Short- and Long-Term Changes in Cognitive Function After Exercise-Based Rehabilitation in People with COPD

Brent Rosenstein

A Thesis
in
The Department
of
Exercise Science

Presented in Partial Fulfillment of the Requirements
for the degree of Master of Science (Exercise Science) at
Concordia University
Montreal, Quebec, Canada

August 2019

CONCORDIA UNIVERSITY
School of Graduate Studies

This is to certify that the thesis prepared

By: Brent Rosenstein

Entitled: Short- and Long-Term Changes in Cognitive Function After Exercise-Based Rehabilitation in People with COPD

and submitted in partial fulfillment of the requirements for the degree of

Master of Science in Exercise Science

complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

Signed by the final examining committee:

Dr. Sylvia Santosa Chair

Dr. Jean-François Gagnon Examiner

Dr. Angela Alberga Examiner

Dr. Véronique Pepin Thesis Supervisor(s)

Approved by _____
Chair of Department or Graduate Program Director

_____
Dean,

Date _____

ABSTRACT

Short- and Long-Term Changes in Cognitive Function After Exercise-Based Rehabilitation in People with COPD

Brent Rosenstein

Objective: To compare the 12-week effects of continuous high-intensity training (**CTHI**), continuous training at the ventilatory threshold (**CTVT**) and high-intensity interval training (**HIIT**) on cognition, and the 1-year maintenance of these effects in people with COPD.

Methods: Participants were randomized to **CTHI, CTVT,** or **HIIT** and underwent 12 weeks of three times weekly training on cycle ergometers. The intensity phase included 25 minutes of pedaling at 80% of peak wattage (W_{peak}) for **CTHI**. For **CTVT**, the intensity was set at the ventilatory threshold, while **HIIT** consisted of 30-second intervals at 100% of W_{peak} alternated with unloaded pedaling. Session duration for **CTVT** and **HIIT** was calculated to ensure comparable total work as for **CTHI**. Assessments were made at baseline (**week 0**), program completion (**week 12**) and 1 year after baseline (**year 1**). Cognition was assessed with a neuropsychological testing battery. Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA).

Results: Thirty-six participants (64% women, mean age: 67.5±9 years) with moderate COPD were randomized. The 12-week effects of exercise training on cognition were small or very small, except for visuospatial abilities, which detected larger effects especially in participants with mild cognitive impairment at baseline. There was considerable heterogeneity between intervention groups. **CTHI** was the only group with medium-to-large effects in each cognitive domain assessed. At year 1, gains and losses in cognition were seen in all groups.

Conclusion: In COPD, 12 weeks of training led to small changes in cognition, with notable heterogeneity between exercise protocols and across cognitive domains.

Keywords: COPD, pulmonary rehabilitation, exercise training, cognitive function

Acknowledgements

This project would not be possible without the support and encouragement from my friends (especially Lucien Fruchtermann and Jake Elituv), colleagues and my family (Mark, Myriam, Michelle, Craig, Michael and Dylan). I must express my deepest gratitude to the following people who in various ways helped make this work possible.

Firstly, I would like to thank my supervisor **Dr. Veronique Pepin**, for her continuous support and moments of encouragement throughout my Master's degree. Thank you for your patience, motivation, and knowledge. Thank you for exceeding your role as a supervisor and helping me be better a student and person. I am extremely grateful to have been your only graduate student these past couple of years and to have gotten the undivided attention of such an amazing individual. You are truly a role model to me, thank you so much Véronique, from the bottom of my heart! This department is very lucky to have you.

Thank you to **Dr. Jean-François Gagnon** and **Dr. Angela Alberga**, members of my thesis committee, for their helpful comments, recommendations and criticism of this project. Thank you for your insight and your encouragement, it is truly appreciated.

Thank you to **Dr. Amanda Rizk, Dr. Frédérique Escudier** and to the **staff of the respiratory physiology laboratory** of Sacré-Coeur hospital, who collected data for the parent project, who helped us extract data from the databases and whose knowledge of data collection process facilitated my work on the current project. Thank you all for your contribution to this study.

I would like to thank **Anna Smyrnova** from the Department of Mathematics and Statistics. Anna and I originally met up in February 2019 for a consultation regarding my statistical analysis, to help with interpretations and for general advice. Since then, Anna had become more enmeshed in the project and helped tremendously for my statistical analysis. Thank you so much Anna for your hard work and for your passion for this project. You were an amazing addition to the team and I am so grateful!

