REVIEW / SYNTHÈSE

Evidence-based risk assessment and recommendations for physical activity clearance: respiratory disease[1]

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Abstract: The 2 most common respiratory diseases are chronic obstructive pulmonary disease (COPD) and asthma. Growing evidence supports the benefits of exercise for all patients with these diseases. Due to the etiology of COPD and the pathophysiology of asthma, there may be some additional risks of exercise for these patients, and hence accurate risk assessment and clearance is needed before patients start exercising. The purpose of this review was to evaluate the available literature regarding the risks of exercise for patients with respiratory disease and provide evidence-based recommendations to guide the screening process. A systematic review of 4 databases was performed. The literature was searched to identify adverse events specific to exercise. For COPD, 102 randomized controlled trials that involved an exercise intervention were included (n = 6938). No study directly assessed the risk of exercise, and only 15 commented on exercise-related adverse events. For asthma, 30 studies of mixed methodologies were included (n = 1278). One study directly assessed the risk of exercise, and 15 commented on exercise-related adverse events. No exercise-related fatalities were reported. The majority of adverse events in COPD patients were musculoskeletal or cardiovascular in nature. In asthma patients, exercise-induced bronchoconstriction and (or) asthma symptoms were the primary adverse events. There is no direct evidence regarding the risk of exercise for patients with COPD or asthma. However, based on the available literature, it would appear that with adequate screening and optimal medical therapy, the risk of exercise for these respiratory patients is low.

Key words: exercise, chronic obstructive pulmonary disease, asthma, rehabilitation, risk assessment, adverse events.

Résumé : La maladie pulmonaire obstructive chronique (COPD) et l'asthme sont les maladies pulmonaires les plus courantes. De plus en plus d'études soulignent les bienfaits que procure l'exercice physique aux patients souffrant de ces maladies. Cependant, si on prend en compte l'étiologie de la COPD et la pathophysiologie de l'asthme, la pratique de l'activité physique peut constituer un risque additionnel chez ces patients; il y a donc lieu de faire une meilleure évaluation du risque et de raffiner le dépistage avant de s'adonner à l'activité physique. Cette analyse documentaire se propose d'évaluer les études disponibles traitant des risques associés à la pratique de l'activité physique chez des individus souffrant de maladie pulmonaire et, pour faciliter le dépistage, de formuler des recommandations basées sur des données probantes.On réalise une analyse documentaire systématique dans quatre bases de données électroniques; on cherche dans les études retenues les événements indésirables associés à l'exercice physique. Dans le cas de la COPD, on retient 102 essais cliniques aléatoires traitant d'intervention au moyen de l'activité physique (n = 6938). Aucune étude ne traite spécifiquement du risque associé à l'exercice physique; seulement quinze études mentionnent des événements indésirables associés à l'exercice physique. Dans le cas de l'asthme, on retient 30 études utilisant diverses méthodes (n = 1278). Une seule étude porte spécifiquement sur le risque associé à l'exercice physique et quinze études mentionnent des événements indésirables associés à l'exercice physique. Aucun décès n'est rapporté. La plupart des événements indésirables notés dans le cas de la COPD sont de nature musculosquelettique ou cardiovasculaire. Au sujet de l'asthme, on note la manifestation de bronchospasme à l'exercice et de symptômes de l'asthme à titre d'événements indésirables primaires. Il n'y a pas d'évidence directe concernant les risques associés à l'exercice physique chez les individus aux prises avec la COPD et l'asthme. Néanmoins, d'après les études disponibles, le risque associé à l'exercice physique chez ces patients est faible si le dépistage est bien fait et si les traitements médicaux sont appropriés.

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Mots-clés : exercice physique, maladie pulmonaire obstructive chronique, asthme, réadaptation, évaluation du risque, événements indésirables.

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Lay synopsis

The number of individuals suffering from lung disease is on the rise. The 2 most prevalent lung diseases are (*i*) chronic obstructive pulmonary disease (COPD), a preventable and treatable respiratory condition characterized by airflow obstruction that is not fully reversible, and (*ii*) asthma, an inflammatory airway disease associated with a narrowing of the airways and unpleasant breathing sensations that are often reversible either spontaneously or with medication. Physical activity (PA) or exercise training are known to reduce the adverse symptoms associated with exertion, improve exercise capacity, and enhance the quality of life of lung disease patients. Consequently, treatment recommendations for both COPD and asthma suggest that all patients should be physically active. However, little information is available to guide patients, exercise specialists, and (or) physicians regarding the risks of becoming more physically active. The purpose of this review was to evaluate previous studies that have reported adverse events to assess the risk of performing PA or exercise in patients with COPD and asthma and to provide recommendations to help guide the screening process. A review of all available literature was performed, and exercise-related adverse events were documented. In the studies reviewed, no patient with lung disease died as a direct cause of performing exercise. The majority of adverse events in COPD patients resulted from muscle soreness and pain or heart disease, while in asthma patients, exercise-induced narrowing of the airways and adverse breathing symptoms were the primary adverse events. Based on this review, we conclude that no study in COPD patients and only 1 in asthma patients has directly investigated the risk of exercise for patients with respiratory disease. Secondary evidence obtained from the reports of adverse events suggests that with adequate screening before starting exercise, the risk of exercise for patients with these lung diseases is low.

Introduction

An aging population and an increase in smoking during the past 50 years has led to a rise in the number of individuals suffering from chronic respiratory disease (Murray and Lopez 1997; PHAC 2007). There is growing interest in treatments that can improve health-related quality of life, symptoms, and functional capacity in these patients. It is estimated that >3.5 million Canadians suffer from respiratory diseases (PHAC 2007). Of the wide range of respiratory disorders, the 2 most common are COPD and asthma, as approximately 750 000 and 2.75 million Canadians are believed to have these conditions, respectively (PHAC 2007). Owing to the heterogeneous nature of both diseases, patients with COPD and (or) asthma present a number of unique challenges for exercise specialists and physicians who are responsible for assessing the risks of PA and prescribing exercise for these patients.

Definition of terms

PA is defined as any movement that increases energy expenditure above resting expenditure. Exercise is a subset of PA that is planned, structured, repetitive, and aimed at improving or maintaining physical fitness (e.g., aerobic capacity or strength) (Thompson et al. 2003). In COPD, risk was considered to be the chance of a cardiovascular or cerebrovascular event, hospitalization, or death. In asthma, risk was considered to be the chance of worsening symptoms, hospitalization, or death.

PA screening and the AGREE guidelines

The following section was written by the consensus panel that guided the overall revision of the PA clearance process. This information is reprinted in each of the systematic review papers so that these reviews can stand alone from the paper describing the overall consensus process (Jamnik et al. 2011).

PA participation is recommended and beneficial for all asymptomatic persons and for persons with chronic diseases (Warburton et al. 2006, 2007). However, the PA participation of persons with certain chronic disease conditions or constraints may need to be restricted. The Physical Activity Readiness Questionnaire (PAR-Q) is a screening tool completed by persons who plan to undergo a fitness assessment or to become “much more physically active”; for example, when initiating PA participation that is beyond a person’s habitual daily activity level or when beginning a structured PA or exercise program. Screening is also recommended when a person is joining a health club, commencing a training program with a fitness professional, or joining a sports team. If a person provides a positive response to any question on the PAR-Q, he or she is directed to consult with his or her physician for clearance to engage in either unrestricted or restricted PA.

The Physical Activity Readiness Medical Evaluation (PARmed-X) is a screening tool developed for use by physicians to assist them in addressing medical concerns regarding PA participation that were identified by the PAR-Q. Recent feedback from PA participants, fitness professionals, and physicians has brought to light substantial limitations to the utility and effectiveness of PA participation screening by the PAR-Q and PARmed-X. In short, the exercise clearance process is not working as intended and at times is a barrier to PA participation for those persons who may be most in need of increased PA. The aim of the present project is for experts in each chronic disease, together with an expert panel, to revise and increase the effectiveness of the PAR-Q and PARmed-X screening process using an evidence-based consensus approach that adheres to the established Appraisal of Guidelines for Research and Evaluation (AGREE).

An important objective of this project is to provide evidence-based support for the direct role of university-educated and qualified exercise professionals (QEPs) in the exercise clearance process. An example of a QEP is the Canadian Society for Exercise Physiology Certified Exercise Physiologist, which is the highest nationally recognized certification in the health and fitness industry. It recognizes the qualifications of those persons who possess advanced formal academic preparation and practical experience in health-related and performance-related PA and exercise science fitness applications for both nonclinical and clinical populations.

The AGREE Instrument was developed by a group of researchers from 13 countries to provide a systematic framework for assessing the quality and impact on medical care of clinical practice guidelines (AGREE Collaboration 2003). The AGREE Collaboration published the rigorous development process and associated reliability and validity data of the AGREE Instrument based on a large-scale study focusing primarily on clinical practice guidelines (AGREE Collaboration 2003). The AGREE Instrument is now a commonly used tool for assessing clinical practice guidelines and other health management guidelines (Lau et al. 2007). The AGREE guidelines were applied in the present project to assess the formulation of risk stratification and PA participation clearance recommendations for each of the critical chronic diseases. One of the authors of this project (J.M.) is an AGREE Instrument Expert, and she was responsible for evaluating the compliance of the overall process to the AGREE guidelines.

In addition to adhering to the AGREE process, the Level of Evidence (1 = randomized control trials (RCTs); 2 = RCTs with limitations or observational trials with overwhelming evidence; 3 =, observational studies; 4 = anecdotal evidence) supporting each PA participation clearance recommendation and the Grade (A = strong; B = intermediate; C = weak) of the PA participation clearance recommendation was assigned by applying the standardized Level and Grade of Evidence detailed in the consensus document (Warburton et al. 2011).

In this series of articles, each chronic disease condition was considered in reference to a continuum of risk from lower-risk to intermediate (moderate) and higher-risk categories. Particular attention was paid to the short-term (acute) risks of PA and exercise versus the long-term (chronic) benefits to the chronic disease. PA participation may transiently increase the risk acutely while leading to physiological and psychological adaptations that markedly reduce the long-term risk. Adverse events were considered to be any adverse change in health status or a side effect that resulted in relation to PA or exercise participation.

COPD: definitions, epidemiology, and clinical significance

COPD is a preventable and treatable condition characterized by partially reversible airflow obstruction (Celli et al. 2004; O'Donnell et al. 2007; GOLD 2009). The airflow limitation is associated with an abnormal inflammatory response of the lung to noxious particles or gases (GOLD 2009). COPD also has significant extrapulmonary manifestations that may affect disease severity (GINA 2009). The term COPD includes the conditions of emphysema — with loss of lung elastic recoil, small airway closure, and destruction of lung parenchyma — and chronic bronchitis — with fibrosis, mucus hypersecretion, and airway narrowing (Barnes 2000). COPD is a heterogeneous disease, and patients often present with varying degrees of both conditions. Cigarette smoking is the primary cause of COPD, and it is well documented that smoking elicits an inflammatory response in the lungs (Mio et al. 1997; Domagała-Kulawik et al. 2003; Glader et al. 2006) that has been causally linked with the pathogenesis of the disease (Hoshino et al. 2007; Macnee 2007).

According to a recent study, 8% of Canadians self-reported having COPD, chronic bronchitis, or emphysema (The Lung Association–Canadian Thoracic Society 2005). However, these numbers are likely vastly underestimated (Buist et al. 2007). For individuals >75 years old, the prevalence of physician-diagnosed COPD is reported to be 9.3%, which is important considering that we have an aging population (PHAC 2007). COPD is currently the fifth leading cause of death worldwide but will be the third by 2020 (Murray and Lopez 1997; Paz-Díaz et al. 2007). In contrast to heart disease, stroke, and cancer, where mortality rates decreased between 1970 and 2002, deaths from COPD increased 103% in North America (Jemal et al. 2005). In Canada, 4.5% of all deaths can be primarily attributable to COPD (Chapman et al. 2003; PHAC 2007), with mortality rates continuing to increase, particularly in women (Nici et al. 2006). In 2003, 3% of all hospitalizations were due to COPD (Fixman et al. 2007), with risk of rehospitalization being around 40% (Nici et al. 2006). The economic burden of COPD is immense, with the direct and indirect costs in Canada estimated at $1.5 billion and $905 million, respectively (Chapman et al. 2003).

Asthma: definition, epidemiology and clinical significance

Asthma is a chronic inflammatory condition that is associated with airway hyperresponsiveness and episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning (GINA 2009). These episodes are usually associated with widespread, but variable, airflow obstruction that is often reversible either spontaneously or with treatment (Lemière et al. 2004; GINA 2009). Several inflammatory cells and mediators identified in the pathogenesis of asthma have been associated with subepithelial fibrosis, mucus hypersecretion, and smooth muscle hypertrophy and hyperplasia, which can lead to structural changes in the airways (Hirst 2000; Jeffery 2001; Fixman et al. 2007). In addition, asthma is associated with airway narrowing, primarily in response to multiple bronchoconstrictor mediators and neurotransmitters but also because of airway remodeling, edema, and mucus hypersecretion (GINA 2009). There are a number of asthma triggers, including exposure to indoor allergens (mites, furred animal, fungi, etc.) and outdoor allergens (pollens, moulds, etc.), tobacco smoke, air pollution, and viral infections (GINA 2009). One of the main asthma triggers is exercise, which can lead to severe bronchoconstriction and asthma symptoms, usually following the exercise bout.

In Canada, at least 8% of the population suffers from asthma, and rates are on the rise in both genders (PHAC 2007). The prevalence of asthma is higher in adult women than in men and is responsible for 146 000 emergency room visits and 250–500 adult deaths per year (PHAC 2007). Asthma affects children of all ages, and it is currently reported that 15.6% of children 4–11 years old and 8.3% of children >12 years old have the disease (PHAC 2007). In contrast to adults, asthma is higher in male children and is one of the primary causes of hospitalization. In Canadian children <4 years old, asthma is the cause of ~10% of all hospitalizations (PHAC 2007). Child death rates from asthma are low (<0.1 deaths per 100 000); however, that is still too many, as asthma is a treatable disease.

Risks of exercise in patients with COPD

As smoking is the primary cause of COPD and a risk factor for a multitude of disorders such as cardiovascular disease, peripheral vascular disease, lung cancer, diabetes, dyslipidemia, hypertension, osteoporosis, and psychological disorders (Briggs 2004; Sin et al. 2006), it is not surprising that patients with COPD commonly present with a wide variety of comorbidities (Chatila et al. 2008). In addition, smoking, medication interactions, and lack of treatment for secondary conditions (Redelmeier et al. 1998) may also increase the incidence of comorbidities in this population (Chatila et al. 2008). As such, patients being referred to exercise or rehabilitation programs could present with a number of contraindications to exercise (i.e., hypoxemia, uncontrolled angina or congestive heart failure, severe hypertension) that a QEP should be aware of. In a large rehabilitation cohort study of 2962 patients with COPD, Crisafulli et al. demonstrated that 51% reported at least 1 comorbidity, with 13% reporting 2 or more (Crisafulli et al. 2008). The 3 most common comorbidities were metabolic disease (62%), heart disease (24%), and musculoskeletal problems (7%). Another study by Foy et al. reported that 36% of 140 patients being randomized to either short- or long-term exercise therapy had heart disease and 44% had hypertension (Foy et al. 2001). These studies highlight the complex nature of COPD and the need for screening techniques that allow identification of patients who may be at risk from exercise.

Considering the high probability that patients with COPD will present with more than 1 chronic condition and be at higher risk of an adverse response to exercise than healthy age-matched individuals, there are a number of contraindications to exercise that a QEP should be aware of (American Thoracic Society and American College of Chest Physicians 2003). For example, patients with more advanced COPD and reduced lung diffusion capacity may present with resting hypoxemia (defined as an oxyhemoglobin saturation (S_pO_2) <90%) while breathing room air. Other patients may not demonstrate hypoxemia until they start to exert themselves, and as such it is important to assess arterial saturation levels to identify those who may need O_2 supplementation with exertion.

