table 2: Overall result for each outcome.

Outcome measure	Weighted mean difference	95% confidence interval	Number of studies contributing to outcome (total participants)
$VO2_{max}$ (ml/kg/min)	4.91	3.98 to 5.84	9 (279)
FEV_1 (l)	0·02	-0·06 to 0·10	11 (756)
FVC (l)	0·03	-0·08 to 0·15	9 (674)
VE_{max} (l/min)	3.08	-0.63 to 6.79	5 (200)
PEFR (l/min)	-6.46	-27.57 to 14.65	5 (161)
HR_{max} (bpm)	3.67	0.90 to 6.44	2 (34)

$VO2_{max}$, maximum oxygen consumption or uptake; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; VE_{max}, maximum expiratory flow; PEFR, peak expiratory flow rate; HR_{max}, maximum heart rate.

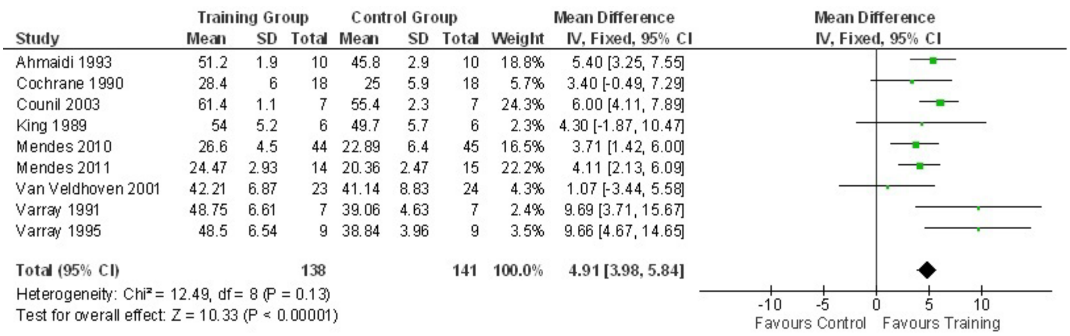

Figure 1: Details of VO2max (ml/kg/min) outcome.

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Study	Training Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cochrane 1990	66	16	18	58	14	18	14.2%	8.00 [-1.82, 17.82]
Counil 2003	102.1	7.4	7	87.3	10.4	7	15.4%	14.80 [5.34, 24.26]
Mendes 2010	57.1	17.4	44	60.8	15	45	30.1%	-3.70 [-10.46, 3.06]
Van Veldhoven 2001	62.58	9.98	23	60.06	13.27	24	30.6%	2.52 [-4.17, 9.21]
Varray 1991	47.26	12.8	7	47.17	9.73	7	9.7%	0.09 [-11.82, 12.00]
Total (95% CI)			**99**			**101**	**100.0%**	**3.08 [-0.63, 6.79]**

Heterogeneity: Chi² = 11.00, df = 4 (P = 0.03)
Test for overall effect: Z = 1.63 (P = 0.10)

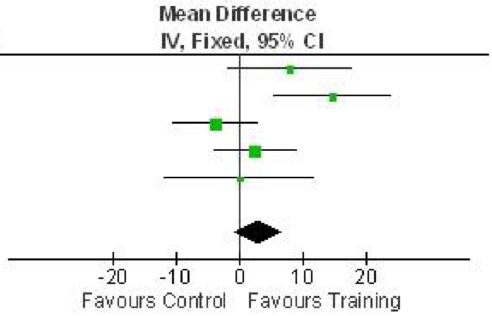

Figure 2: Details of VEmax (l/min) outcome. Although the solid diamond is situated on the right hand side of the line of no effect (favoring exercise/training indicating that regular exercise increases VEmax), it does cross the line of no effect implying that the overall effect in not statistically significant.

Study	Training Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Cochrane 1990	2.97	0.69	18	3.13	0.8	18	2.9%	-0.16 [-0.65, 0.33]
Franca-Pinto 2016	2.1	0.8	22	2.1	0.7	21	3.4%	0.00 [-0.45, 0.45]
Ma 2015	2.8	0.8	165	2.7	0.8	165	22.8%	0.10 [-0.07, 0.27]
Mendes 2010	2.25	0.61	44	2.38	0.62	45	10.4%	-0.13 [-0.39, 0.13]
Mendes 2011	1.832	0.566	14	2.351	0.599	15	3.8%	-0.52 [-0.94, -0.09]
Moreira 2008	2.46	0.58	16	2.57	0.59	15	4.0%	-0.11 [-0.52, 0.30]
Silva 2006	1.8	0.29	23	1.76	0.34	23	20.4%	0.04 [-0.14, 0.22]
Van Veldhoven 2001	2.16	0.51	23	2.18	0.36	24	10.6%	-0.02 [-0.27, 0.23]
Varray 1991	1.66	0.25	7	1.74	0.42	7	5.2%	-0.08 [-0.44, 0.28]
Wang 2009	2.1	0.38	15	1.76	0.35	15	10.0%	0.34 [0.08, 0.60]
Wicher 2010	2.04	0.69	30	1.95	0.59	31	6.5%	0.09 [-0.23, 0.41]
Total (95% CI)			**377**			**379**	**100.0%**	**0.02 [-0.06, 0.10]**