"Choose your team carefully. So much of your success is due to the people who you surround yourself with. Your friends, your family, and the people that you work with – they all play an important role in inspiring you and supporting you and giving you stability." – Tom Ford

Contributions of Authors

Brent Rosenstein is the primary author of the manuscript of this thesis. He was responsible for the literature review, the data extraction and analysis, the presentation and interpretation of the results, and the assembly of the manuscript. **Véronique Pepin** is the thesis supervisor of the primary author and the principal investigator of the larger trial from which this thesis stemmed. She oversaw all stages of the larger trial and of this specific study and its related manuscripts. As the senior author of the manuscript included in the present thesis, she also ensured the accurateness and completeness of its content. **Jean-François Gagnon** is a co-investigator on the larger trial and a member of the primary author's thesis committee. Him and his research team were in charge of the neuropsychological components of the study. **Frédérique Escudier** was responsible for conducting the cognitive tests used for the study under **Dr. Gagnon's** supervision. **Amanda Rizk** was responsible for coordinating the larger trial and for implementing and supervising all exercise interventions. **Anna Smyrnova** helped conduct and interpret the statistical analyses of the study. All authors contributed to draft the manuscript and revised it with helpful recommendations and criticism.

Table of Contents

1. LIST OF FIGURES

2. LIST OF TABLES

3. LIST OF ABBREVIATIONS

BDI	Beck Depression Inventory
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
CO_2	Carbon Dioxide
CTHI	Continuous High-Intensity Training
CTVT	Continuous Training at the Ventilatory Threshold
D_LCO	Lung Diffusion Capacity for Carbon Monoxide
FEV_1	Forced Expiratory Volume in One Second
FEV_1/FVC	Ratio of Forced Expiratory Volume in One Second to Forced Vital Capacity
FVC	Forced Vital Capacity
FRC	Functional Residual Capacity
GOLD	Global Strategy for Obstructive Lung Disease
HIIT	High-Intensity Interval Training
MCI	Mild Cognitive Impairment
MoCA	Montreal Cognitive Assessment
O_2	Oxygen
$PaCO_2$	Partial Pressure of Carbon Dioxide in Arterial Blood
PR	Pulmonary Rehabilitation
RAVLT	Rey Auditory-Verbal Learning Test
RV	Residual Volume
SaO_2	Oxygen Saturation
SCWT	Stroop Color Word Test
TLC	Total Lung Capacity
VCO_2	Carbon Dioxide Production
VO_2	Oxygen Uptake
WAIS	Wechsler Adult Intelligence Scale
W_{peak}	Peak Wattage

4. THEORETICAL CONTEXT

4.1 Chronic Obstructive Pulmonary Disease (COPD)

Chronic obstructive pulmonary disease (COPD) consists of a cluster of lung disorders typified by chronic obstruction of airflow in the airways. More precisely, the Global Initiative for Chronic Obstructive Lung Disease [1] defines COPD as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases”. The main symptoms of COPD include dyspnea (shortness of breath), increased mucus production, and cough [2]. The progression of COPD follows a downward spiral termed the “dyspnea spiral”, which begins with airflow limitation and dyspnea. Once patients start feeling breathless, they tend to avoid exercise and activities of high intensity leading to inactivity and muscular deconditioning. This, in turn, worsens the dyspnea sensation in patients, who then begin to avoid activities of daily living. Eventually this cycle initiates a very poor quality of life as it continues to progress. COPD is currently the fourth leading cause of death worldwide [1] and is predicted to becoming the third cause of worldwide mortality by 2020 [3].

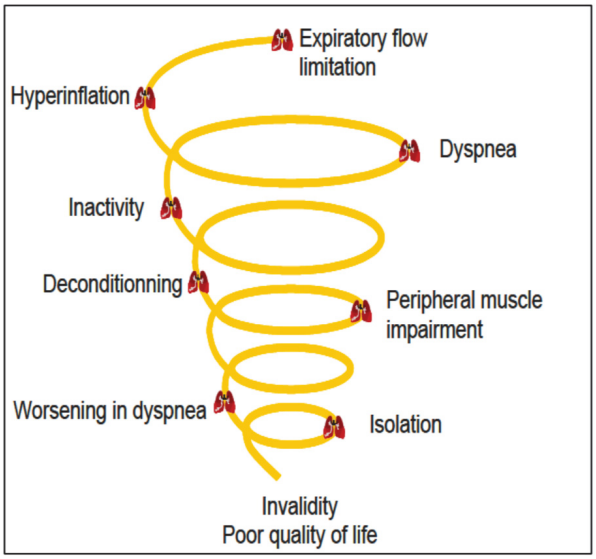

Figure 1 – COPD Downward Spiral

Adapted from la Clinique du Souffle la Solane, Osséja, France.