As ventilatory limitation prematurely limits exercise in many patients (O'Donnell 2001; O'Donnell et al. 2001), it is commonly believed that exercise will be terminated before a cardiovascular limitation to exercise or cardiac ischemia is observed. However, this is not always the case, and a number of previous investigations report excluding COPD patients either before or during exercise interventions because of evidence of ischemia, angina, serious arrhythmia, uncontrolled hypertension, and (or) unstable chronic heart failure (Simpson et al. 1992; Larson et al. 1999; Puhan et al. 2006).

Owing to the destruction of the lung parenchyma in emphysema, the increased dynamic hyperinflation and intrinsic positive end-expiratory pressure associated with gas trapping, and the hypoxemia and hypercapnia due to poor gas exchange, patients with COPD can develop pulmonary hypertension at rest and (or) during exercise (Mahler et al. 1984; Butler et al. 1988; Matthay et al. 1992). Ultimately, pulmonary hypertension can lead to right ventricular hypertrophy, enlargement, and (or) failure (MacNee 1994), which is associated with poor prognosis for those affected (Incalzi et al. 1999). As such, the presence of significant pulmonary hypertension used to be considered a contraindication to exercise (American Thoracic Society and American College of Chest Physicians 2003). More recently it has been documented that exercise can be beneficial for patients with pulmonary hypertension (Mereles et al. 2006). However, careful consideration should be given to exercise prescriptions for these patients (Nici et al. 2006).

Risks of exercise in patients with asthma

As asthma is a disease that often affects children, adolescents, and young adults, the risks associated with participating in exercise or PA is often less complex than for those with COPD, as the majority do not have a significant smoking history or the comorbidities associated with a long-term sedentary and (or) unhealthy lifestyle. The risk of adverse events and complications with asthma do not necessarily increase with increased severity of disease but are more related to the level of asthma control (Peters et al. 2006). Clinical control of asthma can be defined in various ways but usually includes minimal (<2 times per week) daytime symptoms, no limitations of daily activities (including exercise), no nocturnal symptoms or awakening because of asthma, minimal (<2 times per week) need for reliever treatment, normal or near-normal lung function, and no exacerbation (Bateman et al. 2008). Patients with inadequate asthma control are at higher risk of serious morbidity (GINA 2009), and those with inadequately controlled severe persistent asthma are at considerably higher risk of exacerbations and mortality (Chung et al. 1999; GINA 2009). By definition (Lemière et al. 2004), patients with well-controlled asthma will have minimal symptoms, infrequent exacerbations, and no limitations to PAs associated with their asthma. If a patient with controlled asthma has no secondary comorbidities, they should have risks similar to those of a healthy age-matched individual. However, because of the high risks of severe bronchoconstriction triggered by PA in patients with severe uncontrolled asthma, it is considered an absolute contraindication to exercise (American Thoracic Society and American College of Chest Physicians 2003).

Benefits of exercise for patients with COPD and asthma

The benefits of exercise are well documented for patients with COPD, and there is a large body of evidence that demonstrates that exercise can have a variety of clinical and health benefits for these patients (Lacasse et al. 2006; Ries et al. 2007). Performing aerobic exercise does not improve pulmonary function but causes a number of physiological adaptations in skeletal muscle, attenuating ventilatory demand (Casaburi et al. 1991; Vallet et al. 1997) and reducing dynamic hyperinflation (Porszasz et al. 2005; Puente-Maestu et al. 2006) and exertional dyspnea (Porszasz et al. 2005; Puente-Maestu et al. 2006; Ries et al. 2007) at a given workload. While the effects of exercise on maximal oxygen consumption are varied (Maltais et al. 1996; Casaburi et al.

1997; Porszasz et al. 2005), exercise training has consistently been shown to improve exercise tolerance (Puente-Maestu et al. 2000; Emtner et al. 2003; Casaburi et al. 2005; Porszasz et al. 2005) and results in clinically important changes in health-related quality of life (Lacasse et al. 2006; Ries et al. 2007). In the recent evidence-based clinical guidelines by Ries et al., it was reported that there was the highest level of evidence to support that exercise training should be a mandatory component in the treatment of patients with COPD. In addition to the improvements in symptoms and health-related quality of life, there is growing evidence that exercise training can also reduce exacerbations (Güell et al. 2000), health care utilization (Goldstein et al. 1997), and mortality (Ries et al. 1995) but larger well-designed studies are needed to fully address these important questions.

The inclusion of resistance training in the rehabilitation of patients with COPD has also been shown to have a number of benefits that are complimentary but also additional to the physiological benefits associated with endurance training (Bernard et al. 1999). Resistance training has been demonstrated to improve muscle mass and lead to significant improvements in strength (Simpson et al. 1992; Bernard et al. 1999; Kongsgaard et al. 2004) and rate of force development and mechanical efficiency (Hoff et al. 2007). These improvements lead to increased ability to perform tasks of daily living (Kongsgaard et al. 2004) and can improve health-related quality of life (Kongsgaard et al. 2004).

There have been fewer studies that have investigated the benefits of exercise training for patients with asthma, and participation in exercise can present some interesting challenges. Acute bouts of exercise can provoke bronchoconstriction (defined as a reduction in postexercise forced expired volume in 1 second (FEV_1) > 10%) and induce asthma symptoms in the majority of asthma sufferers (Bundgaard et al. 1983; Villaran et al. 1999; Mickleborough et al. 2007), while longer term exercise training, PA, and participation in sports can assist in the management of the disease (Welsh et al. 2005). With the proper education in how to prevent, reduce, and manage the adverse effects of exercise on bronchoconstriction, there are wide variety of physiological and health benefits that can be gained by patients that are similar to those in healthy individuals. A metaanalysis performed by Ram et al. reported that exercise training improved peak oxygen uptake ($\dot{V}O_{2\,max}$) by an average of 5.4 mL·kg^{-1}·min^{-1} (mean age 14.3 years and mean baseline $\dot{V}O_{2max}$~41 mL·kg^{-1}·min^{-1}) in patients with asthma (Ram et al. 2005). However, to date the mechanisms associated with the improved exercise capacity in individuals with asthma have not been addressed.

There is less evidence supporting the benefits of exercise for reducing the prevalence of exercise-induced bronchoconstriction (EIB) and adverse respiratory symptoms postexercise. A number of studies have reported attenuated EIB and (or) asthma symptoms (Matsumoto et al. 1999) following a period of exercise training as assessed by a reduced percent fall in FEV_1 (Henriksen and Nielsen 1983; Svenonius et al. 1983; Fanelli et al. 2007) and peak expired flow rate (Henriksen et al. 1981). However, this is not always the case, as other studies have not observed the same improvements (Sly 1972; Fitch et al. 1976; Schnall et al. 1982; Nickerson et al. 1983; Neder et al. 1999). Other benefits of exercise training for asthmatic individuals can be gleaned from studies that have reported reductions in asthma attacks and number of incidents of wheezing, missed days from school, hospitalizations, and emergency room visits following a period of exercise training (Szentágothai et al. 1987; Huang et al. 1989; Engström et al. 1991; Emtner et al. 1996). There are also a number of studies that have reported improvements in the subjective feelings of anxiety (Emtner et al. 1996) and in health-related quality of life (Cambach et al. 1997; Fanelli et al. 2007).

Purpose of this review

With the relatively large body of evidence supporting the benefits of exercise training for patients with respiratory disease, less information is available to specifically guide the decision-making process around which patients are safe to increase their current level of PA or to begin a structured exercise or rehabilitation program. The purpose of this review was to specifically appraise the available literature regarding the risks of performing PA and exercise for patients with COPD and asthma and to provide evidence-based recommendations to help guide the screening process performed by physicians and QEPs. It was hypothesized that with appropriate screening and understanding of an individual's condition, the benefits of exercise would outweigh the risks for patients with COPD and (or) asthma.

Methodology

To assess the risk of increasing PA levels and (or) initiating a structured exercise program for individuals with COPD and asthma, a systematic review of the literature was performed by 2 independent investigators using 4 different databases (Medline (1950–2008); Sport Discus (1985–2008); EMBASE (1980–2008); and the Cochrane Controlled trials registry). The literature was also searched to identify any adverse events and (or) contraindications to exercise previously reported. Owing to differences in diseases and the potential adverse events that could occur with exercise, a separate review was performed for COPD and asthma. The MeSH terms consistent to each review included exercise, exercise therapy, rehabilitation, motor activity, physical fitness, and weightlifting. Additional non-MESH terms searched included physical activity, pulmonary rehabilitation, exertion, sports, walk, jog, run, resistance training, strength training, circuit training, aerobic exercise, aerobic training, and aerobic fitness. For COPD, the MeSH terms incorporated in the search were obstructive pulmonary disease, COPD, pulmonary emphysema, emphysema, and chronic bronchitis with the additional term chronic airflow obstruction. For asthma, the MeSH term used was asthma, with the additional terms airflow obstruction and reversible airflow obstruction also being searched. Bibliographies of included studies were also checked to identify additional studies.

All studies that used a PA or exercise training intervention that involved large muscle groups in individuals suffering from COPD or asthma were deemed eligible. Studies that incorporated an adjunct therapy in addition to exercise (i.e., oxygen administration) were also considered appropriate. Studies in non-English languages and those only available in abstract form were excluded. Studies associated with other respiratory diseases, review articles, medication comparison trials, cost-effectiveness trials, surgical intervention trials, respiratory muscle training studies (unless performed in combination with exercise), exercise test comparison trials, effect of a pharmaceutical or nonpharmaceutical intervention on exercise performance studies, dose–response trials, and those performed in animals were excluded. If more than 1 manuscript was published from the same data set, only the original study was included. All titles and abstracts identified by the searches as potentially relevant were selected for full-text review. From the publications included in the review, data were abstracted using a standard form by the first reviewer and checked by the second reviewer, with differences resolved through discussion.

Results

Results for COPD

The search was completed in June 2008. The electronic search for COPD yielded 3904 studies. When this was filtered to identify only English-language, randomized controlled trials in adult humans, 807 studies were identified. From reviewing the titles and abstracts of these studies, 137 were considered potentially relevant. On reading the full text of these manuscripts, an additional 8 studies were identified from bibliographies and a total of 102 were considered appropriate for inclusion in this review (Busch and McClements 1988; Lake et al. 1990; Dekhuijzen et al. 1991; Simpson et al. 1992; Patessio et al. 1992; Martinez et al. 1993; Goldstein et al. 1994; Reardon et al. 1994; Wanke et al. 1994; Wijkstra et al. 1994, 1995; Ries et al. 1995, 2003, 2005; Bauldoff et al. 1996, 2005; Berry et al. 1996, 2003; Clark et al. 1996, 2000; Strijbos et al. 1996; Bendstrup et al. 1997; Burdet et al. 1997; Epstein et al. 1997; Rooyackers et al. 1997, 2003; Casaburi et al. 2004, 2005; Elliott et al. 2004; Faager and Larsen 2004; Holland et al. 2004; Kirsten et al. 1998; Nava 1998; Wedzicha et al. 1998; Bernard et al. 1999; Coppoolse et al. 1999; Engström et al. 1999; Larson et al. 1999; Gimenez et al. 2000; Griffiths et al. 2000; Güell et al. 2000; Hernandez et al. 2000; Behnke et al. 2000, 2003; Garrod et al. 2000*a*, 2000*b*; Pompeo et al. 2000; Puente-Maestu et al. 2000*a*, 2000*b*; Ringbaek et al. 2000; Troosters et al. 2000; Carrieri-Kohlman et al. 2001; Etnier and Berry 2001; Finnerty et al. 2001; Foy et al. 2001; Green et al. 2001; Wadell et al. 2001, 2004; Brooks et al. 2002; de Torres et al. 2002; Johnson et al. 2002; Normandin et al. 2002; Spruit et al. 2002; Stulbarg et al. 2002; Vogiatzis et al. 2002, 2005; Creutzberg et al. 2003; Singh et al. 2003; Steiner et al. 2003; Emtner et al. 2003; Monninkhof et al. 2003; Oh 2003; Kongsgaard et al. 2004; Mador et al. 2004, 2005; Man et al. 2004; Bjornshave and Korsgaard 2005; Boxall et al. 2005; Broekhuizen et al. 2005; Fuld et al. 2005; Lindsay et al. 2005; Murphy et al. 2005; Norweg et al. 2005; Sewell et al. 2005, 2006; Arnardóttir et al. 2006, 2007; de Blok et al. 2006; Phillips et al. 2006; Puhan et al. 2006; Romagnoli et al. 2006; Haugen and Stavem 2007; Hoff et al. 2007; Karapolat et al. 2007; Magadle et al. 2007; O'Neill et al. 2007; O'Shea et al. 2007; Paz-Díaz et al. 2007; Varga et al. 2007; Collins et al. 2008; Dolmage and Goldstein 2008). The main reasons for exclusion of trials were as follows: lack of an exercise intervention; investigating the acute effects of pharmaceutical or nonpharmaceutical interventions on exercise performance; cost effectiveness trials; and the use of surgical intervention. Two studies that were relevant to this review were excluded because they combined patients with asthma and COPD within the same rehabilitation program, and adverse events specific to each disease could not be identified (Cambach et al. 1997; Foglio et al. 1999).

The overall characteristics of the studies included for patients with COPD are presented in Table 1. The 102 studies included a total of 6938 patients with COPD. The main exclusion criterion was the presence and (or) symptoms of cardiac disease (e.g., uncontrolled angina, ischemic heart disease, acute myocardial infarction, valvular disease, and (or) the presence of potentially dangerous arrhythmias) in 86% of the trials that mentioned exclusion criteria. Other exclusion criteria identified included musculoskeletal or orthopedic problems that limited an individual's ability to exercise (66%), neurological or cognitive impairment (35%), peripheral vascular disease (27%), uncontrolled hypertension (23%), other pulmonary disorders (23%), cancer (20%), and diabetes (14%). Patients with resting or exertional hypoxemia were excluded in 20% of trials, but the majority allowed inclusion of hypoxemic patients with the administration of O_2 supplementation during exertion to maintain an appropriate oxygen saturation level.

In addition to the aforementioned exclusion criteria, 61 trials (60%) included an incremental exercise test before the start of the exercise program (Table 2). Of these 61 trials, 56% reported using continuous electrocardiogram monitoring and 84% reported assessing arterial saturation either through direct blood gas measurement or indirectly with pulse oximetry. An additional 10 studies (10%) incorporated a 6-min walk test or incremental shuttle walk test with oxyhemoglobin saturation monitoring using pulse oximetry (S_pO_2) that could assist in identifying patients with exertional hypoxemia.

Of the 102 trials included, no study was specifically designed to address the risk of exercise in patients with COPD. Only 15 trials (15%), consisting of a total of 770 patients, made a definite statement regarding adverse events either during exercise testing or an exercise intervention (Table 2). Of these trials, 3 (20%) reported that no adverse events occurred during exercise. In the remaining 12 studies, no deaths directly associated with either exercise were reported. Thirty-three (of 770) patients reported musculoskeletal pain (although 1 study reported that several of their 24 patients experienced arm or lower back pain without quantifying the precise number), 26 were excluded either during testing or training because of cardiovascular-related problems (ischemic events, angina, serious arrhythmia), 17 desaturated (reported as a drop in S_pO_2 below 85%) with exertion, and 2 received exercise-related injuries.

Several trials also reported adverse events that were considered unrelated to the exercise intervention, which highlights the complexity of COPD as a clinical condition (Table 2). In total, there were 605 non-exercise-related adverse events reported, including 85 deaths and 402 exacerbations.

Results for asthma

The electronic search for asthma was also completed in June 2008 and yielded 3227 studies. When this was filtered

Table 1. Characteristics of chronic obstructive pulmonary disease studies (n = 102).

