Exercise for Chronic Obstructive Pulmonary Disease and Obesity

Effects of Exercise or Physical Activity on Overweight and Obese Individuals With Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis

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Abstract

Rationale: The prevalence of obesity among individuals with chronic obstructive pulmonary disease (COPD) is increasing, which contributes to further ventilatory limitations, and compromised exercise capacity, and health-related quality of life (HRQOL) compared to COPD alone.

Objective: To conduct a systematic review to evaluate the effects of exercise interventions on walking capacity, ventilatory parameters, anthropometrics and HRQOL in individuals with COPD and elevated weight.

Methods: A search was conducted on March 16, 2018 of Embase, Medline, CINAHL, AMED and PsycINFO for controlled trials of exercise interventions, involving adults with any stage of severity and stability of COPD with concurrent obesity or overweight. Overall effects were determined with standardized (SMD) and weighted (WMD) mean difference, using Review Manager 5.3.

Results: Nineteen studies with 1716 participants (BMI mean ± SD 28.2 ± 5.1 kg/m^2) were included. Exercise interventions were effective in improving walking capacity measured by the 6-Minute Walk Test (6MWT), Endurance Shuttle Walk Test and Incremental Shuttle walk Test (12 studies, 1215 participants, SMD 0.25 (95% CI [0.06, 0.43]); p=0.01), fat-free mass index (2 studies, 285 participants, WMD 0.33 kg/m^2 (95% CI [0.21, 0.46]); p<0.00001), St. George Respiratory Questionnaire (6 studies, 648 participants, WMD -7.49 points (95% CI [-13.01, -1.98]); p=0.008) and Chronic Respiratory Disease Questionnaire Dyspnea (5 studies, 478 participants, WMD 0.51 points (95% CI [0.00, 1.02]); p=0.05), Emotion (4 studies, 404 participants, WMD 0.28 points, 95% CI [0.03, 0.54]); p=0.03), and Mastery domains (4 studies, 404 participants, WMD 0.31 points (95% CI [0.02, 0.59]); p=0.03). There were no effects on ventilatory parameters or anthropometric measures.

Conclusions: Exercise interventions were effective in improving walking capacity and HRQOL in individuals with COPD and elevated weight. There is an important opportunity to establish effective interventions to minimize the functional and health effects in this subset of the COPD population.

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6MWT	Six-Minute Walk Test
BMI	Body mass index
C	Control
COPD	Chronic Obstructive Pulmonary Disease
CRDQ	Chronic Respiratory Disease Questionnaire
ESWT	Endurance Shuttle Walk Test
FEV_1	Forced expiratory volume in 1 second
FFM	Fat-free mass
FFMI	Fat-free mass index
FVC	Forced vital capacity
HRQOL	Health-related quality of life
I	Intervention
ICCs	Intra-class correlation coefficients
ISWT	Incremental Shuttle Walk Test
kg	Kilogram
L	Liter
m	Meter
MCID	Minimal clinically important difference
MD	Mean difference
ml	Milliliter
PEDro	Physiotherapy Evidence Database
RM	Repetition maximum
RV	Residual volume
SGRQ	St. George's Respiratory Questionnaire
TLC	Total lung capacity
VO2 max	Maximal oxygen consumption
VO2 peak	Peak oxygen consumption
WMD	Weighted mean difference

CHAPTER 1: Introduction

Chronic obstructive pulmonary disease (COPD) is a “preventable and treatable disease state characterized by progressive airflow limitation that is not fully reversible” (Celli et al., 2004). Globally, COPD is the fourth-leading cause of death claiming 3.2 million lives per year and by 2030 it will be the third-leading cause of mortality (Mathers & Loncar, 2006). In 2010, approximately 384 million cases of COPD were reported worldwide among people aged 30 years or older, with a global prevalence of 11.7% (95% confidence interval (CI) [8.4%, 15.0%]) (Adeloye et al., 2015). Across the different geographical regions, the highest prevalence was estimated to be in the Americas (15.2%), and the lowest prevalence was in Southeast Asia (9.7%) (Adeloye et al., 2015). More than 12 million Americans and 1.8 million Canadians are known to be living with COPD, representing 7% (Guarascio, Ray, Finch, & Self, 2013) and 12% (Evans, Chen, Camp, Bowie, & McRae, 2014) of these countries’ populations, respectively.

There are high direct and indirect costs associated with COPD (Mathers & Loncar, 2006; World Health Organization, 2017). In the United States, Canada and South Korea, the annual direct costs associated with COPD are estimated to be $3,000–$4,000 USD per person, and include healthcare costs related to diagnosis, treatment, and inpatient and outpatient care (Guarascio et al., 2013; Yoo et al., 2016; Maleki-Yazdi et al.,2012). Indirect costs include those associated with the reduction or cessation of work productivity due to disability or illness associated with COPD, and is estimated as $300–$1,000 USD annually per person in the United States (Ford et al., 2015) and Canada (Maleki-Yazdi et al., 2012). In total, COPD accounts for $50–

$60 billion USD of economic burden in the United States (Guarascio et al., 2013) and the European Union countries (Lopez-Campos, Tan, & Soriano, 2016), and $440 million USD in South Korea (Kim et al., 2016). By 2020, the total cost of medical care in the United States for individuals with COPD is projected to be double the current cost from $32.1 billion to $49 billion USD (Ford et al., 2015). Little is known regarding the economic burden of COPD in low-income countries, despite the disease prevalence being similar to the middle-income countries (Lopez-Campos et al., 2016).

This chapter will describe in details the COPD's pathophysiology and symptomology, diagnosis and differential diagnosis, risk factors, clinical assessments, effects on functional and psychological status, and health-related quality of life and management of the disease. It will also discuss obesity and overweight in the general population and in COPD and provide a clear rationale for evaluating the role of exercise and physical activity in the outcomes of individuals with COPD and overweight or obesity.

Pathophysiology and Symptomology of COPD

COPD is a condition of ventilatory obstruction characterized by progressive airflow limitation results from an inflammatory response to a noxious stimulus (e.g., cigarette smoke) (Rennard, 1998; Vogelmeier et al., 2017). Neutrophils are increased in the lung tissue and bronchial glands during this inflammatory response (MacNee, 2006; Bourdin et al., 2009), stimulating oxidative metabolism and leading to tissue destruction and fibrosis (MacNee, 2006; Bourdin et al., 2009). The presence of neutrophils also leads to excessive macrophage and epithelial release, causing mucus hypersecretion (MacNee, 2006; Bourdin et al., 2009). Taken together, these changes lead to increased resistance to airflow in the airways, increased compliance of the lungs, air trapping, and progressive airflow obstruction (MacNee, 2006).

Symptoms of COPD begin to manifest clinically when sufficient deterioration and damage have occurred in the lung tissue, and include chronic cough, sputum production, dyspnea, wheezing, and chest tightness (MacNee, 2006; Rennard, 1989; Vogelmeier et al., 2017). These symptoms occur as a result of pulmonary tissue destruction and fibrosis, mucus hypersecretion, and increased resistance to airflow in the airways in response to the inflammation (MacNee, 2006).

Diagnosis and Differential Diagnosis

The diagnosis of COPD is considered in individuals who present with symptoms consistent with COPD and have a history of exposure to known disease risk factors, and is confirmed by spirometry (Vogelmeier et al., 2017). Spirometry is used to measure the volume of air that can be forcibly expelled following full inspiration, and is expressed as volume measured in the first second of forced exhalation (forced expiratory volume in one second; FEV_1, in [L]), and as a total volume (forced vital capacity; FVC, in [L]) (Quanjer et al., 1993). These measures are typically assessed following bronchodilator intake, and a post-bronchodilator FEV_1/FVC spirometry ratio <0.7 confirms the presence of the airflow limitation, and thus the diagnosis of COPD (Vogelmeier et al., 2017).

The diagnosis of COPD is differentiated from other conditions such as asthma, congestive heart failure, and bronchiectasis through careful clinical and spirometric evaluation (Hanania & Sharafkhaneh, 2011). In contrast to asthma, which is characterized by reversible airflow limitation through bronchodilation and tends to start earlier in life, airflow limitation in COPD is irreversible and the onset of disease symptoms mainly starts in mid-life (Price et al., 2010). COPD and congestive heart failure share the same symptoms of wheezing and dyspnea, which increases the challenge of differential diagnosis between these two diseases. However, on pulmonary function tests, individuals with congestive heart failure present with restrictions in lung volume with no airflow limitation, whereas those with COPD present with symptoms of both lung obstruction and airflow limitation (Celli et al., 2004). While sputum production is common in both COPD and bronchiectasis, time course and etiology differ. In COPD, sputum production is chronic and related to the inflammatory response of the lung, whereas sputum in bronchiectasis is commonly purulent and associated with the acute bacterial infection (Hanania & Sharafkhaneh, 2011).

Risk Factors Associated with COPD

There are modifiable and non-modifiable risk factors associated with COPD. Modifiable risk factors include cigarette smoking, occupational hazards, and exposure to smoke and fumes, while non-modifiable risk factors include genetic predisposition and age (Rennard, 1998; Mannino & Buist, 2007).

Cigarette smoking is the most significant COPD modifiable risk factor; whereby, approximately 50% of individuals with history of smoking develop COPD (Mannino & Buist, 2007; Laniado-Laborín, 2009). In addition, passive exposure to cigarette smoke (i.e., second-hand smoke) is associated with an increased risk of COPD (OR 1.24, 95% CI [1.05, 1.47]) (Hooper et al., 2012). Additionally, exposure to outdoor and indoor air pollutants also contributes to the development of COPD (Rennard, 1998; Diaz-Guzman & Mannino, 2014). The World Health Organization estimates that urban air pollution is responsible for 1% of cases of COPD in high-income countries and 2% in low- and middle-income countries (Lopez, Mathers, Ezzati, Jamison & Murray, 2006). The exposure to indoor smoke from biomass fuels accounts for 35% of cases of COPD (Lopez et al., 2006). In a meta-analysis of 6 studies (*n* = 2,543), exposure to indoor smoke from biomass fuels was associated with an increased risk of COPD (OR 2.40, 95% CI [1.47, 3.93]) (Po, FitzGerald, & Carlsten, 2011). In an observational study of 1,202 individuals with COPD, occupational exposure to vapors, gas, dust or fumes was associated with an increased risk of COPD (OR 2.11, 95% CI [1.59, 2.82]) (Blanc et al., 2009).

Non-modifiable risk factors for COPD include the presence of genetic factors, and older age (Hooper et al., 2012; Mannino & Buist, 2007). Alpha-1 antitrypsin deficiency is a common genetic factor present in 1–3% of individuals with COPD (Mannino & Buist, 2007). This enzyme is normally found in the lungs and works to protect the tissue from the damage caused by neutrophils that are released due to inflammation (Stoller & Aboussouan, 2005). Genetic mutations cause Alpha-1 antitrypsin deficiency which leads to lung tissue deterioration in the presence of the neutrophils (Stoller & Aboussouan, 2005).

Finally, a large population-based study of 10,001 individuals with COPD from 14 sites across North America, Europe, Australia, South Africa and Asia found that family history of COPD was associated with an increased risk of the disease (OR 1.50, 95% CI [1.19, 1.90]) (Hooper et al., 2012), suggesting that there may be a genetic predisposition. The same study also found that older age was a risk factor consistently observed across all geographical regions (OR 1.52 for a 10-year age difference, 95% CI [1.35, 1.71]) (Hooper et al., 2012).

Clinical Assessments in COPD

Once the diagnosis has been confirmed with an individual, a comprehensive clinical assessment is conducted that includes a subjective interview, history of presenting illness (past and current symptoms, previous exacerbation events), presence of other comorbidities, as well an objective assessment for airflow limitation (Hanania & Sharafkhaneh, 2011). These assessments aim to determine the severity of the disease, the risk of exacerbation, the comorbidities, and the impact of the disease.

Airflow Limitation

FEV_1 is a standard measure of airflow limitation in the condition of ventilatory obstruction such as in COPD. It is measured by spirometry and used to compare to predicted values to determine the degree of airflow limitation and disease severity. The Global Initiative for Obstructive Lung Disease classification is mainly used to determine the disease severity where an FEV_1 values that are ≥80% of predicted indicates mild severity, 50%–79% indicates moderate severity, 30%–49% indicates severe disease, and <30% indicates a very critical level of the COPD severity (Vogelmeier et al., 2017).

Symptoms

The assessment of COPD symptoms can be performed using generic or disease-specific assessment tools.

The modified Medical Research Council Questionnaire is not specific to COPD but still commonly used with this population due to its ease of administration

(Bestall et al., 1999). This questionnaire uses five statements to assess the disability associated with breathlessness, and classifies individuals from grade 1 ("*I only get breathless during strenuous activities*") to grade 5 ("*I am breathless when dressing or too breathless to leave the house*") (Bestall et al., 1999).

The COPD Assessment Test is the most commonly used disease-specific questionnaire that uses eight items to evaluate the severity of symptoms related to cough, sputum, dyspnea, chest tightness, exercise capacity and activities, confidence, sleep quality, and energy level (Jones et al, 2009). Each item in the test is scored from 0 to 5; the sum is calculated to determine the overall score (Jones et al., 2009). Higher scores indicate higher impact of the disease and are interpreted as follows: <5 standard level of non-smokers, 5–10 low impact, 10–20 moderate impact, 20–30 high impact, >30 very high impact of the disease (Jones et al., 2009).

The correlation and agreement between the modified Medical Research Council Questionnaire and the COPD Assessment Test were evaluated in 257 individuals with COPD (Kim et al., 2013). While correlations between these scales were variable across individual items on the COPD Assessment Test (Spearman correlation coefficients ranged from $rho = 0.290$, for sputum to $rho = 0.731$ for dyspnea, $p < 0.001$), there was a fair agreement in the classification of disease severity (kappa 0.510) (Kim et al., 2013).

Risk for Exacerbation

Assessing the exacerbation risk is a critical strategy for adjusting and refining the management plan for individuals with COPD to reduce the incidence of future exacerbation (Vogelmeier et al., 2017). The history of previous exacerbation events, along with the severity of COPD, are mainly used to predict and assess the risk of exacerbation (Hurst et al., 2010).

In a study involving 2,138 individuals with COPD, a one-year history of a treated exacerbation was a significant predictor of the exacerbation within the following year (OR 4.30, 95% CI [3.58, 5.17]; $p < 0.001$) (Hurst et al., 2010). Moreover, disease severity was also associated with the frequency of exacerbations, where 22% of individuals with mild to moderate COPD, 33% with severe disease, and 47% with very severe COPD experienced two or more exacerbations in a one-year period (Hurst et al., 2010).

Assessment of Other Comorbid Conditions

COPD is often related to other comorbid conditions such as cardiovascular disease, depression and anxiety, metabolic syndrome, and lung cancer (Sin, 2006). The presence of comorbidities is related to higher risk of mortality (Patil et al., 2003). Individuals with at least four comorbidities were at higher risk of hospital mortality compared to those without any comorbidities (OR= 5.70, 99% CI [4.08, 7.89], n = 71,130) (Patil et al., 2003), and deaths in individuals with COPD are frequently attributed to causes other than COPD (Mannino & Buist, 2007). The underlying cause of death among 1,242 persons with COPD was recorded as a respiratory cause (32%), lung cancer (24%), cardiovascular disease (13%) and other causes (32%) (Mannino, Doherty, & Buist, 2006). Thus, a comprehensive assessment and effective management of any comorbidities are important to minimize the interaction with COPD (Vogelmeier et al., 2017).

Effects of COPD on Function, Psychological Status, and Health-Related Quality of Life

COPD also has important effects on an individual's functional abilities, psychological status and health-related quality of life (HRQOL). A Pan-European observational study of 2,441 individuals with COPD reported that more than half had severe symptoms in the morning that affected their usual morning activities such as washing, dressing, and getting out of bed (Kessler et al., 2011). In another study involving 1,100 individuals with COPD, 54% stated that they could not complete activities they like to do because of shortness of breath (Miravitlles et al., 2006).

The symptoms and associated functional limitations of COPD also affect the emotional and psychological health, where 17% of individuals with COPD were afraid that COPD would lead to their death (Miravitlles et al., 2006), and two-thirds perceived that they were a burden to other people (Kessler et al., 2011).

COPD is also associated with sleep and nighttime disturbances, reported by half (Miravitlles et al., 2006) to three-quarters (Price et al., 2013) of individuals with COPD. Disease symptoms, such as coughing (13.4%) and expectoration (12.5%), and an increased rate of hospital admissions (9.5%) were reported by 231 individuals with COPD to have a negative impact on health-related quality of life (Monica et al., 2013).

Management of COPD

There is no direct treatment for COPD but rather, management mainly focuses on controlling its symptoms, reducing exacerbation rate, and preserving lung function (Celli et al., 2004). Typically, the management plans for individuals with COPD include strategies for smoking cessation, pharmacological therapy, oxygen therapy, ventilatory support, surgical treatment, and pulmonary rehabilitation (Vogelmeier et al., 2017).

Smoking Cessation

Smoking cessation slows the development and progression of COPD and thus is strongly recommended for individuals at all levels of disease severity (Hanania & Sharafkhaneh, 2011). The ideal program for smoking cessation should utilize a combination of health professional counseling and pharmacotherapy (Stead, Koilpillai, Fanshawe, & Lancaster, 2016). Choosing the appropriate and effective individualized counseling strategy to facilitate smoking cessation can result in up to 25% higher success in long-term cessation (van Eerd, van der Meer, van Schayck, & Kotz, 2016). Further, pharmacotherapy approaches, such as combining bupropion and nicotine replacement therapy, can increase the rate of long-term cessation by 80% compared to placebo, and vernecicline can increase the cessation rate of by 50% compared to nicotine replacement therapy (Cahill, Stevens, Perera, & Lancaster, 2013). Combining pharmacotherapy together with counseling increases rates of long-term cessation by 70%–100% compared to a minimal intervention or usual care (Stead et al., 2016).

Pharmacological Therapies

Other pharmacological therapies may be used to reduce disease symptoms, increase exercise capacity, reduce the number and severity of exacerbations, and improve health status (Celli et al., 2004). These medications may include bronchodilators (e.g., β-agonists, anticholinergic and methylxanthines) or oral drugs including glucocorticoids and antibiotics (Hanania & Sharafkhane, 2011).

Bronchodilators work by relaxing the smooth muscle of the airways, thus minimizing air trapping during the exhalation, which improves FEV_1 and reduces the dynamic hyperinflation and the dyspnea during exercise (Hanania & Sharafkhaneh, 2011). Combining two or more types of bronchodilators may maximize their benefits (Cazzola & Molimard, 2010). The use of ipratropium bromide (anticholinergic) with albuterol (β-agonists) was more effective in increasing FEV_1 (n=182, mean peak response 0.37 L) compared to ipratropium bromide alone (n=179, mean peak response 0.3 L, $p < 0.001$) or albuterol alone (n=173, mean peak response 0.29L, $p < 0.001$) (COMBIVENT Inhalation Aerosol Study Group, 1994).

Glucocorticoids are anti-inflammatory agents that may be administered orally or through inhalation (Celli et al., 2004). The use of inhaled glucocorticoids with individuals with stable COPD had a minimal effect on lung function (Hanania & Sharafkhaneh, 2011), whereas oral glucocorticoids were effective in shortening recovery time during acute exacerbation (Vogelmeier et al., 2017).

Antibiotics are commonly used to treat respiratory tract infections, and may be taken over the long-term in the event of recurrent infection (Hanania & Sharafkhaneh, 2011). The use of antibiotics after COPD exacerbations was effective in decreasing the relapse rate of COPD symptoms to 19% compared to 32% when antibiotics were not used ($p<0.001$) (Adams, Melo, Luther, & Anzueto, 2000).

Oxygen Therapy

Long-term oxygen therapy is effective in reducing symptoms of dyspnea and hypoxemia and improving exercise tolerance (Hanania & Sharafkhaneh, 2011). The therapeutic goal of the oxygen therapy is to maintain oxygen saturation at >90%

during rest, sleep and exercise (Celli et al., 2004). Oxygen therapy was more effective than room air in increasing exercise capacity (maximal oxygen consumption (VO_2 max) 0.77 L vs. 0.58 L, $p = 0.001$) (Vyas, Banister, Morton, & Grzybowski, 1971). Moreover, using continuous oxygen therapy was nearly twice as effective as nocturnal oxygen therapy at improving survival in individuals with hypoxemia ($p = 0.01$) (Nocturnal Oxygen Therapy Trial Group, 1980).

Ventilatory Support

Noninvasive ventilatory support is used with individuals with severe COPD and persistent hypoxia and/or hypercapnia as a strategy to decrease the need for invasive ventilation (Vogelmeier et al., 2017). In 85 individuals with exacerbation of COPD, using non-invasive ventilation reduced the need for endotracheal intubation (26% vs. 74% requiring endotracheal intubation, $p < 0.001$) and in-hospital mortality rate (9% vs. 29%, $p = 0.02$) when compared to standard treatment of supplemental oxygen only (Brochard et al., 1995). The use of non-invasive ventilatory support with individuals with stable COPD, however is not routinely recommended (Hanania & Sharafkhaneh, 2011).

Surgical Treatment

Surgical interventions are considered the last option when conservative management strategies are no longer effective in individuals with severe deterioration of symptoms and very poor prognosis (Hanania & Sharafkhaneh, 2011). Lung volume reduction surgery and lung transplantation have been shown to improve exercise capacity, dyspnea and HRQOL of persons with severe COPD (Martinez, 1999; Snider, 1996). In a study of 150 individuals with COPD, bilateral lung volume reduction surgery resulted in improvements in FEV_1 by 51% ($p<0.001$), and reduced the need for oxygen therapy in 70% of cases compared to their pre-surgery assessments ($p<0.001$) (Cooper et al., 1996). Lung volume reduction also improved functional exercise capacity compared to routine medical care (Geddes et al., 2000).

Pulmonary Rehabilitation

According to the American Thoracic Society and the European Respiratory Society, pulmonary rehabilitation is "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include -but are not limited to- exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors." (Spruit et al., 2013). Pulmonary rehabilitation programs aim to enhance the well-being of individuals with pulmonary conditions, including COPD, by decreasing the burden of symptoms and improving exercise capacity to allow greater participation in daily activities and enhancing HRQOL (Spruit et al., 2013). Pulmonary rehabilitation interventions must be tailored to the needs of the individual based on initial and ongoing assessments, including disease severity, complexity, and comorbidities (Spruit et al., 2013; Vogelmeier et al., 2017).

There is a large and strong body of evidence of the effectiveness of pulmonary rehabilitation on improving outcomes in individuals with COPD. In a systematic review of 65 randomized controlled trials, pulmonary rehabilitation programs were more effective in increasing functional exercise capacity (mean difference (MD) for Six-Minute Walk Test (6MWT) distance 43.93 m, 95% CI [32.64, 55.21]; 38 studies, *n* = 1879) compared to usual care (McCarthy et al., 2015). Pulmonary rehabilitation was also more effective in improving HRQOL compared to usual care (McCarthy et al., 2015).

Pulmonary rehabilitation programs typically include an interdisciplinary team including physicians, physical therapists, dietitians, exercise specialists and respiratory therapists, and can take place in different settings (hospital inpatient and outpatient settings, in the community, or at home) (Spruit et al., 2013). Both hospital-based and non–hospital-based programs have similar effects in improving individuals function and symptoms, although home-based programs may offer the advantage of greater convenience for participants (Spruit et al., 2013). Thus, the choice of the setting should be made based on the available resources and the individual's condition and preference (Spruit et al., 2013). While the duration of pulmonary rehabilitation programs can vary greatly, studies have shown greater and sustained benefits from longer (>12 weeks) rehabilitation programs (Ries et al., 2007). Indeed, long-term programs (up to 18 months) were more effective in improving physical function measured by faster time climbing two flights of stairs compared to short-term (3 months) programs (11.6 seconds, 95% CI [11.0, 12.2] vs. 12.9 seconds, 95% CI [12.3, 13.5]; $p = 0.05$), and greater exercise capacity measured by 6MWT distance (553 m, 95% CI [533, 573]) vs. (522 m, 95% CI [500, 543]; $p = 0.03$) (Berry et al., 2003).

Exercise Training and Physical Activity in COPD

In the American Association of Cardiovascular and Pulmonary Rehabilitation clinical practice guidelines, exercise training is considered to be an essential, mandatory component of any comprehensive pulmonary rehabilitation program (Ries et al., 2007). The American College of Sports Medicine defines physical activity as “body movement that involves contraction of skeletal muscles and that increases energy expenditure”, and exercise training as “planned, structured and repetitive movement aimed at improving or maintaining one or more components of physical fitness” (Chodzko-Zajko, 2014).

In individuals with COPD, ventilatory limitations and peripheral muscle dysfunction are two major causes of the exercise intolerance and physical inactivity (Hanania & Sharafkhaneh, 2011). With exercise, respiratory rate and ventilatory demand are increased, contributing to shorter exhalation time, and thus greater expiratory flow limitation (O’Donnell, 2001). This leads to more air trapping and hyperinflation of the lungs, further increasing airflow resistance, thereby contributing to the sensation of dyspnea and limited capacity for exercise (O’Donnell, 2001). Additionally, inactivity and sedentary behaviors that are often seen in individuals with COPD, combined with long-term used of corticosteroids, contribute to peripheral muscle atrophy and dysfunction and thus further limitations in exercise capacity (Decramer, Benedetto, Del Ponte, & Marinari, 2005; Gosselink, Troosters, & Decramer, 1996). Lower exercise capacity is associated with negative health consequences, such as poor survival (Oga, Nishimura, Tsukino, Sato, & Hajiro, 2003; Pinto-Plata, Cote, Cabral, Taylor, & Celli, 2003) and increased exacerbation and hospitalization risk (Emtner, Arnardottir, Hallin, Lindberg, & Janson, 2007) in people with COPD.

Assessment of Exercise Capacity

In the COPD population, exercise capacity may be assessed using laboratory-based maximal exercise tests that require advanced technical tools and training, to simple field-based physical tests.

Laboratory-based exercise tests are the criterion standard for evaluating exercise capacity, where maximal or symptom-limited peak oxygen consumption (VO_2max or VO_2peak) are the primary outcome of the test. A longitudinal study found that VO_2peak was the most significant predictor of 5-yr mortality in COPD population (n = 150, risk ratio [RR] 0.994, 95% CI [0.992, 0.996]; p <0.0001) with a 5-yr mortality of 62% when VO_2peak was less than 10 mL/kg/min (Oga et al., 2003).

Field-based exercise tests are often used in clinical and community settings to measure exercise capacity due to their feasibility over laboratory-based tests (Singh et al., 2014). These include tests of functional capacity such as the Six-Minute Walk Test (6MWT) or Incremental Shuttle Walk Test (ISWT) for total distance walked, or the Endurance Shuttle Walk Test (ESWT) for total distance walked or total walking time (Singh et al., 2014). 6MWT distance can be used to predict survival in the COPD population, where a 2-year longitudinal study with 198 individuals with COPD reported an RR of 0.82 (95% CI [0.72, 0.94]; p < 0.003) for survival for every 50 m increase in distance walked (Pinto-Plata et al., 2003). Distance walked on the ISWT was also associated with risk of rehospitalization within 12 months in a study of 21 individuals with severe to very severe COPD (RR 0.8 for every 10 m decrease in the distance, 95% CI [0.67, 0.97]; p < 0.001) (Emtner et al., 2007).

Exercise Training and Physical Activity for COPD

Exercise training is mainly used for individuals with COPD to improve symptoms and outcomes of the disease (Hanania & Sharafkhaneh, 2011), and is a critical component of pulmonary rehabilitation programs (Ries et al., 2007). There is strong meta-analytic data to support the use of exercise training to improve several important outcomes relevant to COPD, including 6MWT distance (weighted mean difference (WMD) 48 meters, 95% CI [32, 65]; $p < 0.00001$; 16 studies, $n = 669$), HRQOL and dyspnea (Lacasse, Goldstein, Lasserson, & Martin, 2006). Moreover, exercise training improved functional mobility, including stair-climbing performance (WMD 1.31 seconds, 95% CI [0.48, 2.13]; $p < 0.002$; $n = 30$), and timed sit-to-stand performance (WMD 1.07 seconds, 95% CI [0.22, 1.92]; $p = 0.01$; $n = 49$) (O'Shea, Taylor, & Paratz, 2009).

Modalities of Exercise Training

Different modalities of exercise are effective in improving exercise capacity, respiratory function and health outcomes in the COPD population. These modalities include aerobic training, resistance training, and respiratory muscle training (Spruit et al., 2013).

Aerobic training. Aerobic training is used to improve cardiorespiratory fitness and respiratory muscle function to reduce symptoms of dyspnea and fatigue (Spruit et al., 2013). This training is ideally delivered as high-intensity continuous training or interval training (Hanania & Sharafkhaneh, 2011; Spruit et al., 2013).