4.1.1 Epidemiology:

The estimated prevalence of COPD in Canadians aged 35-79 years is 17% for mild severity and 8% for moderate severity [4]. Globally, a prevalence of 251 million cases of COPD was reported in 2016 [5]. There are several factors that seem to be associated with a higher prevalence and incidence of COPD, such as age, sex, and smoking status. Overall, studies report an association between older age and COPD prevalence. The prevalence and incidence of COPD increases with age and is most prevalent in individuals aged 75 years or older [6-9]. A systematic review and meta-analysis of prevalence estimates reported between 1990-2004 [7] found a higher prevalence of COPD in people aged 40 years or older compared to people younger than 40 years. In addition, one-year mortality rate of COPD varies from 4.1% in individuals aged 45 years and older, to 27.7% in individuals aged 65-100 years old in Canada [10-12]. Mortality caused by COPD varies across studies with a range between 2.3%-8.4% [6]. These percentages are higher in people aged between 65 and 74 years old [13] and in men than in women [14-16]. A higher incidence of COPD is seen in men compared to women across several additional studies [7, 8, 10, 17, 18]. Furthermore, two studies conducted by the Obstructive Lung Disease in Northern Sweden, stated a two- to three-times higher incidence rate in cigarette smokers than in nonsmokers [19, 20].

4.1.2 Risk Factors:

Cigarette Smoking

Cigarette smoking is the most common risk factor for developing COPD. Approximately 80-90% of COPD cases are attributed to smoking cigarettes [21, 22]. Secondhand smoke is also reported to lead to COPD by inhaling particles and gases, and further burdening the lungs [21]. People who smoke cigarettes have a greater prevalence of respiratory function irregularities and symptoms, and a higher yearly decline in FEV_1 [23]. However, population-based studies report that between 25-45% of people with COPD have never smoked [24]. Therefore, other risk factors play a role in the development of COPD, such as pollution [25].

Pollution and Occupational Exposure

Pollution and/or occupational exposure is a well-known risk factor for COPD contributing to approximately 10-20% of cases by increasing symptoms or functional impairment [26]. Examples of occupational and environmental toxins include fumes, vapors, mineral and organic

dust, and chemical elements [21]. Exposure to these toxins plays a significant role in the development of COPD [27-30].

Alpha$_1$ Antitrypsin Deficiency

Another risk factor is a hereditary deficiency in alpha$_1$ antitrypsin. Alpha$_1$ antitrypsin is an enzyme that regulates the respiratory immune system by protecting the lungs from injury against proteolytic enzymes [21]. Therefore, alpha$_1$ antitrypsin deficiency is a disorder that causes the absence or failure of alpha$_1$ antitrypsin, resulting in damaged lung tissue [21].

Childhood Respiratory Infections

A history of severe respiratory infections and asthma during childhood are significant determinants that possibly increase respiratory symptoms and the risk of obstructive disease in adulthood [31, 32].

4.1.3 Pathogenesis:

COPD mainly involves two underlying diseases: emphysema and chronic obstructive bronchitis. Individuals with COPD typically have features of both these conditions [22]. Lung inflammation, which is commonly initiated by the inhalation of tobacco smoke, particles or gases, induces emphysema and chronic obstructive bronchitis [1]. Inflammation is a normal immune response, however, in COPD it becomes exaggerated and abnormal from the typical protective immune response in the lungs [1, 33]. Overall, the inflammatory and structural changes in the airways worsen with COPD severity [1].