Characteristic	No. of studies, %
No. of patients	6938
Female, %	34±20
Age, y	65±4
Age range, y	49–77
FEV_1, % predicted	42±9
FEV_1 range, % predicted	26–77
Type of exercise used	
Aerobic training	48, 47
General rehabilitation	38, 37
Resistance training	7, 7
Combined training or training comparison trials	8, 8
Circuit	1, 1
Studies prescreening with PAR-Q or PARmed-X	0, 0
Studies performing exercise screening before start of exercise	61, 60
Type of test used for screening	
Cardiopulmonary test with gas exchange analysis	46, 45
Incremental test without gas exchange analysis	15, 15
Exercise monitoring reported during testing	
Electrocardiogram	34, 33
Arterial saturation (either pulse oximetry or blood gases)	51, 50

Note: Data are reported as means ± SD, a range, or the number of studies, percentage of total studies.

Table 2. Adverse events and reasons for patient exclusion in chronic obstructive pulmonary disease (COPD) studies (n = 102).

Characteristic	No. of studies, %
Studies reporting adverse events during exercise	15, 15
Total no. adverse events reported during exercise*	84
Exercise-related adverse events reported	
None	3, 20
Death	0, 0
Cardiovascular (ischemia, angina, arrhythmia, etc.)	4, 27
Arterial desaturation (S_pO_2< 85%)	3, 20
Musculoskeletal	7, 47
Injury	2, 13
No. studies reporting exclusion criteria	86
Reasons for exclusion	
Cardiovascular	74, 86
Peripheral vascular disease	23, 27
Musculoskeletal	57, 66
Hypertension	20, 23
Unstable COPD	33, 38
Other respiratory disorders (including asthma)	20, 23
Cerebrovascular	10, 12
Cancer	17, 20
Diabetes	12, 14
Obesity	3, 4
Neurological and cognitive disorders	30, 35
Hypoxemia	20, 23
Total no. of patients excluded	605
Clinical reasons reported for exclusion (not exercise related)	
Death	85, 14
Exacerbation	412, 68
Cardiovascular	31, 8
Musculoskeletal	12, 2
Other respiratory disorders	9, 2
Cerebrovascular	3, 1
Cancer	11, 2
Hypoxemia	4, 1
Other	38, 6

Note: Data are reported as means ± SD or number of studies, percentage of total studies. In the 15 studies reporting adverse events, mean age was 67 ± 5 years and mean FEV_1 = 38% ± 9% (predicted).

*One study reported that several subjects had arm and lower back pain, but did not quantify the number of subjects with these symptoms. Please note that studies can report more than 1 adverse event and can have more than 1 exclusion criterion.

to identify only English-language, randomized controlled trials in humans, 968 studies were identified. From reviewing the titles and abstracts of these studies, 34 were identified as potentially relevant according to the aforementioned inclusion and exclusion criteria, and of these only 16 were considered appropriate for the review. As this generated few data regarding adverse events, the titles and abstracts of the full 3227 studies were reviewed, and 123 studies were considered potentially relevant. On reading the full text of these manuscripts, an additional 12 studies were identified from bibliographies. After reviewing the additional 135 manuscripts, a total of 30 studies were considered appropriate for inclusion in this review (Fitch et al. 1976; Leisti et al. 1979; Graff-Lonnevig et al. 1980; Bundgaard et al. 1983; Nickerson et al. 1983; Orenstein et al. 1985; Ramazanoglu and Kraemer 1985; Ludwick et al. 1986; Haas et al. 1987; Szentágothai et al. 1987; Freeman et al. 1989; Cochrane and Clark 1990; Engström et al. 1991; Varray et al. 1991,1995; Girodo et al. 1992; Robinson et al. 1992; Ahmaidi et al. 1993; Emtner et al. 1998; Matsumoto et al. 1999; Neder et al. 1999; Bingöl Karakoç et al. 2000; van Veldhoven et al. 2001; Counil et al. 2003; Weisgerber et al. 2003; Basaran et al. 2006; Silva et al. 2006; Fanelli et al. 2007; Bonsignore et al. 2008; Juvonen et al. 2008). The main reasons for exclusion of trials were as follows: lack of an exercise intervention; patients did not have asthma; and studies were in athletes with EIB without a confirmed diagnosis of asthma.

The characteristics of the included studies are presented in Table 3. The 30 studies included a total of 1278 children and adults with chronic asthma. Originally, we separated the studies into those with children (n = 22) or adults (n = 8). However, because of the small number of studies in adults, the comparable disease severity (FEV_1 = 81% ± 5% predicted and 87% ± 9% predicted in adults and children, respectively), and the apparent similarities in the relative number of reports of adverse events, we decided to combine the data. Exclusion criteria were reported by 57% of trials (Table 4). An incremental exercise test with or without gas analysis was performed in 63% of trials before the start of an exercise intervention, and continuous electrocardiogram (ECG) monitoring was performed in 23% of these trials. Twelve studies

Table 3. Characteristics of asthma studies (n = 30).

Characteristic	No. of studies, %
No. of patients	1278
Female, %	37±19
Age, years	16±10
Age range, years	8–38
FEV_1, % predicted	85±8
FEV_1 range, % predicted	69–99
No. of studies in children	22
Severity of asthma recruited (reported in % of studies)	
Severe	14
Moderate to severe	7
Moderate	14
Mild to moderate	50
Mild	7
All severities	7
Study design of included studies	
Randomized controlled trials	16, 53
Quasiexperimental design	4, 13
Single-arm trials	7, 23
Cross-sectional	2, 6
Longitudinal	1, 3
Type of exercise used	
Aerobic	27, 90
Other*	3, 10
Studies prescreening with PAR-Q or PARmed-X	0, 0
Studies performing maximal incremental test before exercise	19, 57
Type of test used for screening	
Cardiopulmonary test with gas exchange analysis	18, 60
Incremental test without gas exchange analysis	1, 3
Exercise monitoring reported during testing	
Electrocardiogram	8, 26
Arterial saturation (either pulse oximetry or blood gases)	2, 7
Exercise provocation test performed before staring exercise training	12, 40

Note: Data are reported as means ± SD, a range, or the number of studies, percentage of total studies unless otherwise stated.

*For other types of training used please see text.

Table 4. Adverse events and reasons for patient exclusion in asthma studies (n = 30).

Characteristic	No. of studies, %
Studies reporting adverse events during exercise	15
Adverse events reported with exercise	
None	1, 7
Death	0, 0
Exercise-induced bronchoconstriction	7, 47
Arterial desaturation	1, 7
Exacerbations	2, 13
Asthma symptoms	2, 13
Decrease in peak flow rates	2, 13
Asthma attacks	1, 7
No. studies reporting exclusion criteria	17
Reasons for exclusion	
Nonclinical diagnosis of asthma	7, 41
Uncontrolled asthma	7, 41
Negative test for exercise-induced bronchoconstriction	1, 6
Severe asthma	4, 23
Other pulmonary diseases	1, 6
Cardiovascular disease	1, 6
Other comorbidities	2, 12
Total no. of patients excluded	41
Reasons reported for exclusion (not exercise related)	
Health problems	23, 56
Exacerbations	10, 24
Upper respiratory tract infections	3, 7
Bone fracture	1, 2
Physical problems	1, 2
Worsening symptoms	3, 7

Note: Data are reported as means ± SD or number of studies, percentage of total studies. In the 15 studies reporting adverse events, mean age was 17 ± 11 years and mean FEV_1 = 87% ± 10% (predicted). Please note that studies can have more than 1 exclusion criterion.

(40%) also performed an exercise provocation test to assess the magnitude of EIB before the initiation of exercise.

One study was specifically designed to determine the safety of exercise in individuals with asthma. This study reported a number of adverse events to exercise, but none were fatal. Following exercise testing, half of all subjects consistently developed EIB, and it was reported that 1 child had a 13 mm Hg drop in transcutaneous oxygen partial pressure during exercise that was associated with a 21% reduction in FEV_1 5 min following exercise. Of the remaining 29 trials, 14 reported adverse events, none of which were fatal. One study reported no adverse events following exercise testing or training. Among the 674 patients in the trials reporting exercise-related adverse events, 103 individuals were reported to have EIB following exercise training sessions. Five additional studies mentioned that subjects had EIB, asthma attacks of various intensities, and reductions in peak flow rates following exercise, but these statements were not quantified. One study reported that 12 patients were hospitalized during the exercise intervention period, but it was not clear whether these were exercise-related hospitalizations or caused by other asthma triggers.

Discussion

This is the first systematic review to evaluate the evidence associated with the risk of performing exercise in patients with respiratory disease. Only 1 study in patients with asthma was directly designed to address this question (Nickerson et al. 1983). As such, secondary-level evidence was obtained by assessing the number of adverse events reported by trials that performed an exercise intervention in patients with COPD or asthma. In total, there were no fatalities and only a minimal number of adverse events directly related to exercise. Owing to exclusion of patients with more severe comorbidities and contraindications to exercise in the majority of studies, it is difficult to make a definitive statement regarding the risk of exercise for all patients with COPD and (or) asthma. However, the available evidence supports that the risk of exercise is low compared with the known benefits of exercise for patients with these disorders, especially when patients have been appropriately cleared to exercise.

Evidence of risks and contraindications to exercise in patients with COPD

The systematic review identified no study that was specifically designed to evaluate the risk of exercise in patients with COPD. Additionally, only 15 of 102 randomized controlled trials made a specific statement regarding whether any adverse events occurred during exercise testing or training (Busch and McClements 1988; Simpson et al. 1992; Martinez et al. 1993; Wedzicha et al. 1998; Larson et al. 1999; Garrod et al. 2000*b*; Johnson et al. 2002; Rooyackers et al. 2003; Singh et al. 2003; Casaburi et al. 2004; Man et al. 2004; Boxall et al. 2005; Phillips et al. 2006; Puhan et al. 2006; Varga et al. 2007). From these 15 studies, potentially more serious cardiovascular adverse events related to exercise occurred in only 3.4% of patients. However, this is likely lower than what would be expected if patients had not been excluded from these studies for known cardiovascular disease, cerebral vascular disease, and hypertension. Interestingly, 23 of 26 cardiovascular adverse events reported were observed during routine incremental cardiopulmonary exercise testing by just 1 study (Larson et al. 1999), which demonstrates the value of this type of testing in determining which patients are safe to exercise. As only 34 studies reported performing an incremental test with continuous ECG monitoring before starting an exercise program, it is possible that additional patients had cardiovascular contraindications to exercise that went undetected. However, as 74 studies reported excluding patients with cardiovascular contraindications and 61 studies performed some form of preexercise incremental test to symptom limitation, it is likely that more studies performed some form of screening process to determine the severity of cardiovascular disease than is actually being reported. Even with the large number of studies reporting that they excluded patients with cardiovascular contraindications to exercise, 34 additional patients were excluded or withdrawn during studies because of cardiovascular or cerebral vascular events unrelated to exercise. These data demonstrate the difficulty in actually evaluating the precise risk of exercise, as a number of cardiovascular adverse events are also reported in those not exercising. It is also impossible to determine how many of the 84 deaths reported were caused by cardiovascular events. The combination of these findings highlight that a number of patients with COPD can present with cardiovascular contraindications to exercise in conjunction with their respiratory disease. As such, appropriate screening before starting exercise appears to be a necessary consideration to reduce the risk of adverse events occurring during exercise in this population.

The majority of events reported were associated with musculoskeletal pain or injury (~41%) related to exercise. A large number of these (71%) were reported in a study that performed eccentric exercise training (Rooyackers et al. 2003). Subsequently, these findings are not particular worrisome and are similar to what might be expected within a group of age-matched healthy but previously sedentary individuals starting exercise. This is especially true considering that the patients with COPD were older (66 years) and a large number likely had secondary comorbidities (Crisafulli et al. 2008) (i.e., arthritis), which could increase their susceptibility to musculoskeletal pain.

A clinically relevant arterial desaturation is often referred to as a decrease in $S_pO_2 > 5\%$ with exercise. However, few studies report this level and only report more significant saturations with exercise, i.e., a decreasing $S_pO_2 < 85\%$. Such a decrease in S_pO_2 was reported in 1 in every 45 patients in trials that reported adverse events. However, it should be noted that 20% of studies reported excluding patients with known hypoxemia at rest or with exertion, and a large number of trials reported that if a patient was hypoxemic or desaturated during exercise they were supplied with supplemental oxygen for testing and training. Nevertheless, the low incidence of exertional hypoxemia reported in these trials supports that, with regular monitoring of S_pO_2 and with the administration of supplemental O_2 to patients who need it during testing or training, the risk of hypoxemia as a contraindication to exercise is relative low.

Based on the literature, there is no direct evidence regarding the risk of performing exercise in patients with COPD and regarding that the evidence was generated from randomized controlled trials that were not specifically designed to assess the risk of exercise in patients with COPD, the evidence can only be considered Level 2, Grade B (Table 5). It should be acknowledged that the risk of an exercise-related adverse event presented by this review is likely biased by the studies that actually reported patients having an adverse event and may actually be lower than that presented. It is feasible that a number of the studies did not make a comment about exercise-related adverse events, as none occurred during the study. However, the overall reporting of exercise-related adverse events in the COPD literature is poor, so this may not be an accurate assumption. Nevertheless, with appropriate screening such as a properly supervised incremental cardiopulmonary exercise test (with ECG monitoring and pulse oximetry), the risks of exercise to patients with COPD is low. Figures 1 and 2 are presented to assist QEPs with the risk stratification of patients with COPD before they initiate PA or an exercise program.

Evidence of risks and contraindications to exercise in patients with asthma

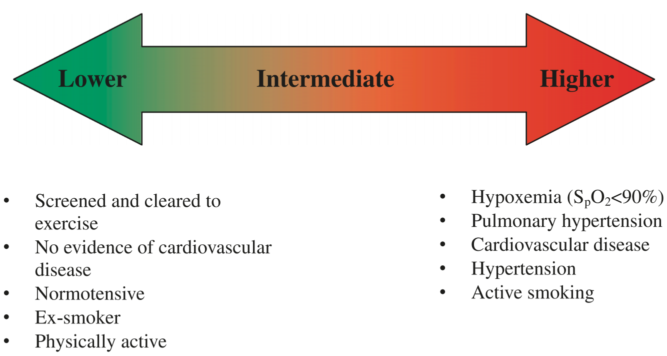
The findings of the systematic review for asthma identified 1 single-armed trial of 15 children (mean age of 11 years) that was specifically designed to determine the safety of exercise in individuals with asthma (Nickerson et al. 1983). This study reported no fatalities during exercise testing or training in children with severe asthma who took part in a 6-week running program. Following outdoor distance running, half of the 15 subjects repeatedly developed EIB, which in all cases was successfully reversed with the administration of a β_2-agonist. One child had a drop of 13 mm Hg in transcutaneous oxygen partial pressure during exercise that was associated with a 21% reduction in FEV_1 following exercise. Although it is promising that there were no serious adverse events reported, some caution is warranted in the interpretation of these findings, as it is not clear whether all children were optimally medically managed.

Fifty percent of studies reporting adverse events documented a worsening of asthma symptoms or EIB in a least 1

Table 5. Levels of Evidence from the chronic obstructive pulmonary disease studies that reported exercise-related adverse events (n = 15).