High-intensity training (>60% of maximal work rate) may be performed using cycling or walking exercise to achieve maximal physiological training effects (Hanania & Sharafkhaneh, 2011, Punzal, Ries, Kaplan, & Prewitt, 1991) but may be difficult to achieve for many individuals with COPD. High-intensity interval training, where intense bouts of exercise as interspersed with periods of rest or active recovery (Gosselink, Troosters, & Decramer, 1998), may also be considered for individuals who are limited by their symptoms and unable to perform high-intensity training continuously for sustained periods (Clark, Cochrane, & Mackay 1996).

Aerobic training is recommended for individuals with COPD three to five times per week at high-intensity continuous exercise for 20 to 60 minutes per session (Garber et al., 2011). Whether cycling or walking exercise is used depends on the goal of training (Spruit et al., 2013). Cycling may be suitable for people who are unable to walk or have poor balance and used to improve limb muscle strength (Man et al. 2003), whereas walking may be preferred for improving walking endurance (Leung, Alison, McKeough, & Peters, 2010).

Resistance training. Individuals with COPD often present with reduced muscle mass and peripheral muscle weakness (O'Shea, Taylor, & Paratz, 2004). Resistance training uses repetitive muscular overload to enhance peripheral muscle strength (Spruit et al., 2013). Resistance training parameters recommended for the general population are also used for persons with COPD and include 2 to 3 days each week of training, 1 to 3 sets of 8 to 12 repetitions with an initial load at 60 to 70% of the one repetition maximum, or at a load that evokes fatigue after 8 to 12 repetitions (American College of Sports Medicine, 2009; Spruit et al., 2013).

Respiratory muscle training. Respiratory muscle training is performed by breathing against the valve of a small hand-held device that impose a resistive or a threshold load on the respiratory muscles (Shoemaker, Donker, & LaPoe, 2009). This training is used to enhance respiratory muscle strength and ventilation to reduce feelings of dyspnea and increase exercise tolerance, and is often implemented in combination with other forms of exercise training (i.e. aerobic and peripheral muscle resistance training) (Shoemaker et al., 2009; Spruit et al., 2013). Respiratory muscle training is recommended for COPD three times per week, with an initial load of at least 30% of the maximal inspiratory pressure (Hill, Cecins, Eastwood, & Jenkins, 2010).

Other modalities. Functional exercise training that uses a circuit training approach of functional movements has been used recently for individuals with COPD (Beauchamp et al., 2013; Marques, Jácome, Cruz, Gabriel, & Figueiredo, 2015; Mkacher, Mekki, Tabka, & Trabelsi, 2015). This type of training aims to improve balance, functional strength and ability to perform physical activities (Beauchamp et al., 2013; Marques et al., 2015; Mkacher et al., 2015). The functional movements used may include standing exercises (e.g. one-leg stance), transition exercises (e.g. sit-to-stand) and gait exercises (e.g. obstacle course training) (Beauchamp et al., 2013; Mkacher et al., 2015). While studies have incorporated functional exercise training in combination with other traditional training (aerobic and resistance exercise) (Marques et al., 2015; Mkacher et al., 2015), it has not yet been included in pulmonary rehabilitation guidelines (Brooks et al., 2007; Spruit et al., 2013).

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Overweight and Obesity

According to the World Health Organization, obesity is described as "excessive or abnormal fat accumulation in the body that might impair health" (World Health Organization, 2000). Body mass index (BMI) is calculated by dividing body mass by the square of a person's height and expressed as kg/m^2 and can be used to classify individuals as being overweight (25–29.9 kg/m^2) or obese ($\geq$ 30 kg/m^2) (World Health Organization, 2000). Obesity can be further classified as Class 1 (BMI 30 to <35 kg/m^2), Class 2 (BMI 35 to <40 kg/m^2), or Class 3 "severe" or "extreme" obesity (BMI 40 kg/m^2 and above) (World Health Organization, 2000).

Globally, the economic burden of obesity accounts for 0.7–2.8% of a country's total healthcare costs, and accrue 30% higher healthcare costs than individuals with normal weight (Withrow & Alter, 2011). In Canada, the total annual costs associated with obesity ranges from $1.3 to $11.1 billion CAD, accounting for 2.2–12.0% of total health expenditures of which 37.2–54.5% are direct costs (Tran, Nair, Kuhle, Ohinmaa, & Veugelers, 2013). In the United States, costs associated with obesity are estimated to be approximately $75 billion USD or 7% of total medical care expenditure (Finkelstein, Fiebelkorn, & Wang, 2004), and, annual costs in the European Union are $41 billion USD, or 2–4% of medical care expenditure (Wang, McPherson, Marsh, Gortmaker, & Brown, 2011).

Over the last four decades, obesity and being overweight have changed from a minor public health problem to one that has a major global impact on public health (Seidell & Halberstadt, 2015). The global prevalence of obesity has almost tripled during the last forty years (World Health Organization, 2017). Indeed, in 2016, approximately 1.9 billion (39%) of the total adult population were estimated to have BMI of >25 and of these, 650 million (13%) were believed to be obese (World Health Organization, 2017). Between 2009 and 2010, data from the National Health and Nutrition Examination Survey indicated that at least one third (35.7%) of all the United States adults were obese (Ogden, Carroll, Kit, & Flegal, 2012). A lower prevalence of obesity has been reported in Canada (approximately 18.3%) (Twells, Gregory, Reddigan, & Midodzi, 2014) but ranges elsewhere, from 27.4% to 31.1% in South America, Central America, southern sub-Saharan Africa, the Middle East, and in North Africa (Seidell & Halberstadt, 2015).

The associations between obesity and mortality and morbidity are well established even for individuals without concurrent COPD (Abdelaal, le Roux, & Docherty, 2017; Di Angelantonio et al., 2016). All-cause mortality increases by approximately 39% for every 5 kg/m^2 increase in BMI above 25 kg/m^2 (HR=1.29, 95% CI [1.26, 1.32] in North America; HR 1.31, 95% CI [1.27, 1.35] in Australia and New Zealand; HR 1.39, 95% CI [1.34, 1.43] in Europe; HR 1.39, 95% CI [1.34, 1.44] in East Asia) (Di Angelantonio et al., 2016). Individuals who are overweight or obese are also at high risk of developing other comorbidities (Abdelaal et al., 2017). The risk of developing type 2 diabetes mellitus increases by 20% for every 1 kg/m^2 increase in the BMI above 23 kg/m^2 (Hartemink, Boshuizen, Nagelkerke, Jacobs & van Houwelingen, 2006). The risk of developing different types of cancers increases with every 5 kg/m^2 increase in BMI (HR 1.62, 99% CI [1.56, 1.69], p <0.0001 for uterine cancer; HR 1.31, 99% CI [1.12, 1.52], p <0·0001 for gallbladder cancer; HR=1.09, 99% CI [1.05, 1.13], p ≤0.0001 for leukaemia) (Bhaskaran et al., 2014). Furthermore, obesity is associated with a 3.5 fold increase in the risk of developing hypertension

(Abdelaal et al., 2017), and morbid obesity with large waist circumferences is associated with 72% increased risk of COPD (Behrens, Matthews, Moore, Hollenbeck, & Leitzmann, 2014).

Obesity as A Restrictive Condition

In individuals with obesity, the presence of the excessive adipose tissue on the thorax and abdomen decreases the compliance of chest wall and lung and reduces the elasticity and the strength of ventilatory muscle that may increase the pulmonary resistance (Collins, Hoberty, Walker, Fletcher, & Peiris, 1995; Lazarus, Sparrow, & Weiss, 1997). Thus, a pulmonary restrictive condition is effectively observed that is reflected by the reduced expiratory reserve volume and functional residual capacity, and reduced residual volume and total lung capacity in very morbid obesity (Melo, Silva, & Calles, 2014; Franssen et al., 2008). During exercise, pulmonary resistance is further increased due to the increase in the ventilatory demand which leads to higher level of work of breathing (Naimark & Cherniack 1960).

Obesity in the COPD Population

Elevated weight has become an increasingly important concern for individuals with COPD. Historically, this population has exhibited symptoms of cachexia (Rutten, Wouters, & Franssen, 2013), but recent studies have reported that the prevalence of obesity in COPD population is on the rise (Franssen et al., 2008; Rutten et al., 2013). In fact, the Canadian National Health Survey reported that obesity is more prevalent in individuals with COPD compared to those without COPD (25% vs. 17%) (Vozoris & O'Donnell, 2012). These findings have been corroborated by data from the Centers for Disease Control and Prevention in Northern California, where obesity rates were 54% in individuals with COPD, compared to 20% in those without COPD (Franssen et al., 2008). While this trend is not observed in all countries (for example, slightly lower prevalence rates were reported in the Netherlands, 18% in individuals with COPD vs. 10-12% in the general population) (Schokker, Visscher, Nooyens, Van Baak, & Seidell, 2007), these data suggest a shift towards elevated weight and higher prevalence of obesity in COPD, and at rates that often exceed those observed in the general population.

The combination of COPD and obesity contributes to a clinical presentation of both obstructive and restrictive pulmonary function that contributes to greater ventilatory limitations, compromised exercise capacity, and lower HRQOL compared to individuals with COPD alone (Franssen et al., 2008). Individuals with both COPD and obesity demonstrated higher minute ventilation compared to those who were not obese (354.6 vs. 221.4 ml/min; p = 0.0001), indicating higher work associated with respiration (Gibson, 2000). Functionally, 6MWT distance was lower in individuals with obesity and COPD compared to those without obesity (203 ± 13 vs. 269 ± 11 m, p <0.0002) (Ramachandran, McCusker, Connors, Zuwallack, & Lahiri, 2008). Hospitalization rates were also higher (OR 1.42, 95% CI [1.10, 1.82]; p <0.05) (Vozoris & O'Donnell, 2012) and HRQOL was reported to be lower (Cecere et al., 2011) in individuals with COPD and obesity compared to those who were not obese. The combined effects of COPD with obesity on health, function, and HRQOL suggest that research is critically needed to better understand this subset of the COPD population such that effective strategies for prevention and management can be established.

The mechanisms underlying the relationship between the obesity and COPD are unclear. Obesity as a metabolic condition increases the systematic and local inflammation in the body including lung tissues (Hanson, Rutten, Wouters, & Rennard 2014). Although not confirmed yet, this inflammation may be a stimulant to the development of COPD in obese individuals (Hanson et al., 2014). A sedentary lifestyle and limitations in exercise capacity may also contribute to incidence of obesity in persons with COPD (Poulain et al., 2006). Individuals with COPD are less likely to be physically active, walking 30 minutes/day less than those without COPD (Pitta et al., 2005). However, the time-course for the development of these health conditions is not clear; that is, whether obesity predisposes a person to develop COPD, or if the pathophysiological or functional consequences of COPD leads to elevated weight (Franssen et al. 2008; Zammit, Liddicoat, Moonsie, & Makker, 2010; Zewari, Vos, van den Elshout, Dekhuijzen, & Heijdra, 2017).

Study Objectives

The growing prevalence of COPD with concurrent elevated weight (overweight or obesity), and the associated adverse consequences of these comorbid conditions, has resulted in a critical need compile the evidence of effective management strategies for this at-risk population. Notably, regular exercise and physical activity have the potential to positively influence health and functional outcomes in these individuals but this has not yet been systematically reviewed specifically for this subgroup.

Thus, the objectives of this research were to conduct a systematic review with meta-analysis to examine the effects of exercise and physical activity interventions on 1) exercise capacity (primary outcome), 2) ventilatory parameters, 3) anthropometric measures, and 4) HRQOL of individuals with COPD and elevated weight (overweight or obesity).

Results from this systematic review will provide important insight into the effects of current exercise and physical activity interventions on improving health and function for individuals who present with concurrent COPD and elevated weight.

CHAPTER 2: Methodology

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42016039037).

Literature Search and Search Strategy

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines were followed. Two independent reviewers (SB and SO) completed a systematic literature search on March 16, 2018, using the following electronic databases: Embase (1974–present), Medline (1946–present), CINAHL (1982–present), AMED (1985–present), and PsycINFO (1987–present). To ensure that a comprehensive search was conducted, the search strategy included terms related to three main domains, 1) COPD, 2) exercise and physical activity, and 3) overweight and obesity. The specific search strategies used for each database are presented in Appendix A.

Study Selection

Two independent reviewers (SB and SO) initially screened the titles and abstracts for eligibility, then conducted full-text assessments to identify relevant studies using the pre-specified eligibility criteria outlined below. Disagreements were resolved through discussion or the inclusion of a third reviewer (AT).

Study Eligibility Criteria

Studies. Studies were eligible to be included if they were controlled or randomized controlled trials published in English. Ongoing trials, study protocols, dissertations, and conference proceedings (posters or abstracts) were excluded from this review.

Participants. Participants were adults with a clinical diagnosis of COPD at any disease severity and stability. Studies with included those with mixed diagnoses were eligible for inclusion if more than 80% of participants had COPD. Studies were eligible if the sample mean BMI were classified as overweight (25–29.9 kg/m^2) or obese ($\geq$ 30 kg/m^2). Studies were excluded if the lower bound of the 95% CI of the BMI was < 18.5 kg/m^2.

Interventions. Studies with any type of physical activity or exercise intervention were eligible for inclusion. Exercise interventions could be traditional interventions such as aerobic and skeletal muscle resistance training, or respiratory muscle training and functional training (e.g. balance training), which could influence the outcomes of interest in individuals with COPD and obesity. Studies that combined exercise with other interventions (e.g. education or smoking cessation) were also eligible for inclusion. Interventions could be conducted in any setting (inpatient, outpatient, community, or home).

Comparators. Studies with any type of comparators were eligible for inclusion. Comparators could be usual care, education, smoking cessation or controlled exercise interventions.

Outcomes. Studies that reported any outcome related to exercise capacity (primary outcome), ventilatory parameters, anthropometric measures, or HRQOL (secondary outcomes) were eligible to be included in the review.

Time. Of primary interest in this review was to examine changes from baseline (i.e. pre-intervention) to immediately following the program.

Primary Outcome: Exercise Capacity

A wide range of methods could be used for evaluating physiological exercise capacity (maximal or peak oxygen consumption) or functional exercise capacity (using functional walk tests).

Maximal or peak oxygen consumption. Maximal oxygen consumption (VO_2max) is defined as the maximal volume of oxygen consumed in one minute of exercise (Hill & Lupton, 1923). VO_2max is the criterion standard measure of cardiorespiratory fitness that reflects aerobic exercise capacity (Shephard et al., 1968). VO_2 max is reached when there are no further increases in oxygen consumption during a progressive incremental exercise test despite further increases in workload (Hill & Lupton, 1923). In some individuals, such as older adults or many clinical populations, functional limitations or other symptoms may limit the ability to reach 'true' physiological VO_2max. In these cases, the highest, or peak, level is referred to as VO_2peak (Zeballos & Weisman, 1994).

VO_2max or VO_2peak can be assessed using validated progressive incremental or ramp test protocols (Shephard et al., 1968) that are most commonly performed on a treadmill or cycle ergometer (Silva, Monteiro, & Farinatti, 2011). To measure oxygen consumption and carbon dioxide production, breath-by-breath analysis is conducted using flow meters and gas analyzers (Shephard et al., 1968). Standardized exercise test procedures are well established to ensure safety and standardization (American Thoracic Society, 2003). The primary outcome of these tests is VO_2max or VO_2peak, which can be expressed in absolute terms (in L/min) or relative to the person's body mass (in ml/kg/min) (Silva et al., 2011).

The Bruce protocol (Bruce, Blackmon, Jones & Strait, 1963) is the most common treadmill-based exercise test. The test is comprised of six 3-minute stages. The first stage of the test starts at 1.7mph and 10% incline, and progresses with incremental increases in velocity at 0.5 and 0.8mph and inclines at 2% with each subsequent stage (Bruce et al., 1963). The test is terminated if the participant is limited by fatigue, difficulties in breathing, muscular tiredness, chest pain, or any factor affecting the exercise effort (Bruce et al., 1963).

Due to the impaired balance ability (Cruz, Marques, Jácome, Gabriel, & Figueiredo, 2015), and reduced walking capacity that associated with an excessively high ventilatory demand in individuals with COPD, cycle ergometry may be preferred to treadmill protocols for conducting exercise tests (Palange et al., 2000). Cycle ergometry offers the advantage of being a seated modality, which may be ideal for those with limited walking or balance ability, and also allows work rate to be easily quantified (e.g. in watts or kilopond meters) (Wasserman, Hansen, Sue, Whipp, & Froelicher, 1987).

Although VO_2max is the criterion standard measure for exercise capacity, there are no standardized, established reference values due in part to lack of randomization or quality control and small sample sizes of studies (American Thoracic Society, 2003). Nonetheless, oxygen consumption can increase from approximately 3.5 ml/kg/min at rest to typical maximum values of 30–50 ml/kg/min in the general population (American Thoracic Society, 2003). In individuals with COPD, VO_2peak values <15 ml/kg/min indicate severe functional disability (Hanania & Sharafkhaneh, 2011).

Six-Minute Walk Test. The 6MWT is one of the commonly used measures of functional exercise capacity in the COPD population (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002; Enright et al., 2003). It is a self-paced test conducted within a 30m enclosed corridor, where total distance walked in 6 minutes is the primary outcome (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002). Participants are provided with standardized instructions to walk continuously for 6 minutes, but are permitted to take rest breaks if needed due to fatigue or dyspnea (ATS Statement: Guidelines for the Six-Minute Walk Test, 2002). The safety of this test has been established in many clinical settings, including those with individuals with chronic lung diseases such as COPD (Jenkins & Čečins, 2011), and heart failure (Bittner et al.,1993). In 741 individuals with chronic lung diseases, oxygen desaturation to <80% were reported in only 5% of cases, and symptoms of intolerable dyspnea, severe wheezing, light-headedness, and severe low back pain were reported in 1% of cases (Jenkins & Čečins, 2011). In 833 individuals with congestive heart failure, while fatigue and dyspnea were reported in 23% and 25% of cases respectively during the 6MWT, the rate of serious adverse events was low (dizziness (4%), angina (5%)) (Bittner et al.,1993).

In a systematic review of the measurement properties of the 6MWT in individuals with COPD, intra-class correlation coefficients (ICCs) for test–retest reliability ranged from 0.72–0.99 (n = 7 studies), and criterion validity with VO_2peak ranged from r = 0.40–0.80 (n = 13 studies) (Singh et al., 2014). The minimal clinically important difference (MCID) of distance walked on the 6MWT in individuals with COPD has been reported to be 30.5 meters (Bohannon & Crouch, 2017).

Incremental Shuttle Walk Test. The Incremental Shuttle Walk Test (ISWT) is an externally-paced, 12-level test that evaluates functional exercise capacity (Parreira et al., 2014). It is measured on a 10m course, where the participant walks with progressively faster speeds according to standardized signals from an audio recording (Singh, Morgan, Scott, Walters, & Hardman, 1992). The test starts at a walking speed of 0.50 m/s, which is increased by 0.17 m/s each minute up to a maximum test duration of 20 minutes (Parreira et al., 2014). The test is over when the participant is limited by dyspnea, has reached >85% of their maximum predicted heart rate, or can no longer keep up with the speed signals (Parreira et al., 2014). The total distance walked is the primary outcome of this test (Singh et al., 1992).

The ISWT has high test–retest reliability (ICCs = 0.80–0.93) and criterion validity with VO_2peak (r = 0.75–0.88) in the COPD population (n = 13 studies) (Singh et al., 2014). The MCID of the ISWT has been reported to be 47.5m in individuals with COPD (Singh et al., 2014).

Endurance Shuttle Walk Test. The Endurance Shuttle Walk Test (ESWT) is a test of exercise endurance in individuals with COPD (Revill, Morgan, Singh, Williams, & Hardman, 1999). Similar to the ISWT, the ESWT uses a 10m course and pre-recorded audio signals, but in contrast to the IWST, it requires participants to walk continuously at a steady pace for as long as possible (Revill et al., 1999). Walking speed is set at 85% of the walking speed measured on an ISWT performed previously (Hill et al., 2012). The test is over when the participant is limited by dyspnea or after a maximum duration of 20 minutes (Revill et al., 1999). The primary outcome of the test is total walking time, but the total distance walked is also commonly reported (Singh et al., 2014).

The reliability and validity of the ESWT have not yet been reported in the literature (Singh et al., 2014), but MCIDs in individuals with COPD have been reported as 65s for total time or 85m for total distance (Pepin et al., 2011).

Secondary Outcome: Ventilatory Parameters

There are several commonly used measures of pulmonary function that are used to reflect changes in obstructive and restrictive disease. The measures of interest for the current systematic review are described below.

Forced expiratory volume in one second and forced vital capacity. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) are the standard outcomes used to quantify the level of pulmonary obstruction and can also indicate the presence of a restrictive condition (Ruppel, 1998). They are usually measured using spirometry, in which volumes of FEV_1 and FVC are expressed in liters or milliliters (Quanjer et al., 1993). Standardized test protocols have been established regarding participant position (sitting with good posture, head slightly elevated), set-up procedures (nasal clip and mouthpiece applied with a good seal), and instructions (rapid and complete inhalation, pause <1s at maximum inhalation, followed by maximal exhalation while maintaining an upright posture) (Miller et al., 2005). The test should be repeated at least three times to check the repeatability, and stopped immediately if the subject reports dizziness or respiratory distress (Miller et al., 2005).

The ratio of the FEV_1 to FVC is used to establish the diagnosis of COPD (when FEV_1/ FVC < 0.7), and values for % predicted FEV_1 have been identified to classify individuals as having mild (≥ 80%), moderate (80% > FEV_1 ≥ 50%), severe

(50% > $FEV_1 \geq$ 30%), or very severe (< 30%) disease (Vogelmeier et al., 2017). When the ratio of FEV_1 to FVC is normal ($\geq$ 0.7), a low % predicted of FVC $\leq$ 80 % indicates ventilatory restriction (Ruppel, 1998).

Total lung capacity, residual volume, and associated ratios. Total lung capacity (total volume of air in the lungs with maximal inhalation, TLC) and residual volume (the amount of gas left in lungs after a complete exhalation, RV) are used to reflect hyperinflation, and air trapping caused by pulmonary obstruction or to confirm pulmonary restriction. These volumes are measured via a body plethysmography (Ranu, Wilde, & Madden, 2011). Plethysmographic measurements are based on Boyle's Law, which states that, under isothermal conditions, when a constant mass of gas is compressed or decompressed, pressure and volume are inversely proportional such that the product of volume and pressure at any given moment is constant (i.e. $P*V=k$, where P is pressure, V is volume, and k is constant) (DuBois, Botelho, Bedell, Marshall & Comroe, 1956). In the measurement of lung volumes, the individual sits inside an airtight glass room wearing a nasal clip, and breathes normally through a shutter valve that contains a transducer to measure mouth pressure and is connected to a spirometer that measures lung volumes (Wanger et al., 2005). The participant takes 3–10 normal breaths, then at the end of the exhalation, the shutter is closed and the individual performs 3–5 gentle pants where mouth pressure is measured (Wanger et al., 2005). The shutter is then opened and individual takes 2-3 normal breaths, followed by a deep inhalation and deep exhalation, concluding with a few normal breaths after which the test is completed (Wanger et al., 2005). By measuring the pressures of the box and at the mouth, RV and TLC can be calculated using Boyle's

Law. The test should be repeated at least three times to check the repeatability (Wanger et al., 2005).

Prediction equations have been developed for TLC and the ratio RV/TLC using height and age (Quanjer et al., 1993):

For men: TLC = 7.99 * Height - 7.08 and RV/TLC = 0.39 * Age + 13.96

For women: TLC = 6.60 * Height - 5.79 and RV/TLC = 0.34 * Age + 18.96

TLC values $\leq$ 80% predicted are indicative of the presence of restrictive disease (Ruppel, 1998). TLC values > 120% predicted is indicative of lung hyperinflation, and RV/TLC > 40% predicted and RV >140% predicted are indicative of air trapping (Ruppel, 1998).

Secondary Outcome: Anthropometrics

Anthropometric measures can be used to reflect nutritional status (Karakas, Bilgin, Polatli, Ozlem, & Tas-Gulen, 2014) and predict prognosis (Landbo, Prescott, Lange, Vestbo, & Almdal, 1999) and functional status (Eisner et al., 2007; Franssen et al., 2008) in individuals with COPD. Different anthropometric measures that are frequently evaluated in persons with COPD are described below.

Body mass index. Body mass index (BMI) is an anthropometric measure commonly used in the COPD population to evaluate the state of underweight or obesity (Celli et al., 2004). It is calculated as weight/height^2 (kg/m^2), which allows individuals to be categorized as being underweight (< 18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese ($\geq$ 30 kg/m^2) (World Health Organization, 1997).

Waist circumference and Waist–hip ratio. Waist circumference is an anthropometric measure of fat deposition around the waist and an indicator of abdominal obesity (World Health Organization, 2011). It can be measured easily in clinical settings by using an anthropometric measuring tape (World Health Organization, 2011). Waist–Hip Ratio is a surrogate measure of fat deposition around the buttocks, hips, and waist, and thus is an indicator of abdominal obesity (World Health Organization, 2011). It is calculated as a ratio of waist and hip circumferences (World Health Organization, 2011). Waist circumference values of > 94 cm and > 80 cm (Han, Van Leer, Seidell, & Lean, 1995), and Waist–Hip Ratio values > 0.90 and > 0.85 (Annex, 2008) are indicative of abdominal obesity in men and women, respectively.

Fat-free mass and Fat-free mass index. Fat-free mass (FFM) and FFM index (FFMI) are used to reflect an individual's functional muscle mass (Steiner, Barton, Singh & Morgan, 2002). FFM can be measured via dual energy X-ray absorptiometry (Steiner, Barton, Singh & Morgan, 2002), which uses two levels of X-rays energies and measures the differential attenuation as they pass through the body (Laskey, 1996). FFM is calculated as the sum of lean mass and bone mineral mass (kg) and is highly variable with changes in height and age (Kyle, Schutz, Dupertuis, & Pichard, 2003). In contrast, FFMI is a height-independent measure that calculated as FFM/height^2 (kg/m^2), and is a preferred measure to use over FFM (Kyle et al., 2003).

FFMI reference values have been identified as 16.7–19.8 kg/m^2 for men and 14.6–16.8 kg/m^2 for women (Kyle et al., 2003), and individuals are considered to be muscle-depleted if they have an FFMI of <14.6 or <16.7 kg/m^2 for women and men, respectively (Kyle et al., 2003).

Secondary Outcome: Health-Related Quality of Life

In the COPD population, HRQOL can be used as a predictor of hospitalization (Fan, Curtis, Tu, McDonell, & Fihn, 2002) and mortality (Domingo-Salvany et al., 2002) . Many disease-specific questionnaires are frequently used with persons having COPD; the most commonly used ones are described below.

St. George's Respiratory Questionnaire. The St. George's Respiratory Questionnaire (SGRQ) is a condition-specific, self-administered assessment tool developed to measure the HRQOL in individuals with obstructive airway diseases, such as COPD, asthma, and bronchiectasis (Jones, Quirk, Baveystock, & Littlejohns, 1992; Jones, Quirk, & Baveystock, 1991). The tool has 76 items that evaluate the disease's effects on three domains: symptoms (frequency and severity), activity (limitation and difficulty), and impact (social and psychological) (Jones et al., 1992, 1991). The total score is calculated and ranges from 0 to 100, where lower scores indicate better HRQOL (Jones et al., 1992, 1991). The questionnaire had an excellent test–retest reliability in the COPD population (ICC = 0.79–0.90) (Barr et al., 2000) and construct validity with the COPD Assessment Test (Pearson's r = 0.73) (Ringbaek, Martinez, & Lange, 2012). The MCID of the St. George's Respiratory Questionnaire has been reported to be 4 points in people with COPD (Jones, 2005).

The Chronic Respiratory Disease Questionnaire. The Chronic Respiratory Disease Questionnaire (CRDQ) is a disease-specific, interviewer-administered questionnaire that measures the impact of COPD on physical functional and emotional limitations (Guyatt, Berman, Townsend, Pugsley, & Chambers, 1987). It uses 20 questions to assess four domains (dyspnea, fatigue, emotions, and mastery), each scored on a 7-point scale ranging from 1 (*severe impairment*) to 7 (*no impairment*)

(Guyatt et al., 1987). The total score and individual subscale scores are used to evaluate the overall and domain-specific effects of the disease, respectively (Guyatt et al., 1987). The questionnaire has excellent test–retest reliability (ICC = 0.83–0.95) (Williams, 2001) and high concurrent validity with the SGRQ (Spearman's *rho* = 0.74–0.86) (Hajiro et al., 1998). The MCID per question is reported as 0.5 points (Wijkstra et al., 1994).

Data Extraction

Standardized data extraction forms were used for both the qualitative synthesis and the quantitative analysis. These are provided in Appendix B and Appendix C, respectively.

For the qualitative synthesis, two independent reviewers (SB and SO) extracted the following information from the identified studies:

- author(s) name(s),
- study title,
- publication year,
- study design,
- sample size,
- participant demographics (number and percentage of men and women, disease severity, and mean ± SD for age and BMI) of the total sample and for each group,
- intervention and comparator details (frequency, intensity, type, time, duration, and setting), and

- Primary and secondary outcomes that were measured at all available time points (baseline, mid-point, post-intervention, and follow-up).