Emphysema is characterized by an enlargement of the distal airspaces past the terminal bronchioles, accompanied by the destruction of alveolar walls and capillary beds [34]. A significant characteristic of emphysema is the breakdown of elastin, a main connective tissue in lung parenchyma [1]. Lung destruction causes hyperinflation (air trapping) of the lungs by reducing the elastic recoil force that pushes air out of the lungs during expiration. As a result, there is an increase in residual volume, functional residual capacity, and total lung capacity. Smoking and alpha$_1$ antitrypsin deficiency have been proposed as causes of emphysema [33]. Smoking causes emphysema by initiating the movement of inflammatory cells into the lungs, resulting in an increased release of proteases. An increase of proteases, inflammatory cells and inflammatory mediators are significant mechanisms that amplify inflammation in COPD. The protease-antiprotease imbalance in COPD, with an excess of proteases, destroy lung tissue [1].

Proteases are a group of enzymes that breakdown elastin and other components of the alveolar walls by digesting proteins. Alpha$_1$ antitrypsin is an antiprotease enzyme that protects the lung from proteases and prevents the breakdown of lung tissue. Therefore, alpha$_1$ antitrypsin deficiency leads to damaged alveolar walls, as there is a decrease in protective alpha$_1$ antitrypsin activity [22].

Chronic bronchitis is characterized by increased mucus and cough production, and obstruction of airways caused by inflammation [33]. Inhaling smoke from tobacco and other pollutants produces an immune reaction leading to hypertrophy of mucus-producing glands and an increase in goblet cells [22]. Increased mucus production leads to a chronic productive cough, and is amplified by inflammatory mediators and proteases [1]. In the lungs, airways and respiratory circulation of individuals with COPD, there is a rise in macrophages, neutrophils and lymphocytes. All together, these inflammatory cells induce the release of inflammatory mediators, which intensify the inflammatory process and initiate structural changes [1].

4.1.4 Pathophysiology:

The pathological changes involved in COPD result in physiological irregularities, such as airflow obstruction and hyperinflation, gas exchange irregularities, pulmonary hypertension, and systemic consequences.

4.1.4.1 – Airflow Obstruction and Hyperinflation

Airway obstruction results from the loss of elastic recoil forces of the lungs and the destruction of alveolar walls caused by inflammation and narrowing in the small airways [35]. As a result, air gets trapped during exhalation, causing hyperinflation (i.e. overinflation of the lungs) during rest and exercise [35]. The degree of inflammation and narrowing of the small airways correlates with the reduction in the FEV_1/FVC ratio, accompanied by a fast decline in FEV_1 [1]. Static hyperinflation decreases inspiratory capacity and is frequently correlated with dynamic (i.e. progressively increasing) hyperinflation during physical activity [1]. These events further contribute to shortness of breath and restricted exercise capacity, which are commonly seen in people with COPD [1].

4.1.4.2 – Gas Exchange Irregularities

Gas exchange irregularities are characterized by hypoxemia with or without hypercapnia. Hypoxemia is defined as a significant decline in arterial blood oxygen concentration, and mediates its effects through hypoxia, an inadequate supply of oxygen to a

tissue [22]. Hypercapnia is defined as a significant increase in arterial blood carbon dioxide concentration [22]. The ventilation perfusion ratio is the amount of air that reaches the alveoli divided by the amount of blood that reaches the alveoli through pulmonary capillaries. A major mechanism in irregular gas exchange in COPD is the abnormal ventilation perfusion ratio due to an increase in physiological dead space from the destruction of lung parenchyma [35]. Airway inflammation, bronchoconstriction and mucus hypersecretion featured in COPD impair ventilation, and cause hypoxic vasoconstriction of respiratory vasculature obstructing circulation [35]. Overall, the transfer of oxygen from pulmonary capillaries into systemic circulation, and the exhalation of carbon dioxide into alveoli worsen with the severity of COPD [1].

4.1.4.3 – Pulmonary Hypertension

Pulmonary hypertension can develop in the late stage of COPD when gas exchange abnormalities are severe [35]. Pulmonary hypertension is caused by hypoxic vasoconstriction of the pulmonary arteries. This leads to structural modifications, such as hyperplasia in blood vessels and in smooth muscles [36]. The structural modifications produce constant hypertension, and right ventricular hypertrophy and dysfunction [35]. The destruction of the pulmonary capillary bed may also contribute to increased pulmonary blood pressure [1].

4.1.4.4 – Systemic Consequences

COPD often progresses into a multisystem disease, with the majority of people with COPD having concomitant diseases that are connected to mutual risk factors, such as aging, smoking, and physical inactivity [1]. The link between COPD and comorbidities is also explained by systemic inflammation [37, 38]. Inflammatory mediators enter the circulation through the peripheral airways and affect the distal organs [39]. The main systemic consequences of COPD include cardiovascular disease, diabetes, osteoporosis, skeletal muscle dysfunction, depression, anxiety and cognitive impairment [29, 40, 70].