Heterogeneity: Chi² = 15.64, df = 10 (P = 0.11)
Test for overall effect: Z = 0.53 (P = 0.60)

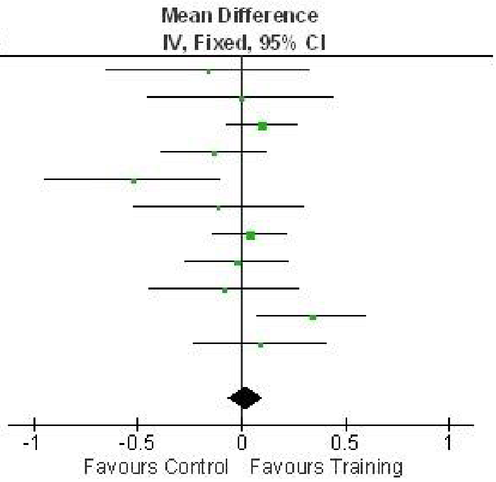

Figure 3: Details of FEV1 (l/min) outcome. The solid diamond crosses the line of no effect therefore indicating that physical training does not alter FEV1.

Study	Training Group Mean	SD	Total	Control Group Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Franca-Pinto 2016	2.79	0.9	22	2.7	0.9	21	4.6%	0.09 [-0.45, 0.63]
Ma 2015	4	1.1	165	3.9	1	165	25.8%	0.10 [-0.13, 0.33]
Mendes 2010	3.12	0.6	44	3.22	0.62	45	20.6%	-0.10 [-0.35, 0.15]
Mendes 2011	2.712	0.632	14	3.319	0.555	15	7.0%	-0.61 [-1.04, -0.17]
Moreira 2008	2.88	0.67	16	2.9	0.71	15	5.6%	-0.02 [-0.51, 0.47]
Van Veldhoven 2001	2.59	0.57	23	2.55	0.48	24	14.5%	0.04 [-0.26, 0.34]
Varray 1991	2.07	0.87	7	2.26	0.55	7	2.3%	-0.19 [-0.95, 0.57]
Wang 2009	2.36	0.41	15	1.97	0.5	15	12.4%	0.39 [0.06, 0.72]
Wicher 2010	2.77	0.9	30	2.53	0.8	31	7.2%	0.24 [-0.19, 0.67]
Total (95% CI)			**336**			**338**	**100.0%**	**0.03 [-0.08, 0.15]**

Heterogeneity: Chi² = 15.63, df = 8 (P = 0.05)
Test for overall effect: Z = 0.55 (P = 0.58)

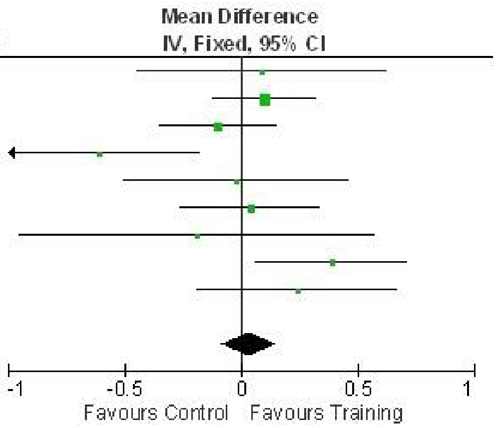

Figure 4: Details of FVC (l) outcome. The solid diamond crosses the line of no effect therefore indicating that physical training does not alter FVC.

or some other non-cardiac factor may have terminated the baseline tests before a true HR_{max} was achieved. The higher heart rate following regular exercise may reflect the ability of subjects to exercise for longer. An alternative explanation, which is improbable, is that the medication taken to prevent EIA caused the increased HR_{max}. Inhaled beta agonists can raise heart rate above resting levels but prophylactic medication was not changed during the study period and there is no evidence that physical training alters the cardiac response to beta-agonists. The significance of the effect of these agents on heart rate lies in their alteration of the workload-heart rate relationship and the possible consequences of this for exercise prescription based on heart rate.