For the quantitative analysis, the number of participants and means ± SD for each outcome of interest were extracted for each group at all available time points (baseline, mid-point, post-intervention, and follow-up).

Qualitative Synthesis

The participants, intervention(s), comparator(s), and outcome(s) data from all of the included studies were extracted by two reviewers (SB and SO).

Study quality and the risk of bias were assessed using the Physiotherapy Evidence Database (PEDro) scale (Appendix D) and the Cochrane Collaboration Risk of Bias tool (Appendix E), respectively. Study quality was assessed by two independent reviewers (SB and SO). Disagreements were solved by discussion, or via the inclusion of a third reviewer (AT). Although Cochrane tool is the preferred assessment tool to evaluate potential sources of bias and the internal validity of clinical trials, the PEDro scale was also selected because it includes elements that evaluate the quality of reporting the trials and provides a numerical score, which can help with the classification of study quality.

The PEDro scale was developed to assess the quality and usefulness of controlled trials that evaluate interventions to inform clinical decision-making in many areas of practice, including physiotherapy (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003), rehabilitation (Gates, Fiatarone Singh, Sachdev, & Valenzuela, 2013), medicine (Pinto et al., 2012), and speech and language pathology (Wong, Ng, &

Tsang, 2012). The scale is widely used in systematic literature reviews published in high-quality journals (Sherrington, Herbert, Maher, & Moseley, 2000)

The PEDro scale includes 11 items and evaluates the generalizability and internal validity of the trials and the interpretability of their results (Verhagen et al., 1998). The total score (maximum score 10) is used to classify the study quality as poor (< 3), fair (4–5), or high (6–10) (Verhagen et al., 1998). The reliability of the PEDro scale for rating the quality of randomized controlled trials has been reported as 0.56 (95% CI [0.47, 0.65]) for the total score when rated by individuals, and 0.68 (95% CI [0.57, 0.76]) for consensus ratings (Maher et al., 2003).

The Cochrane Collaboration Risk of Bias was evaluated using Review Manager 5.3 (Higgins & Green 2011). The Cochrane Collaboration Risk of Bias tool is composed of six domains (selection, performance, detection, attrition, reporting procedures, and other) that are classified as being at high, low or unclear risk of bias for each study (Higgins & Green 2011). Studies were considered of poor quality if they have more than three biases present.

Quantitative Analysis

Review Manager 5.3 was used to conduct the quantitative analysis. Forest plots were generated and the standardized mean difference (SMD) and the weighted mean difference (WMD) using random-effects meta-analysis was used when possible to determine the intervention's overall effects on the outcome of interest.

Secondary analyses were performed to examine differences in effects given different mean BMI, intervention characteristics (e.g., the frequency, intensity, type and duration of sessions and programs), and types of comparators used.

Where possible, sensitivity analyses were conducted to examine the effects of the study quality, as well as participant, intervention, and comparator characteristics on the main results.

CHAPTER 3: Results

Results of Search

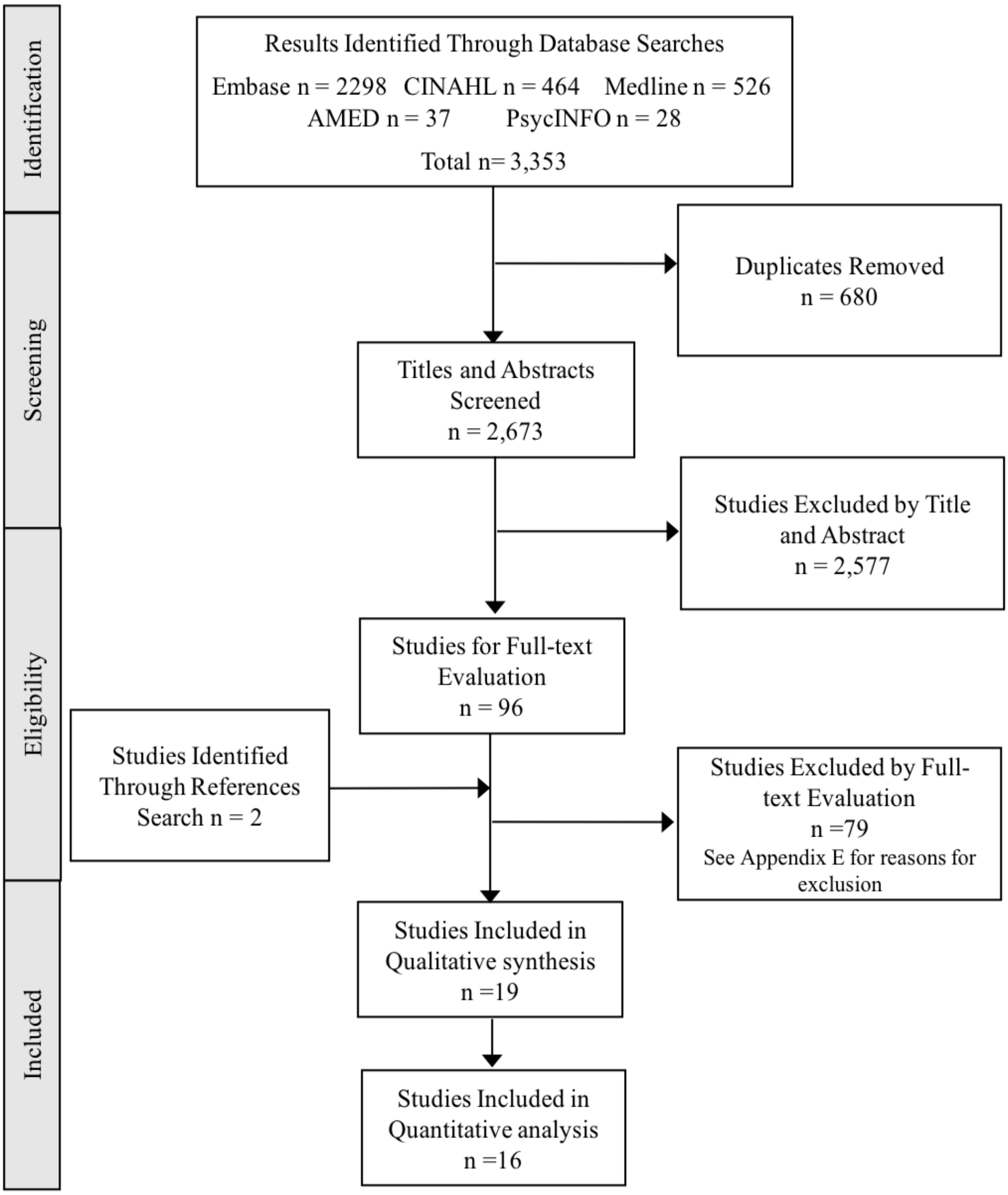
Results from the study search and selection process are presented in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Moher et al, 2009) Flow Diagram (Figure 1). Initially, 3,353 studies were identified from the search. After removing duplicates, 2,673 titles and abstracts were screened, and 98 full-text articles were assessed for eligibility.

During the full-text review, it was noted that two studies (Zakrisson et al., 2011 & Zakrisson et al., 2016) used the same dataset and reported the same outcome measures, but at different time points (Baseline, after 5 and 12 months (Zakrisson et al., 2011); and Baseline, after 1 and 3 years (Zakrisson et al., 2016)). Therefore, to avoid the duplication of participants' data, only the first paper (Zakrisson et al., 2011) was included, which had the larger sample size.

Six studies (Amin et al., 2014; Epstein et al., 1997; Hoff et al., 2007; Paz-Díaz et al., 2007; Wadell et al., 2005a & Weiner et al., 2003) that were otherwise eligible reported aggregate data for height and weight, but not BMI. The corresponding authors were contacted, of which two (Paz-Díaz et al., 2007 & Wadell et al., 2005a) responded but were not able to provide BMI data to be included in the review. The remaining four studies were also excluded. Information regarding the excluded studies is presented in Appendix F.

Two additional articles (Hoogendoorn et al., 2010 & van Wetering et al., 2010b) were identified after reviewing reference lists of included articles. Thus, 19 studies met all eligibility criteria and were included in the qualitative synthesis and 16 studies were included in the quantitative analysis.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Flow Diagram



Qualitative Synthesis

Study Characteristics

Detailed characteristics of the 19 studies included in this review along with group differences for post-intervention effects for all outcomes examined are provided in Table 1. Fifteen studies ([79%]; Covey et al., 2014; Farias et al., 2014; Gottlieb et al., 2011; Guell et al., 2017; Klijn et al., 2013; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Pradella et al., 2015; Ram ́ırez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b; Vorrink et al., 2016; Wilson et al., 2015; Wootton et al., 2014) were randomized controlled trials. The remaining four trials (Elkhateeb et al., 2015; Panton et al., 2004; Wadell et al., 2005b; Zakrisson et al., 2011) were non-randomized controlled trials.

PEDro scores are presented in Table 2. The quality of these studies ranged from fair (*n* = 5, [26%]; Elkhateeb et al., 2015; Panton et al., 2004; Vorrink et al., 2016; Wadell et al., 2005b; Zakrisson et al., 2011) to good (*n* = 14, [74%]; Covey et al., 2014; Farias et al., 2014; Gottlieb et al., 2011; Guell et al., 2017; Klijn et al., 2013; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Pradella et al., 2015; Ram ́ırez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b; Wilson et al., 2015; Wootton et al., 2014).

All studies were judged to have a high risk of bias for at least one item (Table3). Eleven trials reported details on randomization procedures (Covey et al., 2014; Gottlieb et al., 2011; Guell et al., 2017; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b; Vorrink et al., 2016; Wilson et al., 2015 & Wootton et al., 2014), and only six reported allocation concealment, (Farias et al., 2014; Gottlieb et al 2011; Klijn et al

2013; McNamara et al., 2013; Monninkhof et al., 2003 & O'Shea et al., 2007) indicating possible selection bias. Due to the nature of the interventions, blinding the participants and the therapist is not possible. Thus, all the studies had a high risk of performance bias. Blinding of outcome assessors was reported in most of the studies (Covey et al., 2014; Farias et al., 2014; Guell et al., 2017; Klijn et al 2013; McNamara et al., 2013; O'Shea et al., 2007; Pradella et al., 2015; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b; Vorrink et al., 2016; Wilson et al., 2015 & Wootton et al., 2014), and was unclear in five studies (Elkhateeb et al., 2015; Panton et al., 2004; Ram´ırez-Sarmiento et al., 2002; Wadell et al., 2005b & Zakrisson et al., 2011). Due to the high dropout rate (20-53%), attrition bias was high in nine studies (Covey et al., 2014; Elkhateeb et al., 2015; Gottlieb et al., 2011; Guell et al., 2017; O'Shea et al., 2007; Vorrink et al., 2016; Wadell et al., 2005b; Wilson et al., 2015 & Zakrisson et al., 2011). The selective reporting bias was high in only one study (Elkhateeb et al., 2015).

Therefore, twelve studies (Covey et al., 2014; Farias et al., 2014; Guell et al., 2017; Klijn et al 2013; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Pradella et al., 2015; Ram´ırez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b & Wootton et al., 2014) were considered good quality studies. Four studies (Gottlieb et al., 2011; Panton et al., 2004; Vorrink et al., 2016 & Wilson et al., 2015) were with fair quality, and three (Elkhateeb et al., 2015; Wadell et al., 2005b & Zakrisson et al., 2011) were poor quality studies.

Table 1. Studies Included in The Qualitative Analysis

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
Covey et al 2014	RCT	Total n = 75 **I:** n= 20, 18 (90%) men, Age 68±6 years, BMI 28.1±7.1 kg/m^2 **C_1:** n= 28, 24 (86%) men, Age 68±8 years, BMI 29.2±6.7 kg/m^2 **C_2:** n=27, 25 (93%) men, Age 68±7 years, BMI 28.4±6.2 kg/m^2 University or Outpatient Hospital Setting	**Frequency:** 3 sessions/week for 16 weeks **Intensity:** Resistance: 70% 1RM x2 weeks, 80% 1RM x2 weeks, 80% of re-evaluated 1RM x4 weeks Aerobic: 50% peak work rate with weekly progression as tolerated **Time:** Resistance: 2-3 sets of 8-10 repetitions	**C_1: Frequency:** 3 sessions/week for 16 weeks **Intensity:** Sham: Light intensity Resistance: 70% of 1RM x 2 weeks, 80% 1RM x2 weeks, 80% of re-evaluated 1RM x4 weeks Aerobic: 50% peak work rate progressed weekly to highest work rate as tolerated	6MWT, *p* = 0.44 CRDQ, *p* = 0.85 *p* reported for intervention vs. both control groups

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		Baseline, 8 weeks, 16 weeks	Aerobic: 26-32 minutes **Type:** Resistance x8 weeks, followed by interval cycling performed as 4 work sets of moderate intensity for 5 minutes separated by 2-4 minutes of unloaded cycling x8 weeks	**Time:** Sham: NR Resistance: 2-3 sets of 8-10 repetitions Aerobic: 26-32 minutes **Type:** Sham chair stretching x8 weeks followed by Combination of resistance and interval cycling performed as 4 work sets of moderate intensity for 5 minutes separated by 2-4 minutes of	

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
				unloaded cycling x8 weeks **C_2: Frequency:** 3 sessions/week for 16 weeks **Intensity:** Sham: Light intensity Aerobic: 50% peak work rate progressed weekly to highest work rate as tolerated **Time:** Sham: NR Aerobic: 26-32min	

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
				Type: Sham chair stretching x8 weeks followed by Interval cycling performed as 4 work sets of moderate intensity for 5 minutes separated by 2-4 minutes of unloaded cycling x8 weeks	
Elkhateeb et al 2015	CT	Total n = 45 **I_1:** n= 15, n (%) men NR, Age 58.9±8.8 years, BMI 25.5±3.9 kg/m^2 **I_2:** n=15, n (%) men NR, Age	**I_1: Frequency:** Session frequency NR for total duration of intervention (6-8 weeks) **Intensity:** 80-85% of max HR	Optimized medical therapy	6MWT, *p* =NR % Predicted of FEV_1, *p* =0.01* % Predicted of FVC, *p* =0.002*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		59.8±7.9 years, BMI 26.9±4.9 kg/m^2 **C:** n= 15, n (%) men NR, Age 60.5±8.1 years, BMI 25.7±5.1 kg/m^2 Hospital Outpatient Setting Baseline, post-intervention (6-8 weeks)	**Type:** Aerobic **Time:** NR **I_2: Frequency:** Session frequency NR for total duration of intervention 6-8 weeks **Intensity:** NR **Time:** NR **Type:** Respiratory training		FEV_1/FVC, *p* =0.36 BMI, *p* =0.66 *p* reported for both intervention groups vs. control
Farias et al	RCT	Total n = 34	**Frequency:** 5 sessions/week	2 educational classes	6MWT, *p*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
2014		**I:** n= 18, 11 (32%) men, Age 64.6±10.1 years, BMI 28.1±5.1 kg/m^2 **C:** n= 16, 6 (18%) men, Age 70.5±8.1 years, BMI 26.4±5.3 kg/m^2 Community Baseline, 8 weeks	for 8 weeks **Intensity:** Borg Rating of Perceived Exertion 5/10 **Time:** 40-60 minutes **Type:** Aerobic walking **Other**: 2 educational classes		<0.05* SGRQ, *p* <0.05* Skeletal muscle mass, *p* <0.05*
Gottlieb et al 2011	RCT	Total n = 42 **I:** n= 22, 7 (32%) men, Age	**Frequency:** 3 sessions/week for 7 weeks + 1 maintenance session/month for 6 months	Standard Care	6MWT, *p* =0.19 Sit to stand time,

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		Mean 74.1 years ±SD NR, BMI 25.6±4.2 kg/m^2 **C:** n=20, 7 (35%) men, Age Mean 73.2 years ±SD NR, BMI 26.4±3.9 kg/m^2 Healthcare Centre Outpatient Setting Baseline and post rehab (rehab group only) or 6 months (control group only), with follow-up at 12 and 18 months	**Intensity:** Borg Rating of Perceived Exertion 16-17/20 **Time:** 90 minutes **Type:** Aerobic: static circuit training, brisk walking, breathing technique (2 sessions/week) **Other**: Education (1session/week), smoking cessation and dietary		*p* = 0.13 SGRQ, *p* =NR

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
			intervention if needed		
Guell et al. 2017	RCT	Total n =138 **I:** n= 87, 59 (32%) men, Age 64±9 years, BMI 27±5 kg/m^2 **C:** n=70, 64 (91%) men, Age 64±8 years, BMI 28±5 kg/m^2 Home Baseline, 12 months, 24 months, and after 36 months	**Frequency:** 3 sessions/week for 3 years **Intensity:** 50% of maximum work rate **Time:** 60 minutes **Type:** Aerobic: arm and leg training using cycle ergometers **Other**: chest physiotherapy for 15 minutes and receiving	Advice to exercise at home	6MWT, *p* =0.12 CRDQ: Dyspnea, *p* =0.29 Fatigue, *p* =0.19 Emotion, *p* =0.27 Mastery, *p* =0.89

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
			an encouragement call from physiotherapist every 15 days		
Klijn et al 2013	RCT	Total n = 110 **I:** n= 55, 19 (35%) men, Age 61±7 years, BMI 26±6 kg/m^2 **C:** n= 55, 19 (35%) men, Age 61±6 years, BMI 25±5 kg/m^2 Hospital Inpatients Settings Baseline, 12 weeks	**Frequency:** 3 sessions/week for 10 weeks **Intensity:** Aerobic: 50-60% of maximum work rate for the first 3 sessions progressed up to 95% of maximum work rate for the rest of the trainings sessions Resistance: 40-50% of 1RM **Time:** 45-90 minutes	**Frequency:** 3 sessions/week for 10 weeks **Intensity:** Aerobic: 30% of maximum work rate progressed to 75% of maximum work in each session Resistance: 50% 1RM **Time:** 45-90 minutes	CRDQ: Dyspnea & Fatigue, $p <$ 0.001* Emotion & Mastery, $p <$ 0.01* BMI, *p* reported not significant Fat-Free Mass Index, $p <$0.05*

Study	**Design**	**Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points**	**Intervention Frequency, Intensity, Time, Type**	**Comparator Frequency, Intensity, Time, Type**	**Outcome, *p* value**
			Type: Aerobic: cycling Resistance: leg press training	**Type:** Aerobic: cycling and walking Resistance: leg press training	
McNamara et al 2013	RCT	Total n = 53 **I:** n= 18, 5 (28%) men, Age 72±1 years, BMI 33±6 kg/m^2 **C_1:** n=15, 32 (59.3%) men, Age 70±9 years, BMI 33±6 kg/m^2 **C_2:** n=20, 10(50%) men, Age 73±7 years, BMI 32±5 kg/m^2 Hospital Outpatients Settings	**Frequency:** 3 sessions/week for 8 weeks **Intensity:** Borg Rating of Perceived Exertion 3-5/10 **Time:** 60 minutes **Type:** Aerobic (Water-based upper and lower limb exercise training)	**C_1:** Usual medical care with no training intervention and no alteration in exercise level **C_2: Frequency:** 3 sessions/week for 8 weeks **Intensity:** 3-5 on the modified Borg, 80% of the average 6MWT **Time:** 60 minutes	6MWT, *p* <0.001* ISWT, *p* =0.01* ESWT (m), *p* =0.01* CRDQ: Dyspnea, *p* =0.026* Fatigue, *p*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		Baseline, 8 weeks		**Type:** Aerobic (Land-based over-ground walking or treadmill exercise training)	=0.001* Emotion, *p* =0.07 Mastery, *p* =0.18 *p* reported for intervention vs. both control groups
Monninkhof et al 2003	RCT	Total n = 248 **I:** n= 127, 85 (67%) men, Age 65±7 years, BMI 27±4 kg/m^2 **C:** n= 121, 84 (69.4%) men, Age	**Frequency:** 1-2 sessions/week for 2 years **Intensity:** Individualized (not specified)	Usual Care	6MWT, *p* > 0.05 SGRQ, *p* > 0.05

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		65±7 years, BMI 27±4 kg/m^2 Outpatient Clinic Settings Baseline, 6 months, 12 months	**Time:** 60 minutes **Type:** Aerobic: cycling and walking with breathing exercise **Other**: Self-management education		
O'Shea et al 2007	RCT	Total n = 54 **I:** n= 27, n (%) men NR, Age 66.9±7 years, BMI 25.5±5.1 kg/m^2 **C:** n= 27, n (%) men NR, Age	**Frequency:** 3 sessions/week for 12 weeks **Intensity:** 3 sets of 8-12 repetitions, using elastic band **Time:** NR	No training intervention, no alteration in exercise level	6MWT, $p > 0.05$ Time Up and Go, $p > 0.05$ CRDQ, $p > 0.05$

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		68.4±9.9 years, BMI 27.8±7.9 kg/m^2 Outpatient Clinic and Home Settings Baseline,12 weeks with follow-up at 24 weeks	**Type:** Progressive resistance: hip abdomen, sit to stand, simulated lifting, seated row, lunges, chest press		
Panton et al 2004	CT	Total n = 17 **I:** n= 9, 6 (67%) men, Age 61±7 years, BMI 32.5±9.6 kg/m^2 **C:** n= 8, 2 (25%) men, Age 63±8 years, BMI 30±6.5 kg/m^2	**Frequency:** 2 sessions/week for 12 weeks **Intensity:** Aerobic: 50-70% HR reserve Resistance: 3 sets of 10-12	**Frequency:** 2 sessions/week for 12 weeks **Intensity:** 50-70% HR reserve **Time:** 60 minutes	12-minute walk test, $p < 0.05$* FEV_1, $p < 0.05$* % Predicted of FEV_1, $p < 0.05$*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		Outpatient Clinic Settings Baseline, 12 weeks	repetitions **Time:** 1:45-2hrs Aerobic: 60 minutes, Resistance: 45-60 minutes **Type:** Aerobic: arm ergometer, cycling, treadmill, walking, chair aerobics with light dumbbells Resistance: leg press, calf press, leg curl, leg extension, chest press, shoulder press,	**Type:** Aerobic: arm ergometer, cycling, treadmill, walking, chair aerobics with light dumbbells	FVC, *p* >0.05 BMI, *p* >0.05 Body Fat %, *p* <0.05*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
			seated row		
Pradella et al 2015	RCT	Total n = 44 **I:** n= 29, 23 (79.3%) men, Age 62.4±10.7 years, BMI 25.2±5 kg/m^2 **C:** n= 15, 13 (87%) men, Age 65.3±8 years, BMI 26.7 ± 5.3 kg/m^2 Rehabilitation Center, then Home	**Frequency:** 3 sessions/week for 8 weeks **Intensity:** 60-70% of max HR **Time:** 70 minutes **Type:** Aerobic: walking, stair climbing and upper limb exercises **Other**: a weekly	No intervention	6MWT, $p < 0.05$* SGRQ, $p < 0.05$*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		Baseline, 8 weeks	encouragement call from physiotherapist		
Ram ́ırez-Sarmiento et al 2002	RCT	Total n = 14 **I:** n= 7, 7 (100%) men, Age 65±5 years, BMI 29±4 kg/m^2 **C:** n= 7, 7 (100%) men, Age 66±6 years, BMI 26±4 kg/m^2 Hospital Outpatient Settings Baseline, 5 weeks	**Frequency:** 5 sessions/week for 5 weeks **Intensity:** 60% of maximal sustainable inspiratory pressure, or 40 to 50% of maximal inspiratory pressure **Time:** 30 minutes **Type:** Inspiratory muscle training using a threshold inspiratory device	**Frequency:** 5 sessions/week for 5 weeks **Intensity:** no additional load **Time:** 30 minutes **Type:** placebo sham training using a threshold inspiratory device	6MWT, Maximum Oxygen Consumption, FEV_1, % Predicted of FEV_1, Total Lung Capacity, % Predicted of Total Lung Capacity,

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
					p >0.05 for all
Torres-Sánchez et al 2016	RCT	Total n = 49 **I:** n= 24, 24 (100%) men, Age 72.4±8.9 years, BMI 33.6±1.1 kg/m^2 **C:** n= 25, 23(92%) men, Age 73.7±7.1 years, BMI 34.3± 2 kg/m^2 Hospital Inpatient Settings Baseline (admission), at	**Frequency:** 2 sessions/day for a minimum of 7 sessions until discharge day **Intensity:** Repetitions adapted to the subject response (not specified) **Time:** 30–45 minutes Resistance: 20–30 minutes Breathing: 15 minutes	Standard medical and pharmacological care, no exercise	Two-minute step-in-place, *p* =0.013* FEV_1, *p* =0.12 % Predicted of FEV_1, *p* =0.26 EuroQOL, *p* <0.05*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		discharge	**Type:** Resistance: knee flexion-extension, hip and upper limbs flexion-extension, and abduction-adduction **Other:** deep breathing exercises		
Van Wetering et al 2010b	RCT	Total n = 199 **I:** n= 102, 73 (71%) men, Age 65.9±8.8 years, BMI 26.1±4.4 kg/m^2 **C:** n= 98, 69 (71%) men, Age 67.2±8.9 years, BMI 27.3±4.7	**Frequency:** 2 sessions/week for 4 months then 1 visit/month for 20 months **Intensity:** NR **Time:** 30 minutes	Usual care, pharmacotherapy according to guidelines, short smoking cessation advice	6MWT, *p* =0.02* % Predicted of FEV_1, *p* =0.03* SGRQ: Total, *p* =0.004*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		kg/m^2 Community Baseline, 4 months, with follow-up at 12 and 24 months	**Type:** Aerobic: cycling and walking Resistance: upper and lower limbs training **Other**: education		Activity, *p* =0.01* Symptoms, *p* =0.64 Impact, *p* <0.01* BMI, *p* =0.13 Fat-Free Mass Index, *p* =0.01*
Vorrink et al 2016	RCT	Total n = 157 **I:** n= 84, 42 (50%) men, Age 62±9 years, BMI 27.7±0.6 kg/m^2	**Frequency:** Session frequency NR for total duration of 6 months of intervention **Intensity:** Steps/day goal:	Usual Care	6MWT, *p* =0.58 CRDQ: Dyspnea, *p* =0.18

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		C: n= 73, 36 (49%) men, Age 63±8 years, BMI 26.7±0.6 kg/m^2 Home Baseline, 3 months, 6 months, and follow-up at 12 months	average plus 20% of steps during 1 min of intense physical activity or average over 30 min plus 20% of steps **Time:** 30 minutes **Type:** Accelerometer to track steps and communication by text message to provide feedback and encouragement.		Fatigue, *p* =0.02* Emotion, *p* =0.59 Mastery, *p* =0.15 BMI, *p* = 0.46
Wadell et al 2005b	CT	Total n = 43 **I:** n= 30, 9 (30%) men, Age 65±5 years, BMI mean± SD NR	**Frequency:** 3 sessions/week for 3 months **Intensity:** NR	No exercise intervention	Peak Oxygen Consumption, ISWT and ESWT(m)

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		C: n= 13, 7 (54%) men, Age 63±7 years, BMI mean± SD NR Hospital Outpatient Settings Baseline, 3 months	**Time:** 45 min **Type:** Endurance and strength training in water and on land		FEV_1 % Predicted of FEV_1 FEV_1/FVC BMI *p*=NR
Wilson et al 2015	RCT	Total n = 148 **I:** n= 73, 41 (56%) men, Age 67.3±15.1 years, BMI 28.7±5.8 kg/m^2 **C:** n= 75, 50 (67%) men, Age 69.3±8.9 years, BMI 28.6±6.3	**Frequency:** 1 session every 3 months for 12 months **Intensity:** Individualized (not specified) **Time:** 2 hours Exercise: 1 hour	Advice to exercise at home and optional attendance at Breath Easy Group	ESWT(s), *p* =0.91 ESWT (m), *p* =0.30 CRDQ: Dyspnea, *p*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		kg/m^2 Outpatient Settings Baseline, 3 months, 6 months, 9 moths, 12 months	Education: 1 hour **Type:** Aerobic and Resistance: walking, cycling, standing from sitting and arm exercises. **Other**: education		=0.39 Fatigue, *p* =0.59 Emotion, *p* =0.93 Mastery, *p* =0.80 EuroQOL, *p* =0.007* BMI, *p* =0.62 Body Fat %, *p* =0.916
Wootton et al 2014	RCT	Total n = 143	**Frequency:** 3 sessions/week for 8-10 weeks	No exercise intervention	6MWT, *p* =0.01*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		I: n= 95, 56 (59%) men, Age 69±8 years, BMI 25±5 kg/m^2 **C:** n= 48, 28 (58%) men, Age 68±9 years, BMI 27±6 kg/m^2 Hospital Outpatient Settings Baseline, post intervention (8-10 weeks)	**Intensity:** 80% of average speed from 6MWT, progressed to Borg 3-4/10 **Time:** 30-45 minutes **Type:** Aerobic track walking		ISWT, *p* =0.052 ESWT (s), *p* <0.001* SGRQ, *p* =0.003* CRDQ: Total, *p* = 0.01* Dyspnea, *p* =0.15 Fatigue, *p* =0.18 Emotion, *p*

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
					=0.01* Mastery, *p* =0.04*
Zakrisson et al 2011	CT	Total n = 103 **I:** n= 49, 25 (51%) men, Age 67±4 years, BMI 28±6 kg/m^2 **C:** n= 54, 32 (59%) men, Age 68±5 years, BMI 27±6 kg/m^2 Primary Health Care Outpatient Settings Baseline, 2 months, follow-up at	**Frequency:** 1 session/week for 6 weeks **Intensity:** NR **Time:** 2 hours Exercise: 1 hour Education: 1 hour **Type:** Resistance muscle training	Usual Care	6MWT, *p* =0.23 Clinical COPD Questionnaire, *p* =0.86

Study	Design	Participants Total n, Group n, n (%) men, mean± SD Age, mean± SD BMI, Setting, Assessment Time Points	Intervention Frequency, Intensity, Time, Type	Comparator Frequency, Intensity, Time, Type	Outcome, *p* value
		5 months and 12 months	**Other**: education, breathing & coughing techniques, relaxation, with home exercise prescription		

*$P<0.05$

Abbreviations. 1-RM: 1-Repetition maximum, NR: Not Reported, 6MWT: 6-Minute Walk Test, ISWT: Incremental Shuttle Walk Test, ESWT: Endurance Shuttle Walk Test, SGRQ: St George’s Respiratory Questionnaire, CRDQ: Chronic Respiratory Disease Questionnaire, FEV_1: Forced Expiratory Volume in 1s, FVC: Forced Vital Capacity, BMI: Body Mass Index.