Cardiovascular Comorbidities

Cardiovascular comorbidities of COPD include systemic arterial hypertension, congestive heart failure, stroke, coronary heart disease, atrial fibrillation, and venous thromboembolism [41]. Hypertension is a common comorbidity in COPD and is potentially the most frequent comorbidity [1]. Hypertension is associated with airflow obstruction [42], increased dyspnea scores, and decreased exercise capacity [43]. Congestive heart failure is one of the main reasons for hospitalization and death for individuals with COPD [44]. People

with stable COPD have a lower prevalence of congestive heart failure compared to those experiencing an exacerbation [45, 46]. Individuals with COPD are at a higher risk for ischemic stroke due to COPD-induced systemic inflammation and impaired coagulation [47, 48]. In addition, airflow obstruction and risk of stroke have a linear relationship [49], and approximately 4% of deaths in people with COPD are associated with an ischemic stroke [50]. Coronary heart disease, venous thromboembolism and atrial fibrillation are three consequences of COPD that have a prevalence of 30%, 29%, 23.3% in individuals with COPD, respectively [41, 51-53].

Metabolic Comorbidities

Metabolic comorbidities of COPD include diabetes, osteoporosis, loss of fat-free mass (cachexia) and skeletal muscle dysfunction. Individuals with COPD have a higher risk of developing diabetes [54, 55], and individuals with diabetes have a higher risk of developing COPD [56]. This simultaneous development of COPD and diabetes results from a combination of common risk factors and the presence of systemic inflammation [57, 58]. The development of osteoporosis and COPD also results from common risk factors and systemic inflammation. However, decreased physical activity is another factor that contributes to the link between COPD and osteoporosis [59]. Additionally, inhaled and systemic corticosteroid treatment increases the risk of developing osteoporosis [1]. Low bone mineral density and fractures are often seen in people with COPD even after being adjusted for age, smoking history and status, exacerbations and steroid treatment [1, 60]. Improving muscle function in people with COPD is vital because of the prevalence of cachexia and myopathy in this population. The prevalence of skeletal muscle dysfunction ranges from 10-15% in mild-to-moderate COPD to 50% in severe COPD [61]. Myopathy is a skeletal muscle disorder characterized by muscle atrophy, weakness and abnormal cell structure. Myopathy has a prevalence of 32% in people with stable COPD [62]. Myopathy has similar risk factors as COPD, such as smoking and age, however it is also influenced by systemic inflammation, physical inactivity, and oxidative stress [62].

Psychological Comorbidities

Psychological comorbidities of COPD include depression and anxiety, which are both commonly seen in people with COPD [63, 64]. The prevalence of depression and anxiety ranges widely from 10 to 42% and 10 to 19% in stable COPD, respectively [65]. Individuals with COPD and anxiety and/or depression show worse dyspnea after a 6-minute walk test than individuals with COPD without these psychological comorbidities [66]. Depression decreases quality of life, adherence to treatment, and physical activity [67-69]. Furthermore, depression is

more prevalent in people with COPD who exacerbate more often than in those with stable COPD [70].

Cognitive impairment is another common systemic consequence of COPD [71], with past studies demonstrating a higher rate of cognitive impairment in individuals with COPD overall [72-75], and versus age-matched healthy controls [76]. This topic is discussed in further details below.

4.2 Cognitive Impairment:

Cognitive impairment can be defined as the decline of intellectual functions of impactful severity with daily functional influences [77]. There are various levels of cognitive impairment ranging from mild cognitive impairment to dementia. Mild cognitive impairment (MCI) is defined as significant cognitive decline without notable functional influences on activities of daily living [78, 79]. Dementia is defined as having several cognitive impairments with memory impairment and one or more other cognitive deficits that significantly influence occupational and social functioning [80].