Level of Evidence	Grade	No. of studies	Proportion
1	A	0	0
1	B	0	0
1	C	0	0
2	A	6	6/15 (40%)
2	B	9	9/15 (60%)
2	C	0	0
3	A	0	0
3	B	0	0
3	C	0	0
4	A	0	0
4	B	0	0
4	C	0	0

Fig. 1. Risk continuum for patients with diagnosed chronic obstructive pulmonary disease. Patients who have been screened and cleared to exercise are at lower risk of an adverse event if they have no comorbidities, are free from cardiovascular disease, and are non-hypoxemic at rest or with exertion. The risk of initiating a physical activity or any exercise program increases with the severity of disease, and if the patient is a smoker, has other risk factors for (or known) cardiovascular disease, pulmonary, and (or) systemic hypertension and (or) hypoxemia. The level of risk refers to the chance of a cardiovascular or cerebrovascular event or death.



subject during or following exercise (Fitch et al. 1976; Bundgaard et al. 1983; Nickerson et al. 1983; Orenstein et al. 1985; Szentágothai et al. 1987; Freeman et al. 1989; Girodo et al. 1992; Emtner et al. 1998; Larson et al. 1999; Neder et al. 1999; van Veldhoven et al. 2001; Counil et al. 2003; Basaran et al. 2006; Silva et al. 2006; Fanelli et al. 2007; Bonsignore et al. 2008). The large majority of these adverse events appeared to be of minimal severity, as almost all were associated with either the development of EIB and (or) asthma symptoms and all were reported to be relieved following the administration of a bronchodilator. One study (Svenonius et al. 1983) reported that 12 patients were hospitalized because of their asthma symptoms during the duration of the study, but it is not clear whether any of these were exercise related. A further 4 studies (2 each) reported asthma attacks and exacerbations associated with exercise, but these are difficult to quantify, as the specific number of patients that these adverse events apply to were not reported. In the 4 studies that recruited patients with severe asthma, only 1 study reported adverse events, and these were all associated with EIB in 65% of patients. How the severity of airflow obstruction changes the risk of performing exercise independently of the level of asthma control is difficult to interpret from the available literature. Furthermore, even though 41% of studies reported excluding patients with uncontrolled asthma, very few studies actual reported that patients were optimally controlled. As such, it is likely that a number of the adverse events reported in these studies are due to suboptimal asthma control.

No cardiovascular contraindications to exercise were reported; however, this is not surprising considering that 22 of 30 studies were performed in children. Eight studies were performed in adults, with the mean age of individuals in these studies (31 ± 7 years) being below that traditionally associated with an increased risk of cardiovascular disease (AHA–ACSM 1998). To date, no investigation has studied older individuals exclusively with asthma, as these individuals have commonly been included in rehabilitation trials with patients who have COPD (Cambach et al. 1997; Foglio et al. 1999).

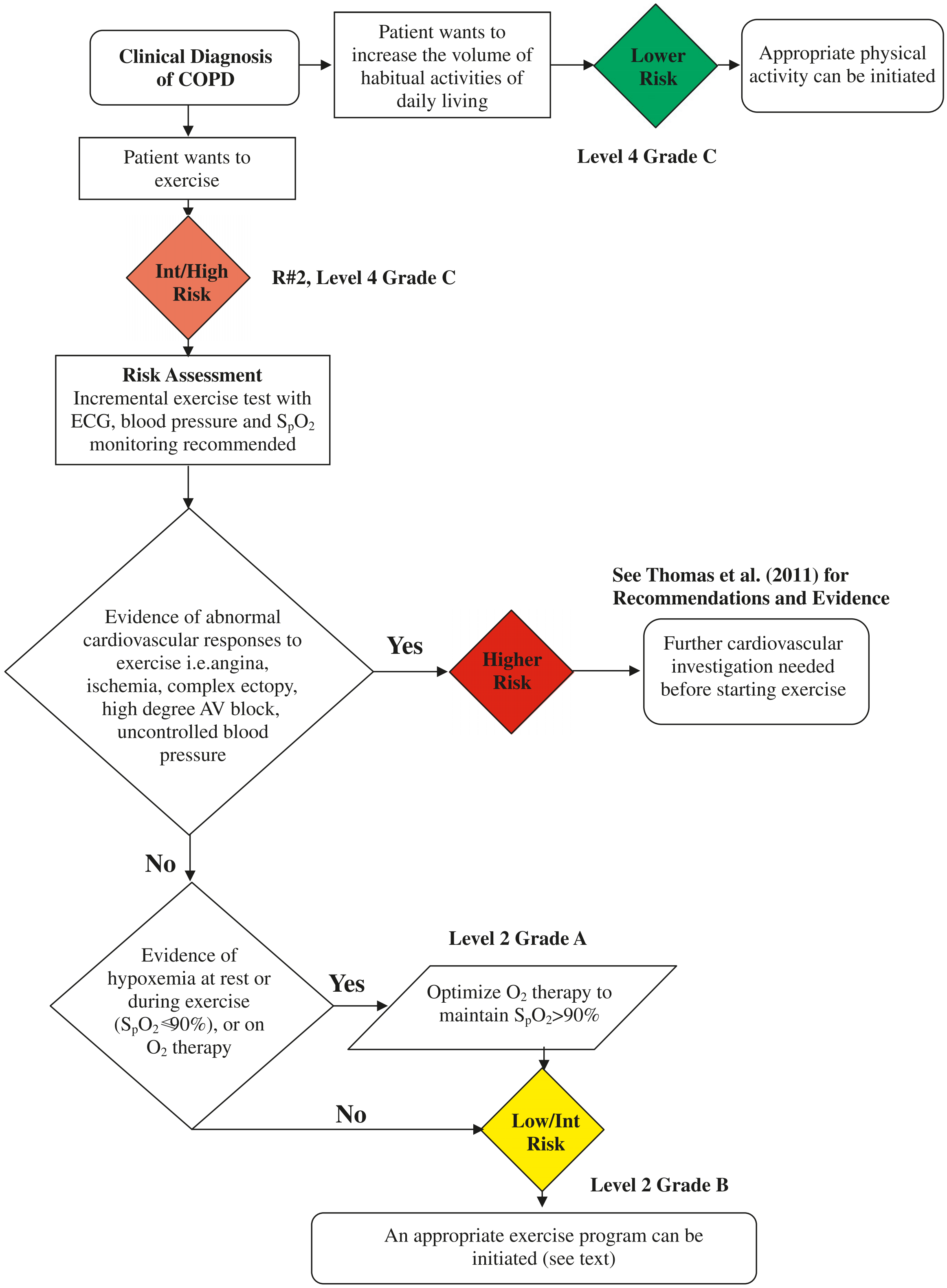
Based on the available literature, there is little direct evidence regarding the risk of exercise in patients with asthma, and the evidence can only be considered Level 2, Grade B (Table 6). Nevertheless, based on the best available information generated by this review, it would appear that even though a number of patients with asthma experienced asthma symptoms or bronchoconstriction with exercise, when their asthma was under optimal medical control the risk for patients with all severities of the disease appeared to be low. Based on the best available information generated by this review and the opinions of the authors, Figs. 3 and 4 are presented to assist QEPs with the risk stratification of patients with asthma before initiating PA or an exercise program.

Clearing patients with COPD and asthma to perform exercise using the PAR-Q and PARmed-X

In the 132 studies reviewed in this systematic review, no study reported using the PAR-Q for screening individuals before they participated in an exercise program. As such, it is impossible to base any decision on the appropriateness of the PAR-Q on available evidence. There are a number of possible reasons why the PAR-Q was not used by any study in this review. First, the PAR-Q is intended for healthy individuals, 15–69 years old, with no known disease. The majority of individuals included in this review were older and had known respiratory disease. Second, 54% of all studies used an incremental exercise test with some objective monitoring of the patient's physiological condition, which allowed risk assessment before the start of an exercise program. Finally, the 7 questions that make up the PAR-Q are focused on screening for the presence of cardiovascular disease, musculoskeletal abnormalities, and hypertension. A diagnosis of respiratory disease is not a question on the current PAR-Q, and in theory a patient with severe hypoxemia or uncontrolled asthma who has no known cardiovascular disease or musculoskeletal problem could answer in the negative to all questions and be cleared for exercise.

Recommendation no. 1: To help identify persons with respiratory disease (or individuals who may have respiratory

Fig. 2. Decision tree for the screening of patients with chronic obstructive pulmonary disease before they become more physically active.



disease and not be aware of their condition), questions directly asking whether an individual has a diagnosis of respiratory disease or if they experience adverse respiratory symptoms during or following exertion (i.e., shortness of breath, chest tightness, wheeze or cough) should be added to the PAR-Q (Level 4, Grade C).

A positive answer to these questions would not necessarily exclude patients from starting PA, but it would allow a QEP

Table 6. Levels of Evidence from the asthma studies that reported exercise-related adverse events (n = 15).

Level of Evidence	Grade	No. of studies	Proportion
1	A	0	0
1	B	0	0
1	C	0	0
2	A	7	7/15 (47%)
2	B	2	2/15 (13%)
2	C	1	1/15 (7%)
3	A	2	2/15 (13%)
3	B	1	1/15 (7%)
3	C	2	2/15 (13%)
4	A	0	0
4	B	0	0
4	C	0	0

to assess whether physician clearance and further evaluation is necessary (Figs. 2 and 4).

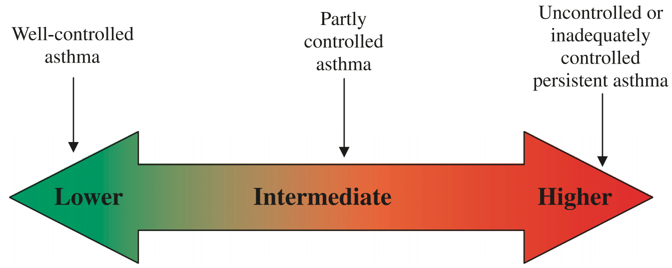
Similar to the PAR-Q, no study in this review reported using the PARmed-X for screening of patients with respiratory disease. The use of such a document may not be considered necessary in clinical trial research, where commonly at least 1 member of the investigative team is a physician who often may know a patient's medical history and (or) can help evaluate a patient's risk of performing exercise. However, with more respiratory disease patients being encouraged to perform PA, it is essential that there is a simple, accurate screening tool that can identify individuals at risk from exercise while minimizing the barriers for lower-risk patients to start exercising quickly.

The current PARmed-X has no specific absolute or relative contraindications associated with respiratory disease to make decisions on the risk of exercise for these patients. Although no direct evidence was found to support any contraindication to exercise in either COPD or asthma, the secondary evidence supports the notion that patients with significant hypoxemia (S_pO_2 < 90%) at rest and (or) exertion, uncontrolled asthma, and the presence of pulmonary hypertension should be properly optimally medically managed before starting exercise (Level 4, Grade C) (Tables 5, 6).

The decision trees provided in Figs. 2 and 4 are designed to help guide some of the decision-making process regarding patients of any age with a known diagnosis of COPD or asthma who want to start exercise training or performing a greater amount of PA. The joint ATS–ERS statement on pulmonary rehabilitation (Nici et al. 2006) states that all patients with COPD should perform a maximal cardiopulmonary exercise test (which includes continuous ECG monitoring) to evaluate the patient's safety before they initiate a rehabilitation program. Considering (*i*) the secondary evidence of the prevalence of cardiovascular disease in these patients, (*ii*) the known risks of long-term habitual cigarette smoking, (*iii*) the higher number of comorbidities associated with COPD, and (*iv*) the prevalence of exertional hypoxemia, there is little evidence to reject such a recommendation for patients who want to start exercising at an intensity above habitual levels. Consequently, we make the following recommendation:

Recommendation no. 2: Persons with known COPD who want to become more physically active ideally should be evaluated using a properly supervised incremental cardiopulmonary exercise test (with ECG monitoring and pulse oximetry) (Level 4, Grade C) (Table 5).

Fig. 3. Risk continuum for patients with asthma. Patients with well-controlled asthma have a similar risk of an adverse event as those in the "healthy" population. Patients with uncontrolled asthma are at a higher risk of an adverse event from their disease. There is currently little evidence to comment on how the severity of airflow obstruction may change the risk of exercise to patients with asthma. The level of risk refers to the increased likelihood of worsening symptoms, hospitalization, or death.



This recommendation is not taken lightly, as it clearly imposes a barrier to patients becoming more physically active and may involve patients having to pay for the test to be performed. If a patient presents with known cardiovascular disease, then the QEP should appropriately assess the patient according to the accompanying systematic review on the recommendations for PA clearance in established cardiovascular disease (Thomas et al. 2011).

In patients with asthma, if the disease is well controlled, then the risk of exercise with a few disease-specific considerations (see exercise guidelines for patients with asthma) are likely similar to those for a healthy nonasthmatic individual.

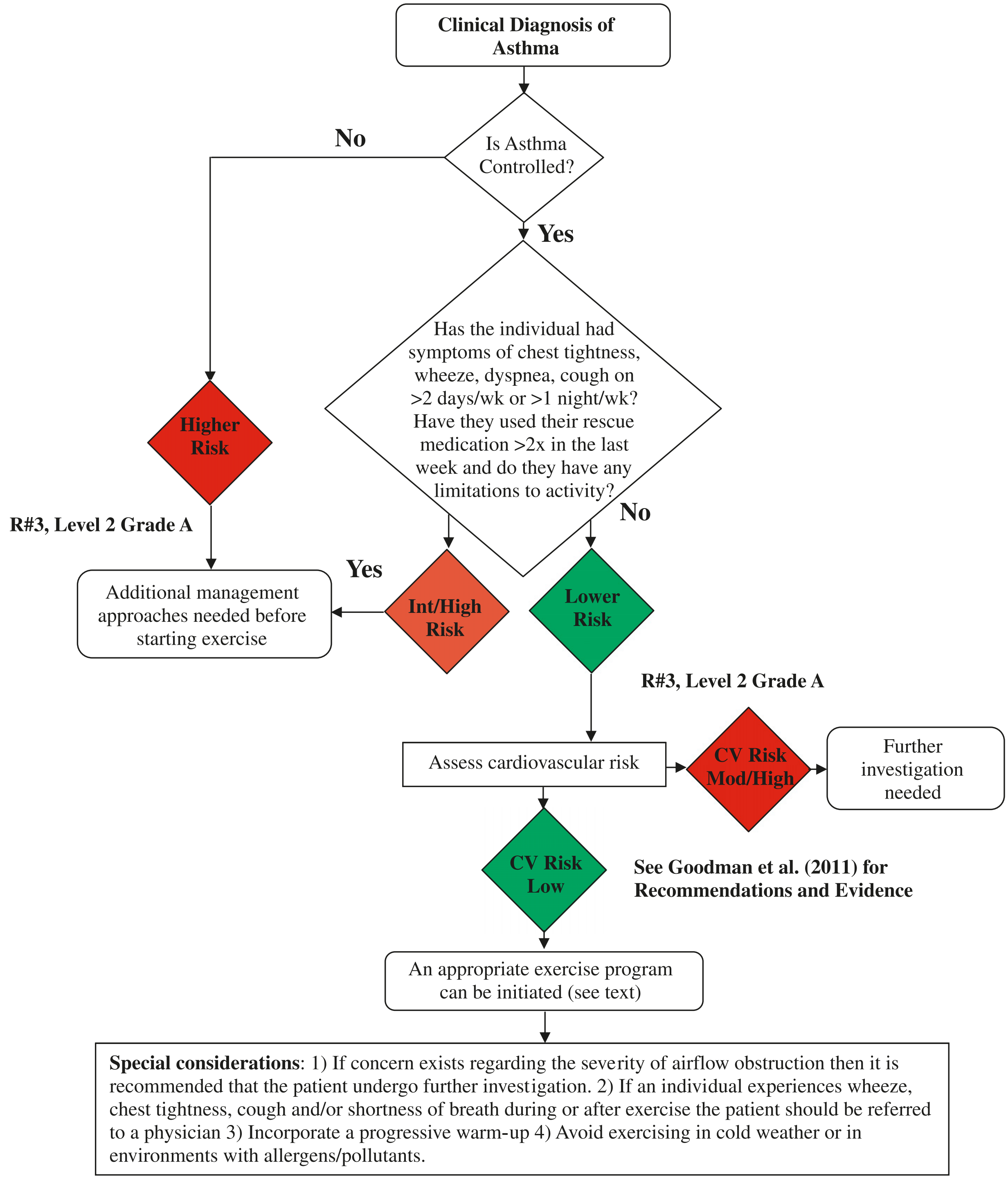
Recommendation no. 3: To reduce the risk of an exercise-related adverse event, persons with asthma should make sure that their disease is properly controlled before becoming more physically active. Persons with poor or partial control of their asthma should be referred back to their physician before becoming more active (Level 2, Grade A) (Table 6).