Table 2. Quality Assessment of Included Studies Using Physiotherapy Evidence Database Scale

Item / Studies	Eligibility criteria	Random allocation	Concealed allocation	Similar baseline indicators	Blinding of all subjects	Blinding of all therapists	Blinding of all assessors	One key measure obtained from more than 85% of the participants	Intention to treat analysis	Between-group statistical comparisons	Provides point measures and measures of variability	**Score**
Covey et al 2015	Y	Y	N	Y	Y	N	Y	N	N	Y	Y	**7**
Elkhateeb et al 2015	Y	N	N	Y	N	N	N	Y	N	Y	Y	**5**
Farias et al 2014	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	**8**
Gottlieb et al 2011	Y	Y	Y	Y	N	N	N	N	Y	Y	Y	**7**
Guell et al 2017	Y	Y	N	Y	N	Y	Y	N	Y	Y	Y	**8**
Klijn et al 2013	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**9**
McNamara et al 2013	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**9**
Monninkhof et al 2003	Y	Y	Y	Y	N	N	N	Y	Y	Y	Y	**8**
O'Shea et al 2007	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	**8**
Panton et al 2004	N	N	N	Y	N	N	N	Y	N	Y	Y	**4**
Pradella et al 2015	Y	Y	N	Y	N	N	N	Y	N	Y	Y	**6**
Ram´ırez-Sarmiento et al 2002	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	**7**
Torres-Sánchez et al 2016	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**9**
Van Wetering et al 2010b	Y	Y	Y	Y	N	N	Y	Y	Y	Y	N	**8**
Vorrink et al 2016	Y	Y	N	N	N	N	Y	N	N	Y	Y	**5**

Wadell et al 2005b	Y	N	N	N	N	N	N	Y	Y	Y	N	**4**
Wilson et al 2015	Y	Y	Y	Y	N	N	Y	N	Y	Y	Y	**8**
Wootton et al 2014	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	**9**
Zakrisson et al 2011	Y	N	N	Y	N	N	N	N	N	Y	Y	**4**

Table 3. Risk of Bias Assessment of Included Studies Using the Cochrane Collaboration Risk of Bias Tool

Study	Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting
Covey et al 2014	Low	Unclear	High	Low	High	Low
Elkhateeb et al 2015	High	High	High	Unclear	High	High
Farias et al 2014	Unclear	Low	High	Low	Low	Low
Gottlieb et al 2011	Low	Low	High	High	High	Low
Guell et al 2017	Low	Unclear	High	Low	High	Low
Klijn et al 2013	Unclear	Low	High	Low	Low	Low
McNamara et al 2013	Low	Low	High	Low	Low	Low
Monninkhof et al 2003	Low	Low	High	High	Low	Low
O'Shea et al 2007	Low	Low	High	Low	High	Low
Panton et al 2004	High	High	High	Unclear	Unclear	Low
Pradella et al 2015	Unclear	High	High	Low	Low	Low
Ram´ırez-	Unclear	High	High	Unclear	Low	Low

Sarmiento et al 2002						
Torres-Sánchez et al 2016	Low	High	High	Low	Low	Low
Van Wetering et al 2010b	Low	Unclear	High	Low	Low	Low
Vorrink et al 2016	Low	High	High	Low	High	Low
Wadell et al 2005b	High	High	High	Unclear	High	Low
Wilson et al 2015	Low	High	High	Low	High	Low
Wootton et al 2014	Low	Unclear	High	Low	Unclear	Low
Zakrisson et al 2011	High	High	High	Unclear	High	Low

Participants

A total of 1,716 participants were included in the identified trials. The age of participants ranged from 44 to 88 years, with men (*n* = 1,043) representing 61% of the total sample. Six studies ([32%]; Farias et al., 2014; Monninkhof et al., 2003; Van Wetering et al., 2010b; Vorrink et al., 2016; Wadell et al., 2005b; Zakrisson et al., 2011), included participants with moderate to severe COPD according to Global Initiative for Chronic Obstructive Lung Disease criteria (Vogelmeier et al., 2017). Another 6 studies ([32%]; Guell et al., 2017; McNamara et al., 2013; O'Shea et al., 2007; Panton et al., 2004; Pradella et al., 2015; Wilson et al., 2015), included moderate to very severe COPD, four studies ([21%]; Covey et al., 2014; Klijn et al., 2013; Ram´ırez-Sarmiento et al., 2002; Wootton et al., 2014), with severe to very severe COPD. Of the remaining 3 studies, participants had mild to severe (Elkhateeb et al., 2015), moderate (Gottlieb et al., 2011), or severe disease (Torres-Sánchez et al., 2016) COPD. The mean ± SD of the participants' BMI was 28.2 ± 5.1 kg/m^2.

Interventions

Exercise interventions are described with respect to exercise frequency, intensity, type, duration of sessions, the total duration of intervention, and intervention setting.

Intervention Frequency. The frequency of exercise primarily ranged from 1-2 sessions/week (*n* = 3, [16%]; Monninkhof et al., 2003; Panton et al., 2004; Zakrisson et al., 2011), to 3-5 sessions/week (*n* = 10, [53%]; Covey et al., 2014; Farias et al., 2014; Guell et al., 2017; Klijn et al., 2013; McNamara et al., 2013; O'Shea et al., 2007; Pradella et al., 2015; Ram´ırez-Sarmiento et al., 2002; Wadell et al., 2005b; Wootton et al., 2014). The study with the highest frequency delivered the interventions twice a day (Torres-Sánchez et al., 2016), and the lowest frequency intervention provided 1 session every 3 months (Wilson et al., 2015). Two studies (11%) used weaning schedules (2 times per week for 4 months, then 1 session/month for 20 months (Van Wetering et al., 2010b); 3 sessions per week for 7 weeks, then 1 session/month for 6 months (Gottlieb et al., 2011)). Two studies ([11%]; Elkhateeb et al., 2015; Vorrink et al., 2016) did not provide information regarding the frequency of their interventions.

Intervention Intensity. Training were provided at moderate level intensities in nine (47%) studies (50-70% of maximal HR or 50-60% of maximal work rate (Guell et al., 2017; Klijn et al., 2013; Panton et al., 2004; Pradella et al., 2015; Vorrink et al., 2016), 40-70% of 1-repetition maximum (O'Shea et al., 2007), or 3-5 on the modified Borg Rating of Perceived Exertion scale (Farias et al., 2014; McNamara et al., 2013; Wootton et al., 2014)). Four (21%) studies provided high-intensity exercise training (> 70% of maximal HR or >60% of maximal work rate (Elkhateeb et al., 2015), >15/20 on the Borg Rating of Perceived Exertion scale (Gottlieb et al., 2011), >70 of 1-repetition maximum (Covey et al., 2014), or 60% of maximal sustainable inspiratory pressure (Ram ́ırez-Sarmiento et al., 2002)). Three (16%) studies mentioned that exercise intensity was individualized based on the participants' goals, but did not specify how intensity was prescribed (Monninkhof et al., 2003; Torres-Sánchez et al., 2016; Wilson et al., 2015). The remaining 3 (16%) studies (Van Wetering et al., 2010b; Wadell et al., 2005b; Zakrisson et al., 2011) did not specify the exercise intensities used in the interventions.

Intervention Types. Interventions included aerobic training (*n* = 6, [32%]; Farias et al., 2014; Gottlieb et al., 2011; Guell et al., 2017; McNamara et al., 2013;

Pradella et al., 2015; Wootton et al., 2014), resistance training (*n* = 3, [16%]; Monninkhof et al., 2003; O'Shea et al., 2007; Zakrisson et al., 2011), and combined aerobic and resistance training (n=6, [32%]; Covey et al., 2014; Klijn et al., 2013; Panton et al., 2004; Van Wetering et al., 2010b; Wadell et al., 2005b; Wilson et al., 2015). Respiratory muscle training alone was provided in one study (Ram´ırez-Sarmiento et al., 2002), and combined with resistance training in another study (Torres-Sánchez et al., 2016). One study (Elkhateeb et al., 2015) included two interventions arms (aerobic training, respiratory muscle training). Another study (Vorrink et al., 2016) focused on increasing physical activity using accelerometers to track step counts and text message communication to provide encouragement.

Eight studies used a combination approach where exercise was combined with education (n=5 studies (26%); Farias et al., 2014; Monninkhof et al., 2003; Van Wetering et al., 2010b; Wilson et al., 2015; Zakrisson et al., 2011), combined with education, dietary counselling and smoking cessation (Gottlieb et al., 2011), or combined with regular phone calls to provide continues encouragement (Guell et al., 2017; Pradella et al., 2015).

Duration of the Intervention Sessions. There was a broad range of session durations used. Approximately half of the studies included short sessions for 30 minutes (*n* = 4, [21%]; Covey et al., 2014; Ram´ırez-Sarmiento et al., 2002; Van Wetering et al., 2010b; Vorrink et al., 2016) or 30-60 minutes (*n* = 6, [32%]; Farias et al., 2014; McNamara et al., 2013; Monninkhof et al., 2003; Torres-Sánchez et al., 2016; Wadell et al., 2005b; Wootton et al., 2014). Seven studies (37%) provided long sessions that lasted between 1-2 hours (Gottlieb et al., 2011; Guell et al., 2017; Klijn et al., 2013; Panton et al., 2004; Pradella et al., 2015; Wilson et al., 2015; Zakrisson et al., 2011). The remaining two (11%) studies (Elkhateeb et al., 2015; O'Shea et al., 2007) did not provide information regarding the duration of their intervention sessions.

Duration of the Total Intervention. The total duration of the interventions ranged from 1-3 months (*n* = 11, [58%]; Elkhateeb et al., 2015; Farias et al., 2014; Klijn et al., 2013; McNamara et al., 2013; O'Shea et al., 2007; Panton et al., 2004; Pradella et al., 2015; Ram´ırez-Sarmiento et al., 2002; Wadell et al., 2005b; Wootton et al., 2014; Zakrisson et al., 2011), 4-8 months (*n* = 3, [16%]; Covey et al., 2014; Gottlieb et al., 2011; Vorrink et al., 2016) and 1-3 years (*n* = 4, [21%]; Guell et al., 2017; Monninkhof et al., 2003; Van Wetering et al., 2010b; Wilson et al., 2015). One study (Torres-Sánchez et al., 2016) did not provide information regarding the total duration of the intervention.

Intervention Settings. Most of the interventions (*n* = 11, [58%]; Covey et al., 2014; Elkhateeb et al., 2015; Gottlieb et al., 2011; McNamara et al., 2013; Monninkhof et al., 2003; Panton et al., 2004; Ram´ırez-Sarmiento et al., 2002; Wadell et al., 2005b; Wilson et al., 2015; Wootton et al., 2014; Zakrisson et al., 2011) were provided in outpatient settings. In two studies ([11%]; O'Shea et al., 2007; Pradella et al., 2015), interventions were provided in a combination of outpatient settings and at home. The remaining studies were conducted in the community (*n* =2, Farias et al., 2014; Van Wetering et al., 2010b), at home (*n* =2, Guell et al., 2017; Vorrink et al., 2016), or in inpatient facilities (*n* =2, Klijn et al., 2013; Torres-Sánchez et al., 2016).

Comparators

Comparator groups received usual medical care (*n* = 7, [37%]; Elkhateeb et al., 2015; Gottlieb et al., 2011; Monninkhof et al., 2003; Torres-Sánchez et al., 2016; Van

Wetering et al., 2010b; Vorrink et al., 2016; Zakrisson et al., 2011) or education (*n* = 3, [16%]; Farias et al., 2014; Guell et al., 2017; Wilson et al., 2015). Four studies (21%) included no intervention comparator groups (O'Shea et al., 2007; Pradella et al., 2015; Wadell et al., 2005b; Wootton et al., 2014).

Five studies (26%) used other controlled exercise interventions for the comparator groups (Covey et al., 2014; Klijn et al., 2013; McNamara et al., 2013; Panton et al., 2004; Ramírez-Sarmiento et al., 2002). Of these, two (Covey et al., 2014; McNamara et al., 2013) had two comparator groups. Covey et al. (2014) used sham training as a primer for exercise training (aerobic training or combined aerobic and resistance training). McNamara et al. (2013) used usual medical care or aerobic land-based training for the comparator groups.

Exercise frequency, intensity, type, session duration and total intervention duration for the studies that used comparator exercise interventions are described below.

Intervention Frequency. Three of the five studies (60%; Covey et al., 2014; Klijn et al., 2013; McNamara et al., 2013) provided interventions 3 times/week. The remaining two provided the training 2 sessions/week (Panton et al., 2004) and 5 sessions/week (Ramírez-Sarmiento et al., 2002).

Intervention Intensity. The intensities used for the comparator interventions were low (<40% of maximal work rate) in two studies ([40%]; Klijn et al., 2013; Ramírez-Sarmiento et al., 2002), moderate intensity in three (60%) studies (50-60% of maximal work rate and 40-70% of 1 repetition maximum (Covey et al., 2014), 50-60% of maximal work rate (Panton et al., 2004), or 3-5 on the modified Borg scale (McNamara et al., 2013).

Types of Interventions. The exercise interventions provided for the control groups were sham training alone (Ramírez-Sarmiento et al., 2002), sham as a primer for aerobic or aerobic and resistance training (Covey et al., 2014). Two studies (40%) provided aerobic exercise alone (Panton et al., 2004; McNamara et al., 2013), and one (20%) used a combined low-intensity aerobic and resistance training program (Klijn et al., 2013).

Duration of the Comparator Intervention Sessions. Sessions were 30 minutes (*n* = 2, [40%]; Covey et al., 2014; Ramírez-Sarmiento et al., 2002), or 45-90 minutes in length (*n* = 3, [60%]; Klijn et al., 2013; McNamara et al., 2013; Panton et al., 2004).

Duration of the Total Intervention. The duration of the comparator interventions ranged from 5-10 weeks (*n* = 3, [60%]; Klijn et al., 2013; McNamara et al., 2013; Ramírez-Sarmiento et al., 2002) to 12-16 weeks (*n* = 2, [40%]; Covey et al., 2014; Panton et al., 2004).

Outcomes

Exercise Capacity. 6MWT distance was the most commonly reported outcome measure (*n* = 14 studies, [74%]; Covey et al., 2014; Elkhateeb et al., 2015; Farias et al., 2014; Gottlieb et al., 2011; Guell et al., 2017; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Pradella et al., 2015; Ramírez-Sarmiento et al., 2002; Van Wetering et al., 2010b; Vorrink et al., 2016; Wootton et al., 2014; Zakrisson et al., 2011). Three studies examined changes in ISWT ([16%]; McNamara et al., 2013; Wadell et al., 2005b; Wootton et al., 2014). Four studies examined changes in ESWT distance and time ([21%]; McNamara et al., 2013; Wadell et al., 2005b; Wilson et al., 2015; Wootton et al., 2014). Two studies measured changes in VO_2peak ([11%]; Ramírez-Sarmiento et al., 2002; Wadell et al., 2005b) and the remaining outcomes related to exercise capacity were used in single studies only: 12-Minute Walk Test (Panton et al., 2004), a 2-Minute Step-In-Place Test (Torres-Sánchez et al. 2016), a Time Up and Go Test (O'Shea et al., 2007), and a Sit to Stand Time (Gottlieb et al., 2011).

Ventilatory Parameters. Changes in FEV_1 were reported in 5 studies ([26%]; Panton et al., 2004; Ramírez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Van Wetering et al., 2010b; Wadell et al., 2005b), and % predicted of FEV_1 was examined in 5 studies ([26%]; Elkhateeb et al., 2015; Panton et al., 2004; Ramírez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Wadell et al., 2005b). Two studies measured changes in FVC ([11%]; Elkhateeb et al., 2015; Panton et al., 2004), and FEV_1/FVC ([11%]; Elkhateeb et al., 2015; Wadell et al., 2005b). Changes in TLC were measured in one study (Ramírez-Sarmiento et al., 2002).

Anthropometrics. BMI was used as an outcome in six studies ([32%]; Klijn et al., 2013; Panton et al., 2004; Van Wetering et al., 2010b; Vorrink et al., 2016; Wadell et al., 2005b; Wilson et al., 2015). Two studies reported changes in FFMI ([11%]; Klijn et al., 2013; Van Wetering et al., 2010b) and body fat percentage ([11%]; Panton et al., 2004; Wilson et al., 2015). Changes in Skeletal muscle mass were measured in one study (Farias et al., 2014).

Health-Related Quality of Life. Most of the studies that evaluated HRQOL used disease-specific questionnaires, such as CRDQ (*n* = 8, [42%]; Covey et al., 2014; Guell et al., 2017; Klijn et al., 2013; McNamara et al., 2013; O'Shea et al., 2007; Vorrink et al., 2016; Wilson et al., 2015; Wootton et al., 2014) and SGRQ (*n* =6, [32%]; Farias et al., 2014; Gottlieb et al., 2011; Monninkhof et al., 2003; Pradella et al., 2015; Van Wetering et al., 2010b; Wootton et al., 2014). The EuroQOL was used as an outcome in 2 studies ([11%]; Torres-Sánchez et al., 2016; Wilson et al., 2015), and Clinical COPD Questionnaire was used in one study (Zakrisson et al., 2011).

Quantitative analyses

Sixteen studies (Covey et al., 2014; Elkhateeb et al., 2015; Farias et al., 2014; Gottlieb et al., 2011; Klijn et al., 2013; McNamara et al., 2013; Monninkhof et al., 2003; O'Shea et al., 2007; Panton et al., 2004; Pradella et al., 2015; Ram´ırez-Sarmiento et al., 2002; Torres-Sánchez et al., 2016; Van Wetering et al., 2010; Wilson et al., 2015; Wootton et al., 2014; Zakrisson et al., 2011) were included in the quantitative analyses. Three studies (Guell et al., 2017; Vorrink et al., 2016 and Wadell et al., 2005) from the qualitative synthesis were not included in the meta-analysis because standard deviation or standard error values were not reported for any of the outcomes.

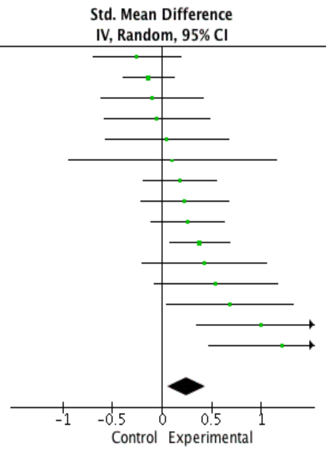
Random effects models were used for all analyses due to the presence of high heterogeneity in most of the included studies.

Primary Analyses: Effects of Exercise on Outcomes of Interest

Results from the primary analyses are described in detail below and also summarized in Appendix G.

Primary Outcome

Exercise Capacity. There was a significant improvement in the distance walked on the 6MWT, ISWT and ESWT as measured by the SMD (12 studies, n= 1215 participants, SMD= 0.25 (95% CI [0.06, 0.43]); p = 0.01) (Figure 2).

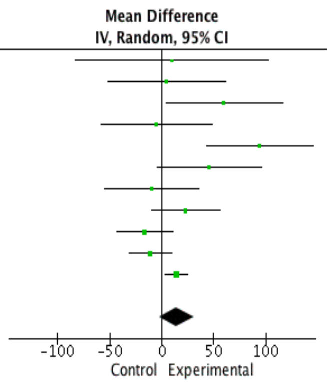


Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Zakrisson et al 2011	22	44	38	38	76	42	7.7%	-0.25 [-0.69, 0.19]
Monninkhof et al 2003	-13	84	122	-2	78	118	10.8%	-0.14 [-0.39, 0.12]
Covey et al 2015	10	85.28	20	19.6	99.68	55	6.7%	-0.10 [-0.61, 0.41]
O'Shea et al 2007	4	112.36	27	9	87.01	27	6.4%	-0.05 [-0.58, 0.48]
McNamara et al 2013	48	78.92	15	43	112.2	30	5.4%	0.05 [-0.57, 0.67]
Ramı́rez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	2.6%	0.11 [-0.94, 1.15]
Wootton et al 2014	25	121.95	74	3	121.27	47	8.8%	0.18 [-0.19, 0.55]
Wilson et al 2015	-70.22	487.59	40	-179.29	451.37	40	7.7%	0.23 [-0.21, 0.67]
Wootton et al 2014	9	87.99	77	-14	89.49	45	8.8%	0.26 [-0.11, 0.63]
Van Wetering et al 2010	-1.4	36.39	87	-15.3	36.58	88	10.0%	0.38 [0.08, 0.68]
McNamara et al 2013	49	91.31	15	6.5	102	30	5.3%	0.42 [-0.20, 1.05]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	5.4%	0.54 [-0.08, 1.17]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	5.2%	0.68 [0.04, 1.32]
McNamara et al 2013	321	271.6	15	33	289.2	30	5.0%	1.00 [0.34, 1.65]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	4.3%	1.21 [0.47, 1.95]
Total (95% CI)			**605**			**610**	**100.0%**	**0.25 [0.06, 0.43]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 31.24$, df = 14 (P = 0.005); $I^2 = 55\%$
Test for overall effect: Z = 2.58 (P = 0.010)

Figure 2. Effects of Exercise Interventions on 6-Minute Walk Test Distance, Incremental Shuttle Walk Test Distance and Endurance Shuttle Walk Test Distance

There was no overall effect of exercise on the distance walked on the 6MWT (11 studies, n= 924 participants, MD=14.19 m (95% CI [-2.58, 30.97]); *p* = 0.10) (Figure 3), and the ISWT (2 studies, n=166 participants, MD=29.44 m (95% CI [-6.03, 64.90]); *p* = 0.10) (Figure 4).



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ramı́rez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	2.8%	10.00 [-82.97, 102.97]
McNamara et al 2013	48	78.92	15	43	112.2	30	6.0%	5.00 [-51.63, 61.63]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	6.1%	60.10 [4.20, 116.00]
O'Shea et al 2007	4	112.36	27	9	87.01	27	6.5%	-5.00 [-58.60, 48.60]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	6.9%	94.00 [42.77, 145.23]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	7.1%	45.58 [-4.70, 95.86]
Covey et al 2015	10	85.28	20	19.6	99.68	55	7.9%	-9.60 [-55.33, 36.13]
Wootton et al 2014	9	87.99	77	-14	89.49	45	11.1%	23.00 [-9.71, 55.71]
Zakrisson et al 2011	22	44	38	38	76	42	12.9%	-16.00 [-42.91, 10.91]
Monninkhof et al 2003	-13	84	122	-2	78	118	14.9%	-11.00 [-31.50, 9.50]
Van Wetering et al 2010	-1.4	36.39	87	-15.3	36.58	88	17.8%	13.90 [3.09, 24.71]
Total (95% CI)			**461**			**463**	**100.0%**	**14.19 [-2.58, 30.97]**

Heterogeneity: $Tau^2 = 380.87$; $Chi^2 = 25.09$, df = 10 (P = 0.005); $I^2 = 60\%$
Test for overall effect: Z = 1.66 (P = 0.10)

Figure 3. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m)

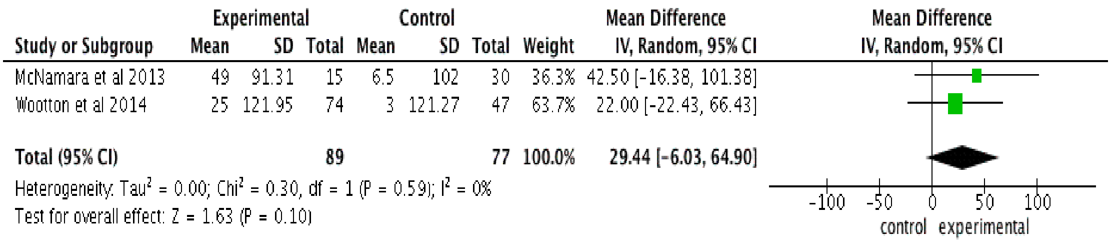


Figure 4. Effects of Exercise Interventions on Incremental Shuttle Walk Test Distance (m)

Exercise interventions were effective in improving the distance walked in the ESWT (2 studies, n=125 participants, MD= 207.84 m (95% CI [33.45, 382.24]); p = 0.02) (Figure 5) but not in increasing the total time of the ESWT (2 studies, n= 208 participants, MD=112.04 s (95% CI [-96.77, 320.85]); p = 0.29) (Figure 6).

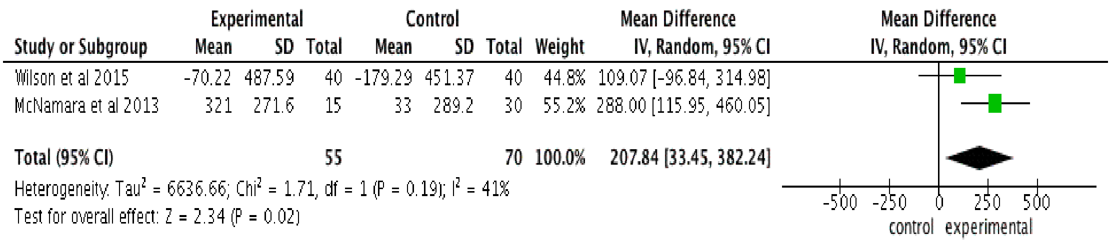


Figure 5. Effects of Exercise Interventions on Endurance Shuttle Walk Test Distance (m)

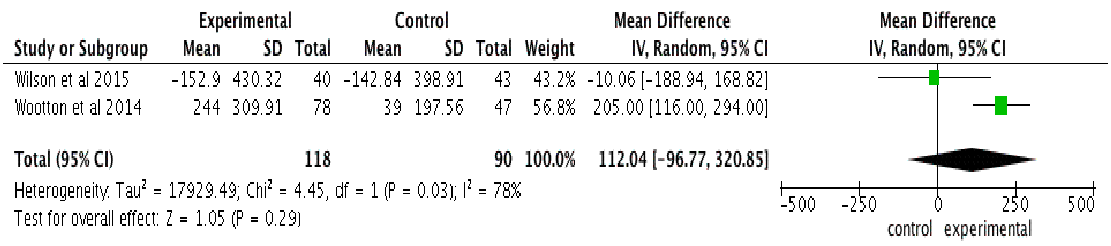


Figure 6. Effects of Exercise Interventions on Endurance Shuttle Walk Test Time (s)

Secondary Outcomes

Ventilatory Parameters. Exercise interventions were not superior over control interventions for improving FEV_1 (3 studies, n= 80 participants, MD= -0.01 L (95% CI [-0.07, 0.05]); p = 0.76) (Figure 7) or % predicted of FEV_1 (4 studies, n= 255 participants, MD= - 0.18% (95% CI [-3.82, 3.46]); p = 0.92) (Figure 8).

