CME review

Benefits of exercise in asthma

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Learning Objectives:
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- Discuss the evidence that exercise is beneficial for patients with asthma
- Improve potential quality of life for asthma patients by encouraging an appropriate exercise regimen

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Introduction

Exercise-induced bronchospasm (EIB) is a condition in which individuals experience shortness of breath, wheezing, and chest tightness within or after physical exertion. EIB is formally defined as
the airway obstruction that occurs in association with exercise without regard to the presence of chronic asthma. Diagnosis of EIB may be made by a detected decrease in forced expiratory volume in 1 second (FEV<sub>1</sub>) of 10% to 15% with exercise. Decreases in FEV<sub>1</sub> correlate with symptoms; FEV<sub>1</sub> decreases markedly within minutes after the cessation of exercise, reaches peak impairment within 5 to 10 minutes, and slowly recovers in 10 minutes to 1 hour. As its definition implies, EIB is seen in both individuals with asthma and those without underlying asthma. Nonasthmatic individuals with EIB may have a normal FEV<sub>1</sub> at baseline and only experience symptoms during exercise. In contrast, an impaired FEV<sub>1</sub> at baseline with bronchodilator reversibility indicates underlying asthma, and the classification of asthma depends on the degree of FEV<sub>1</sub> impairment. Roughly 90% of adults who have been diagnosed as having asthma report EIB. In addition, EIB is a marker of poor asthma control, according to the National Asthma Education and Prevention Program.

The distinction between EIB and exercise-induced asthma (EIA) should be made. Historically, EIA has been defined as the condition in which exercise induces symptoms of asthma in patients who have asthma. The term EIA is problematic for several reasons. First, it implies that exercise causes asthma when it is more appropriate to state that exercise is a trigger of asthma symptoms that can be controlled in the same way as symptoms from other triggers. Second, EIB is not exclusive to asthma as the term EIA might suggest. Finally, EIB in both asthmatic and nonasthmatic individuals has considerable overlap in symptoms, pathophysiologic mechanisms, and treatment. Thus, EIB and EIA are now commonly grouped together under the term EIB. The diagnosis, prevalence, and treatment of EIB have been recently reviewed. This review summarizes the pathophysiologic mechanisms of EIB and the most recent data that demonstrate the potential benefits of exercise in humans and animal models.

Pathophysiologic Mechanisms of EIB

Osmotic Theory of EIB

It has long been known that the humidity content of environmental air has a major effect on EIB. Exercise in dry air is more likely to cause EIB than exercise in humid air (efig 1). The osmotic theory of EIB postulates that water and electrolyte imbalance within the bronchial mucosa leads to inflammatory reactions that cause smooth muscle contraction of the airways [Fig 1]. Water loss from humidifying inspired air creates a hyperosmolar surface airway environment with increased Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, and Ca<sup>2+</sup> ions and mucus production. Water diffuses out of cells to restore airway surface osmolality, thus creating a hyperosmolar intracellular environment that precipitates the increase of inflammatory mediators. The key players in this response appear to be epithelial cells, eosinophils, and mast cells. Higher mean concentrations of columnar epithelial cells, mast cells, and eosinophils have been detected in the airways of individuals with EIB compared with healthy controls. In addition, the number of eosinophils in the sputum correlate with severity of EIB. Mast cells and eosinophils release inflammatory mediators, including histamine, leukotrienes, and prostaglandins. Patients with EIB have increased levels of histamine, tryptase, and cysteinyl leukotrienes in their sputum after 30 minutes of exercise compared with baseline.

Bronchial smooth muscle contraction follows with symptoms of shortness of breath, cough, wheezing, and chest tightness. The osmotic theory may explain why competitive athletes have a high prevalence of EIB. Elite athletes are more likely than casual athletes or sedentary individuals to engage in extremely strenuous exercise with a high minute ventilation. In addition, the osmotic theory would explain why some sports are more asthmogenic than others. A study by Storms et al found that the most asthmogenic sports are those with the highest minute ventilation (basketball, cycling, soccer) and those that take place in cold weather (cross-country skiing, hockey, skating). Weiler et al reported that among US Olympic athletes, 15.3% of the 699 polled summer games athletes reported asthma symptoms, whereas 22.4% of winter games athletes reported asthma symptoms, suggesting that the low humidity of cold air is an important trigger of EIB.