Exercise guidelines for patients with COPD

There are considerable data to support the idea that PA of any kind can have some benefit for reducing exertional symptoms and improving quality of life in patients with COPD (Lacasse et al. 2002, 2006; Ries et al. 2007). Current recommendations suggest that aerobic exercise of a moderate to high intensity (60%–80% of workload maximum, W_{max}) (Casaburi et al. 1991; Maltais et al. 1997) leads to many positive physiological adaptations, if performed on at least 3 days of the week (Ringbaek et al. 2000; Nici et al. 2006). However, it should be highlighted that because of ventilatory limitation occurring in a large number of patients around the point of respiratory compensation, these intensities are often more reflective of a percentage of ventilatory threshold than a workload associated with a true maximal oxygen consumption.

Owing to the large heterogeneity in where ventilatory limitation occurs in patients with COPD, it is difficult to prescribe exercise routinely from a generic prescription for heart rate reserve or as a percentage of maximal heart rate. A potentially more appropriate way to prescribe exercise in this

Fig. 4. Decision tree for the screening of patients with asthma before they become more physically active.



population is to use symptom rating, as a moderate intensity can be determined by having patients exercise at dyspnea levels between 4 and 6 on the modified Borg Scale (Borg 1982). However, the QEP must describe the scale in detail and should be aware of those who are more desensitized to the sensation of dyspnea or who are less motivated, as in these individuals this method for gauging exercise intensity may not be appropriate.

Although higher intensity exercise of a continuous nature may result in better outcomes for patients with COPD, it can often reduce adherence because of the adverse exertional symptoms that accompany it (Maltais et al. 1997). A practical alternative may be interval training, as many studies have demonstrated that interval training is well tolerated by patients with COPD and results in similar physiological adaptations to a continuous endurance exercise (Coppoolse et al. 1999; Gimenez et al. 2000; Vogiatzis et al. 2002, 2005; Puhan et al. 2006; Arnardóttir et al. 2007). The intermittent nature of interval training allows patients to work at higher intensities than can normally be achieved, but allows dynamic hyperinflation to be reduced during recovery, which gives patients relief from their dyspnea. As a result the average dyspnea reported through an interval training session is lower (Vogiatzis et al. 2005). Intervals of 30 s to 3 min, working at 80%–100% W_{max} with either complete rest or active recover at 30%–40% W_{max} have been shown to be tolerable for patients with COPD (Coppoolse et al. 1999; Vogiatzis et al. 2002, 2005; Arnardóttir et al. 2007).

As mentioned above, resistance training has also been shown to be beneficial for patients with COPD. Similar to interval training, resistance training allows patients to avoid dyspnea due to the short periods of work being separated by periods of recovery. As a result, resistance training has been reported to be well tolerated by patients of all severities (Simpson et al. 1992; Bernard et al. 1999; Kongsgaard et al. 2004; Arnardóttir et al. 2007; Hoff et al. 2007) and is often associated with good adherence rates (Phillips et al. 2006). Resistance exercise of 1–4 sets of 6–12 repetitions at 50%–80% of 1RM have been shown to be appropriate for patients with COPD (Simpson et al. 1992; Bernard et al. 1999; Arnardóttir et al. 2006; Phillips et al. 2006). In some patients, alterations in loading and the type of exercises may be needed, especially for upper-body exercise, to avoid musculoskeletal injury. Progression to heavy resistance exercises (>80% of 1RM), especially for the lower extremities, may also produce greater benefits for some individuals (Phillips et al. 2006; Hoff et al. 2007).

Exercise guidelines for patients with asthma

When controlled, patients with asthma are not often ventilatory-limited and can achieve similar types, intensities, and durations of exercise as their age-matched peers. Subsequently, exercise of any type can be prescribed depending on the desired goal of exercise. In general, exercise prescription for patients with asthma who are participating in exercise for general health can follow guidelines supplied by the American College of Sports Medicine, which recommends exercise of 20–60 min duration at 55%–90% of maximum heart rate on 3–5 days per week (Pollock et al. 1998). Exercise of higher intensities, frequencies, and durations are also applicable to individuals who want to improve their physical fitness or want to participate in sporting competition. A number of studies included in this review have demonstrated that aerobic exercise of intensities associated with the ventilatory threshold or higher are well tolerated in patients with asthma and can result in considerable improvement in maximal oxygen consumption (Cochrane and Clark 1990; Varray et al. 1991; Ahmaidi et al. 1993; Matsumoto et al. 1999; Counil et al. 2003; Fanelli et al. 2007). For individuals who may have developed more fixed airway obstruction, the recommendations provided above for patients with COPD are probably more realistic and would result in similar benefits for these patients.

Even though all types and intensities of exercise appear to be appropriate for individuals with well-controlled asthma, a number of special considerations are recommended for individuals wanting to perform exercise (Miller et al. 2005). For individuals who develop EIB and (or) asthma-like symptoms with exercise, a rapid-acting β_2-agonist (salbutamol, formoterol, terbutaline) should be taken before exercise. Individuals with asthma should also incorporate a progressive warmup and should try and avoid exercising in the excessive cold or environments with known asthma triggers.

Areas of research requiring additional evidence

From the current review, a number of important areas can be identified where there is a need for future investigation. (*i*) There is an need for well-designed trials that can better identify the specific risk of exercise for individuals with respiratory disease, including COPD and asthma, to clearly guide the PA screening and clearance process. With these data it may be feasible to design more economical and practical evaluation procedures, especially for COPD patients, to provide clearance to lower-risk patients to initiate PA and exercise programs safely. (*ii*) The limited data in this area also necessitate that patients with mild to very severe COPD who want to start exercising are treated in a similar fashion for the PA screening process. Intuitively, patients with milder disease would seem at lower risk of exercise-related complications (i. e., exercise-induced arterial desaturation and pulmonary arterial hypertension), but this group is still at risk of associated underlying cardiovascular disease. Consequently, there is a need for research that documents the risk of performing exercise in patients with a variety of disease severities. (*iii*) Similarly, in individuals with asthma, research is needed to better understand the risk of exercise in controlled patients with different severities of airflow obstruction. In addition, as more asthma phenotypes are identified, studies are needed to determine the benefits and risks of exercise in these specific subgroups of patients. (*iv*) Finally, although the benefits of PA and exercise are well documented for both asthma and COPD, research needs to determine more optimal exercise prescriptions to maximize the benefits of exercise for disease modification in both these populations.

Summary

The findings of this systematic review demonstrate that there is little direct evidence regarding the risk of exercise in patients with COPD or asthma. However, secondary evidence supports that with the appropriate screening of patients with respiratory disease, the benefits of exercise appear to outweigh the risk and can help a patient to manage their disease and live a healthy life.

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References

AGREE Collaboration. 2003. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual. Saf. Health Care, **12**(1): 18–23. doi:10.1136/qhc.12.1.18. PMID:12571340.

AHA–ACSM. 1998. Joint position statement: recommendations for cardiovascular screening, staffing, and emergency policies at health/fitness facilities. Med. Sci. Sports Exerc. **30**(6): 1009–1018 . doi:10.1097/00005768-199806000-00034. PMID:9624663.

Ahmaidi, S.B., Varray, A.L., Savy-Pacaux, A.M., and Prefaut, C.G. 1993. Cardiorespiratory fitness evaluation by the shuttle test in asthmatic subjects during aerobic training. Chest, **103**(4): 1135–1141. doi:10.1378/chest.103.4.1135. PMID:8131453.

American Thoracic Society and American College of Chest Physicians. 2003. ATS–ACCP Statement on cardiopulmonary exercise testing. Am. J. Respir. Crit. Care Med. **167**(2): 211–277. doi:10.1164/rccm.167.2.211. PMID:12524257.

Arnardóttir, R.H., Sorensen, S., Ringqvist, I., and Larsson, K. 2006. Two different training programmes for patients with COPD: a randomised study with 1-year follow-up. Respir. Med. **100**(1): 130–139. doi:10.1016/j.rmed.2005.03.043. PMID:15885996.

Arnardóttir, R.H., Boman, G., Larsson, K., Hedenstrom, H., and Emtner, M. 2007. Interval training compared with continuous training in patients with COPD. Respir. Med. **101**(6): 1196–1204. doi:10.1016/j.rmed.2006.11.004. PMID:17188853.

Barnes, P.J. 2000. Chronic obstructive pulmonary disease. N. Engl. J. Med. **343**(4): 269–280. doi:10.1056/NEJM200007273430407. PMID:10911010.

Basaran, S., Guler-Uysal, F., Ergen, N., Seydaoglu, G., Bingol-Karakoc, G., and Ufuk Altintas, D. 2006. Effects of physical exercise on quality of life, exercise capacity and pulmonary function in children with asthma. J. Rehabil. Med. **38**(2): 130–135. doi:10.1080/16501970500476142. PMID:16546771.

Bateman, E.D., Hurd, S.S., Barnes, P.J., Bousquet, J., Drazen, J.M., FitzGerald, M., et al. 2008. Global strategy for asthma management and prevention: GINA executive summary. Eur. Respir. J. **31**(1): 143–178. doi:10.1183/09031936.00138707.

Bauldoff, G.S., Hoffman, L.A., Sciurba, F., and Zullo, T. 1996. Home-based, upper-arm exercise training for patients with chronic obstructive pulmonary disease. Heart Lung, **25**(4): 288–294. doi:10.1016/S0147-9563(96)80064-1. PMID:8836744.

Bauldoff, G.S., Rittinger, M., Nelson, T., Doehrel, J., and Diaz, P.T. 2005. Feasibility of distractive auditory stimuli on upper extremity training in persons with chronic obstructive pulmonary disease. J. Cardiopulm. Rehabil. **25**(1): 50–55. doi:10.1097/00008483-200501000-00011. PMID:15714113.

Behnke, M., Taube, C., Kirsten, D., Lehnigk, B., Jörres, R.A., and Magnussen, H. 2000. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. Respir. Med. **94**(12): 1184–1191. doi:10.1053/rmed.2000.0949. PMID:11192954.

Behnke, M., Jorres, R.A., Kirsten, D., and Magnussen, H. 2003. Clinical benefits of a combined hospital and home-based exercise programme over 18 months in patients with severe COPD. Monaldi Arch. Chest Dis. **59**(1): 44–51. PMID:14533282.

Bendstrup, K.E., Ingemann Jensen, J., Holm, S., and Bengtsson, B. 1997. Out-patient rehabilitation improves activities of daily living, quality of life and exercise tolerance in chronic obstructive pulmonary disease. Eur. Respir. J. **10**(12): 2801–2806. doi:10.1183/09031936.97.10122801. PMID:9493664.

Bernard, S., Whittom, F., Leblanc, P., Jobin, J., Belleau, R., Berube, C., et al. 1999. Aerobic and strength training in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **159**(3): 896–901. PMID:10051269.

Berry, M.J., Adair, N.E., Sevensky, K.S., Quinby, A., and Lever, H. M. 1996. Inspiratory muscle training and whole-body reconditioning in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **153**(6 Pt 1): 1812–1816. PMID:8665039.

Berry, M.J., Rejeski, W.J., Adair, N.E., Ettinger, W.H., Jr, Zaccaro, D.J., and Sevick, M.A. 2003. A randomized, controlled trial comparing long-term and short-term exercise in patients with chronic obstructive pulmonary disease. J. Cardiopulm. Rehabil. **23**(1): 60–68. doi:10.1097/00008483-200301000-00011. PMID:12576914.

Bingöl Karakoç, G., Yilmaz, M., Sur, S., Ufuk Altintas, D., Sarpel, T., and Guneter Kendirli, S. 2000. The effects of daily pulmonary rehabilitation program at home on childhood asthma. Allergol. Immunopathol. (Madr.), **28**(1): 12–14. PMID:10757852.

Bjornshave, B., and Korsgaard, J. 2005. Comparison of two different levels of physical training in patients with moderate to severe COPD. Lung, **183**(2): 101–108. doi:10.1007/s00408-004-2523-2. PMID:16026014.

Bonsignore, M.R., La Grutta, S., Cibella, F., Scichilone, N., Cuttitta, G., Interrante, A., et al. 2008. Effects of exercise training and montelukast in children with mild asthma. Med. Sci. Sports Exerc. **40**(3): 405–412. doi:10.1249/MSS.0b013e31815d9670. PMID:18379200.

Borg, G.A. 1982. Psychophysical bases of perceived exertion. Med. Sci. Sports Exerc. **14**(5): 377–381. PMID:7154893.

Boxall, A.M., Barclay, L., Sayers, A., and Caplan, G.A. 2005. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. J. Cardiopulm. Rehabil. **25**(6): 378–385. doi:10.1097/00008483-200511000-00012. PMID:16327534.

Broekhuizen, R., Wouters, E.F., Creutzberg, E.C., Weling-Scheepers, C.A., and Schols, A.M. 2005. Polyunsaturated fatty acids improve exercise capacity in chronic obstructive pulmonary disease. Thorax, **60**(5): 376–382. doi:10.1136/thx.2004.030858. PMID:15860712.

Briggs, D.D., Jr. 2004. Chronic obstructive pulmonary disease overview: prevalence, pathogenesis, and treatment. J. Manag. Care Pharm. **10**(4 Suppl.): S3–S10. PMID:15253681.

Brooks, D., Krip, B., Mangovski-Alzamora, S., and Goldstein, R.S. 2002. The effect of postrehabilitation programmes among individuals with chronic obstructive pulmonary disease. Eur. Respir. J. **20**(1): 20–29. doi:10.1183/09031936.02.01852001. PMID:12166571.

Buist, A.S., McBurnie, M.A., Vollmer, W.M., Gillespie, S., Burney, P., Mannino, D.M., et al. 2007. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. Lancet, **370**(9589): 741–750. doi:10.1016/S0140-6736(07)61377-4. PMID:17765523.

Bundgaard, A., Ingemann-Hansen, T., Halkjaer-Kristensen, J., Schmidt, A., Bloch, I., and Andersen, P.K. 1983. Short-term physical training in bronchial asthma. Br. J. Dis. Chest, **77**(2): 147–152. doi:10.1016/0007-0971(83)90020-7. PMID:6135442.

Burdet, L., de Muralt, B., Schutz, Y., Pichard, C., and Fitting, J.W. 1997. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. Am. J. Respir. Crit. Care Med. **156**(6): 1800–1806. PMID:9412558.

Busch, A.J., and McClements, J.D. 1988. Effects of a supervised home exercise program on patients with severe chronic obstructive pulmonary disease. Phys. Ther. **68**(4): 469–474. PMID:3353456.

Butler, J., Schrijen, F., Henriquez, A., Polu, J.M., and Albert, R.K. 1988. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. **138**(2): 350–354. PMID:3195834.

Cambach, W., Chadwick-Straver, R.V., Wagenaar, R.C., van Keimpema, A.R., and Kemper, H.C. 1997. The effects of a community-based pulmonary rehabilitation programme on exercise tolerance and quality of life: a randomized controlled trial. Eur. Respir. J. **10**(1): 104–113. doi:10.1183/09031936.97.10010104. PMID:9032501.

Carrieri-Kohlman, V., Gormley, J.M., Eiser, S., Demir-Deviren, S., Nguyen, H., Paul, S.M., and Stulbarg, M.S. 2001. Dyspnea and the affective response during exercise training in obstructive pulmonary disease. Nurs. Res. **50**(3): 136–146. doi:10.1097/00006199-200105000-00002. PMID:11393635.