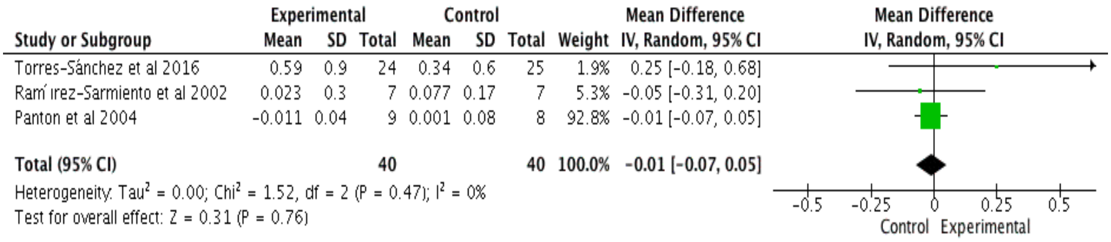


Figure 7. Effects of Exercise Interventions on Forced Expiratory Volume in One Second (L)

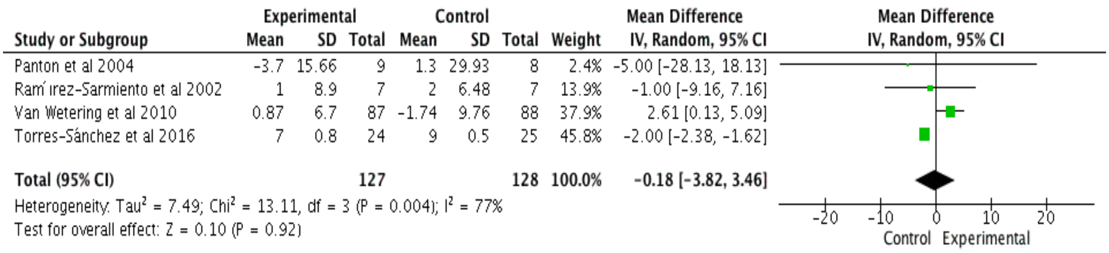


Figure 8. Effects of Exercise Interventions on Percent Predicted of Forced Expiratory Volume in One Second (%)

Anthropometrics. There was no overall effect of exercise interventions on improving BMI (5 studies, n= 420 participants, MD= 0.21 kg/m^2 (95% CI [-0.02, 0.44]); p = 0.08) (Figure 9), but the effects of interventions on increasing FFMI was observed (2 studies, n= 285 participants, MD= 0.33 kg/m^2 (95% CI [0.21, 0.46]); $p <$ 0.00001) (Figure 10).

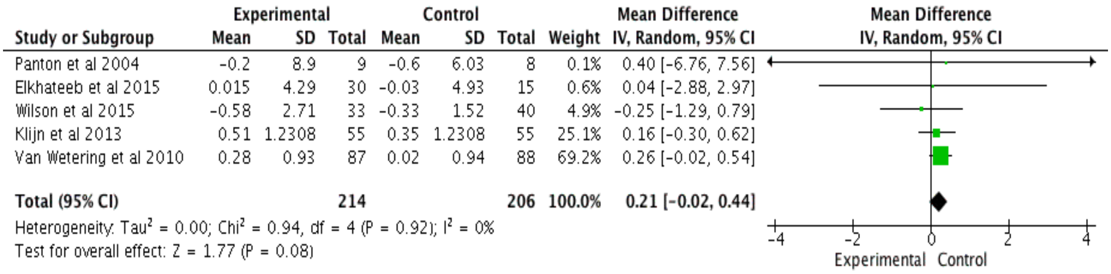


Figure 9. Effects of Exercise Interventions on Body Mass Index (kg/m^2)

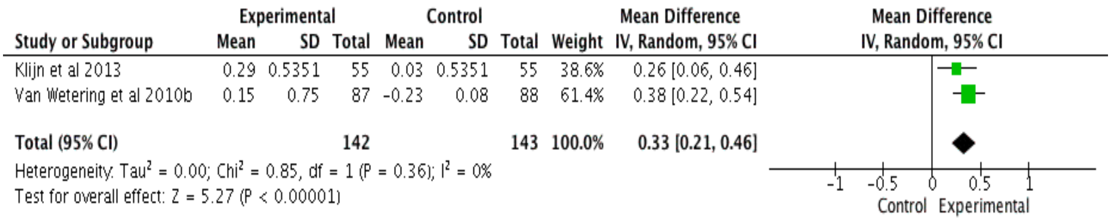


Figure 10. Effects of Exercise Interventions on Fat Free Mass Index (kg/m^2)

Health-Related Quality of Life. Exercise interventions were effective in improving HRQOL as measured by the SGRQ (6 studies, n= 648 participants, MD= -7.49 points (95% CI [-13.01, -1.98]); p = 0.008) (Figure 11).

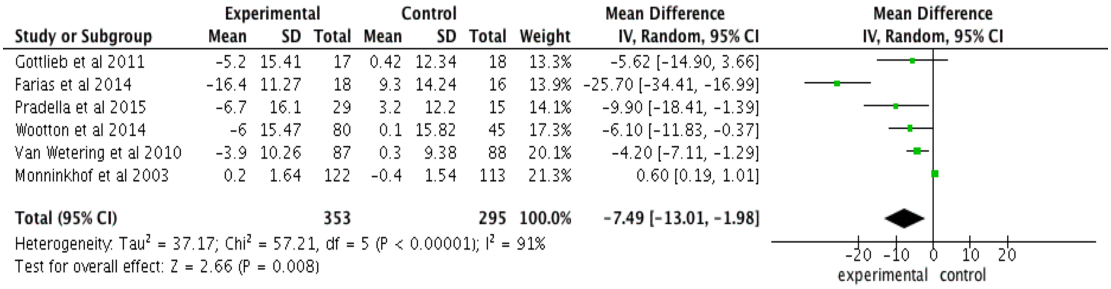


Figure 11. Effects of Exercise Interventions on St. George Respiratory Questionnaire Score

The benefits of exercise were also observed in three of the four domains of the CRDQ: Dyspnea (5 studies, n= 478 participants, MD= 0.51 points (95% CI [0.00, 1.02]); *p* = 0.05) (Figure 12), Emotion (4 studies, n= 404 participants, MD= 0.28 points, 95% CI [0.03, 0.54]); *p* = 0.03) (Figure 13), and Mastery (4 studies, n= 404 participants MD= 0.31 points (95% CI [0.02, 0.59]); *p* = 0.03) (Figure 14). There was no effect of exercise on improving the Fatigue domain of the CDRQ (5 studies, 479 participants, MD= 0.39 points (95% CI [-0.12, 0.89]); *p* = 0.13) (Figure 15).

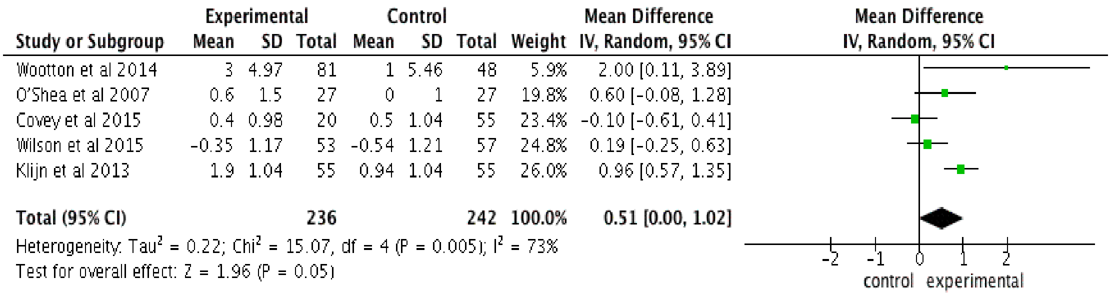


Figure 12. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Dyspnea Domain)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wootton et al 2014	2	7.47	53	1	8.9	48	0.6%	1.00 [-2.22, 4.22]
Wilson et al 2015	0	1.46	81	0.02	1.32	58	24.1%	-0.02 [-0.49, 0.45]
O'Shea et al 2007	0.4	0.8	27	0.2	0.7	27	30.3%	0.20 [-0.20, 0.60]
Klijn et al 2013	1.32	0.8	55	0.83	0.8	55	45.0%	0.49 [0.19, 0.79]
Total (95% CI)			**216**			**188**	**100.0%**	**0.28 [0.03, 0.54]**

Heterogeneity: Tau² = 0.01; Chi² = 3.79, df = 3 (P = 0.29); I² = 21%
Test for overall effect: Z = 2.16 (P = 0.03)

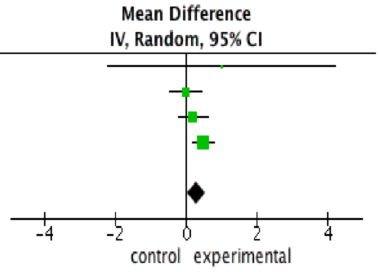


Figure 13. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Emotion Domain)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wootton et al 2014	1	4.97	81	0	4.95	48	2.5%	1.00 [-0.77, 2.77]
Wilson et al 2015	0.01	1.42	53	-0.06	1.49	58	21.6%	0.07 [-0.47, 0.61]
O'Shea et al 2007	0.3	0.8	27	0.2	0.8	27	30.6%	0.10 [-0.33, 0.53]
Klijn et al 2013	1.39	0.83	55	0.87	0.83	55	45.3%	0.52 [0.21, 0.83]
Total (95% CI)			**216**			**188**	**100.0%**	**0.31 [0.02, 0.59]**

Heterogeneity: Tau² = 0.02; Chi² = 3.99, df = 3 (P = 0.26); I² = 25%
Test for overall effect: Z = 2.11 (P = 0.03)

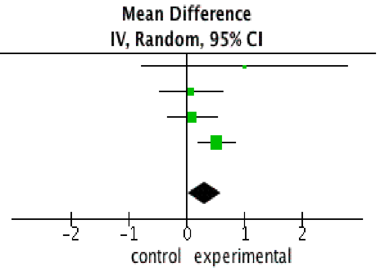


Figure 14. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Mastery Domain)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wootton et al 2014	2	5.49	81	0	3.96	48	7.1%	2.00 [0.36, 3.64]
O'Shea et al 2007	0.4	1.2	27	-0.1	1	27	20.9%	0.50 [-0.09, 1.09]
Covey et al 2015	0	0.98	20	0.35	1.18	55	22.1%	-0.35 [-0.88, 0.18]
Wilson et al 2015	-0.3	1.09	53	-0.41	1.19	58	24.2%	0.11 [-0.31, 0.53]
Klijn et al 2013	1.64	0.94	55	0.9	0.94	55	25.6%	0.74 [0.39, 1.09]
Total (95% CI)			**236**			**243**	**100.0%**	**0.39 [-0.12, 0.89]**

Heterogeneity: Tau² = 0.23; Chi² = 16.76, df = 4 (P = 0.002); I² = 76%
Test for overall effect: Z = 1.50 (P = 0.13)

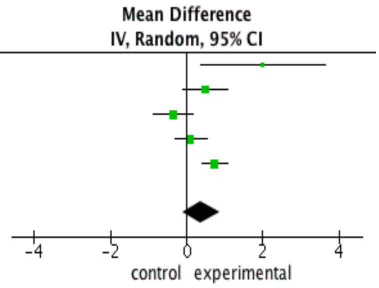


Figure 15. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Fatigue Domain)

Secondary Analyses

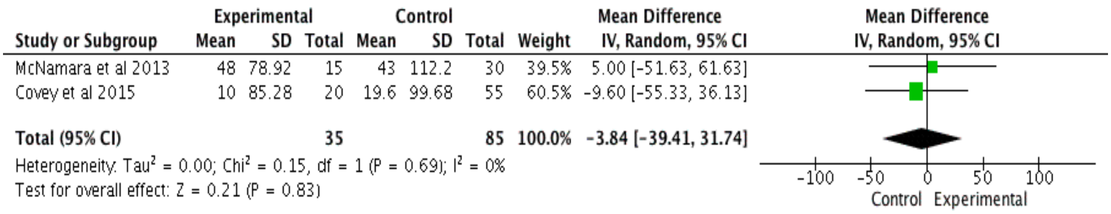
Due to the small number of studies for the majority of the outcomes, subgroup analyses were performed only for the primary outcome measured by 6MWT. Sensitivity analyses were performed where possible ($\geq$ 3 studies in the main analysis) for the secondary outcomes only except for the analyses of high quality studies which were performed for both primary and secondary outcomes.

Subgroup Analyses for the Primary Outcome 6MWT

Subgroup analyses were performed to examine the differential effects of participant characteristics (BMI) and exercise training characteristics (frequency and intensity of the intervention, duration of each session, total duration of the intervention, and type of comparators). For a summary of the sub-group analyses results see Appendix H.

Body Mass Index. To evaluate differences in the effect of exercise interventions on 6MWT distance among individuals with different BMI, studies included participants with mean BMI of 28 kg/m^2 or more were compared to studies that enrolled participants with mean BMI of less than 28 kg/m^2. The BMI of 28 kg/m^2 was selected as a cut-off to ensure that studies with participants who are closer to the obesity category were compared to those in the overweight or normal weight categories.

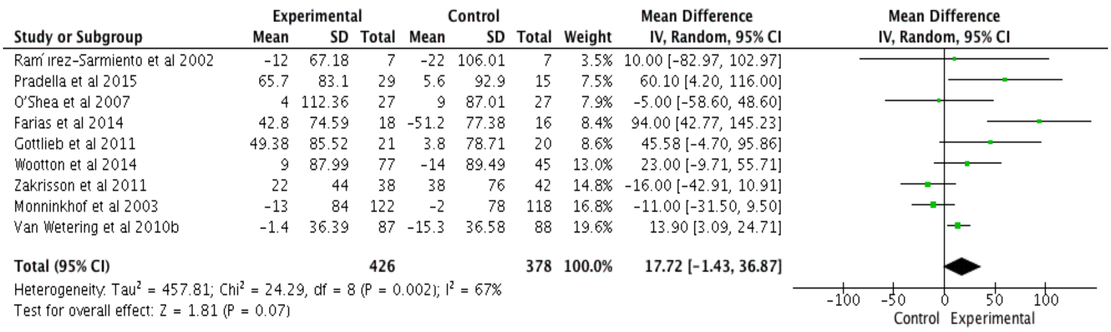
There was no overall effect of exercise on 6MWT distance in either subgroup (2 studies, n= 120 participants, MD= -3.84 m (95% CI [-39.41, 31.74]); p = 0.83 for mean BMI $\geq$ 28 kg/m^2, Figure 16; 9 studies, n= 804 participants, MD= 17.72 m (95% CI [-1.43, 36.87]); p = 0.07 for mean BMI < 28 kg/m^2, Figure 17).



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
McNamara et al 2013	48	78.92	15	43	112.2	30	39.5%	5.00 [-51.63, 61.63]
Covey et al 2015	10	85.28	20	19.6	99.68	55	60.5%	-9.60 [-55.33, 36.13]
Total (95% CI)			**35**			**85**	**100.0%**	**-3.84 [-39.41, 31.74]**

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 1 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)

Figure 16. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Participants with Mean Body Mass Index of ≥ 28 kg/m²



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ramírez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	3.5%	10.00 [-82.97, 102.97]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	7.5%	60.10 [4.20, 116.00]
O'Shea et al 2007	4	112.36	27	9	87.01	27	7.9%	-5.00 [-58.60, 48.60]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	8.4%	94.00 [42.77, 145.23]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	8.6%	45.58 [-4.70, 95.86]
Wootton et al 2014	9	87.99	77	-14	89.49	45	13.0%	23.00 [-9.71, 55.71]
Zakrisson et al 2011	22	44	38	38	76	42	14.8%	-16.00 [-42.91, 10.91]
Monninkhof et al 2003	-13	84	122	-2	78	118	16.8%	-11.00 [-31.50, 9.50]
Van Wetering et al 2010b	-1.4	36.39	87	-15.3	36.58	88	19.6%	13.90 [3.09, 24.71]
Total (95% CI)			**426**			**378**	**100.0%**	**17.72 [-1.43, 36.87]**

Heterogeneity: Tau² = 457.81; Chi² = 24.29, df = 8 (P = 0.002); I² = 67%
Test for overall effect: Z = 1.81 (P = 0.07)

Figure 17. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Participants with Mean Body Mass Index of < 28 kg/m²

Exercise Frequency. Studies that offered the interventions at frequencies of 3 days/week or greater were compared to those that were conducted less frequently at 1-2 days/week or 1 session/month. Although not significant, studies with higher frequency training (3-5 sessions/week) may demonstrate a beneficial effect of exercise on 6MWT distance (7 studies, n= 388 participants, MD= 25.90 m (95% CI [-2.34, 54.14]); $p = 0.07$) (Figure 18).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ramírez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	7.0%	10.00 [-82.97, 102.97]
McNamara et al 2013	48	78.92	15	43	112.2	30	13.3%	5.00 [-51.63, 61.63]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	13.5%	60.10 [4.20, 116.00]
O'Shea et al 2007	4	112.36	27	9	87.01	27	14.1%	-5.00 [-58.60, 48.60]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	14.8%	94.00 [42.77, 145.23]
Covey et al 2015	10	85.28	20	19.6	99.68	55	16.4%	-9.60 [-55.33, 36.13]
Wootton et al 2014	9	87.99	77	-14	89.49	45	20.8%	23.00 [-9.71, 55.71]
Total (95% CI)			**193**			**195**	**100.0%**	**25.90 [-2.34, 54.14]**

Heterogeneity: $Tau^2 = 719.97$; $Chi^2 = 12.48$, df = 6 (P = 0.05); $I^2 = 52\%$
Test for overall effect: Z = 1.80 (P = 0.07)

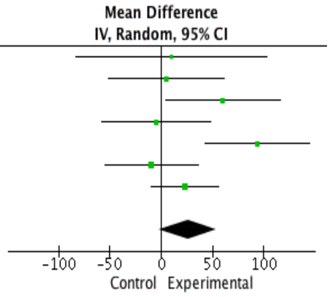


Figure 18. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Frequency of 3-5 Sessions/Week

There was no effect among studies with interventions provided with less frequency (1-2 sessions/week, 2 studies, n= 320 participants, MD= -12.84 m (95% CI [-29.14, 3.47]); $p = 0.12$, Figure 19; 1 session/month, 2 studies, n= 216 participants, MD= 19.83 m (95% CI [-4.39, 44.06]); $p = 0.11$, Figure 20).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Zakrisson et al 2011	22	44	38	38	76	42	36.7%	-16.00 [-42.91, 10.91]
Monninkhof et al 2003	-13	84	122	-2	78	118	63.3%	-11.00 [-31.50, 9.50]
Total (95% CI)			**160**			**160**	**100.0%**	**-12.84 [-29.14, 3.47]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.08$, df = 1 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 1.54 (P = 0.12)

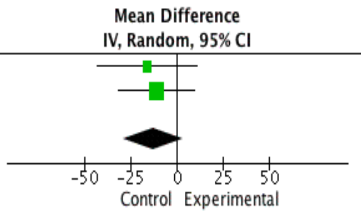


Figure 19. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Frequency of 1-2 Sessions/Week

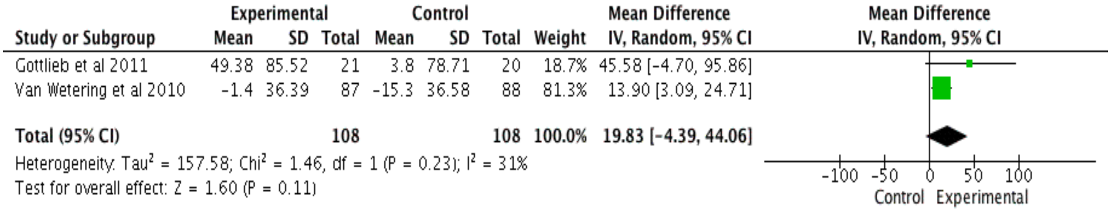


Figure 20. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Frequency of 1 Session/Month

Intervention Intensity. Studies utilizing moderate-intensity and high-intensity exercise were compared. A significant change in the 6MWT distance was observed with studies employing moderate intensity exercise (5 studies, n= 299 participants, MD= 35.03 m (95% CI [1.23, 68.82]); p = 0.04) (Figure 21), but no effect was observed with high-intensity training (3 studies, n= 130 participants, MD= 15.24 m (95% CI [-21.89, 52.38]); p = 0.42) (Figure 22).

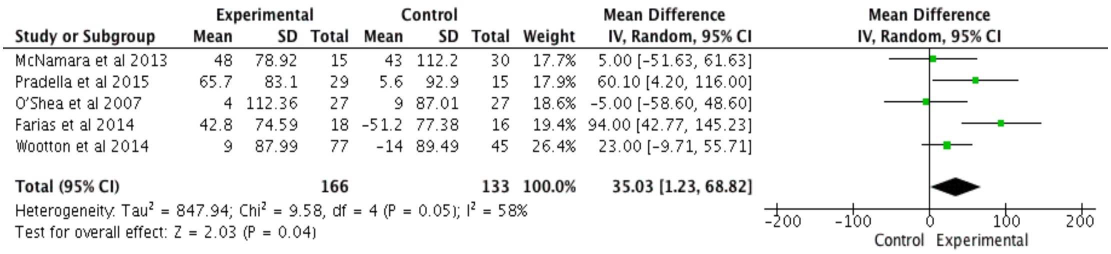


Figure 21. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies Utilizing Moderate Intensity Exercise

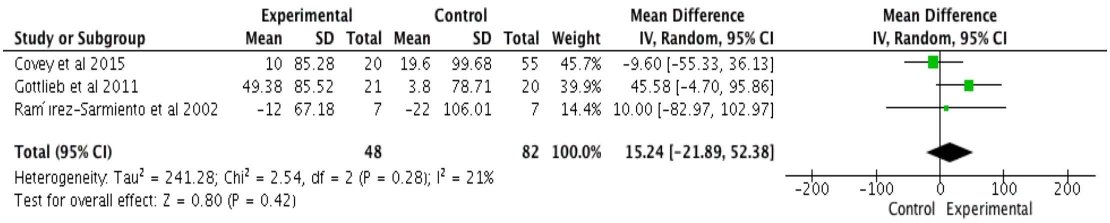


Figure 22. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies Utilizing High Intensity Exercise

Exercise with or without Other Interventions. Studies that provided exercise interventions alone were compared to those that delivered other interventions (e.g. education, dietary counselling and smoking cessation) in addition to exercise. There was no overall effect on 6MWT distance in either group (exercise alone: 5 studies, n= 310 participants, MD=8.17 m (95% CI [-13.21, 29.55]); p = 0.45) (Figure 23); mixed interventions: 6 studies, n= 416 participants, MD= 21.59 m (95% CI [-3.37, 46.55]); p = 0.09) (Figure 24).

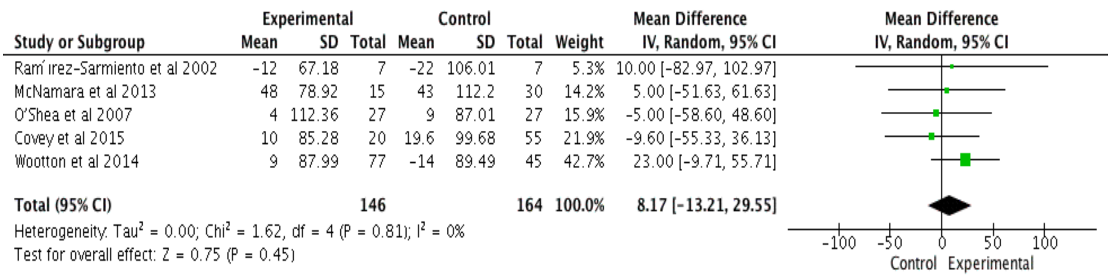


Figure 23. Effects of Exercise Interventions Alone on 6-Minute Walk Test Distance (m)

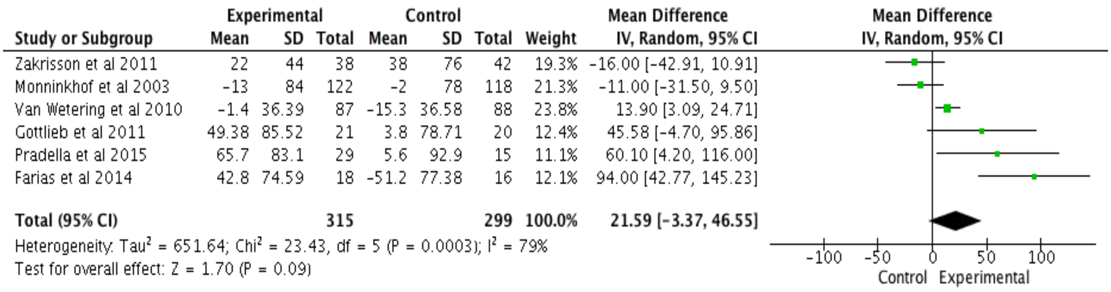


Figure 24. Effects of Exercise with Other Interventions (Mixed Interventions) on 6-Minute Walk Test Distance (m)

Exercise Type. The effects of aerobic exercise training, resistance training, and combined aerobic and resistance exercise training on 6MWT distance were compared. Among the studies that used aerobic exercise alone, there was a positive effect of exercise on 6MWT distance (5 studies, n= 2826 participants, MD= 43.91 m (95% CI [14.84, 72.98]); p = 0.003) (Figure 25). This positive effect was also observed in studies that utilized a combined aerobic and resistance training program (2 studies, n= 250 participants, MD= 12.66 m (95% CI [2.13, 32.18]; p = 0.02) (Figure 26), but not observed in studies that utilized resistance training alone (3 studies, n= 374 participants, MD= -12.17 m (95% CI [-27.77, 3.43]); p = 0.13) (Figure 27).