Small-Airway Damage

Other than osmotic influences, dry air may be damaging by other mechanisms. In normal conditions, air is fully humidified in the respiratory tract by the 12th airway generation. Very dry air requires the use of smaller airways to condition the air. Excessive ventilation causes stress in very small airways (<1 mm) and thus injures the epithelium. Evidence of this has been shown by increases in the ratio of cysteinyl leukotrienes to prostaglandin E<sub>2</sub> identified in the airways of individuals with EIB compared with controls. Recurrent injury over time damages the contractile properties of the bronchial smooth muscle. In addition, mast cell numbers increase with each generation of airway, so higher generations may also have an increased probability of causing EIB due to higher local production of
inflammatory mediators. This mechanism of recurrent small airway injury may be another contributing factor to the higher rate of EIB in elite athletes compared with the general population, especially when superimposed on osmotic mechanisms from high minute ventilation during strenuous exercise.

Vasoconstriction and Reactive Hyperemia

It has been proposed that thermal gradients in the airways may contribute to EIB.19 According to this hypothesis, hyperpnea during exercise causes airway cooling, leading to vasoconstriction in the bronchial circulation (Fig 1). Rapid rewarming and reactive hyperemia result in edema of the airway wall. Although there is some evidence to support this hypothesis, it has been largely discounted in favor of the hypertonicity hypothesis.19

Atopy

As mentioned, EIB is defined as bronchospasm regardless of the presence or absence of asthma. However, even in athletes with EIB and no underlying diagnosis of asthma, atopy appears to play a role in both risk and symptom severity. The presence of asthma or allergic rhinitis greatly increases the risk of having EIB. In one study by Helenius et al,20 the number of positive reactions on a skin prick test with aeroallergens were directly correlated with the odds ratio of increased bronchial responsiveness and asthma.20 Thus, although atopy may not be the primary cause of EIB, it may be an aggravant.

Irritants

Aside from humidity and allergenic antigens, other environmental components likely play a role in EIB. Some Olympic swimmers with EIB have coincident eosinophilia in their airways, suggesting an allergic or irritant mechanism.21 As mentioned, rates of EIB are higher in urban populations compared with rural populations. This effect is presumably a consequence of increased air pollution in urban environments because various pollutants have been found to exacerbate asthma and EIB. Particular matter from combustion engines up-regulates cysteinyl leukotrienes and oxidizes glutathione.22 Both of these factors can cause localized inflammation and EIB. Even normal atmospheric components may be irritating; ozone is an oxidant that depletes antioxidants, leading to a reduction of intracellular antioxidant capability.23,24

Because dry air is known to be a causative factors in EIB, then it could be postulated that swimming and other water sports, where the environmental air is humid, would have lower potential for causing EIB. In fact, the data on EIB prevalence in swimmers are controversial. Some studies have found higher rates of EIB in swimmers compared with land sport athletes, which has been explained as a result of the irritation of airways by chlorine compounds in swimming pools. Chemicals that are used to disinfect pools, including hypochlorite, chlorine gas, chloramines, and chloroisocyanates (collectively termed chlorine), have been found to damage lung epithelium.25 Many researchers have argued that exposure to chlorinated pools as infants causes airway changes that predispose children to developing asthma and recurrent bronchitis, whereas others have found no such increased risk.25–29 Interestingly, among studies that measured the concentrations of chlorine in the swimming pools, the mean levels of chemicals were below the 500-μg/m3 level that the World Health Organization delineated in their guidelines for safe swimming environments.30,31 Still, discrepancies in these findings could be accounted for by differences in the maximum recommended levels between countries.

Benefits of Exercise in EIB

Despite the fact that exercise is a causative factor in EIB, there is increasing evidence that regular exercise and aerobic conditioning reduce the frequency and severity of EIB. Data from both animal models and human studies support this concept.