Casaburi, R., Patessio, A., Ioli, F., Zanaboni, S., Donner, C.F., and Wasserman, K. 1991. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am. Rev. Respir. Dis. **143**(1): 9–18. PMID:1986689.

Casaburi, R., Porszasz, J., Burns, M.R., Carithers, E.R., Chang, R.S., and Cooper, C.B. 1997. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **155**(5): 1541–1551. PMID:9154855.

Casaburi, R., Bhasin, S., Cosentino, L., Porszasz, J., Somfay, A., Lewis, M.I., et al. 2004. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **170**(8): 870–878. doi:10.1164/rccm.200305-617OC. PMID:15271690.

Casaburi, R., Kukafka, D., Cooper, C.B., Witek, T.J., Jr, and Kesten, S. 2005. Improvement in exercise tolerance with the combination of tiotropium and pulmonary rehabilitation in patients with COPD. Chest, **127**(3): 809–817. doi:10.1378/chest.127.3.809. PMID:15764761.

Celli, B.R., MacNee, W., Agusti, A., Anzueto, A., Berg, B., Buist, A.S., et al. 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS–ERS position paper. Eur. Respir. J. **23**(6): 932–946. doi:10.1183/09031936.04.00014304. PMID:15219010.

Chapman, K.R., Bourbeau, J., and Rance, L. 2003. The burden of COPD in Canada: results from the Confronting COPD survey. Respir. Med. **97**(Suppl. C): S23–S31. doi:10.1016/S0954-6111(03)80022-7. PMID:12647940.

Chatila, W.M., Thomashow, B.M., Minai, O.A., Criner, G.J., and Make, B.J. 2008. Comorbidities in chronic obstructive pulmonary disease. Proc. Am. Thorac. Soc. **5**(4): 549–555. doi:10.1513/pats.200709-148ET. PMID:18453370.

Chung, K.F., Godard, P., Adelroth, E., Ayres, J., Barnes, N., Barnes, P., et al. 1999. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. Eur. Respir. J. **13**(5): 1198–1208. PMID:10414427.

Clark, C.J., Cochrane, L., and Mackay, E. 1996. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. Eur. Respir. J. **9**(12): 2590–2596. doi:10.1183/09031936.96.09122590. PMID:8980974.

Clark, C.J., Cochrane, L.M., Mackay, E., and Paton, B. 2000. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. Eur. Respir. J. **15**(1): 92–97. doi:10.1183/09031936.00.15109200. PMID:10678627.

Cochrane, L.M., and Clark, C.J. 1990. Benefits and problems of a physical training programme for asthmatic patients. Thorax, **45**(5): 345–351. doi:10.1136/thx.45.5.345. PMID:2116678.

Collins, E.G., Langbein, W.E., Fehr, L., O'Connell, S., Jelinek, C., Hagarty, E., et al. 2008. Can ventilation-feedback training augment exercise tolerance in patients with chronic obstructive pulmonary disease? Am. J. Respir. Crit. Care Med. **177**(8): 844–852. doi:10.1164/rccm.200703-477OC. PMID:18202351.

Coppoolse, R., Schols, A.M., Baarends, E.M., Mostert, R., Akkermans, M.A., Janssen, P.P., and Wouters, E.F. 1999. Interval versus continuous training in patients with severe COPD: a randomized clinical trial. Eur. Respir. J. **14**(2): 258–263. doi:10.1034/j.1399-3003.1999.14b04.x. PMID:10515398.

Counil, F.P., Varray, A., Matecki, S., Beurey, A., Marchal, P., Voisin, M., and Préfaut, C. 2003. Training of aerobic and anaerobic fitness in children with asthma. J. Pediatr. **142**(2): 179–184. doi:10.1067/mpd.2003.83. PMID:12584541.

Creutzberg, E.C., Wouters, E.F., Mostert, R., Pluymers, R.J., and Schols, A.M. 2003. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest, **124**(5): 1733–1742. doi:10.1378/chest.124.5.1733. PMID:14605042.

Crisafulli, E., Costi, S., Luppi, F., Cirelli, G., Cilione, C., Coletti, O., et al. 2008. Role of comorbidities in a cohort of patients with COPD undergoing pulmonary rehabilitation. Thorax, **63**(6): 487–492. doi:10.1136/thx.2007.086371. PMID:18203818.

de Blok, B.M., de Greef, M.H., ten Hacken, N.H., Sprenger, S., Postema, K., and Wempe, J. 2006. The effects of a lifestyle physical activity counseling program with feedback of a pedometer during pulmonary rehabilitation in patients with COPD: a pilot study. Patient Educ. Couns. **61**(1): 48–55. doi:10.1016/j.pec.2005.02.005. PMID:16455222.

de Torres, J.P., Pinto-Plata, V., Ingenito, E., Bagley, P., Gray, A., Berger, R., and Celli, B. 2002. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest, **121**(4): 1092–1098. doi:10.1378/chest.121.4.1092. PMID:11948037.

Dekhuijzen, P.N., Folgering, H.T., and van Herwaarden, C.L. 1991. Target-flow inspiratory muscle training during pulmonary rehabilitation in patients with COPD. Chest, **99**(1): 128–133. doi:10.1378/chest.99.1.128. PMID:1984942.

Dolmage, T.E., and Goldstein, R.S. 2008. Effects of one-legged exercise training of patients with COPD. Chest, **133**(2): 370–376. doi:10.1378/chest.07-1423. PMID:17925417.

Domagała-Kulawik, J., Maskey-Warzęchowska, M., Kraszewska, I., and Chazan, R. 2003. The cellular composition and macrophage phenotype in induced sputum in smokers and ex-smokers with COPD. Chest, **123**(4): 1054–1059. doi:10.1378/chest.123.4.1054. PMID:12684293.

Elliott, M., Watson, C., Wilkinson, E., Musk, A.W., and Lake, F.R. 2004. Short- and long-term hospital and community exercise programmes for patients with chronic obstructive pulmonary disease. Respirology, **9**(3): 345–351. doi:10.1111/j.1440-1843.2004.00595.x. PMID:15363006.

Emtner, M., Herala, M., and Stalenheim, G. 1996. High-intensity physical training in adults with asthma. A 10-week rehabilitation program. Chest, **109**(2): 323–330. doi:10.1378/chest.109.2.323. PMID:8620700.

Emtner, M., Finne, M., and Stålenheim, G. 1998. High-intensity physical training in adults with asthma. A comparison between training on land and in water. Scand. J. Rehabil. Med. **30**(4): 201–209. doi:10.1080/003655098443940. PMID:9825384.

Emtner, M., Porszasz, J., Burns, M., Somfay, A., and Casaburi, R. 2003. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. Am. J. Respir. Crit. Care Med. **168**(9): 1034–1042. doi:10.1164/rccm.200212-1525OC. PMID:12869359.

Engström, I., Fällström, K., Karlberg, E., Sten, G., and Bjure, J. 1991. Psychological and respiratory physiological effects of a physical exercise programme on boys with severe asthma. Acta Paediatr. Scand. **80**(11): 1058–1065. doi:10.1111/j.1651-2227.1991.tb11783.x. PMID:1750339.

Engström, C.P., Persson, L.O., Larsson, S., and Sullivan, M. 1999. Long-term effects of a pulmonary rehabilitation programme in outpatients with chronic obstructive pulmonary disease: a randomized controlled study. Scand. J. Rehabil. Med. **31**(4): 207–213. doi:10.1080/003655099444371. PMID:10599897.

Epstein, S.K., Celli, B.R., Martinez, F.J., Couser, J.I., Roa, J., Pollock, M., and Benditt, J.O. 1997. Arm training reduces the VO2 and VE cost of unsupported arm exercise and elevation in chronic obstructive pulmonary disease. J. Cardiopulm. Rehabil. **17**(3): 171–177. doi:10.1097/00008483-199705000-00004. PMID: 9187983.

Etnier, J.L., and Berry, M. 2001. Fluid intelligence in an older COPD sample after short- or long-term exercise. Med. Sci. Sports Exerc. **33**(10): 1620–1628. doi:10.1097/00005768-200110000-00002. PMID:11581543.

Faager, G., and Larsen, F.F. 2004. Performance changes for patients with chronic obstructive pulmonary disease on long-term oxygen therapy after physiotherapy. J. Rehabil. Med. **36**(4): 153–158. doi:10.1080/16501970410023443. PMID:15370730.

Fanelli, A., Cabral, A.L., Neder, J.A., Martins, M.A., and Carvalho, C.R. 2007. Exercise training on disease control and quality of life in asthmatic children. Med. Sci. Sports Exerc. **39**(9): 1474–1480. PMID:17805077.

Finnerty, J.P., Keeping, I., Bullough, I., and Jones, J. 2001. The effectiveness of outpatient pulmonary rehabilitation in chronic lung disease: a randomized controlled trial. Chest, **119**(6): 1705–1710. doi:10.1378/chest.119.6.1705. PMID:11399694.

Fitch, K.D., Morton, A.R., and Blanksby, B.A. 1976. Effects of swimming training on children with asthma. Arch. Dis. Child. **51** (3): 190–194. doi:10.1136/adc.51.3.190. PMID:782376.

Fixman, E.D., Stewart, A., and Martin, J.G. 2007. Basic mechanisms of development of airway structural changes in asthma. Eur. Respir. J. **29**(2): 379–389. doi:10.1183/09031936.00053506. PMID:17264325.

Foglio, K., Bianchi, L., Bruletti, G., Battista, L., Pagani, M., and Ambrosino, N. 1999. Long-term effectiveness of pulmonary rehabilitation in patients with chronic airway obstruction. Eur. Respir. J. **13**(1): 125–132. doi:10.1183/09031936.99.13112599. PMID:10836336.

Foy, C.G., Rejeski, W.J., Berry, M.J., Zaccaro, D., and Woodard, C. M. 2001. Gender moderates the effects of exercise therapy on health-related quality of life among COPD patients. Chest, **119**(1): 70–76. doi:10.1378/chest.119.1.70. PMID:11157586.

Freeman, W., Nute, M.G., and Williams, C. 1989. The effect of endurance running training on asthmatic adults. Br. J. Sports Med. **23**(2): 115–122. doi:10.1136/bjsm.23.2.115. PMID:2605441.

Fuld, J.P., Kilduff, L.P., Neder, J.A., Pitsiladis, Y., Lean, M.E., Ward, S.A., and Cotton, M.M. 2005. Creatine supplementation during pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax, **60**(7): 531–537. doi:10.1136/thx.2004.030452. PMID:15994258.

Garrod, R., Mikelsons, C., Paul, E.A., and Wedzicha, J.A. 2000. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **162**(4 Pt 1): 1335–1341. PMID:11029341.

Garrod, R., Paul, E.A., and Wedzicha, J.A. 2000. Supplemental oxygen during pulmonary rehabilitation in patients with COPD with exercise hypoxaemia. Thorax, **55**(7): 539–543. doi:10.1136/thorax.55.7.539. PMID:10856310.

Gimenez, M., Servera, E., Vergara, P., Bach, J.R., and Polu, J.M. 2000. Endurance training in patients with chronic obstructive pulmonary disease: a comparison of high versus moderate intensity. Arch. Phys. Med. Rehabil. **81**(1): 102–109. PMID: 10638884.

GINA. 2009. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2009. Available from http://www.ginasthma.org.

Girodo, M., Ekstrand, K.A., and Metivier, G.J. 1992. Deep diaphragmatic breathing: rehabilitation exercises for the asthmatic patient. Arch. Phys. Med. Rehabil. **73**(8): 717–720. PMID: 1642520.

Glader, P., von Wachenfeldt, K., and Lofdahl, C.-G. 2006. Systemic CD4+ T-cell activation is correlated with FEV_1 in smokers. Respir. Med. **100**(6): 1088–1093. doi:10.1016/j.rmed.2005.09.025. PMID:16246539.

Goldstein, R.S., Gort, E.H., Stubbing, D., Avendano, M.A., and Guyatt, G.H. 1994. Randomised controlled trial of respiratory rehabilitation. Lancet, **344**(8934): 1394–1397. doi:10.1016/S0140-6736(94)90568-1. PMID:7968075.

Goldstein, R.S., Gort, E.H., Guyatt, G.H., and Feeny, D. 1997. Economic analysis of respiratory rehabilitation. Chest, **112**(2): 370–379. doi:10.1378/chest.112.2.370. PMID:9266871.

Graff-Lonnevig, V., Bevegårrd, S., Eriksson, B.O., Kraepelien, S., and Saltin, B. 1980. Two years' follow-up of asthmatic boys participating in a physical activity programme. Acta Paediatr. Scand. **69**(3): 347–352. doi:10.1111/j.1651-2227.1980.tb07091.x. PMID:7376860.

Green, R.H., Singh, S.J., Williams, J., and Morgan, M.D. 2001. A randomised controlled trial of four weeks versus seven weeks of pulmonary rehabilitation in chronic obstructive pulmonary disease. Thorax, **56**(2): 143–145. doi:10.1136/thorax.56.2.143. PMID:11209104.

Griffiths, T.L., Burr, M.L., Campbell, I.A., Lewis-Jenkins, V., Mullins, J., Shiels, K., et al. 2000. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet, **355**(9201): 362–368. doi:10.1016/S0140-6736(99)07042-7. PMID:10665556.

Güell, R., Casan, P., Belda, J., Sangenis, M., Morante, F., Guyatt, G. H., and Sanchis, J. 2000. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest, **117**(4): 976–983. doi:10.1378/chest.117.4.976. PMID:10767227.

Haas, F., Pasierski, S., Levine, N., Bishop, M., Axen, K., Pineda, H., and Haas, A. 1987. Effect of aerobic training on forced expiratory airflow in exercising asthmatic humans. J. Appl. Physiol. **63**(3): 1230–1235. PMID:3654468.

Haugen, T.S., and Stavem, K. 2007. Rehabilitation in a warm versus a colder climate in chronic obstructive pulmonary disease: a randomized study. J. Cardiopulm. Rehabil. Prev. **27**(1): 50–56. PMID:17474645.

Henriksen, J.M., and Nielsen, T.T. 1983. Effect of physical training on exercise-induced bronchoconstriction. Acta Paediatr. Scand. **72**(1): 31–36. doi:10.1111/j.1651-2227.1983.tb09659.x. PMID:6858683.

Henriksen, J.M., Nielsen, T.T., and Dahl, R. 1981. Effects of physical training on plasma citrate and exercise-induced asthma. Scand. J. Clin. Lab. Invest. **41**(3): 225–229. doi:10.3109/00365518109092038. PMID:7313506.

Hernandez, M.T., Rubio, T.M., Ruiz, F.O., Riera, H.S., Gil, R.S., and Gómez, J.C. 2000. Results of a home-based training program for patients with COPD. Chest, **118**(1): 106–114. doi:10.1378/chest.118.1.106. PMID:10893367.

Hirst, S.J. 2000. Airway smooth muscle as a target in asthma. Clin. Exp. Allergy, **30**(Suppl 1): 54–59. doi:10.1046/j.1365-2222.2000.00099.x. PMID:10849477.

Hoff, J., Tjønna, A.E., Steinshamn, S., Høydal, M., Richardson, R.S., and Helgerud, J. 2007. Maximal strength training of the legs in COPD: a therapy for mechanical inefficiency. Med. Sci. Sports Exerc. **39**(2): 220–226. doi:10.1249/01.mss.0000246989.48729.39. PMID:17277584.

Holland, A.E., Hill, C.J., Nehez, E., and Ntoumenopoulos, G. 2004. Does unsupported upper limb exercise training improve symptoms and quality of life for patients with chronic obstructive pulmonary disease? J. Cardiopulm. Rehabil. **24**(6): 422–427. doi:10.1097/00008483-200411000-00010. PMID:15632778.