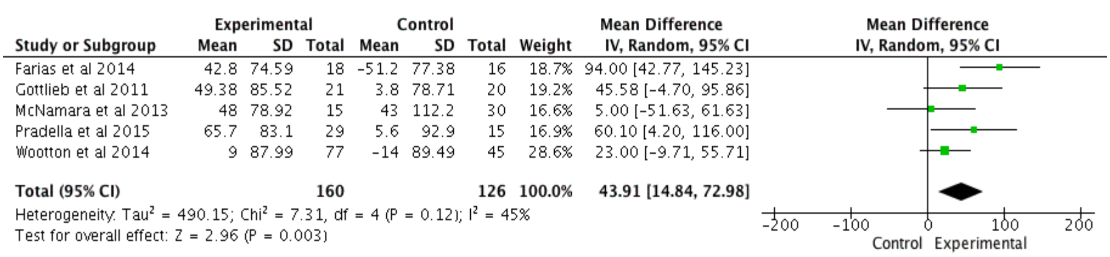


Figure 25. Effects of Aerobic Exercise Interventions on 6-Minute Walk Test Distance (m)

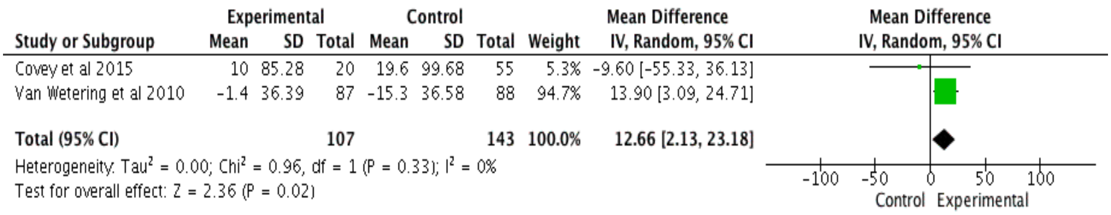


Figure 26. Effects of Combined Aerobic and Resistance Exercise Interventions on 6-Minute Walk Test Distance (m)

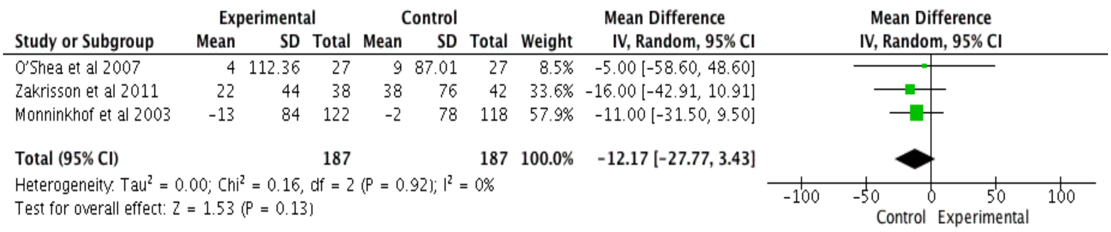


Figure 27. Effects of Resistance Exercise Interventions on 6-Minute Walk Test Distance (m)

Exercise Session Duration. Studies with short training sessions (≤30 minutes) were effective in improving 6MWT distance (3 studies, n= 264 participants, MD= 12.62 m (95% CI [2.17, 23.08]); p = 0.02) (Figure 28), whereas there was no effect with moderate (>30-60 minutes, 4 studies, n= 441 participants, MD= 24.49 m (95% CI [-16.75, 65.73]); p = 0.24) (Figure 29) and long duration training (>1-2 hours, 3 studies, n= 165 participants, MD= 25.52 m (95% CI [-26.56, 77.59]); p = 0.34) (Figure 30).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Covey et al 2015	10	85.28	20	19.6	99.68	55	5.2%	-9.60 [-55.33, 36.13]
Ramírez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	1.3%	10.00 [-82.97, 102.97]
Van Wetering et al 2010	-1.4	36.39	87	-15.3	36.58	88	93.5%	13.90 [3.09, 24.71]
Total (95% CI)			**114**			**150**	**100.0%**	**12.62 [2.17, 23.08]**

Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 2 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.37 (P = 0.02)

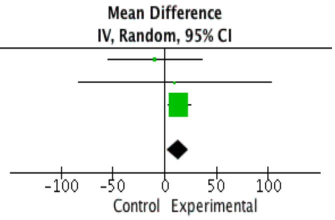


Figure 28. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Short Exercise Session Duration (≤30 Minutes)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	21.9%	94.00 [42.77, 145.23]
McNamara et al 2013	48	78.92	15	43	112.2	30	20.3%	5.00 [-51.63, 61.63]
Monninkhof et al 2003	-13	84	122	-2	78	118	30.5%	-11.00 [-31.50, 9.50]
Wootton et al 2014	9	87.99	77	-14	89.49	45	27.3%	23.00 [-9.71, 55.71]
Total (95% CI)			**232**			**209**	**100.0%**	**24.49 [-16.75, 65.73]**

Heterogeneity: Tau² = 1342.60; Chi² = 14.94, df = 3 (P = 0.002); I² = 80%
Test for overall effect: Z = 1.16 (P = 0.24)

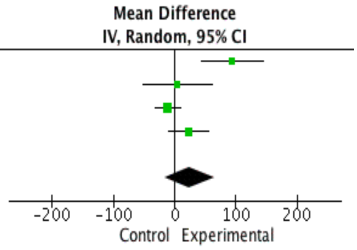


Figure 29. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Moderate Exercise Session Duration (>30-60 Minutes)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	31.3%	45.58 [-4.70, 95.86]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	29.3%	60.10 [4.20, 116.00]
Zakrisson et al 2011	22	44	38	38	76	42	39.5%	-16.00 [-42.91, 10.91]
Total (95% CI)			**88**			**77**	**100.0%**	**25.52 [-26.56, 77.59]**

Heterogeneity: Tau² = 1599.43; Chi² = 8.53, df = 2 (P = 0.01); I² = 77%
Test for overall effect: Z = 0.96 (P = 0.34)

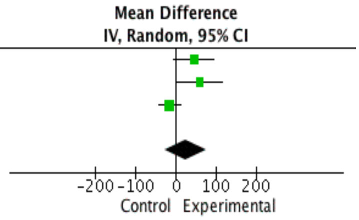


Figure 30. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Long Exercise Session Duration (>1-2 Hours)

Duration of the Total Intervention. There was no effect of exercise interventions on 6MWT distance in studies with different total durations of the exercise interventions: <4 months (7 studies, n= 393 participants, MD= 23.05 m (95% CI [-7.52, 53.62]), p = 0.14) (Figure 31), 4-8 months (2 studies, n= 116 participants, MD=16.96 m (95% CI [-37.08, 71.00]); p = 0.54) (Figure 32), or 1-2 years (2 studies, n= 415 participants, MD=3.04 m (95% CI [-21.17, 27.24]); p = 0.81) (Figure 33).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	14.2%	94.00 [42.77, 145.23]
McNamara et al 2013	48	78.92	15	43	112.2	30	13.0%	5.00 [-51.63, 61.63]
O'Shea et al 2007	4	112.36	27	9	87.01	27	13.7%	-5.00 [-58.60, 48.60]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	13.2%	60.10 [4.20, 116.00]
Ram´ırez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	7.4%	10.00 [-82.97, 102.97]
Wootton et al 2014	9	87.99	77	-14	89.49	45	18.6%	23.00 [-9.71, 55.71]
Zakrisson et al 2011	22	44	38	38	76	42	19.9%	-16.00 [-42.91, 10.91]
Total (95% CI)			**211**			**182**	**100.0%**	**23.05 [-7.52, 53.62]**

Heterogeneity: Tau² = 1032.00; Chi² = 17.63, df = 6 (P = 0.007); I² = 66%
Test for overall effect: Z = 1.48 (P = 0.14)

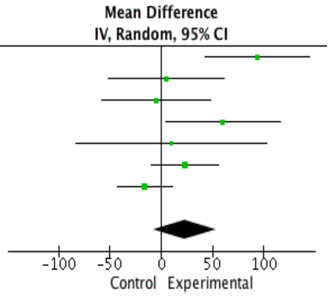


Figure 31. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Durations of <4 Months

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Covey et al 2015	10	85.28	20	19.6	99.68	55	51.9%	-9.60 [-55.33, 36.13]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	48.1%	45.58 [-4.70, 95.86]
Total (95% CI)			**41**			**75**	**100.0%**	**16.96 [-37.08, 71.00]**

Heterogeneity: Tau² = 921.25; Chi² = 2.53, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.62 (P = 0.54)

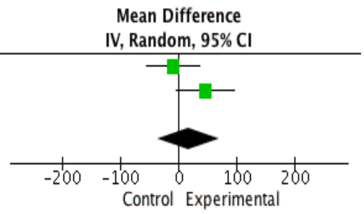


Figure 32. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Durations of 4-8 Months

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Monninkhof et al 2003	-13	84	122	-2	78	118	43.6%	-11.00 [-31.50, 9.50]
Van Wetering et al 2010	-1.4	36.39	87	-15.3	36.58	88	56.4%	13.90 [3.09, 24.71]
Total (95% CI)			**209**			**206**	**100.0%**	**3.04 [-21.17, 27.24]**

Heterogeneity: Tau² = 240.09; Chi² = 4.43, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.25 (P = 0.81)

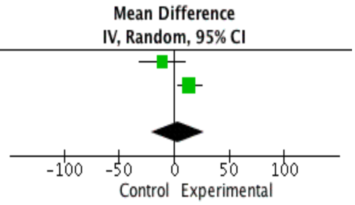


Figure 33. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Intervention Duration of 1-2 Years

Type of Comparator. Differences in the effects of exercise on 6MWT distance across different comparator interventions were examined. There were no effects in studies that used usual medical care as the comparator intervention (4 studies, n= 536 participants, MD= 3.42 m (95% CI [-17.01, 23.84]); *p* = 0.74) (Figure 34), no intervention (3 studies, n= 220 participants, MD=24.72 m (95% CI [-5.93, 55.37]); *p* = 0.11) (Figure 35), or controlled exercise interventions (3 studies, n=134 participants, MD= -2.07 m (95% CI [-35.30, 31.16]); *p* = 0.90) (Figure 36).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	11.7%	45.58 [-4.70, 95.86]
Monninkhof et al 2003	-13	84	122	-2	78	118	28.6%	-11.00 [-31.50, 9.50]
Van Wetering et al 2010	-1.4	36.39	87	-15.3	36.58	88	36.1%	13.90 [3.09, 24.71]
Zakrisson et al 2011	22	44	38	38	76	42	23.7%	-16.00 [-42.91, 10.91]
Total (95% CI)			**268**			**268**	**100.0%**	**3.42 [-17.01, 23.84]**

Heterogeneity: Tau² = 270.54; Chi² = 9.60, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 0.33 (P = 0.74)

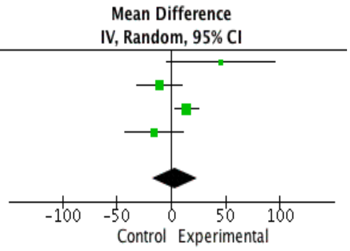


Figure 34. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies Where the Comparator Intervention Was Usual Medical Care

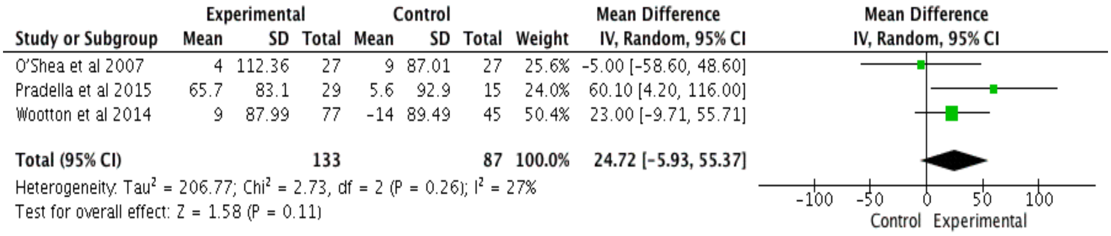


Figure 35. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies with Non-Interventional Comparator Group

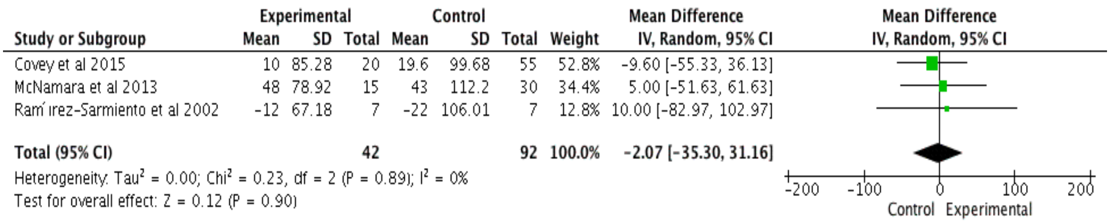


Figure 36. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) in Studies Where the Comparator Intervention Was an Exercise Intervention

Sensitivity Analyses

Sensitivity analyses were conducted when applicable (if ≥3 studies were available in the primary analysis) to examine the effects of study quality on the primary and secondary outcomes and the effects of exercise on the secondary outcomes. For a summary of the sensitivity analyses results, see Appendix I.

Study Quality. When studies with poor quality were excluded, the effects on 6MWT, ISWT and ESWT distance were maintained (11 studies, n= 1135 participants, SMD= 0.28 (95% CI [0.10, 0.47]); p = 0.003) (Figure 37). Additionally, a positive effect of exercise on the 6MWT distance was now observed (10 studies, n= 844 participants, MD= 18.55 m (95% CI [[0.77, 36.33]); p = 0.04) (Figure 38). There was no change in the overall effect on BMI (Appendix J).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
Monninkhof et al 2003	-13	84	122	-2	78	118	12.0%	-0.14 [-0.39, 0.12]
Covey et al 2015	10	85.28	20	19.6	99.68	55	7.2%	-0.10 [-0.61, 0.41]
O'Shea et al 2007	4	112.36	27	9	87.01	27	6.9%	-0.05 [-0.58, 0.48]
McNamara et al 2013	48	78.92	15	43	112.2	30	5.8%	0.05 [-0.57, 0.67]
Ramírez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	2.7%	0.11 [-0.94, 1.15]
Wootton et al 2014	25	121.95	74	3	121.27	47	9.7%	0.18 [-0.19, 0.55]
Wilson et al 2015	-70.22	487.59	40	-179.29	451.37	40	8.3%	0.23 [-0.21, 0.67]
Wootton et al 2014	9	87.99	77	-14	89.49	45	9.6%	0.26 [-0.11, 0.63]
Van Wetering et al 2010b	-1.4	36.39	87	-15.3	36.58	88	11.0%	0.38 [0.08, 0.68]
McNamara et al 2013	49	91.31	15	6.5	102	30	5.7%	0.42 [-0.20, 1.05]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	5.7%	0.54 [-0.08, 1.17]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	5.5%	0.68 [0.04, 1.32]
McNamara et al 2013	321	271.6	15	33	289.2	30	5.4%	1.00 [0.34, 1.65]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	4.6%	1.21 [0.47, 1.95]
Total (95% CI)			**567**			**568**	**100.0%**	**0.28 [0.10, 0.47]**

Heterogeneity: Tau² = 0.06; Chi² = 27.23, df = 13 (P = 0.01); I² = 52%
Test for overall effect: Z = 2.95 (P = 0.003)

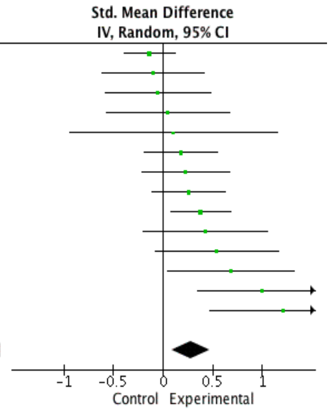


Figure 37. Effects of Exercise Interventions on 6-Minute Walk Test Distance, Incremental Shuttle Walk Test Distance and Endurance Shuttle Walk Test Distance (m) After Excluding Studies with Poor Quality

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Covey et al 2015	10	85.28	20	19.6	99.68	55	9.0%	-9.60 [-55.33, 36.13]
Farias et al 2014	42.8	74.59	18	-51.2	77.38	16	7.8%	94.00 [42.77, 145.23]
Gottlieb et al 2011	49.38	85.52	21	3.8	78.71	20	8.0%	45.58 [-4.70, 95.86]
McNamara et al 2013	48	78.92	15	43	112.2	30	6.8%	5.00 [-51.63, 61.63]
Monninkhof et al 2003	-13	84	122	-2	78	118	17.3%	-11.00 [-31.50, 9.50]
O'Shea et al 2007	4	112.36	27	9	87.01	27	7.4%	-5.00 [-58.60, 48.60]
Pradella et al 2015	65.7	83.1	29	5.6	92.9	15	7.0%	60.10 [4.20, 116.00]
Ramírez-Sarmiento et al 2002	-12	67.18	7	-22	106.01	7	3.1%	10.00 [-82.97, 102.97]
Van Wetering et al 2010b	-1.4	36.39	87	-15.3	36.58	88	20.7%	13.90 [3.09, 24.71]
Wootton et al 2014	9	87.99	77	-14	89.49	45	12.8%	23.00 [-9.71, 55.71]
Total (95% CI)			**423**			**421**	**100.0%**	**18.55 [0.77, 36.33]**

Heterogeneity: Tau² = 366.62; Chi² = 21.04, df = 9 (P = 0.01); I² = 57%
Test for overall effect: Z = 2.04 (P = 0.04)

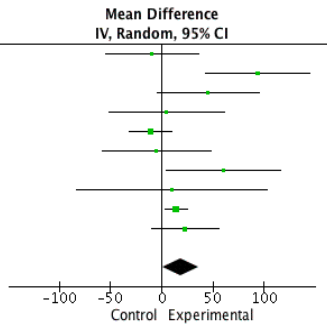


Figure 38. Effects of Exercise Interventions on 6-Minute Walk Test Distance (m) After Excluding Studies with Poor Quality

Exercise Frequency. In a meta-analysis of studies that delivered exercise interventions with greater frequency (≥3-5 sessions/week), there was no change in the overall effect on the FEV_1 (Appendix J). However, a significant reduction in % predicted of FEV_1 level in the control arm was observed (2 studies, n= 63 participants, MD= -2.00% (95% CI [-2.37, -1.62]); $p < 0.00001$) (Figure 39).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Ramírez-Sarmiento et al 2002	1	8.9	7	2	6.48	7	0.2%	-1.00 [-9.16, 7.16]
Torres-Sánchez et al 2016	7	0.8	24	9	0.5	25	99.8%	-2.00 [-2.38, -1.62]
Total (95% CI)			**31**			**32**	**100.0%**	**-2.00 [-2.37, -1.62]**

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 10.44 (P < 0.00001)

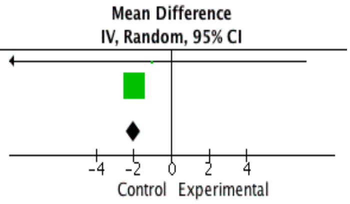
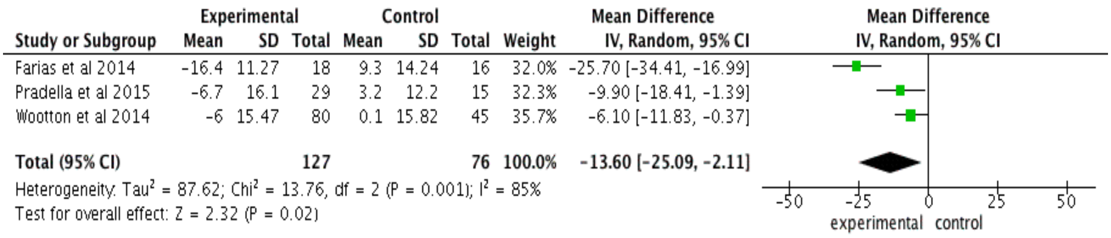


Figure 39. Effects of Exercise Interventions on Percent Predicted of Forced Expiratory Volume in One Second (%) in Studies with High Intervention Frequency (≥3-5 Sessions/Week)

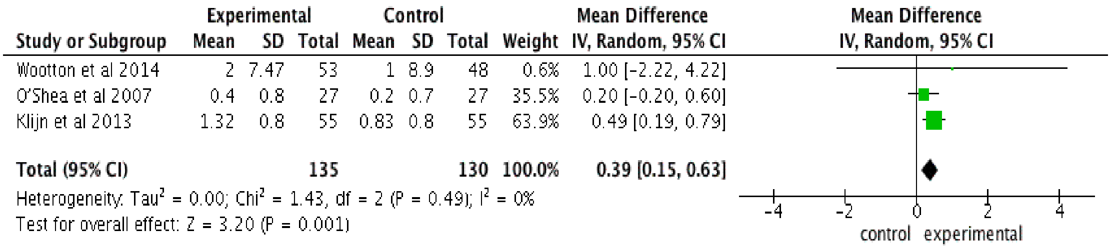
The positive effects of exercise on SGRQ score (3 studies, n= 203 participants, MD= -13.60 points (95% CI [-25.09, -2.11]); p = 0.02) (Figure 40) and the CRDQ Emotion (3 studies, n= 265 participants, MD= 0.39 points (95% CI [0.15, 0.63]); p = 0.001) (Figure 41) and Mastery domains (3 studies, n= 293 participants, MD= 0.37 (95% CI [0.02, 0.72]); p = 0.04) (Figure 42) were maintained among studies that delivered interventions with greater frequency. Additionally, a positive effect of exercise on the CRDQ Fatigue domain was now observed (4 studies, n= 368 participants, MD= 0.47 points (95% CI [0.21, 0.72]); p = 0.0004) (Figure 43), but the effect on the CRDQ Dyspnea domain was not maintained (4 studies, n= 368 participants, MD=0.64 points (95% [-0.03, 1.31]); p = 0.06) (Figure 44).



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Farias et al 2014	-16.4	11.27	18	9.3	14.24	16	32.0%	-25.70 [-34.41, -16.99]
Pradella et al 2015	-6.7	16.1	29	3.2	12.2	15	32.3%	-9.90 [-18.41, -1.39]
Wootton et al 2014	-6	15.47	80	0.1	15.82	45	35.7%	-6.10 [-11.83, -0.37]
Total (95% CI)			**127**			**76**	**100.0%**	**-13.60 [-25.09, -2.11]**

Heterogeneity: $Tau^2 = 87.62$; $Chi^2 = 13.76$, df = 2 (P = 0.001); $I^2 = 85\%$
Test for overall effect: Z = 2.32 (P = 0.02)

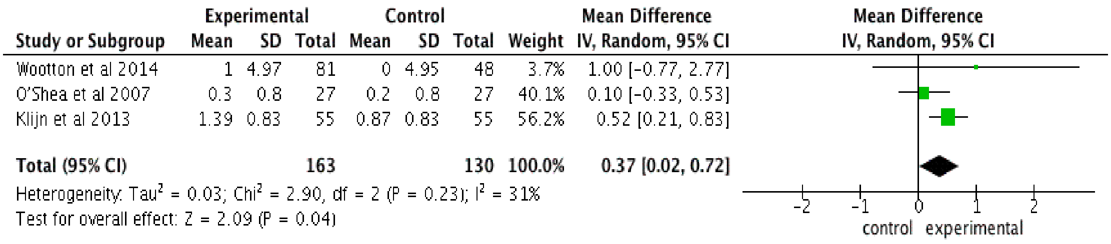
Figure 40. Effects of Exercise Interventions on St. George Respiratory Questionnaire Score in Studies with Intervention Frequency ≥3-5 Sessions/Week



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Wootton et al 2014	2	7.47	53	1	8.9	48	0.6%	1.00 [-2.22, 4.22]
O'Shea et al 2007	0.4	0.8	27	0.2	0.7	27	35.5%	0.20 [-0.20, 0.60]
Klijn et al 2013	1.32	0.8	55	0.83	0.8	55	63.9%	0.49 [0.19, 0.79]
Total (95% CI)			**135**			**130**	**100.0%**	**0.39 [0.15, 0.63]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.43$, df = 2 (P = 0.49); $I^2 = 0\%$
Test for overall effect: Z = 3.20 (P = 0.001)

Figure 41. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire (Emotion Domain) in Studies with Intervention Frequency ≥3-5 Sessions/Week



Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Wootton et al 2014	1	4.97	81	0	4.95	48	3.7%	1.00 [-0.77, 2.77]
O'Shea et al 2007	0.3	0.8	27	0.2	0.8	27	40.1%	0.10 [-0.33, 0.53]
Klijn et al 2013	1.39	0.83	55	0.87	0.83	55	56.2%	0.52 [0.21, 0.83]
Total (95% CI)			**163**			**130**	**100.0%**	**0.37 [0.02, 0.72]**

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 2.90$, df = 2 (P = 0.23); $I^2 = 31\%$
Test for overall effect: Z = 2.09 (P = 0.04)

Figure 42. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire (Mastery Domain) in Studies with Intervention Frequency ≥3-5 Sessions/Week

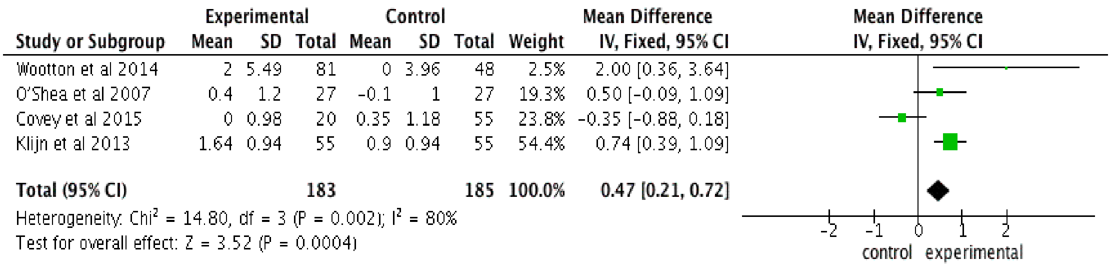


Figure 43. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire (Fatigue Domain) in Studies with Intervention Frequency >3-5 Sessions/Week

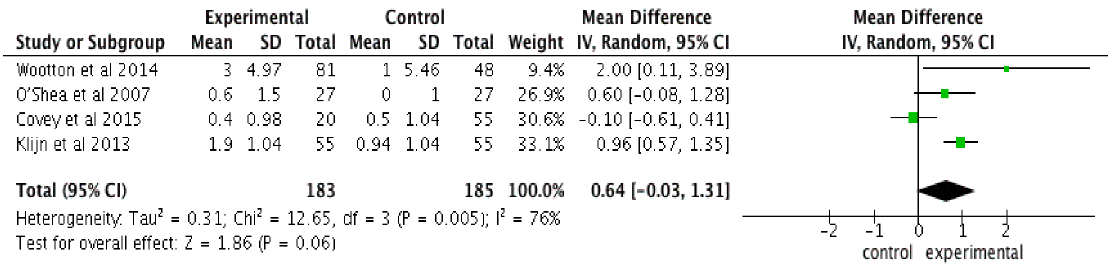


Figure 44. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire (Dyspnea Domain) in Studies with Intervention Frequency >3-5 Sessions/Week

Exercise Intensity. To determine the effects when only studies employing moderate-intensity exercise training were included, studies with high or non-specified intensity were removed. The positive effect of exercise was maintained on SGRQ (3 studies n= 203 participants, MD= -13.60 points (95% CI [-25.09, -2.11]); p = 0.02) (Figure 45), and on CRDQ Dyspnea (3 studies n= 293 participants, MD= 0.90 points (95% CI [0.54, 1.27]); p < 0.00001) (Figure 46), Emotion (3 studies n= 265 participants, MD= 0.39 points (95% CI [0.15, 0.63]); p = 0.001) (Figure 47), and

Mastery domains (3 studies n= 293 participants, MD= 0.37 points (95% CI [0.03, 0.72]); p = 0.04) (Figure 48). A positive effect of exercise was also observed on the CRDQ Fatigue domain (3 studies n= 293 participants, MD= 0.74 points (95% CI [0.31, 1.17]); p = 0.0007) (Figure 49). There was no change on the overall effect on BMI (Appendix J).

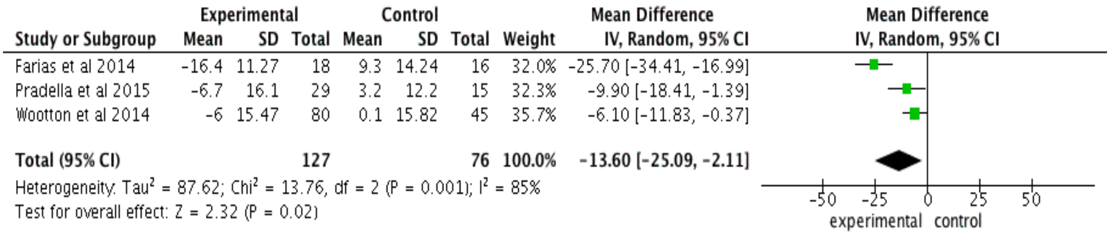


Figure 45. Effects of Moderate Intensity Exercise Interventions on St. George Respiratory Questionnaire Score

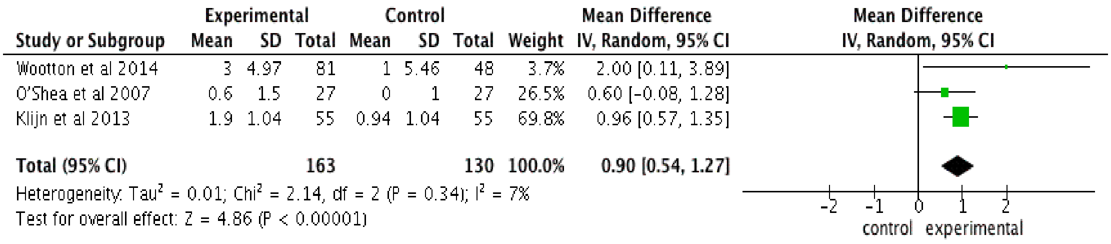


Figure 46. Effects of Moderate Intensity Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Dyspnea Domain)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Wootton et al 2014	2	7.47	53	1	8.9	48	0.6%	1.00 [-2.22, 4.22]
O'Shea et al 2007	0.4	0.8	27	0.2	0.7	27	35.5%	0.20 [-0.20, 0.60]
Klijn et al 2013	1.32	0.8	55	0.83	0.8	55	63.9%	0.49 [0.19, 0.79]
Total (95% CI)			**135**			**130**	**100.0%**	**0.39 [0.15, 0.63]**

Heterogeneity: Tau² = 0.00; Chi² = 1.43, df = 2 (P = 0.49); I² = 0%
Test for overall effect: Z = 3.20 (P = 0.001)

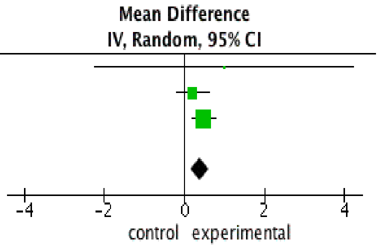


Figure 47. Effects of Moderate Intensity Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Emotion Domain)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Wootton et al 2014	1	4.97	81	0	4.95	48	3.7%	1.00 [-0.77, 2.77]
O'Shea et al 2007	0.3	0.8	27	0.2	0.8	27	40.1%	0.10 [-0.33, 0.53]
Klijn et al 2013	1.39	0.83	55	0.87	0.83	55	56.2%	0.52 [0.21, 0.83]
Total (95% CI)			**163**			**130**	**100.0%**	**0.37 [0.02, 0.72]**

Heterogeneity: Tau² = 0.03; Chi² = 2.90, df = 2 (P = 0.23); I² = 31%
Test for overall effect: Z = 2.09 (P = 0.04)

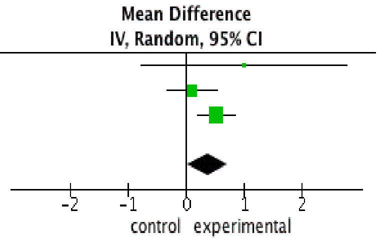


Figure 48. Effects of Moderate Intensity Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Mastery Domain)

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Wootton et al 2014	2	5.49	81	0	3.96	48	6.4%	2.00 [0.36, 3.64]
O'Shea et al 2007	0.4	1.2	27	-0.1	1	27	34.3%	0.50 [-0.09, 1.09]
Klijn et al 2013	1.64	0.94	55	0.9	0.94	55	59.3%	0.74 [0.39, 1.09]
Total (95% CI)			**163**			**130**	**100.0%**	**0.74 [0.31, 1.17]**

Heterogeneity: Tau² = 0.05; Chi² = 2.89, df = 2 (P = 0.24); I² = 31%
Test for overall effect: Z = 3.38 (P = 0.0007)

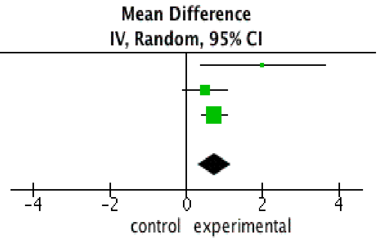


Figure 49. Effects of Moderate Intensity Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Fatigue Domain)

Exercise Interventions only. For studies that included exercise interventions only (i.e. not combined with non-exercise interventions), an effect in the control intervention was observed for % Predicted of FEV_1 (3 studies n= 80 participants, MD= -2.00% (95% CI [-2.37, -1.62]); $p < 0.00001$) (Figure 50). However, the effect of exercise on SGRQ scores was maintained (2 studies n= 169 participants, MD= -7.29 points (95% CI [-12.04, -2.53]); $p = 0.003$) (Figure 51). There was no change in the overall effect on BMI (Appendix J).