Evidence from Animal Models

There are surprisingly few studies that have investigated the effects of exercise on asthma in animal models. Much of the work has been performed by the Schweibert Laboratory at the University of Alabama. This laboratory uses a mouse model for allergen-mediated asthma by sensitizing mice to ovalbumin peptide by intraperitoneal injection and challenging with aerosolized ovalbumin, a method that mimics human asthma by inducing hallmark lung changes, including increased mucous production, basement membrane thickening, and eosinophil and neutrophil infiltrates.31 Pastva et al31 investigated the effects of exercise training on these inflammatory changes in the lungs. Mice underwent a 4-week aerobic conditioning period in which they ran on motorized treadmills for 30 to 45 minutes a day, 3 times a week at 50% to 75% maximum oxygen consumption. Compared with sedentary mice, the aerobically trained mice experienced significantly fewer inflammatory changes in their lungs after subsequent ovalbumin aerosol challenge (Fig 2, A, B, and C). Trained mice had significantly down-regulated expression of the murine homologue of interleukin (IL) 8 and of vascular cell adhesion molecule 1 in their lung tissue, resulting in a decrease in infiltrating macrophages, lymphocytes, and eosinophils.31,32 In bronchial lavage fluid, IL-4 and IL-5 levels were decreased by 13- and 3-fold, respectively. Finally, exercise significantly decreased serum ovalbumin specific IgE levels but did not affect total IgE levels (Fig 2, D and E). These effects were postulated to be partially due to the finding that exercise decreased nuclear factor-κB nuclear translocation and DNA binding in the lung tissue of ovalbumin-sensitized mice.

Pastva and colleagues later found that the exercise training increased plasma concentrations of endogenous cortisol in ovalbumin-sensitized mice for 24 hours after each training session. In addition, the beneficial effects of exercise were attenuated by treatment with the glucocorticoid receptor antagonist RU486, indicating that exercise training reduces inflammation through activation of the glucocorticoid receptor.33 These data suggest that exercise induces a temporary anti-inflammatory hormonal response, which has long-term consequences on gene transcription. They also validate the mechanism by which inhaled corticosteroids are thought to reduce the frequency and severity of asthma attacks in humans.

From the same laboratory, Lowder et al32 investigated the effects of exercise training on regulatory T (Treg) cells in ovalbumin-sensitized Foxp3-reporter mice. They found that exercise increased the number of CD4+Foxp3+ T cells in the lung tissue and the draining mediastinal lymph nodes of ovalbumin-treated mice compared with sedentary mice (Fig 3, A and B). These Treg cells also significantly enhanced suppressive function as indicated by lymphocyte proliferation assays (Fig 3, C and D). This enhanced suppression was accompanied by increased production of TGF-β and decreased production of IL-17 and IL-10 by T cells.

Using a similar allergen-mediated mouse model, Vieira and coworkers found that exercise training decreased chronic allergic lung inflammation and remodeling in mice. Mice were sensitized to ovalbumin peptide by intraperitoneal injection and challenged by aerosolized ovalbumin. They were subjected to a low- or moderate-intensity exercise program (respectively, 50% or 75% of maximal speed) for 60 minutes per day, 5 days per week. Their data indicate that mice that exercised had significantly less collagen and elastic fiber deposition in their airway walls in response to ovalbumin challenge compared with sedentary mice14 (Fig 4). In addition, exercise training reduced epithelial and airway smooth muscle
hypertrophy in response to ovalbumin challenge. These effects were coupled with a reduction in ovalbumin-induced up-regulation of particular growth factors that are associated with airway remodeling, including the growth factors insulin-like growth factor 1, epithelial growth factor receptor, vascular endothelial growth factor, and TGF-β (Fig 5, A and B). Intriguingly, Vieira et al also demonstrated an effect of exercise on the amount of oxidative stress in the lung tissue of ovalbumin-sensitized mice. Aerobic training reduced expression of GP91phox and 3-nitrotyrosine, which are markers of oxidative and nitrosative stress, respectively, and levels of the oxidative damage marker 8-isoprostane (Fig 5, C and D).