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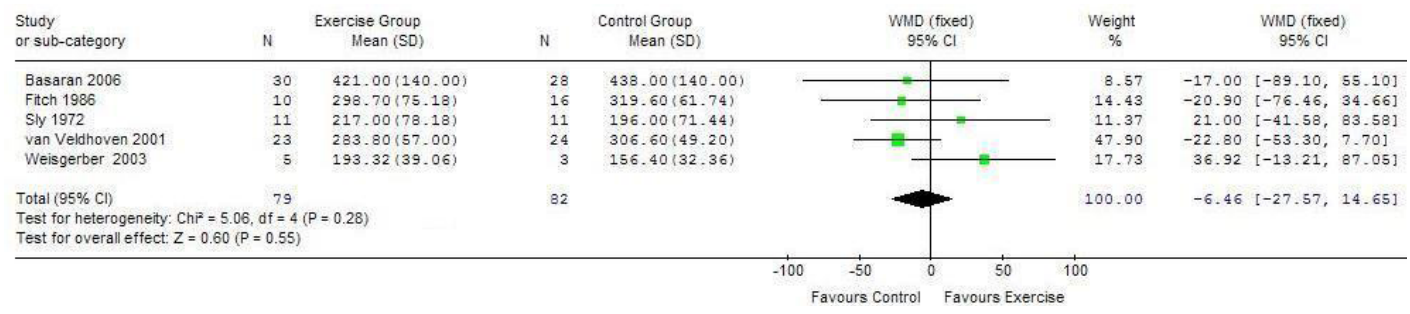

Figure 5: Details of PEFR (l/min) outcome. The solid diamond crosses the line of no effect indicating that physical training does not significantly alter PEFR in patients with asthma.

Unfortunately, there were no data available on a number of outcome measures of interest for this review, the list included exercise endurance (as distinct from VO_{2max}), diary symptoms (other than frequency of wheeze), quality of life and bronchodilator use. This review has revealed an important gap in our knowledge about the effects of regular exercise in the management of asthma. There is, however, evidence from one study [43] which was excluded from this review, suggesting that regular exercise may improve these outcomes. The study by Cambach et al., [43], included subjects with asthma, but was not included in our review because they also received education about their disease and breathing retraining. This means that any benefit could not be ascribed solely to regular physical exercise. Nonetheless, the intervention resulted in significant improvements in exercise endurance time and the total score for the Chronic Respiratory Disease Questionnaire increased by 17 points compared to the control group. In subjects with COPD, pulmonary rehabilitation does not lead to an improvement in these parameters unless the subjects undertake regular exercise training [44] and the same may be true of asthma. A study from Brazil [45], allocated children to physical exercise or a control group. The study was not included in the review because the allocation of the subjects was not truly random, but it did find that regular physical exercise led to significant reductions in the use of both inhaled and oral steroids.

Although there are a number of pitfalls in conducting a systematic review (e.g. incomplete electronic databases, bias in selection of relevant studies and quality of included studies), we believe these were adequately dealt with the methodology employed. Hand searching of journals was used including reference check of all studies obtained, two reviewers independently reviewed all studies obtained for inclusion and the review was restricted to randomized controlled trials only, thus eliminating a substantial source of lower quality study data. Another potential weakness of this review is the small number of subjects included. However, the studies which measured VO_{2max} were not heterogeneous and all studies showed a similar effect which was statistically significant ($p < 0.00001$).

Conclusion

This review has shown that aerobic power and ventilation improves following regular exercise in patients with asthma. The evidence included in this review suggests that a minimum of 20 minutes of exercise, two or more times a week will lead to improvement in cardiorespiratory fitness in patients with asthma providing the same level of benefit afforded to people who do not have asthma. This appears to be a normal training effect and is not due to an improvement in resting lung function. Examples of regular exercise that provided this benefit included whole body aerobic exercise (for example, running or jogging, gymnastics, basketball, cycling and swimming).

What is also clear from the evidence included in this review is that regular exercise should not be limited due to perceived (and unsubstantiated) limitations of asthma. Fear of inducing an episode of breathlessness inhibits many asthmatic patients from taking part in exercise. However, we found no evidence of any detrimental effect on lung function, deterioration or worsening symptoms in asthmatic patients included in this review. There is no reason to withhold regular physical exercise in patients with asthma. Therefore, it is recommended that all patients with asthma should participate in regular exercise without the fear of asthma inhibiting their participation. This will not only improve asthma management but also provide associated general health benefits.

There still remains a need for further trials for assessment of the role of exercise in the management of asthma. It is particularly important to determine whether the improved exercise performance that follows regular exercise is translated into fewer symptoms and an improvement in quality of life. Further studies are required to confirm the improvements seen in this systematic review especially symptoms and quality of life.

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Citation: McDonald EM, Ram FSF (2017) Pulmonary Rehabilitation Using Regular Physical Exercise for the Management of Patients with Asthma. J Nov Physiother Phys Rehabil 4(1): 001-008. DOI: http://doi.org/10.17352/2455-5487.000038

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