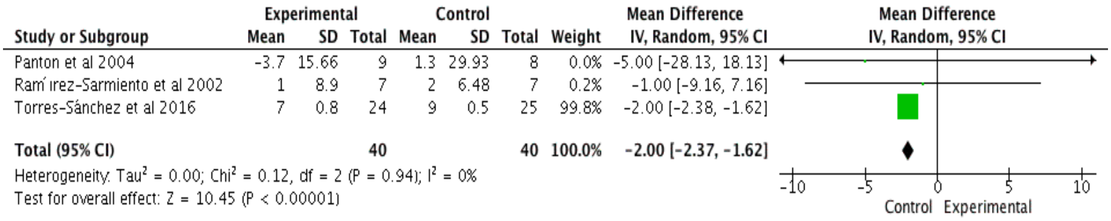


Figure 50. Effects of Exercise Interventions Alone on Percent Predicted of Forced Expiratory Volume in One Second (%)

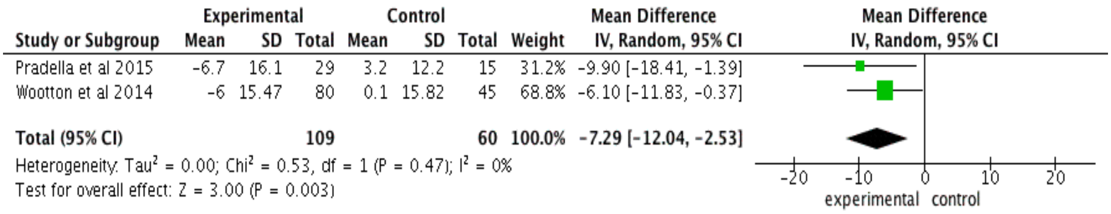


Figure 51. Effects of Exercise Interventions Alone on St. George Respiratory Questionnaire Score

Exercise Session Duration. When studies with shorter exercise session duration (≤1 hour) were removed, the effects on SGRQ was maintained (2 studies n= 79 participants, MD= -7.94 points (95% CI [-14.22, -1.67]); $p = 0.01$) (Figure 52). However, the effects on CRDQ Dyspnea (2 studies n= 220 participants, MD= 0.58

points (95% CI [-0.17, 1.34]); *p* = 0.13) (Figure 53), Emotion (2 studies n= 249 participants, MD= 0.27 points (95% CI [-0.23, 0.76]); *p* = 0.29) (Figure 54), and Mastery domains (2 studies n= 221 participants, MD= 0.35 points (95% CI [-0.07, 0.78]); *p* = 0.11) (Figure 55) were lost. The effects on the BMI and the CRDQ Fatigue domain did not change (Appendix J).

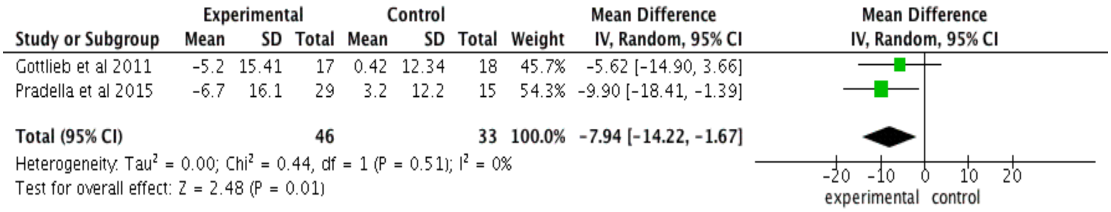


Figure 52. Effects of Exercise Interventions on St. George Respiratory Questionnaire Score in Studies with Exercise Session Duration >1 Hour

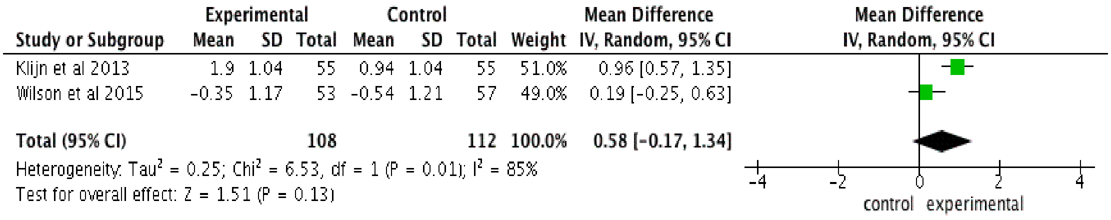


Figure 53. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Dyspnea Domain) in Studies with Exercise Session Duration >1 Hour

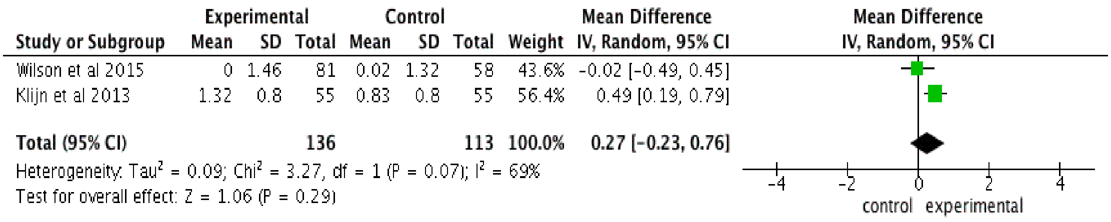


Figure 54. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Emotion Domain) in Studies with Exercise Session Duration >1 Hour

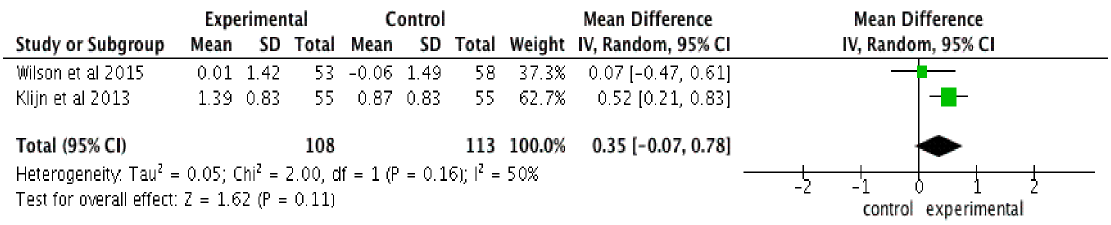


Figure 55. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Mastery Domain) in Studies with Exercise Session Duration >1 Hour

Duration of the Total Intervention. In meta-analyses that included studies with longer (>4 months) duration, the effect of exercise intervention previously observed on SGRQ (3 studies n= 445 participants, MD= -2.16 points (95% CI [-6.44, 2.12]); p = 0.32) (Figure 56), and CRDQ Dyspnea domain (2 studies n= 185 participants, MD= 0.06 points (95% CI [-0.27, 0.40]); p = 0.71) (Figure 57) were lost. There was no change in the overall effect of exercise on the BMI and CRDQ Fatigue domain (Appendix J).

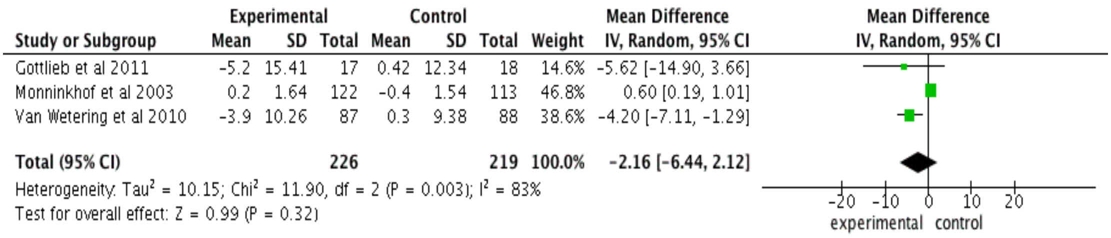


Figure 56. Effects of Exercise Interventions on St. George Respiratory Questionnaire Score in Studies with Intervention Durations >4 Months

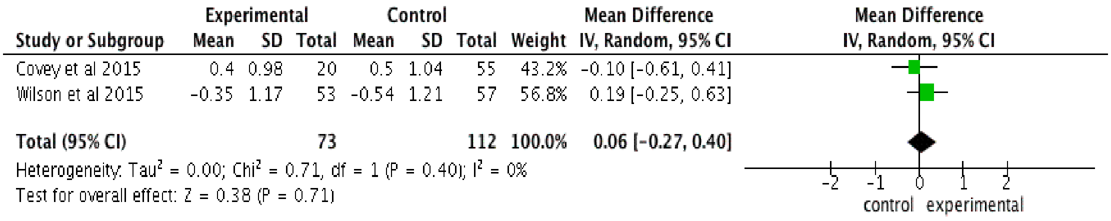


Figure 57. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Dyspnea Domain) in Studies with Intervention Durations >4 Months

Comparator Interventions. The effect of the type of the provided intervention to the comparator group was evaluated. When studies that included non-interventional comparator group were removed, the positive effects of exercise interventions on SGRQ score were maintained (4 studies, n= 479 participants, MD= -7.44 points (95% CI [-14.36, -0.53]); p = 0.03) (Figure 58), but the benefits effect of exercise on CRDQ Dyspnea (3 studies, n= 295 participants, MD= 0.37 points (95% CI [-0.28, 1.01]); p = 0.26) (Figure 59), Emotion (2 studies, n= 249 participants, MD= 0.27 points (95% CI [-0.23, 0.76]); p = 0.29) (Figure 60), and Mastery (2 studies, n= 221 participants, MD= 0.35 points (95% CI [-0.07, 0.78]); p = 0.11) (Figure 61) domains were lost. There was no change on the effect of the intervention on the Fatigue domain (Appendix J).

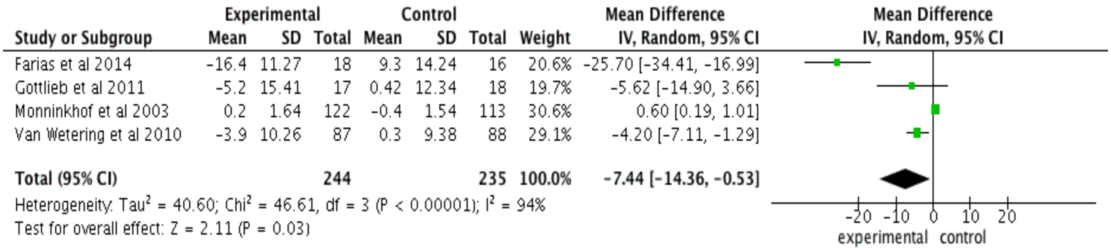


Figure 58. Effects of Exercise Interventions on St. George Respiratory Questionnaire Score in Studies with Interventional Comparator Groups

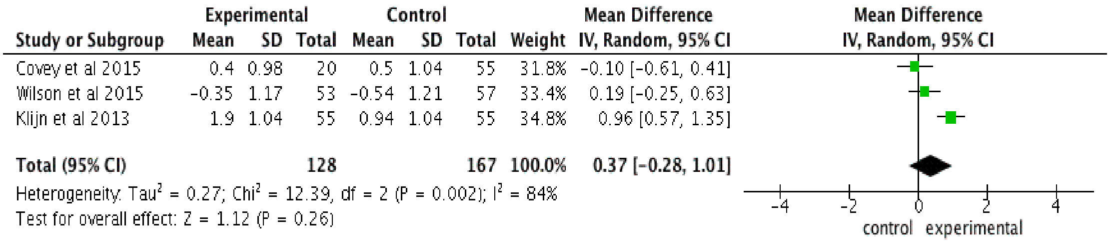


Figure 59. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Dyspnea Domain) in Studies with Interventional Comparator Groups

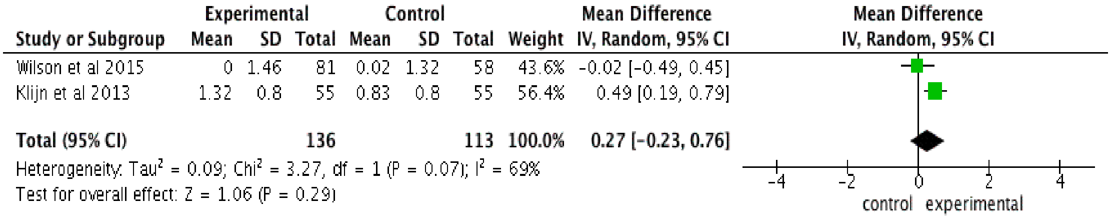


Figure 60. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Emotion Domain) in Studies with Interventional Comparator Groups

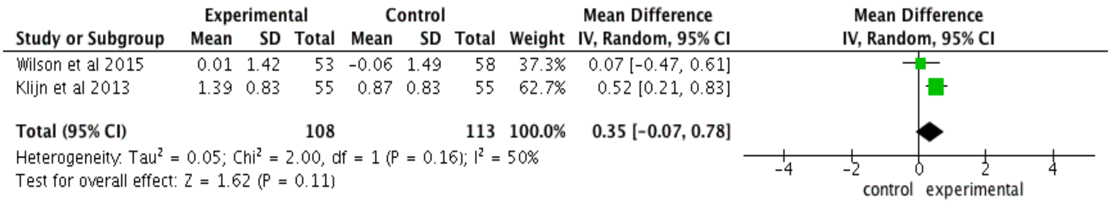


Figure 61. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Mastery Domain) in Studies with Interventional Comparator Groups

CHAPTER 4: Discussion

The prevalence of obesity has been increasing in the COPD population such that it now exceeds the prevalence in the general population (Franssen et al., 2008; Rutten et al., 2013). Moreover, the combination of COPD and obesity contributes to greater functional and ventilatory limitations than COPD alone (Franssen et al., 2008). To the best of our knowledge, this is the first systematic review to report on the effectiveness of exercise interventions in improving the walking capacity and HRQOL of individuals with COPD and elevated weight.

Exercise Interventions Appear to Be Effective in Improving Walking Capacity

Our meta-analysis showed that exercise interventions were effective in improving walking capacity as an indicator of functional exercise capacity. This finding is aligned with results of previous reviews that did not have a specific BMI criterion but rather focused on the general COPD population (Lacasse et al., 2006; McCarthy et al., 2015; Salman et al., 2003).

A previous review of 20 randomized controlled trials also reported positive effects of exercise on measures of walking capacity, but with a larger effect size (SMD = 0.25; 95% CI [0.06, 0.43] in the current study vs. SMD = 0.71; 95% CI [0.43 to 0.99]) (Salman et al., 2003). Another review also observed greater improvement in measures of functional and maximal exercise capacity in individuals with COPD after exercise training compared to control groups (65 randomized controlled trials) (McCarthy et al., 2015). However, they reported mean differences in 6MWT and ISWT separately, and did not include studies examining changes on other walk tests such as the ESWT.

When meta-analyses for each of the walk tests were conducted separately, we found that ESWT distance was the only outcome that improved after exercise. This finding is aligned with previous research suggesting that ESWT is more sensitive to change than 6MWT following pulmonary rehabilitation and exercise interventions for the general COPD population (Eaton et al., 2006; Holland et al., 2014). Importantly, although the mean change in ESWT distance was slightly lower than that reported by Eaton et al. (2006), (MD = 207.84 m, 95% CI [33.45, 382.24] in our study vs. 302 m, 95% CI [104, 501]), the difference still exceeded the MCID of 85 m (Pepin et al., 2011).

In contrast to findings from previous reviews of the general COPD population (Lacasse et al., 2006; McCarthy et al., 2015; Salman et al., 2003), it is notable that we did not observe changes in 6MWT distance in people with elevated weight. It is known that individuals with COPD and elevated weight have lower distances walked on the 6MWT compared to those with normal weight (Bautista, Ehsan, Normandin, ZuWallack, & Lahiri, 2011; Maatman et al., 2016) and thus may need more intense interventions for significant benefits to be observed.

Positive effects of exercise were observed with 2 studies that focused on the ESWT, and both followed a standardized protocol to administer the test (Revill et al., 1999). However, these results should be interpreted with caution since the psychometric measures of ESWT have not yet been established, and there is high risk of type II error due to the small number of studies included.

Exercise Interventions Are Effective in Improving Fat-Free Mass Index and Health-Related Quality of Life but Not Ventilatory Parameters

Exercise interventions were effective at improving FFMI in individuals with coexisting COPD and elevated weight. Although only two studies were included in our analysis, the size of the effect was similar to that reported in previous studies focused on individuals with COPD without concurrent obesity (Berton et al., 2013; Emtner, Hallin, Arnardottir, & Janson, 2015). Improvement in FFMI may be due to reductions in fat mass, but this variable was not examined in the included studies.

We did not observe changes in BMI in the current review. This may be partially explained by the exercise training parameters employed by the included studies. Whereas studies conducted in the general obese and overweight populations (i.e. without COPD) have reported that longer exercise durations (≥14 weeks) are needed for significant reductions in BMI to be observed (Donnelly et al., 2003; Ross et al., 2004; Slentz et al., 2004), programs employed in most of the studies in the current analysis were 12 weeks in length or less. Additionally, as is generally recommended for individuals with elevated weight, it is likely that exercise needs to be combined with dietary interventions for reductions in BMI to be realized (Geliebter et al., 1997; Ross et al., 2004; Shaw, Gennat, O'Rourke, & Del Mar, 2006). The increasing incidence of obesity concurrent with COPD could result from different behavioral factors such as sedentary lifestyle and high caloric intake (Poulain et al., 2006); thus exercise may need to be combined with dietary interventions to effectively reduce BMI in this population.

Health related quality of life, as measured by the SGRQ and the dyspnea, emotion, and mastery domains of the CRDQ, improved with exercise interventions.

The improvements observed in the dyspnea domain of the CRDQ may be attributed to improvements in ventilatory muscle strength, which decreases the ventilatory demand, expiratory flow limitation, and dynamic hyperinflation that in turn reduce sensations of dyspnea (Cooper, 2009; Porszasz et al., 2005; Puente-Maestu et al., 2006; Ries et al., 2007). Combined, reduced feelings of dyspnea and improved respiratory muscle strength contribute to less fatigue, improved activity tolerance to perform activities of daily living, and thus greater sense of mastery (Eves & Davidson, 2011; Porszasz et al., 2005; Ries et al., 2007). This provides support of the non-physical benefits of exercise, allowing mood and self-efficacy to improve, which enhances health-related quality of life (Dekhuijzen, Beek, Folgering, & Van, 1990; Derom, Marchand, & Troosters 2007; Kozora, Tran, & Make 2002). Individuals with COPD and obesity are more likely to express greater fatigue compared to those with COPD and normal weight (Cecere et al., 2011; Franssen et al., 2008; García-Rio et al., 2014; Ramachandran et al., 2008), which may explain the neutral findings in the CDRQ fatigue domain. The improvements in SGRQ and CRDQ dyspnea domain were also clinically significant, as the changes observed exceeded the MCIDs for SGRQ (4 points) (Jones, 2005) and CRDQ domains (0.5 points) (Wijkstra et al., 1994).

That we did not observe exercise-associated improvements in ventilatory outcomes (measured by FEV_1 or % predicted of FEV_1) is similar to previous findings in individuals with COPD without elevated weight (Berry, Rejeski, Adair, & Zaccaro, 1999; Kaymaz et al., 2018; Xu et al., 2017). Arguably, given that COPD is a progressive and irreversible disease, it would be expected that FEV_1 would decline over time (Fletcher & Peto, 1977; Soriano et al., 2007; Vestbo et al., 2011). Whereas previous studies have reported that interventions, including exercise, may stem the rate of decline in FEV_1 (Cote & Celli, 2005; Foglio et al., 2007; Stav, Raz, & Shpirer, 2009), these improvements would be most likely observed in those with mild, rather than moderate or severe, COPD (Berry et al., 1999).

Exercise Program Characteristics Have Different Effects on 6MWT

In subgroup analyses, there were no differences in the effects on 6MWT distance comparing programs that used exercise alone or combined with other interventions (such as education on self-management, smoking cessation and nutrition). These findings are similar to previous reviews of individuals with COPD without elevated weight (Lahham, McDonald, & Holland, 2016; McCarthy et al., 2015).

Regarding the type of exercise interventions, our results suggest that aerobic training was more effective in improving 6MWT distance than resistance training. These changes in aerobic interventions were similar in magnitude to those reported in previous reviews of aerobic exercise interventions in the general COPD population (McCarthy et al., 2015; Paneroni, Simonelli, Vitacca, & Ambrosino, 2017) and importantly, exceeded the MCID of 30.5 m for the 6MWT (Bohannon & Crouch, 2017). That 6MWT is a functional test that is more indicative of aerobic capacity than muscle strength could explain the observed effect. Combining aerobic and resistance training resulted in very small improvements in 6MWT that were not clinically significant though arguably, there were only two studies in this analysis, which may explain the small effect. Despite these findings, resistance training should still be considered an essential component of a comprehensive exercise program for individuals with COPD (Derom et al., 2007; O'Shea, Taylor, & Paratz, 2004; Spruit et al., 2013), and highlights the need for more research in this area.

Interestingly, moderate-intensity interventions appeared to be more effective in improving 6MWT distance compared to high-intensity interventions. This finding was unexpected and stood in contrast to previous findings involving the general COPD population where high-intensity continuous or interval training resulted in greater benefits to muscle strength and walking endurance (Garber et al., 2011; Hanania & Sharafkhaneh, 2011; Punzal et al, 1991; Spruit et al., 2013). The results should be interpreted with caution however, as the findings may be explained by the characteristics of the studies included in this review. Most studies of moderate-intensity interventions primarily focused on aerobic training, whereas high-intensity protocols typically used aerobic, aerobic and resistance, and respiratory muscle training, which may not lead directly to improvements in aerobic 6MWT.

Programs offered at higher frequencies of three to five sessions per week may be more effective in improving 6MWT distance than those offered at lower frequency, although this finding was not statistically significant. It is possible that the heterogeneity in the types of programs may partially explain this finding, as aerobic and mixed training programs were included in this analysis. There is no clear evidence of the optimal frequency of exercise sessions for the COPD population. Typical pulmonary rehabilitation programs offer two to three sessions per week (Spruit et al., 2013), although participation is recommended three sessions per week (Nici et al., 2006). Although it is likely that higher frequencies are more effective, they could be difficult to apply pragmatically, especially in outpatient or community settings.

When we evaluated the effect of session duration, it appeared that shorter sessions ($\leq$ 30 minutes) were slightly more effective than longer ones at improving 6MWT distance although arguably, there were only three studies included in this analysis and the measured effect was very small and did not reach clinical importance. Moreover, the heterogeneity of the interventions delivered in studies with longer session durations may also account for the absence of effect on 6MWT distance. The typical duration of exercise sessions used with the general COPD population typically ranges from 20 to 60 minutes, but there is no clear evidence of the optimal duration (Hanania & Sharafkhaneh, 2011).

There were no differences between programs of shorter ($\leq$ 4 months) or longer durations. In the general COPD population, the ideal program duration has not been clearly established (Beauchamp, Janaudis-Ferreira, Goldstein, & Brooks, 2011), although greater improvements in 6MWT have been observed following longer programs (> 6–18 months) (Berry et al., 2003; Ries et al., 2007; Verrill, Barton, Beasley, & Lippard, 2005).

There Were No Differences in 6MWT Distance Between Different Mean Body Mass Index and Types of Comparators

There were no differences in 6MWT distance when studies of individuals with mean BMI $\geq$ 28 kg/m^2 were compared with studies that included those with BMI within normal ranges. These results suggest that when individuals with extreme elevated weight are considered alone, the effects are not maintained and that the observed changes were likely influenced by individuals who were in normal weight categories. Arguably, there were only two studies included in the analysis of higher

BMI, thus more research is needed that specifically focuses on the elevated weight categories. Moreover, we noted that the interventions included in these studies incorporated different types of exercise (aerobic (McNamara et al., 2013) and mixed aerobic and resistance training (Covey et al., 2014)). This may also partially explain the neutral effect on 6MWT, given our findings that aerobic interventions appear to be most effective in improving 6MWT in this population.

Similarly, we did not observe a greater effect among studies that used usual care or no interventions as the comparator groups compared to those that used other active interventions such as education or controlled exercise training. In previous systematic reviews, authors have excluded studies with active comparator groups from their analysis to prevent masking of the true effects of the exercise intervention (Lacasse et al., 2006; McCarthy et al., 2015). In this review however, we included studies that utilized a comparator group but did not place limitations on the type of comparator used. This subgroup analysis allowed us to compare the effects of different comparator interventions, although more research is needed.

Exercise Characteristics Have Different Effects on Secondary Outcomes

That statistically and clinically important effects on SGRQ were maintained in sensitivity analysis of exercise without co-interventions suggests that exercise alone may be sufficient for improving HRQOL. Similarly, there were significant benefits of exercise on % predicted FEV_1 when it was not supplemented with other interventions. This finding aligns with those from previous reviews in the general COPD population without elevated weight (Cote & Celli, 2005; Foglio et al., 2007; Stav et al., 2009) in which exercise was effective in preventing or stemming the progressive reduction of FEV_1.

That we did not see an effect of exercise without other interventions on BMI is aligned with the hypotheses that individuals with obesity with concurrent COPD, similar to those without COPD (Geliebter et al., 1997; Ross et al., 2004; Shaw et al., 2006), would benefit more from combined programs of exercise and dietary intervention for reductions in BMI to be observed.

The benefits of exercise on HRQOL were maintained when studies with moderate-intensity interventions were included. A noteworthy improvement was also seen in the fatigue domain of the CRDQ that was not initially observed in the primary analysis. Moreover, the improvements were also clinically significant for the SGRQ and the CRDQ dyspnea and fatigue domains, although they were slightly lower for the mastery and emotion domains. These specific improvements in dyspnea and fatigue, similar to benefits observed in 6MWT distance, may have been a product of improvements in muscle strength and functional capacity following exercise (Cooper, 2009; Eves & Davidson, 2011; Porszasz et al., 2005; Puente-Maestu et al., 2006; Ries et al., 2007).

Similarly, in the analysis that included studies with higher frequency interventions ($\geq$ 3–5 sessions/week), the effect on the SGRQ and the emotion and mastery domains of the CRDQ was maintained, and an improvement in the CRDQ fatigue domain was also observed. However, the observed effect on the dyspnea domain was not maintained. It is worth noting that the improvement in the SGRQ, although not the CRDQ emotion, mastery, or fatigue domains, was also clinically significant. These findings are consistent with published recommendations for pulmonary rehabilitation programs to offer at least three exercise sessions per week for the general COPD population (Nici et el., 2006), and may be explained by improvements observed in functional capacity and exercise tolerance (Cooper, 2009; Eves & Davidson, 2011; Porszasz et al., 2005; Puente-Maestu et al., 2006; Ries et al., 2007).

In contrast, we did not observe any improvement on the FEV_1 or the % predicted of FEV_1 with higher frequency interventions. Previous studies of individuals with COPD without obesity reported similar findings (Cote & Celli, 2005; Foglio et al., 2007; Stav et al., 2009), providing further support that exercise does not directly improve FEV_1 or the % predicted of FEV_1 but rather helps in mitigating their deterioration.

Among studies of long session duration (>1 hour), the positive effect on SGRQ was maintained, but not for the CRDQ domains. In studies of longer program duration (> 4 months), the effects previously observed in the SGRQ and CRDQ domains of dyspnea and fatigue were lost. There is no clear evidence of the optimal duration of exercise sessions (Hanania & Sharafkhaneh, 2011) or duration of programs for individuals with COPD with normal weight (Beauchamp et al., 2011), although greater improvement in HRQOL is typically expected from longer programs (Beauchamp et al., 2011; Ries et al., 2007). Of note, the positive effect of exercise interventions on HRQOL was maintained more often with studies that used the SGRQ compared to those that used the CRDQ, suggesting that SGRQ could be more sensitive to change in this population. However, it is important to note that the SGRQ is a self-administered questionnaire that includes 76 items and typically takes 30 minutes to complete compared to 15 minutes for the CRDQ. This may pose a high burden on participants, and limit the research and clinical utility of this tool.

Interventional Comparators Could Mask the Observed Effects, but Quality of the Study Did Not Affect Our Findings

In the sensitivity analysis that included studies with interventional comparators (education or controlled exercise), the exercise effect previously measured in CRDQ's domain was not maintained. This was expected as masking the effect of exercise by having interventional comparator was discussed previously and hypothesized in previous reviews (Lacasse et al., 2006; McCarthy et al., 2015). However, the previously measured effect on SGRQ was maintained in this analysis. Arguably, only few studies included in these analyses which may cause this result.

When studies of poor quality exhibiting multiple risks of bias were excluded, there was no change in the observed effect on walking capacity, but a significant improvement in 6MWT distance was revealed. The effect size was very small and not clinically important, which may be due to the high heterogeneity of the delivered interventions. There were no changes in the original effects observed with BMI, suggesting that the findings were not biased by study quality.