In contrast to these data, Olivo et al found that in a guinea pig model of allergic asthma, aerobic exercise reduced inflammation but did not affect remodeling in airways. One marked difference in their model from the aforementioned ones is that they sensitized the guinea pigs by aerosolized ovalbumin instead of by intraperitoneal injection. On challenge with aerosolized ovalbumin, exercised guinea pigs had significantly decreased peribronchial edema, eosinophil and lymphocyte infiltration of airway walls, and expression of IL-4 and IL-13. However, aerobic training did not prevent the challenge-induced increase in smooth muscle area or bronchoconstriction index. In addition, exercise actually increased the thickness of the airway epithelium compared with non-exercised animals. It is unknown whether these discrepancies between mouse and guinea pig models are due to differences in lung physiology or the route of ovalbumin sensitization. Olivo et al also acknowledge that because they only examined peripheral and not central airway epithelia, they could have missed changes induced by aerobic exercise in the cartilaginous airways.

Collectively, these data from both mouse and guinea pig models of asthma indicate that aerobic exercise training significantly reduces Th2 cytokine-mediated inflammation, inflammatory cell infiltration, and peribronchial edema compared with non-exercised animals. In mice, this was associated with an enhanced suppressive
Treg response. Aerobic exercise training was also associated with an increased physical exercise capacity in both species, although this was not different between ovalbumin-sensitized and nonsensitized training groups. However, there are conflicting data between animal models on the long-term beneficial effects of exercise training on smooth muscle hypertrophy and airway remodeling.

Evidence from Human Data

Two recently published reviews have explored the effects of exercise in adults with EIB. There is no standard exercise protocol for investigating these effects, so it is difficult to compare trials because each one has used different training programs, study outcomes, methods, and study lengths. To address these discrepancies, a Cochrane database systematic review by Chandratilleke et al performed a meta-analysis of the quantitative evidence in the literature of the benefits of exercise on lung function in individuals with EIB. Primary outcomes were symptoms of asthma, including episodes of shortness of breath or wheezing and symptom assessment scores. Secondary outcomes included bronchodilator use, exercise endurance, work capacity, walking distance, quality of life (QOL), and lung function measurements. The authors found only 19 studies that fulfilled the inclusion criteria for the review. The others were excluded based on methodologic grounds, including inadequate controls, lack of randomization, and other such defects. The 19 included studies were randomized controlled trials that represented a total of 695 study participants and were published between 1980 and 2011. Many of these studies had small or only modest sample sizes, ranging from 14 to 101. The exercise training programs all consisted of aerobic exercise for 20 to 30 minutes, 2 to 3 times a week, for 6 to 16 weeks total.

Because asthma symptoms and severity were measured with varying techniques among the studies, data could not be pooled from multiple studies for meta-analysis of this parameter. Of 7 trials (n = 251 participants), only 1 reported significant improvement in asthma severity based on National Heart, Lung, and Blood Institute criteria after 6 weeks of exercise training (n = 30), although the results may have been biased by the fact that the exercise intervention group had higher adherence to maintenance medications (eTable 1). Three trials (n = 151) reported significant improvement in asthma symptom frequency as assessed by the monthly sum of symptom-free days. Three reported no improvement after exercise training: the first assessed asthma control scores (6-point Asthma Screening Questionnaire scores), the second measured daily asthma symptom scores, and the third reported only the frequency of asthma attacks.

Evidence of improvement in FEV1 with aerobic exercise training was not conclusive. Meta-analysis of these data was difficult because of inconsistent methods of reporting FEV1 across studies, with absolute values, percentage predicted, and percent changes all being reported. Collective data from 12 studies (n = 204) failed to show improvement in FEV1 measurements after training interventions (eTable 1). However, the authors point out that the high variability in the meta-analysis precludes ruling out a beneficial effect. Pooled data also found no improvements in forced vital capacity (n = 122) or peak expiratory flow rate (153 L/min).
In patients with asthma, QOL trended toward improvement in the Cochrane review, with 4 of 5 studies reporting improvement in health-related QOL scores after an exercise training program \((n = 212)\). Four scales of QOL measures were included in the report: the Pediatric Asthma Quality of Life Questionnaire, the Asthma Quality of Life Questionnaire, the Medical Outcomes Study 36-Item Short Form Health Survey, and the Quality of Life—Escola Paulista de Medicina. Again, because outcome reporting was highly heterogeneous, pooling of data was not possible, and meta-analysis could not make conclusions regarding the results.