Hoshino, T., Kato, S., Oka, N., Imaoka, H., Kinoshita, T., Takei, S., et al. 2007. Pulmonary inflammation and emphysema: role of the cytokines IL-18 and IL-13. Am. J. Respir. Crit. Care Med. **176**(1): 49–62. doi:10.1164/rccm.200603-316OC. PMID:17400729.

Huang, S.W., Veiga, R., Sila, U., Reed, E., and Hines, S. 1989. The effect of swimming in asthmatic children–participants in a swimming program in the city of Baltimore. J. Asthma, **26**(2): 117–121. doi:10.3109/02770908909073240. PMID:2702218.

Incalzi, R.A., Fuso, L., De Rosa, M., Di Napoli, A., Basso, S., Pagliari, G., and Pistelli, R. 1999. Electrocardiographic signs of chronic cor pulmonale: anegative prognostic finding in chronic obstructive pulmonary disease. Circulation, **99**(12): 1600–1605. PMID:10096937.

Jamnik, V.J., Warburton, D.E.R., Makarski, J., McKenzie, D.C., Shephard, R.J., Stone, J., et al. 2011. Enhancing the effectiveness of clearance for physical activity: background and overall process. Appl. Physiol. Nutr. Metab. **36**(Suppl. 1). This issue.

Jeffery, P.K. 2001. Remodeling in asthma and chronic obstructive lung disease. Am. J. Respir. Crit. Care Med. **164**(10 Pt. 2): S28–S38. PMID:11734464.

Jemal, A., Ward, E., Hao, Y., and Thun, M. 2005. Trends in the leading causes of death in the United States, 1970–2002. JAMA, **294**(10): 1255–1259. doi:10.1001/jama.294.10.1255. PMID: 16160134.

Johnson, J.E., Gavin, D.J., and Adams-Dramiga, S. 2002. Effects of training with heliox and noninvasive positive pressure ventilation on exercise ability in patients with severe COPD. Chest, **122**(2): 464–472. doi:10.1378/chest.122.2.464. PMID:12171818.

Juvonen, R., Bloigu, A., Peitso, A., Silvennoinen-Kassinen, S., Saikku, P., Leinonen, M., et al. 2008. Training improves physical fitness and decreases CRP also in asthmatic conscripts. J. Asthma, **45**(3): 237–242. doi:10.1080/02770900701883790. PMID: 18415833.

Karapolat, H., Atasever, A., Atamaz, F., Kirazlı, Y., Elmas, F., and Erdinç, E. 2007. Do the benefits gained using a short-term pulmonary rehabilitation program remain in COPD patients after participation? Lung, **185**(4): 221–225. doi:10.1007/s00408-007-9011-4. PMID:17487535.

Kirsten, D.K., Taube, C., Lehnigk, B., Jörres, R.A., and Magnussen, H. 1998. Exercise training improves recovery in patients with COPD after an acute exacerbation. Respir. Med. **92**(10): 1191–1198. doi:10.1016/S0954-6111(98)90420-6. PMID:9926148.

Kongsgaard, M., Backer, V., Jorgensen, K., Kjaer, M., and Beyer, N. 2004. Heavy resistance training increases muscle size, strength and physical function in elderly male COPD-patients–a pilot study. Respir. Med. **98**(10): 1000–1007. doi:10.1016/j.rmed.2004.03.003. PMID:15481277.

Lacasse, Y., Brosseau, L., Milne, S., Martin, S., Wong, E., Guyatt, G. H., and Goldstein, R.S. 2002. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst. Rev. (3): CD003793. PMID:12137716.

Lacasse, Y., Goldstein, R., Lasserson, T.J., and Martin, S. 2006. Pulmonary rehabilitation for chronic obstructive pulmonary disease. Cochrane Database Syst. Rev. (4): CD003793. PMID: 17054186.

Lake, F.R., Henderson, K., Briffa, T., Openshaw, J., and Musk, A.W. 1990. Upper-limb and lower-limb exercise training in patients with chronic airflow obstruction. Chest, **97**(5): 1077–1082. doi:10.1378/chest.97.5.1077. PMID:2184993.

Larson, J.L., Covey, M.K., Wirtz, S.E., Berry, J.K., Alex, C.G., Langbein, W.E., and Edwards, L. 1999. Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **160**(2): 500–507. PMID: 10430720.

Lau, D.C., Douketis, J.D., Morrison, K.M., Hramiak, I.M., Sharma, A.M., and Ur, E.2007. Synopsis of the 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children. CMAJ, **176**(8): 1103–1106. PMID: 17420493.

Leisti, S., Finnila, M.J., and Kiuru, E. 1979. Effects of physical training on hormonal responses to exercise in asthmatic children. Arch. Dis. Child. **54**(7): 524–528. doi:10.1136/adc.54.7.524. PMID:485194.

Lemière, C., Bai, T., Balter, M., Bayliff, C., Becker, A., Boulet, L.P., et al. 2004. Adult Asthma Consensus Guidelines Update 2003. Can. Respir. J. **11**(Suppl. A): 9A–18A. PMID:15254605.

Lindsay, M., Lee, A., Chan, K., Poon, P., Han, L.K., Wong, W.C.W., and Wong, S. 2005. Does pulmonary rehabilitation give additional benefit over tiotropium therapy in primary care management of chronic obstructive pulmonary disease? Randomized controlled clinical trial in Hong Kong Chinese. J. Clin. Pharm. Ther. **30**(6): 567–573. doi:10.1111/j.1365-2710.2005.00686.x. PMID: 16336289.

Ludwick, S.K., Jones, J.W., Jones, T.K., Fukuhara, J.T., and Strunk, R.C. 1986. Normalization of cardiopulmonary endurance in severely asthmatic children after bicycle ergometry therapy. J. Pediatr. **109**(3): 446–451. doi:10.1016/S0022-3476(86)80115-9. PMID:3746532.

MacNee, W. 1994. Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One. Am. J. Respir. Crit. Care Med. **150**(3): 833–852. PMID:8087359.

Macnee, W. 2007. Pathogenesis of chronic obstructive pulmonary disease. Clin. Chest Med. **28**(3): 479–513, v. doi:10.1016/j.ccm.2007.06.008. PMID:17720039.

Mador, M.J., Bozkanat, E., Aggarwal, A., Shaffer, M., and Kufel, T.J. 2004. Endurance and strength training in patients with COPD. Chest, **125**(6): 2036–2045. doi:10.1378/chest.125.6.2036. PMID: 15189919.

Mador, M.J., Deniz, O., Aggarwal, A., Shaffer, M., Kufel, T.J., and Spengler, C.M. 2005. Effect of respiratory muscle endurance training in patients with COPD undergoing pulmonary rehabilitation. Chest, **128**(3): 1216–1224. doi:10.1378/chest.128.3.1216. PMID:16162709.

Magadle, R., McConnell, A.K., Beckerman, M., and Weiner, P. 2007. Inspiratory muscle training in pulmonary rehabilitation program in COPD patients. Respir. Med. **101**(7): 1500–1505. doi:10.1016/j.rmed.2007.01.010. PMID:17329091.

Mahler, D.A., Brent, B.N., Loke, J., Zaret, B.L., and Matthay, R.A. 1984. Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. **130**(5): 722–729. PMID:6388444.

Maltais, F., LeBlanc, P., Simard, C., Jobin, J., Berube, C., Bruneau, J., et al. 1996. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **154**(2Pt. 1): 442–447. PMID:8756820.

Maltais, F., LeBlanc, P., Jobin, J., Berube, C., Bruneau, J., Carrier, L., et al. 1997. Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **155**(2): 555–561. PMID:9032194.

Man, W.D., Polkey, M.I., Donaldson, N., Gray, B.J., and Moxham, J. 2004. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. BMJ, **329**(7476): 1209. doi:10.1136/bmj.38258.662720.3A. PMID:15504763.

Martinez, F.J., Vogel, P.D., Dupont, D.N., Stanopoulos, I., Gray, A., and Beamis, J. 1993. Supported arm exercise vs. unsupported arm exercise in the rehabilitation of patients with severe chronic airflow obstruction. Chest, **103**(5): 1397–1402. doi:10.1378/chest.103.5.1397. PMID:8486017.

Matsumoto, I., Araki, H., Tsuda, K., Odajima, H., Nishima, S., Higaki, Y., et al. 1999. Effects of swimming training on aerobic capacity and exercise induced bronchoconstriction in children with bronchial asthma. Thorax, **54**(3): 196–201. doi:10.1136/thx.54.3.196. PMID:10325893.

Matthay, R.A., Arroliga, A.C., Wiedemann, H.P., Schulman, D.S., and Mahler, D.A. 1992. Right ventricular function at rest and during exercise in chronic obstructive pulmonary disease. Chest, **101**(5 Suppl.): 255S–262S. doi:10.1378/chest.101.5.255S. PMID:1576846.

Mereles, D., Ehlken, N., Kreuscher, S., Ghofrani, S., Hoeper, M.M., Halank, M., et al. 2006. Exercise and respiratory training improve exercise capacity and quality of life in patients with severe chronic pulmonary hypertension. Circulation, **114**(14): 1482–1489. doi:10.1161/CIRCULATIONAHA.106.618397. PMID:16982941.

Mickleborough, T.D., Lindley, M.R., and Turner, L.A. 2007. Comparative effects of a high-intensity interval warm-up and salbutamol on the bronchoconstrictor response to exercise in asthmatic athletes. Int. J. Sports Med. **28**(6): 456–462. doi:10.1055/s-2006-924583. PMID:17111314.

Miller, M.G., Weiler, J.M., Baker, R., Collins, J., and D'Alonzo, G. 2005. National Athletic Trainers' Association position statement: management of asthma in athletes. J. Athl. Train. **40**(3): 224–245. PMID:16284647.

Mio, T., Romberger, D.J., Thompson, A.B., Robbins, R.A., Heires, A., and Rennard, S.I. 1997. Cigarette smoke induces interleukin-8 release from human bronchial epithelial cells. Am. J. Respir. Crit. Care Med. **155**(5): 1770–1776. PMID:9154890.

Monninkhof, E., van der Valk, P., van der Palen, J., van Herwaarden, C., and Zielhuis, G. 2003. Effects of a comprehensive self-management programme in patients with chronic obstructive pulmonary disease. Eur. Respir. J. **22**(5): 815–820. doi:10.1183/09031936.03.00047003. PMID:14621090.

Murphy, N., Bell, C., and Costello, R.W. 2005. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. Respir. Med. **99**(10): 1297–1302. doi:10.1016/j.rmed.2005.02.033. PMID:16140230.

Murray, C.J., and Lopez, A.D. 1997. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet, **349**(9064): 1498–1504. doi:10.1016/S0140-6736(96)07492-2. PMID:9167458.

Nava, S. 1998. Rehabilitation of patients admitted to a respiratory intensive care unit. Arch. Phys. Med. Rehabil. **79**(7): 849–854. doi:10.1016/S0003-9993(98)90369-0. PMID:9685104.

Neder, J.A., Nery, L.E., Silva, A.C., Cabral, A.L., and Fernandes, A. L. 1999. Short-term effects of aerobic training in the clinical management of moderate to severe asthma in children. Thorax, **54** (3): 202–206. doi:10.1136/thx.54.3.202. PMID:10325894.

Nici, L., Donner, C., Wouters, E., Zuwallack, R., Ambrosino, N., Bourbeau, J., et al. 2006. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am. J. Respir. Crit. Care Med. **173**(12): 1390–1413. doi:10.1164/rccm.200508-1211ST. PMID:16760357.

Normandin, E.A., McCusker, C., Connors, M., Vale, F., Gerardi, D., and ZuWallack, R.L. 2002. An evaluation of two approaches to exercise conditioning in pulmonary rehabilitation. Chest, **121**(4): 1085–1091. doi:10.1378/chest.121.4.1085. PMID:11948036.

Norweg, A.M., Whiteson, J., Malgady, R., Mola, A., and Rey, M. 2005. The effectiveness of different combinations of pulmonary rehabilitation program components: a randomized controlled trial. Chest, **128**(2): 663–672. doi:10.1378/chest.128.2.663. PMID:16100152.

Nickerson, B.G., Bautista, D.B., Namey, M.A., Richards, W., and Keens, T.G. 1983. Distance running improves fitness in asthmatic children without pulmonary complications or changes in exercise-induced bronchospasm. Pediatrics, **71**(2): 147–152. PMID:6823415.

O'Donnell, D.E. 2001. Ventilatory limitations in chronic obstructive pulmonary disease. Med. Sci. Sports Exerc. **33**(7 Suppl.): S647–S655. PMID:11462073.

O'Donnell, D.E., Revill, S.M., and Webb, K.A. 2001. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care Med. **164**(5): 770–777. PMID:11549531.

O'Donnell, D.E., Aaron, S., Bourbeau, J., Hernandez, P., Marciniuk, D.D., Balter, M., et al. 2007. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. Can. Respir. J. **14**(Suppl. B): 5B–32B. PMID:17885691.

O'Neill, B., McKevitt, A., Rafferty, S., Bradley, J.M., Johnston, D., Bradbury, I., and McMahon, J. 2007. A comparison of twice-versus once-weekly supervision during pulmonary rehabilitation in chronic obstructive pulmonary disease. Arch. Phys. Med. Rehabil. **88**(2): 167–172. doi:10.1016/j.apmr.2006.11.007. PMID:17270513.

O'Shea, S.D., Taylor, N.F., and Paratz, J.D. 2007. A predominantly home-based progressive resistance exercise program increases knee extensor strength in the short-term in people with chronic obstructive pulmonary disease: a randomised controlled trial. Aust. J. Physiother. **53**(4): 229–237. doi:10.1016/S0004-9514(07)70003-X. PMID:18047457.

Oh, E.G. 2003. The effects of home-based pulmonary rehabilitation in patients with chronic lung disease. Int. J. Nurs. Stud. **40**(8): 873–879. PMID:14568368.

Orenstein, D.M., Reed, M.E., Grogan, F.T., Jr, and Crawford, L.V. 1985. Exercise conditioning in children with asthma. J. Pediatr. **106**(4): 556–560. doi:10.1016/S0022-3476(85)80071-8. PMID:3981308.

Patessio, A., Carone, M., Ioli, F., and Donner, C.F. 1992. Ventilatory and metabolic changes as a result of exercise training in COPD patients. Chest, **101**(5 Suppl): 274S–278S. PMID:1576849.

Paz-Díaz, H., Montes de Oca, M., López, J.M., and Celli, B.R. 2007. Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. Am. J. Phys. Med. Rehabil. **86**(1): 30–36. doi:10.1097/PHM.0b013e31802b8eca. PMID:17304686.

Peters, S.P., Ferguson, G., Deniz, Y., and Reisner, C. 2006. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. Respir. Med. **100**(7): 1139–1151. doi:10.1016/j.rmed.2006.03.031. PMID:16713224.

PHAC. 2007. Life and breath: respiratory disease in Canada. Public Health Agency of Canada, Ottawa, Ont.

Phillips, W.T., Benton, M.J., Wagner, C.L., and Riley, C. 2006. The effect of single set resistance training on strength and functional fitness in pulmonary rehabilitation patients. J. Cardiopulm. Rehabil. **26**(5): 330–337. doi:10.1097/00008483-200609000-00011. PMID:17003602.

Pollock, M.L., Gaesser, G.A., Butcher, J.D., Després, J., Dishman, R. K., Franklin, B.A., et al. 1998. ACSM Position Stand: the recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med. Sci. Sports Exerc. **30**(6): 975–991 . doi:10.1097/00005768-199806000-00032. PMID:9624661.

Pompeo, E., Marino, M., Nofroni, I., Matteucci, G., and Mineo, T.C. Pulmonary Emphysema Research Group. 2000. Reduction pneumoplasty versus respiratory rehabilitation in severe emphysema: a randomized study. Pulmonary Emphysema Research Group. Ann. Thorac. Surg. **70**(3): 948–953, discussion 954. doi:10.1016/S0003-4975(00)01646-5. PMID:11016339.