Limitations of the Review and Recommendations for Future Studies

Despite the rising prevalence of obesity in the COPD population, only a few studies to date have specifically focused on this extreme end of the body mass continuum (i.e., BMI $\geq$ 30 kg/m^2). As such, we included studies in which the mean BMI of the study sample fell within the range of elevated weight (overweight and obese) but acknowledge that participants were not exclusively in these ranges. Thus, it is possible that some of the intervention effects observed may have be influenced by individuals within normal weight ranges. Indeed, in our subgroup analyses, we observed no overall effect of exercise on 6MWT distance in studies where the mean BMI of the sample exceeded 28 kg/m^2, and a trend towards positive effects when the mean sample BMI was less than 28 kg/m^2. More research is needed that focuses exclusively on individuals with elevated weight in overweight and obese categories to establish the effects of exercise on this subset of the COPD population.

More research is needed that specifically focuses on individuals with COPD who are overweight or obese only in order to determine the effects of exercise with a less heterogeneous sample that includes people in normal weight categories as well.

Additionally, in this developing body of evidence, a broad range of outcomes were studied. Most of the outcomes analyzed included a small number of studies (2–4 studies), and as such, many of the results should be interpreted with caution. Most of the included studies where of high quality, however, they lacked the blindness of the participants and interventions' provider which increased the risk of bias of these studies. Given the rising prevalence of obesity among individuals with COPD, further research is needed with high quality evidence to establish the effects of exercise as a strategy to improve health outcomes in this at-risk population.

Conclusion

This was the first systematic review to examine the effect of exercise interventions on exercise capacity, anthropometrics, HRQOL, and ventilatory parameters of individuals with COPD and elevated weight. These results suggest that individuals with COPD and elevated weight may benefit from exercise interventions to improve walking capacity and aerobic exercise in particular is an important factor in improving 6MWT distance beyond clinically important thresholds. These results should be interpreted with caution however, as the effect on specific walk tests and the clinical significance of the improvements are unclear given that the magnitude of effects was generally small and below MCID thresholds, and smaller than that observed in those without elevated weight.

The results also suggest that exercise interventions can also improve overall and specific domains of HRQOL, as measured by disease-specific questionnaires in individuals with COPD and elevated weight. Traditional exercise interventions may need to be tailored to help manage the multiple comorbidities presented in this population and target other important outcomes such as blood glucose level and blood pressure.

The results from this review provide insight for future research into the importance of establishing effective interventions and optimal training parameters to minimize the functional and health effects among individuals who present with both COPD and obesity.

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Appendixes

Appendix A. Search Strategy

Search strategy for Embase, Medline, AMED and PsycINFO databases

A	Terms Related to Chronic Obstructive Pulmonary Disease
1	chronic obstructive pulmonary disease.mp. or *chronic obstructive lung disease/
2	Pulmonary Disease, Chronic Obstructive.mp.
3	Lung Diseases, Obstructive.mp.
4	Pulmonary Emphysema.mp. or *lung emphysema/
5	chronic bronchitis.mp.
6	(COPD or COAD or COBD or AECB).mp
7	1 or 2 or 3 or 4 or 5 or 6

B	Terms Related to Exercise and Physical Activity
8	exp exercise tolerance/ or Exercise*.mp. or exp exercise test/
9	Exercises.mp. or exp exercise/
10	Exercise Therapy.mp.
11	Exercise.mp. or exercise/
12	exp physical activity/ or physical activ*.mp. or exp fitness/
13	Physical Endurance.mp.
14	Physical Fitness.mp.
15	Physical exer*.mp.

16	fitness*.mp.
17	pulmonary rehabilitation.mp. or exp pulmonary rehabilitation/
18	Physical ed*.mp.
19	physical train*.mp.
20	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

C	**Terms Related to Overweight and Obesity**
21	exp body weight/ or exp obesity/ or exp body mass/ or Obes*.mp.
22	adiposity.mp.
23	Overweight.mp. or Overweight/
24	(BMI adj6 ("25" or "24:")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
25	("body mass index" adj6 ("25" or "24:")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
26	(BMI adj6 ("30" or "29:")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
27	("body mass index" adj6 ("30" or "29:")).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]

28	body composition.mp. or exp body composition/
29	Body fat.mp. or Adipose Tissue/
30	(Body weight and measures).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
31	Waist-hip ratio.mp. or exp Waist-Hip Ratio/
32	waist circumference.mp. or exp Waist Circumference/
33	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34	7 and 20 and 33
35	Limit to English

Search strategy for CINAHL database

A	**Terms Related to Chronic Obstructive Pulmonary Disease**
1	(MM "Pulmonary Disease, Chronic Obstructive") OR (MM "Lung Diseases, Obstructive") OR "chronic obstructive pulmonary disease"
2	(MM "Emphysema") OR "Pulmonary Emphysema"
3	(MM "Bronchitis, Chronic") OR "chronic bronchitis"
4	COPD
5	COAD
6	COBD
7	AECB

8	1 or 2 or 3 or 4 or 5 or 6 or 7

B	**Terms Related to Exercise and Physical Activity**
9	(MM "Exercise+") OR "exercise" OR (MH "Therapeutic Exercise+") OR (MH "Exercise Test") OR (MH "Rehabilitation Exercise (Saba CCC)") OR (MH "Exercise Tolerance+")
10	(MH "Physical Activity") OR "physical activity" OR (MH "Physical Endurance") OR (MH "Physical Fitness") OR (MH "Physical Education and Training")
11	(MH "Rehabilitation, Pulmonary+") OR "pulmonary rehabilitation"
12	fitness
13	Physical exer*
14	9 or 10 or 11 or 12 or 13

C	**Terms Related to Overweight and Obesity**
15	(MH "Obesity+") OR "obesity" OR (MH "Obesity, Morbid")
16	(MH "Body Weight+") OR "body weight" OR (MH "Body Weights and Measures") OR (MH "Body Mass Index")
17	(MH "Body Mass Index") OR "body mass index"
18	Obes*
19	adiposity
20	Overweight

21	BMI adj6 "25 or 24"
22	BMI adj6 "30 or 29"
23	(MH "Body Composition+") OR "body composition"
24	(MH "Adipose Tissue") OR "Body fat" OR (MH "Body Weights and Measures")
25	(MH "Waist-Hip Ratio") OR "Waist-hip ratio"
26	(MH "Waist Circumference") OR "waist circumference"
27	15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28	8 and 14 and 27
29	Limit to English

Appendix B. Data extraction form used for qualitative synthesis

			Participants																													Intervention (FITTTS)						Control1 (FITTTS)							Outcomes																
				Intervention									Control(1) N, age, BMI(kg/m2)									Control (2) N, age, BMI(kg/m2)																								Exercis Capasity					Ventilatory Parameters			HRQL				Body composition			
				Total			Male			Female			Total			Male			Female			Total			Male			Female																																			
N	Author, Date	Design	Total N, Male N (%)	N	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	N	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	N	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	N (%)	age mean,SD	BMI mean,SD (min-max)	Notes	Frequency	Intensity	Type	Time/session	Time for the total intervention	Setting	Frequency	Intensity	Type	Time/session	Time for the total intervention	Setting	Notes	Timeline	6MWT	ISWT	ESWT(S)	ESWT(m)	Others	FEV_1	% Pred FEV_1	Others	SGRQ	CRDQ	EQ5D	Others	BMI	Body Fat %	Others	Others

Appendix C. Data extraction form used for quantitative analysis

N	Author, Date	Outcome	Intervention														Control (1)														Control (2)									
			PRE			Post			1st Follow up				2nd Follow up				PRE			Post			1st Follow up				2nd Follow up				PRE			Post			1st Follow up			
			Total N	Mean	SD	Total N	Mean	SD	Total N	Mean	SD	Notes	Total N	Mean	SD	Notes	Total N	Mean	SD	Total N	Mean	SD	Total N	Mean	SD	Notes	Total N	Mean	SD	Notes	Total N	Mean	SD	Total N	Mean	SD	Total N	Mean	SD	Notes

Appendix D. Physiotherapy Evidence Database Scale Form

Title: ______________________________	Yes	No	Where
1- eligibility criteria were specified			
2- subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)			
3- allocation was concealed			
4- the groups were similar at baseline regarding the most important prognostic indicators			
5- there was blinding of all subjects			
6- there was blinding of all therapists who administered the therapy			
7- there was blinding of all assessors who measured at least one key outcome			
8- measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups			
9- all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one			

key outcome was analysed by "intention to treat"			
10- the results of between-group statistical comparisons are reported for at least one key outcome			
11- the study provides both point measures and measures of variability for at least one key outcome			
Total			

Appendix E. The Cochrane Collaboration Risk of Bias Tool Form

Title: ___________________________	Low Risk	High Risk	Unclear
1- Random Sequence Generation			
2- Allocation Concealment			
3- Blinding of Participants and Personnel			
4- Blinding of Outcome Assessment			
5- Incomplete Outcome Data			
6- Selective Reporting			
7- Other source of Bias			

Appendix F. Reasons for Exclusion Following Full-Text Evaluation

Reasons for exclusion	***n***	**Studies**
Not controlled trials	14	Alexander et al 2008; Alfaro et al 1996; Bertici et al 2013; Cesari et al 2012; Cooke et al 2009; Cote et al 2005; Croitoru et al 2013; Ko et al 2011; McNamara et al 2015; Mertens et al 1978; Shakur 2003; Swenson et al 1967; Vagaggini et al 2009 & Wouters et al 2011
Not published in English	2	Ren et al 2011 & Sivori et al 2011
Studies included mixed or non-relevant population	5	Cox et al 1993; Finnerty et al 2001; Foglio et al 2001; Mathew et al 2011 & Ries et al 2003
Study sample did not meet BMI eligibility criteria	35	Behnke et al 2005; Borges et al 2014; Deslée et al 2016; Dourado et al 2009; Eaton et al 2009; Elmorsi 2016; Embarak et al 2015; Emtner et al 2015; Gupta et al 2014; Gurgun et al 2013a; Gurgun et al 2013b; He et al 2015; Huang et al 2011; Kaymaz et al 2015; Li et al 2014; Lin et al 2012; Lou et al 2015; Mineo et al 2010; Nakamura et al 2008; Napolis et al 2011; Nasis et al 2009; Neder et al 2002; Ng et al 2011; Ng et al 2014; Nikoletou et al 2016; Petersen et al 2008; Pitta et al 2004; Rooyackers et al 2003; Senjyu et al 1999; Shahin et al 2008; Sillen et al 2014; Spielmanns et al 2017;

		Stav et al 2009; Suzana et al 2008; van Wetering et al 2010a; Wang, K. et al 2017 & Zanotti et al 2003
Sample BMI not provided	12	Amin et al 2014; Donesky et al 2014; Donesky-Cuenco et al 2009; Epstein et al 1997 Güell et al 2000; Hoogendoorn et al 2010; Hoff et al 2007; Kozora et al 2002; Paz-Díaz et al 2007; Strijbos et al 1996; Wadell et al a2005 & Weiner et al 2003
Article used dataset of another included study	1	Zakrisson et al 2016
Trials did not include exercise or physical activity intervention	7	Alexander et al 2012; Bjørgen et al 2009; Carrieri-Kohlman et al 2005; Casaburi et al 2004; Collins et al 2003; Norweg et al 2005 & Stulbarg et al 2002
Did not examine outcomes of interest	1	Camillo et al 2011

Appendix G. Summary of Results of the Primary Analyses

Outcome or Subgroup Title	No. of studies	No. of participants	Effect size MD (95% CI)	*P* Value
1- Exercise Capacity				
1.1 Standardized mean Difference of Walking Distance	12	1215	0.25 (0.06, 0.43)	$p = 0.01$*
1.2 6MWT (m)	11	924	14.19 m (-2.58, 30.97)	$p = 0.10$
1.3 ISWT (m)	2	166	29.44 m (-6.03, 64.90)	$p = 0.10$
1.4 ESWT (s)	2	208	112.04 s (-96.77, 320.85)	$p = 0.29$
1.5 ESWT (m)	2	125	207.84 m (33.45, 382.24)	$p = 0.02$*
2- Ventilatory Parameters				
2.1 FEV1 (L)	3	80	-0.01 L (-0.07, 0.05)	$p = 0.76$
2.2 % Predicted FEV_1 (%)	4	255	-0.18% (-3.82, 3.46)	$p = 0.92$
3- Anthropometrics				
3.1 BMI (kg/m2)	5	420	0.21 kg/m^2 (-0.02, 0.44)	$p = 0.08$
3.2 FFMI (kg/m^2)	2	285	0.33 kg/m^2 (0.21, 0.46)	$p < 0.001$*
4- Health-Related Quality of Life				
4.1 SGRQ	6	648	-7.49 points (-13.01, -1.98)	$p = 0.008$*
4.2 CRDQ (Dyspnea)	5	478	0.51 points (0.00, 1.02)	$p = 0.05$*
4.3 CRDQ (Fatigue)	5	479	0.39 points (-0.12, 0.89)	$p = 0.13$
4.4 CRDQ (Emotion)	4	404	0.28 points (0.03, 0.54)	$p = 0.03$*
4.5 CRDQ (Mastery)	4	404	0.31 points (0.02, 0.59)	$p = 0.03$*

*$p<0.05$

Appendix H. Summary of Results of the Subgroup Analyses for the Primary Outcome 6-Minute Walk Test

Subgroup Title	No. of studies	No. of participants	Effect size MD (95% CI)	*P* Value
1- Body Mass Index				
1.1 Mean BMI ≥ 28 kg/m²	2	120	-3.84 m (-39.41, 31.74)	*p* = 0.83
1.2 Mean BMI < 28 kg/m²	9	804	17.72 m (-1.43, 36.87)	*p* = 0.07
2- Exercise Frequency				
2.1 3-5 Sessions/Week	7	388	25.90 m (-2.34, 54.14)	*p* = 0.07
2.2 1-2 Sessions/Week	2	320	-12.84 m (-29.14, 3.47)	*p* = 0.12
2.3 1 Sessions/Month	2	216	19.83 m (-4.39, 44.06)	*p* = 0.11
3- Intervention Intensity				
3.1 Moderate Intensity Exercise	5	299	35.03 m (1.23, 68.82)	*p* = 0.04*
3.2 High Intensity	3	130	15.24 m (-21.89, 52.38)	*p* = 0.42
4- Exercise with or without Other Intervention				
4.1 Exercise Interventions Alone	5	310	8.17 m (-13.21, 29.55)	*p* = 0.45
4.2 Mixed Interventions	6	416	21.59 m (-3.37, 46.55)	*p* = 0.09
5- Exercise Type				
5.1 Aerobic Exercise	5	2826	43.91 m (14.84, 72.98)	*p* = 0.003*
5.2 Combined Aerobic and Resistance Exercise	2	250	12.66 m (2.13, 32.18)	*p* = 0.02*
5.3 Resistance Exercise	3	374	-12.17 m (-27.77, 3.43)	*p* = 0.13

5- Exercise Session Duration				
5.1 Short Exercise Session Duration (30 Minutes)	3	264	12.62 m (2.17, 23.08)	*p* = 0.02*
5.2 Moderate Exercise Session Duration (30-60 Minutes)	4	441	24.49 m (-16.75, 65.73)	*p* = 0.24
5.3 Long Exercise Session Duration (1-2 Hours)	3	165	25.52 m (-26.56, 77.59)	*p* = 0.34
6- Duration of the Total Intervention				
6.1 Intervention Durations of <4 Months	7	393	23.05 m (-7.52, 53.62)	*p* = 0.14
6.2 Intervention Durations of 4-8 Months	2	116	16.96 m (-37.08, 71.00)	*p* = 0.54
6.3 Intervention Duration of 1-2 Years	2	415	3.04 m (-21.17, 27.24)	*p* = 0.81
7- Type of Comparator Intervention				
7.1 Usual Medical Care	4	536	3.42 m (-17.01, 23.84)	*p* = 0.74
7.2 No Intervention	3	220	24.72 m (-5.93, 55.37)	*p* = 0.10
7.3 Exercise Intervention	3	134	-2.07 m (-35.30, 31.16)	*p* = 0.90

*$p<0.05$

Appendix I. Summary of Results of the Sensitivity Analyses for the Secondary Outcomes

Sensitivity Analyses	No. of studies	No. of participants	Effect size MD (95% CI)	*P* Value
1- Excluding Studies with Poor Quality				
1.1 Standardized mean Difference of Walking Distance	11	1135	0.28 m (0.10, 0.47)	*p* = 0.003*
1.2 6MWT (m)	10	884	18.55 m (0.77, 36.33)	*p* = 0.04*
1.3 BMI (kg/m^2)	4	375	0.21 kg/m^2 (-0.02, 0.44)	*p* = 0.08
2- More Frequent Exercise Sessions (≥3-5 sessions/week)				
2.1 FEV$_1$ (L)	2	63	-2.00L (-3.37, -1.62)	*p* = 0.74
2.2 % Predicted FEV1 (%)	2	63	-2.00% (-2.37, -1.62)	*p* < 0.001*
2.3 SGRQ	3	203	-13.60 points (-25.09, -2.11)	*p* = 0.02*
2.4 CRDQ (Dyspnea)	4	368	0.64 points (-0.03, 1.31)	*p* = 0.06
2.5 CRDQ (Fatigue)	4	368	0.47 points (0.21, 0.72)	*p* = 0.004*
2.6 CRDQ (Emotion)	3	265	0.39 points (0.15, 0.63)	*p* = 0.001*
2.7 CRDQ (Mastery)	3	293	0.37 points (0.02, 0.72)	*p* = 0.04*
3- Moderate Intensity Exercise Interventions				
3.1 BMI (kg/m^2)	2	127	0.16 kg/m^2 (-0.30, 0.62)	*p* = 0.49
3.2 SGRQ	3	203	-13.60 points (-25.09, -2.11)	*p* = 0.02*
3.3 CRDQ (Dyspnea)	3	293	0.90 points (0.54, 1.27)	*p* < 0.0001*
3.4 CRDQ (Fatigue)	3	293	0.74 points (0.31, 1.17)	*p* < 0.0001*
3.5 CRDQ (Emotion)	3	265	0.39 points (0.15, 0.63)	*p* = 0.001*
3.6 CRDQ (Mastery)	3	293	0.37 points (0.03, 0.72)	*p* = 0.04*
4- Exercise Interventions Alone				

4.1 % Predicted FEV_1 (%)	3	80	-2.00% (-2.37, -1.62)	$p < 0.0001$*
4.2 BMI (kg/m^2)	3	172	0.16 kg/m^2 (-0.30, 0.61)	$p = 0.49$
4.3 SGRQ	2	169	-7.29 points (-12.04, -2.53)	$p = 0.003$*
5- Long Exercise Sessions (>1 Hour)				
5.1 BMI (kg/m^2)	3	200	0.09 kg/m^2 (-0.33, 0.51)	p =0.66
5.2 SGRQ	2	79	-7.94 points (-14.22, -1.67)	$p = 0.01$*
5.3 CRDQ (Dyspnea)	2	220	0.58 points (-0.17, 1.34)	$p = 0.13$
5.4 CRDQ (Fatigue)	2	221	0.44 points (-0.18, 1.05)	$p = 0.17$
5.5 CRDQ (Emotion)	2	249	0.27 points (-0.23, 0.76)	$p = 0.29$
5.6 CRDQ (Mastery)	2	221	0.35 points (-0.07, 0.78)	$p = 0.11$
6- Total Exercise Interventions ($\geq$4 Months)				
6.1 BMI (kg/m^2)	2	248	0.23 kg/m^2 (-0.04, 0.49)	$p = 0.10$
6.2 SGRQ	3	445	-2.16 points (-6.44, 2.12)	$p = 0.32$
6.3 CRDQ (Dyspnea)	2	185	0.06 points (-0.27, 0.40)	$p = 0.71$
6.4 CRDQ (Fatigue)	2	186	-0.09 points (-0.54, 0.36)	$p = 0.69$
7- Interventional Control Groups				
7.1 SGRQ	4	479	-7.44 points (-14.36, -0.53)	$p = 0.03$*
7.2 CRDQ (Dyspnea)	3	295	0.37 points (-0.28, 1.01)	$p = 0.26$
7.3 CRDQ (Fatigue)	3	296	0.19 points (-0.43, 0.81)	$p = 0.55$
7.4 CRDQ (Emotion)	2	249	0.27 points (-0.23, 0.76)	$p = 0.29$
7.5 CRDQ (Mastery)	2	221	0.35 points (-0.07, 0.78)	$p = 0.11$

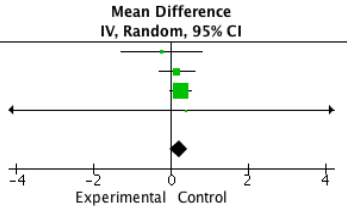
*p<0.05

Abbreviations. SGRQ: St George's Respiratory Questionnaire, CRDQ: Chronic Respiratory Disease Questionnaire, FEV_1: Forced Expiratory Volume in 1s, BMI: Body Mass Index.

Appendix J. Additional Forest Plots from the Sensitivity Analyses

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Wilson et al 2015	−0.58	2.71	33	−0.33	1.52	40	5.0%	−0.25 [−1.29, 0.79]
Klijn et al 2013	0.51	1.2308	55	0.35	1.2308	55	25.3%	0.16 [−0.30, 0.62]
Van Wetering et al 2010b	0.28	0.93	87	0.02	0.94	88	69.7%	0.26 [−0.02, 0.54]
Panton et al 2004	−0.2	8.9	9	−0.6	6.03	8	0.1%	0.40 [−6.76, 7.56]
Total (95% CI)			**184**			**191**	**100.0%**	**0.21 [−0.02, 0.44]**

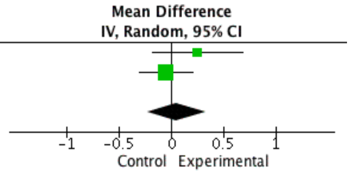
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.93$, $df = 3$ ($P = 0.82$); $I^2 = 0\%$
Test for overall effect: $Z = 1.78$ ($P = 0.08$)



1. Effects of Exercise Interventions on Body Mass Index (Kg/m^2) After Excluding Studies of Poor Quality

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Torres-Sánchez et al 2016	0.59	0.9	24	0.34	0.6	25	33.1%	0.25 [−0.18, 0.68]
Ramírez-Sarmiento et al 2002	0.023	0.3	7	0.077	0.17	7	66.9%	−0.05 [−0.31, 0.20]
Total (95% CI)			**31**			**32**	**100.0%**	**0.05 [−0.23, 0.33]**

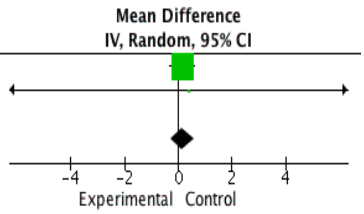
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.42$, $df = 1$ ($P = 0.23$); $I^2 = 30\%$
Test for overall effect: $Z = 0.33$ ($P = 0.74$)



2. Effects of Exercise Interventions on Forced Expiratory Volume in 1 Second (L) in Studies with High Intervention Frequency (≥ 3-5 Sessions/Week)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Klijn et al 2013	0.51	1.2308	55	0.35	1.2308	55	99.6%	0.16 [−0.30, 0.62]
Panton et al 2004	−0.2	8.9	9	−0.6	6.03	8	0.4%	0.40 [−6.76, 7.56]
Total (95% CI)			**64**			**63**	**100.0%**	**0.16 [−0.30, 0.62]**

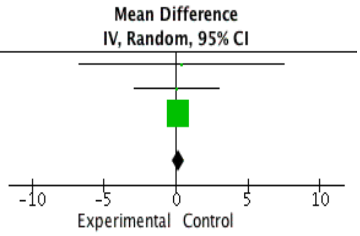
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, $df = 1$ ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: $Z = 0.69$ ($P = 0.49$)



3. Effects of Exercise Interventions on Body Mass Index (Kg/m^2) in Studies Utilizing Moderate Intensity Exercise

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Panton et al 2004	-0.2	8.9	9	-0.6	6.03	8	0.4%	0.40 [-6.76, 7.56]
Elkhateeb et al 2015	0.015	4.29	30	-0.03	4.93	15	2.4%	0.04 [-2.88, 2.97]
Klijn et al 2013	0.51	1.2308	55	0.35	1.2308	55	97.2%	0.16 [-0.30, 0.62]
Total (95% CI)			**94**			**78**	**100.0%**	**0.16 [-0.30, 0.61]**

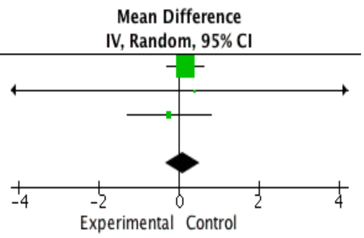
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.49)



4. Effects of Exercise Interventions Alone on Body Mass Index (Kg/m^2)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Klijn et al 2013	0.51	1.2308	55	0.35	1.2308	55	83.3%	0.16 [-0.30, 0.62]
Panton et al 2004	-0.2	8.9	9	-0.6	6.03	8	0.3%	0.40 [-6.76, 7.56]
Wilson et al 2015	-0.58	2.71	33	-0.33	1.52	40	16.4%	-0.25 [-1.29, 0.79]
Total (95% CI)			**97**			**103**	**100.0%**	**0.09 [-0.33, 0.51]**

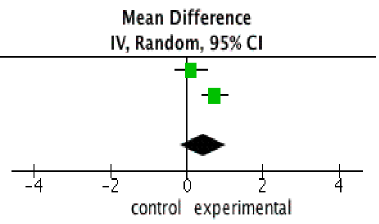
Heterogeneity: Tau² = 0.00; Chi² = 0.51, df = 2 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)



5. Effects of Exercise Interventions on Body Mass Index (Kg/m^2) in Studies with Long Exercise Session Duration (>1 Hour)

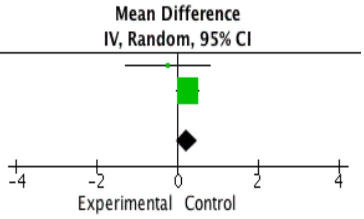
Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Wilson et al 2015	-0.3	1.09	53	-0.41	1.19	58	48.1%	0.11 [-0.31, 0.53]
Klijn et al 2013	1.64	0.94	55	0.9	0.94	55	51.9%	0.74 [0.39, 1.09]
Total (95% CI)			**108**			**113**	**100.0%**	**0.44 [-0.18, 1.05]**

Heterogeneity: Tau² = 0.16; Chi² = 5.03, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 1.39 (P = 0.17)



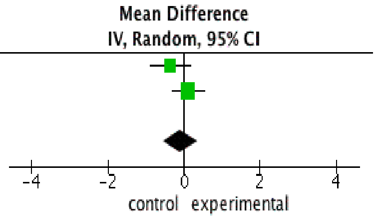
6. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Fatigue Domain) in Studies with Long Exercise Session Duration (>1 Hour)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Wilson et al 2015	-0.58	2.71	33	-0.33	1.52	40	6.7%	-0.25 [-1.29, 0.79]
Van Wetering et al 2010	0.28	0.93	87	0.02	0.94	88	93.3%	0.26 [-0.02, 0.54]
Total (95% CI)			**120**			**128**	**100.0%**	**0.23 [-0.04, 0.49]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.87$, df = 1 (P = 0.35); $I^2 = 0\%$								
Test for overall effect: Z = 1.66 (P = 0.10)								



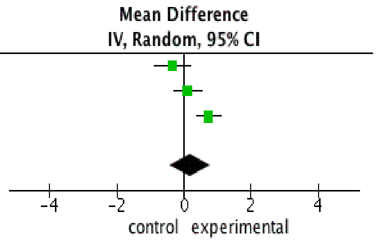
7. Effects of Exercise Interventions on Body Mass Index (Kg/m^2) in Studies with long Intervention Durations (>4 Months)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Covey et al 2015	0	0.98	20	0.35	1.18	55	43.7%	-0.35 [-0.88, 0.18]
Wilson et al 2015	-0.3	1.09	53	-0.41	1.19	58	56.3%	0.11 [-0.31, 0.53]
Total (95% CI)			**73**			**113**	**100.0%**	**-0.09 [-0.54, 0.36]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.76$, df = 1 (P = 0.18); $I^2 = 43\%$								
Test for overall effect: Z = 0.40 (P = 0.69)								



8. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Fatigue Domain) in Studies with long Intervention Durations (>4 Months)

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Covey et al 2015	0	0.98	20	0.35	1.18	55	30.9%	-0.35 [-0.88, 0.18]
Wilson et al 2015	-0.3	1.09	53	-0.41	1.19	58	33.7%	0.11 [-0.31, 0.53]
Klijn et al 2013	1.64	0.94	55	0.9	0.94	55	35.4%	0.74 [0.39, 1.09]
Total (95% CI)			**128**			**168**	**100.0%**	**0.19 [-0.43, 0.81]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 12.55$, df = 2 (P = 0.002); $I^2 = 84\%$								
Test for overall effect: Z = 0.60 (P = 0.55)								



9. Effects of Exercise Interventions on Chronic Respiratory Disease Questionnaire Score (Fatigue Domain) in Studies with Interventional Comparator Groups