A second systematic review by Pacheco et al, which was published around the same time as the Cochrane review, also analyzed literature published on the effects of exercise training on measures of QoL in asthmatic patients. Nine studies were included in their analysis. Of the 4 studies that included children, 3 demonstrated a statistically significant improvement in QOL scores in patients undergoing an exercise program over those receiving only conventional treatment (eTable 2). Among adults, all 3 studies that used aerobic conditioning programs reported statistically significant increases in QOL scores over controls. Three studies used nonaerobic exercise interventions (e.g., yoga). Of these 3, only 1 study reported improved QOL over controls, although the intervention may not be practical for some individuals (1.5 hours of yoga daily).

Aside from QOL, aerobic exercise programs improved measures of cardiopulmonary fitness in asthma patients. The Cochrane review included 9 studies that measured such parameters during exercise challenge. Pooled data from 6 studies that reported maximum oxygen consumption demonstrated a statistically significant increase, with a mean increase of 5.57 mL \((n = 149)\) (eTable 1). Maximum expiratory volume was also significantly increased, with a mean increase of 6.00 mL \((n = 111)\). Finally, maximum heart rate increased by a mean of 3.67/min \((n = 34)\). At rest, however, the analysis found no difference in lung function. Not included in the Cochrane analysis, a recent pilot study by Boyd et al found similar results benefits of exercise on the maximum oxygen consumption in asthma patients \((n = 16)\). In addition, Lochte et al found increases in aerobic capacity in asthmatic children who had undergone a 10-month exercise program \((n = 26)\). Although these data indicate that exercise programs increase cardiopulmonary fitness in asthmatic individuals, the Cochrane authors point out that these results are similar to those seen in healthy individuals without asthma who undergo aerobic training programs.

Overall, the Cochrane meta-analysis gave an evidence grade of low for recommending exercise training to improve cardiopulmonary fitness in asthmatic individuals and very low for recommending it for improving QOL, asthma symptoms, and pulmonary function. As mentioned previously, it is difficult to make definitive recommendations for exercise in individuals with asthma due to variation among published trials. The authors of the Cochrane review made the conclusion that in the short term (3 or 4 months) exercise has benefits in overall health and QOL in asthmatic individuals but not necessarily in pulmonary function or asthma severity. They also point out that the studies that found improvement in asthma symptoms were ones that used educational program and breathing exercises in conjunction with aerobic training. However, several studies found improvement in asthma symptoms and QOL. Because their analysis revealed that exercise is well tolerated in asthma patients, there is no reason to discourage patients from exercising. Although these conclusions are
conservative at best, it is important to remember that the Cochrane meta-analysis excluded many studies based on reporting heterogeneity. In addition, it only included individuals with diagnosed asthma. Elite athletes and other individuals who have EIB without underlying asthma have not been studied as extensively; thus, these conclusions cannot be extended to this subgroup. Finally, the longest randomized trial measured outcomes for only 16 weeks. The exercise protocols used in the studies were minimal in duration, frequency per week, and degree of intensity. As of yet, no randomized controlled trials have evaluated the effects of long-term or high-intensity exercise in asthmatic individuals.

The Vicious Cycle of Inactivity

Individuals with asthma often actively avoid exercise due to symptoms. In one poll, 52% of asthmatic individuals indicated that their health limits their participation in activities, including recreational outdoor sports, going to the gym, and normal physical exertion (eg, walking up stairs). This same poll found that 40% of adults and 26% of children avoid sports and other activities because of their EIB symptoms. This long-term avoidance ultimately results in physical deconditioning. Thus, exercise becomes more difficult with time, and patients become increasingly frustrated with their EIB symptoms, causing them to continue their avoidance.