Porszasz, J., Emtner, M., Goto, S., Somfay, A., Whipp, B.J., and Casaburi, R. 2005. Exercise training decreases ventilatory requirements and exercise-induced hyperinflation at submaximal intensities in patients with COPD. Chest, **128**(4): 2025–2034. doi:10.1378/chest.128.4.2025. PMID:16236851.

Puente-Maestu, L., Sanz, M.L., Sanz, P., Cubillo, J.M., Mayol, J., and Casaburi, R. 2000*a*. Comparison of effects of supervised versus self-monitored training programmes in patients with chronic obstructive pulmonary disease. Eur. Respir. J. **15**(3): 517–525. doi:10.1034/j.1399-3003.2000.15.15.x. PMID:10759446.

Puente-Maestu, L., Sanz, M.L., Sanz, P., Ruíz de Oña, J., Rodríguez-Hermosa, J., and Whipp, B. 2000*b*. Effects of two types of training on pulmonary and cardiac responses to moderate exercise in patients with COPD. Eur. Respir. J. **15**(6): 1026–1032. doi:10.1034/j.1399-3003.2000.01509.x. PMID:10885420.

Puente-Maestu, L., Abad, Y.M., Pedraza, F., Sanchez, G., and Stringer, W.W. 2006. A controlled trial of the effects of leg training on breathing pattern and dynamic hyperinflation in severe COPD. Lung, **184**(3): 159–167. doi:10.1007/s00408-005-2576-x. PMID:16902841.

Puhan, M.A., Busching, G., Schunemann, H.J., VanOort, E., Zaugg, C., and Frey, M. 2006. Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. Ann. Intern. Med. **145**(11): 816–825. PMID:17146066.

Ram, F.S., Robinson, S.M., Black, P.N., and Picot, J. 2005. Physical training for asthma. Cochrane Database Syst. Rev. (4): CD001116. PMID:16235280.

Ramazanoglu, Y.M., and Kraemer, R. 1985. Cardiorespiratory response to physical conditioning in children with bronchial asthma. Pediatr. Pulmonol. **1**(5): 272–277. doi:10.1002/ppul.1950010510. PMID:4069817.

Reardon, J., Awad, E., Normandin, E., Vale, F., Clark, B., and ZuWallack, R.L. 1994. The effect of comprehensive outpatient pulmonary rehabilitation on dyspnea. Chest, **105**(4): 1046–1052. doi:10.1378/chest.105.4.1046. PMID:8162723.

Redelmeier, D.A., Tan, S.H., and Booth, G.L. 1998. The treatment of unrelated disorders in patients with chronic medical diseases. N. Engl. J. Med. **338**(21): 1516–1520. doi:10.1056/NEJM199805213382106. PMID:9593791.

Ries, A.L., Kaplan, R.M., Limberg, T.M., and Prewitt, L.M. 1995. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann. Intern. Med. **122**(11): 823–832. PMID:7741366.

Ries, A.L., Kaplan, R.M., Myers, R., and Prewitt, L.M. 2003. Maintenance after pulmonary rehabilitation in chronic lung disease: a randomized trial. Am. J. Respir. Crit. Care Med. **167** (6): 880–888. doi:10.1164/rccm.200204-318OC. PMID:12505859.

Ries, A.L., Make, B.J., Lee, S.M., Krasna, M.J., Bartels, M., Crouch, R., and Fishman, A.P.National Emphysema Treatment Trial Research Group. 2005. The effects of pulmonary rehabilitation in the national emphysema treatment trial. Chest, **128**(6): 3799–3809. doi:10.1378/chest.128.6.3799. PMID:16354848.

Ries, A.L., Bauldoff, G.S., Carlin, B.W., Casaburi, R., Emery, C.F., Mahler, D.A., et al. 2007. Pulmonary rehabilitation: joint ACCP–AACVPR evidence-based clinical practice guidelines. Chest, **131** (5 Suppl.): 4S–42S. doi:10.1378/chest.06-2418. PMID:17494825.

Ringbaek, T.J., Broendum, E., Hemmingsen, L., Lybeck, K., Nielsen, D., Andersen, C., and Lange, P. 2000. Rehabilitation of patients with chronic obstructive pulmonary disease. Exercise twice a week is not sufficient! Respir. Med. **94**(2): 150–154. doi:10.1053/rmed.1999.0704. PMID:10714421.

Robinson, D.M., Egglestone, D.M., Hill, P.M., Rea, H.H., Richards, G.N., and Robinson, S.M. 1992. Effects of a physical conditioning programme on asthmatic patients. N. Z. Med. J. **105**(937): 253–256. PMID:1620508.

Roca, J., Whipp, B.J., Agusti, A.G., Andersen, S.D., Casaburi, R., Cotes, J.E., et al. 1997. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on Standardization of Clinical Exercise Testing. European Respiratory Society. Eur. Respir. J. **10**(11): 2662–2689. PMID:9426113.

Romagnoli, M., Dell'Orso, D., Lorenzi, C., Crisafulli, E., Costi, S., Lugli, D., and Clini, E.M. 2006. Repeated pulmonary rehabilitation in severe and disabled COPD patients. Respiration, **73**(6): 769–776. doi:10.1159/000092953. PMID:16636528.

Rooyackers, J.M., Dekhuijzen, P.N., Van Herwaarden, C.L., and Folgering, H.T.M. 1997. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. Eur. Respir. J. **10**(6): 1278–1284. doi:10.1183/09031936.97.10061278. PMID:9192929.

Rooyackers, J.M., Berkeljon, D.A., and Folgering, H.T. 2003. Eccentric exercise training in patients with chronic obstructive pulmonary disease. Int. J. Rehabil. Res. **26**(1): 47–49. doi:10.1097/00004356-200303000-00006. PMID:12601267.

Sewell, L., Singh, S.J., Williams, J.E., Collier, R., and Morgan, M.D. 2005. Can individualized rehabilitation improve functional independence in elderly patients with COPD? Chest, **128**(3): 1194–1200. doi:10.1378/chest.128.3.1194. PMID:16162706.

Sewell, L., Singh, S.J., Williams, J.E., Collier, R., and Morgan, M.D. L. 2006. How long should outpatient pulmonary rehabilitation be? A randomised controlled trial of 4 weeks versus 7 weeks. Thorax, **61**(9): 767–771. doi:10.1136/thx.2005.048173. PMID:16449270.

Schnall, R., Ford, P., Gillam, I., and Landau, L. 1982. Swimming and dry land exercises in children with asthma. Aust. Paediatr. J. **18**(1): 23–27. PMID:7103876.

Silva, C.S., Torres, L.A., Rahal, A., Terra Filho, J., and Vianna, E.O. 2006. Comparison of morning and afternoon exercise training for asthmatic children. Braz. J. Med. Biol. Res. **39**(1): 71–78. doi:10.1590/S0100-879X2006000100008. PMID:16400466.

Simpson, K., Killian, K., McCartney, N., Stubbing, D.G., and Jones, N.L. 1992. Randomised controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax, **47**(2): 70–75. doi:10.1136/thx.47.2.70. PMID:1549826.

Sin, D.D., Anthonisen, N.R., Soriano, J.B., and Agusti, A.G. 2006. Mortality in COPD: Role of comorbidities. Eur. Respir. J. **28**(6): 1245–1257. doi:10.1183/09031936.00133805. PMID:17138679.

Singh, V., Khandelwal, D.C., Khandelwal, R., and Abusaria, S. 2003. Pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Indian J. Chest Dis. Allied Sci. **45**(1): 13–17. PMID:12683707.

Sly, R.M. 1972. Induction of increased airway obstruction by exercise or voluntary hyperventilation in asthmatic children. Ann. Allergy, **30**(12): 668–675. PMID:4635241.

Spruit, M.A., Gosselink, R., Troosters, T., De Paepe, K., and Decramer, M. 2002. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. Eur. Respir. J. **19**(6): 1072–1078. doi:10.1183/09031936.02.00287102. PMID:12108859.

Steiner, M.C., Barton, R.L., Singh, S.J., and Morgan, M.D. 2003. Nutritional enhancement of exercise performance in chronic obstructive pulmonary disease: a randomised controlled trial. Thorax **58**: 745-751.

Strijbos, J.H., Postma, D.S., van Altena, R., Gimeno, F., and Koeter, G.H. 1996. A comparison between an outpatient hospital-based pulmonary rehabilitation program and a home-care pulmonary rehabilitation program in patients with COPD. A follow-up of 18 months. Chest, **109**(2): 366–372. doi:10.1378/chest.109.2.366. PMID:8620707.

Stulbarg, M.S., Carrieri-Kohlman, V., Demir-Deviren, S., Nguyen, H. Q., Adams, L., Tsang, A.H., et al. 2002. Exercise training improves outcomes of a dyspnea self-management program. J. Cardiopulm. Rehabil. **22**(2): 109–121. doi:10.1097/00008483-200203000-00010. PMID:11984209.

Svenonius, E., Kautto, R., and Arborelius, M., Jr. 1983. Improvement after training of children with exercise-induced asthma. Acta Paediatr. Scand. **72**(1): 23–30. doi:10.1111/j.1651-2227.1983.tb09658.x. PMID:6407276.

Szentágothai, K., Gyene, I., Szócska, M., and Osváth, P. 1987. Physical exercise program for children with bronchial asthma. Pediatr. Pulmonol. **3**(3): 166–172. doi:10.1002/ppul.1950030310. PMID:3615039.

The Lung Association–Canadian Thoracic Society. 2005. A National Report Card. Available from http://www.lung.ca/_resources/2005.copd_reportcard.pdf.

Thomas, S.G., Goodman, J.M., and Burr, J. 2011. Evidence-based risk assessment and recommendations for physical activity clearance: established cardiovascular disease. Appl. Physiol. Nutr. Metab. **36**(Suppl. S1): This issue..

Thompson, P.D., Buchner, D., Pina, I.L., Balady, G.J., Williams, M.A., Marcus, B.H., et al. 2003. Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease: a statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity). Circulation, **107**(24): 3109–3116. doi:10.1161/01.CIR.0000075572.40158.77. PMID:12821592.

Troosters, T., Gosselink, R., and Decramer, M. 2000. Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial. Am. J. Med. **109**(3): 207–212. doi:10.1016/S0002-9343(00)00472-1. PMID:10974183.

Vallet, G., Ahmaidi, S., Serres, I., Fabre, C., Bourgouin, D., Desplan, J., et al. 1997. Comparison of two training programmes in chronic airway limitation patients: standardized versus individualized protocols. Eur. Respir. J. **10**(1): 114–122. doi:10.1183/09031936.97.10010114. PMID:9032502.

van Veldhoven, N.H., Vermeer, A., Bogaard, J.M., Hessels, M.G., Wijnroks, L., Colland, V.T., and van Essen-Zandvliet, E.E.M. 2001. Children with asthma and physical exercise: effects of an exercise programme. Clin. Rehabil. **15**(4): 360–370. doi:10.1191/026921501678310162. PMID:11518437.

Varga, J., Porszasz, J., Boda, K., Casaburi, R., and Somfay, A. 2007. Supervised high intensity continuous and interval training vs. self-paced training in COPD. Respir. Med. **101**(11): 2297–2304. doi:10.1016/j.rmed.2007.06.017. PMID:17689948.

Varray, A.L., Mercier, J.G., Terral, C.M., and Prefaut, C.G. 1991. Individualized aerobic and high intensity training for asthmatic children in an exercise readaptation program. Is training always helpful for better adaptation to exercise? Chest, **99**(3): 579–586. doi:10.1378/chest.99.3.579. PMID:1995211.

Varray, A.L., Mercier, J.G., and Prefaut, C.G. 1995. Individualized training reduces excessive exercise hyperventilation in asthmatics. Int. J. Rehabil. Res. **18**(4): 297–312. doi:10.1097/00004356-199512000-00002. PMID:8748052.

Villaran, C., O'Neill, S.J., Helbling, A., van Noord, J.A., Lee, T.H., Chuchalin, A.G., et al.; Montelukast/Salmeterol Exercise Study Group. 1999. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast/Salmeterol Exercise Study Group. J. Allergy Clin. Immunol. **104**(3): 547–553. doi:10.1016/S0091-6749(99)70322-2. PMID:10482826.

Vogiatzis, I., Nanas, S., and Roussos, C. 2002. Interval training as an alternative modality to continuous exercise in patients with COPD. Eur. Respir. J. **20**(1): 12–19. doi:10.1183/09031936.02.01152001. PMID:12166558.

Vogiatzis, I., Terzis, G., Nanas, S., Stratakos, G., Simoes, D.C., Georgiadou, O., et al. 2005. Skeletal muscle adaptations to interval training in patients with advanced COPD. Chest, **128**(6): 3838–3845. doi:10.1378/chest.128.6.3838. PMID:16354852.

Wadell, K., Henriksson-Larsen, K., and Lundgren, R. 2001. Physical training with and without oxygen in patients with chronic obstructive pulmonary disease and exercise-induced hypoxaemia. J. Rehabil. Med.**33**: 200–205.

Wadell, K., Sundelin, G., Henriksson-Larsen, K., and Lundgren, R. 2004. High intensity physical group training in water–an effective training modality for patients with COPD. Respir. Med. **98**(5): 428–438. doi:10.1016/j.rmed.2003.11.010. PMID:15139572.

Wanke, T., Formanek, D., Lahrmann, H., Brath, H., Wild, M., Wagner, C., and Zwick, H. 1994. Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. Eur. Respir. J. **7**(12): 2205–2211. doi:10.1183/09031936.94.07122205. PMID:7713205.

Warburton, D.E., Nicol, C., and Bredin, S.S. 2006. Health benefits of physical activity: the evidence. CMAJ, **174**(6): 801–809. PMID:16534088.

Warburton, D.E.R., Katzmarzyk, P.T., Rhodes, R.E., and Shephard, R.J. 2007. Evidence-informed physical activity guidelines for Canadian adults. Appl. Physiol. Nutr. Metab. **32**(Suppl. 2E): S16–S68. doi:10.1139/h07-123.

Warburton, D.E.R., Gledhill, N., Jamnik, V.K., Bredin, S.S.D., McKenzie, D.C., Stone, J., et al. 2011. Evidence-based risk assessment and recommendations for physical activity participation clearance: Consensus Document 2011. Appl. Physiol. Nutr. Metab. **36**(Suppl. 1). This issue.

Wedzicha, J.A., Bestall, J.C., Garrod, R., Garnham, R., Paul, E.A., and Jones, P.W. 1998. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur. Respir. J. **12**(2): 363–369. doi:10.1183/09031936.98.12020363. PMID:9727786.

Weisgerber, M.C., Guill, M., Weisgerber, J.M., and Butler, H. 2003. Benefits of swimming in asthma: effect of a session of swimming lessons on symptoms and PFTs with review of the literature. J. Asthma, **40**(5): 453–464. doi:10.1081/JAS-120018706. PMID:14529095.

Welsh, L., Kemp, J.G., and Roberts, R.G. 2005. Effects of physical conditioning on children and adolescents with asthma. Sports Med. **35**(2): 127–141. doi:10.2165/00007256-200535020-00003. PMID:15707377.

Wijkstra, P.J., Van Altena, R., Kraan, J., Otten, V., Postma, D.S., and Koeter, G.H. 1994. Quality of life in patients with chronic obstructive pulmonary disease improves after rehabilitation at home. Eur. Respir. J. **7**(2): 269–273. doi:10.1183/09031936.94.07020269. PMID:8162979.

Wijkstra, P.J., Ten Vergert, E.M., van Altena, R., Otten, V., Kraan, J., Postma, D.S., and Koeter, G.H. 1995. Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease. Thorax, **50**(8): 824–828. doi:10.1136/thx.50.8.824. PMID:7570431.