This phenomenon is all the more concerning because of increasing data revealing correlations between obesity and asthma incidence. In addition, there is evidence that inhaled corticosteroids may not be as effective in controlling asthma symptoms in obese patients as they are in normal weight patients. Given these data and the overall benefits of regular exercise, we believe that it is reasonable to recommend exercise to asthmatic patients. Breaking the cycle of inactivity is difficult, but health care practitioners can help their patients engage in physical activity through education, support, guidance, and optimal control of their underlying asthma.

Conclusions and Future Considerations

In conclusion, EIB is a common phenomenon, especially in asthmatic patients and elite athletes. Data from mouse models demonstrate that exercise down-regulates inflammatory mediators and up-regulates suppressive Treg responses. However, definitive data on the benefits of aerobic exercise in asthmatic patients are lacking. Although meta-analyses of the literature fail to show any significant changes in pulmonary function or asthma severity, individual studies in asthmatic patients have found positive effects. Studies reveal trends of increased QOL scores and improved cardiopulmonary fitness in patients after undergoing an exercise training program, although this effect is not unique to asthma patients and can be seen in the general population. Because the data are limited, there is a need for large randomized controlled trials to quantify the physiologic benefits of aerobic exercise training in EIB, especially for longer periods. What is known for certain is that exercise is not detrimental to asthma control. This fact, along with the numerous other health benefits of an active lifestyle, is reason enough to recommend regular exercise to all patients, including asthmatic patients.

Supplementary Data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.anai.2012.10.023

References


Figure 1. Interactions between the intensity of exercise and the thermal environment in which it is performed. Changes in forced expiratory volume in 1 second (FEV₁) are plotted for increasingly strenuous levels of exertion (walking, jogging, and running) in different climactic conditions. Obstruction severity increases proportionally to the strenuousness of activity; maximal obstruction occurs with cold and dry weather, whereas minimal obstruction occurs in warm and humid weather. VE indicates expiratory volume. Reprinted from McFadden et al.⁹

eTable 1
Summary of the cochrane meta-analysis by Chandratilleke et al⁸

<table>
<thead>
<tr>
<th>Study</th>
<th>Measured outcomes</th>
<th>No. of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of Life</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fanelli, 2007</td>
<td>PAQLQ scores</td>
<td>38</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Moreira, 2008</td>
<td>PAQLQ Scores</td>
<td>34</td>
<td>No difference</td>
</tr>
<tr>
<td>Turner, 2010</td>
<td>AQOL scores</td>
<td>35</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Turner, 2010</td>
<td>SF-36 scores</td>
<td>35</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Mendes, 2010</td>
<td>QOL-EPM scores</td>
<td>101</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Gonçalves, 2008</td>
<td>QOL-EPM scores</td>
<td>23</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Asthma Symptoms</td>
<td></td>
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</tr>
<tr>
<td>Wang, 2009</td>
<td>Severity (NHLBI criteria)</td>
<td>30</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Moreira, 2008; Mendes, 2010; Mendes, 2011</td>
<td>Symptom-free days</td>
<td>151</td>
<td>Significant improvement</td>
</tr>
<tr>
<td>Turner, 2010</td>
<td>ASQ scores</td>
<td>35</td>
<td>No difference</td>
</tr>
<tr>
<td>Swann, 1983</td>
<td>Daily symptom scores</td>
<td>27</td>
<td>No difference</td>
</tr>
<tr>
<td>Varray, 1991</td>
<td>Frequency of attacks</td>
<td>14</td>
<td>No difference</td>
</tr>
<tr>
<td>Pulmonary Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochrane, 1990; Moreira, 2008; Silva, 2006; van Veldhoven, 2001; Varray, 1991; Wang, 2009</td>
<td>FEV₁</td>
<td>204</td>
<td>No difference</td>
</tr>
<tr>
<td>Moreira, 2008; van Veldhoven, 2001; Varray, 1991; Wang, 2009</td>
<td>FVC</td>
<td>122</td>
<td>No difference</td>
</tr>
<tr>
<td>Mendes, 2011; van Veldhoven, 2001; Wang, 2009; Weisgerber, 2003</td>
<td>PEFR</td>
<td>153</td>
<td>No difference</td>
</tr>
<tr>
<td>Cardiopulmonary Fitness</td>
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<td></td>
<td></td>
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<tr>
<td>Ahmadi, 1993, Cochrane, 1990; Council, 2003; van Veldhoven, 2001; Varray, 1991; Varray, 1995</td>
<td>VO₂max</td>
<td>149</td>
<td>Mean increase 5.57 mL/kg/min</td>
</tr>
<tr>
<td>Cochrane, 1990; Council, 2003; van Veldhoven, 1991; Varray, 2001</td>
<td>VE₁max</td>
<td>111</td>
<td>Mean increase 6.00 L/min</td>
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<tr>
<td>Ahmadi, 1993; Varray, 1991</td>
<td>HR₁max</td>
<td>34</td>
<td>Mean increase 3.67/min</td>
</tr>
</tbody>
</table>

Abbreviations: AQOL, Asthmato Quality of Life Questionnaire; FEV₁, forced expiratory volume; FVC, forced vital capacity; HR₁max, maximum heart rate; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; PEFR, peak expiratory flow rate; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; VO₂max, maximum oxygen consumption; VE₁max, maximum expiratory volume.
## eTable 2
Summary of the systemic review by Pacheco et al.52

<table>
<thead>
<tr>
<th>Study</th>
<th>QoL score</th>
<th>No. of patients</th>
<th>Type</th>
<th>Frequency and duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basaran, 2006</td>
<td>PAQLQ</td>
<td>62</td>
<td>Aerobic, moderate</td>
<td>1 hour 3 times per week for 8 weeks</td>
<td>Significant improvement in both EG and CG, but improvement was higher in EG (P &lt; .001)</td>
</tr>
<tr>
<td>Fanelli, 2007</td>
<td>PAQLQ</td>
<td>38</td>
<td>Aerobic to 70%</td>
<td>1.5 hours 2 times per week for 16 weeks</td>
<td>Significant improvement in EG over CG for activity limitation (P &lt; .03), symptoms (P &lt; .02), and emotions (P &lt; .03)</td>
</tr>
<tr>
<td>Flapper, 2008</td>
<td>TACQOL- generic and asthma forms; DUX-25</td>
<td>36</td>
<td>Aerobic</td>
<td>2.5 hours once per week for 12 weeks</td>
<td>Significant improvement in EG over CG for TACQOL-asthma (P &lt; .023) and DUX-25 (P &lt; .02) scores</td>
</tr>
<tr>
<td>Moreira, 2008</td>
<td>PAQLQ</td>
<td>34</td>
<td>Aerobic</td>
<td>50 minutes 2 times per week for 12 weeks</td>
<td>Significant improvement in EG for all domains and nonsignificant trend in toward improvement in EG for activity but not different from CG</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turner, 2010</td>
<td>AQLQ; SF-36</td>
<td>34</td>
<td>Aerobic, moderate</td>
<td>1.5 hours 3 times per week for 6 weeks</td>
<td>Significant improvement in EG for total score, activity limitation (P = .04) and symptoms (P = .001)</td>
</tr>
<tr>
<td>Goncalves, 2008</td>
<td>QQL-EPM</td>
<td>20</td>
<td>Aerobic to 70%</td>
<td>0.5 hour 2 times per week for 12 weeks</td>
<td>Significant improvement in EG over CG for total score (P &lt; .001), activity limitation (P &lt; .001), symptoms (P &lt; .002), and psychosocial (P &lt; .003)</td>
</tr>
<tr>
<td>Mendes, 2010</td>
<td>QQL-EPM</td>
<td>101</td>
<td>Aerobic to 70%</td>
<td>0.5 hour 2 times per week for 12 weeks</td>
<td>Significant improvement (P &lt; .001) in EG for total score, activity limitation, symptoms, and psychosocial</td>
</tr>
</tbody>
</table>

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CG, control group; DUX-25, Dutch Children Quality of Life Questionnaire; EG, exercise group; PAQLQ, Pediatric Asthma Quality of Life Questionnaire; QoL, quality of life; QQL-EPM, Quality of Life—Escola Paulista de Medicina; SF-36, Medical Outcomes Study 36-Item Short Form Health Survey; TACQOL, TNO-AZL Children Quality of Life Questionnaire.