4.2.1 Frequency/Prevalence in COPD

Cognitive impairment is a very common manifestation of COPD [71], with past studies demonstrating a higher rate of cognitive impairment in individuals with COPD overall [72-75], and versus age-matched healthy controls [76]. A systematic review by Yohannes et al. [72] found a pooled prevalence of 25% for MCI and 32% for any cognitive impairment in those with COPD. A study by Martinez et al. [73], analyzing the 2006-2008 waves of the Health and Retirement Study, reported that 17.5% of participants with COPD had MCI. In addition, MCI was detected three times more in people with COPD (36%) compared to age-, sex- and education-matched healthy controls (12%) in a study using validated diagnostic criteria [76]. Singh et al. [74] found a higher prevalence of MCI in elderly people with COPD (27%) compared to people without COPD (15%), even after adjusting for age, sex and education. Martinez et al. [73] define prevalent disability as dependency in one or more activities of daily living at baseline. Results showed a higher prevalence of prevalent disability in participants with COPD (12.8%) compared to those without COPD (5.2%), with MCI being a main confounder [73]. Additionally, cognitive scores of people with COPD on the Mini-Mental State Examination were shown to be inversely related with the severity of COPD and were significantly lower in people with COPD compared to healthy controls [75]. Therefore, people with COPD seem to have a higher prevalence of

cognitive impairment compared to healthy individuals, and elderly people with COPD have a higher risk of developing MCI compared to their counterparts without COPD. People with COPD experience cognitive decline in domains such as attention, memory and executive dysfunctions [71, 76].

4.2.2 Causal Mechanisms

The link between COPD and cognitive impairment is multifaceted as there is no clear pathological mechanism causing cognitive decline in this population. However, there are several factors that enhance the risk of cerebral injury in individuals with COPD, such as hypoxemia and hypercapnia, exacerbations of COPD, vascular disease, inflammatory mediators, and smoking [71].

4.2.2.1 – Hypoxemia and Cognitive Function

Hypoxemia is defined as a significant decline in arterial blood oxygen concentration, and exerts its effects on cognition through hypoxia, an inadequate supply of oxygen to a tissue [22]. Thakur et al. [81] investigated the role of hypoxemia and oxygen therapy in people with COPD. The study revealed that people with a lower baseline oxygen saturation had a higher risk of cognitive impairment. In addition, results revealed that home oxygen therapy lowered the risk of cognitive impairment in people with COPD and was a protective treatment against cognitive impairment. Dodd et al. [71] hypothesized that hypoxia to brain tissue was possibly a central factor causing neuronal injury. Hypoxia may affect oxygen-dependent enzymes that produce significant neurotransmitters, such as acetylcholine [71]. However, there is evidence that goes against the hypothesis proposed by Dodd et al. [71]. A weak correlation was found between cognition and arterial oxygen saturation in two studies [82, 83], with oxygen saturation only accounting for 5% of the predicted variance in cognitive functioning. Overall, reports about the relationship between cognitive decline and hypoxemia are inconsistent. The relationship remains uncertain as cognitive impairment in people with COPD is caused by several factors and not solely by hypoxemia [71]. Therefore, some people without hypoxemia have cognitive impairment.

4.2.2.2 – Hypercapnia and Cognitive Function

Similar to hypoxemia, the correlation between arterial carbon dioxide tension and cognition varies between studies. Incalzi et al. (1997) found an inverse correlation between arterial carbon dioxide tension and complex attention, processing speed and memory, but not motor function, language and simple attention in people with hypercapnic respiratory failure [84].

Incalzi et al. (1993) also found a direct correlation between lower arterial carbon dioxide tension and higher function in attention, verbal memory and executive function [85]. Hypercapnia possibly causes the formation of free radicals and oxygen-dependent enzymes that could lead to neuronal damage [86]. However, in several studies no correlation was shown between hypercapnia and cognitive impairment [87, 88].

4.2.2.3 – COPD Exacerbations and Cognitive Function

In 2008, Ranieri et al. [89] conducted a study investigating elderly patients with acute exacerbation of COPD. After measuring cognitive status, results showed that the patients had low cognitive performance scores, a mean and standard deviation of 21±5 (range 0-30) on the Mini-Mental State Examination. In addition, Ranieri et al. [89] found that inflammatory mediators were significantly higher in patients with acute exacerbation of COPD than in patients with other illnesses. Inflammation plays a vital role in acute exacerbation of COPD as exacerbations are thought to represent the symptoms of increased inflammation [90]. Donaldson et al. [91] revealed that mucus purulence increases as the severity of exacerbation increases, suggesting further inflammation in patients with high severity exacerbations. Therefore, there may be a link between increased inflammation in patients with high severity exacerbations of COPD and cognitive impairment. Another study conducted in 2002 by Ambrosino et al. [92] investigated patients with COPD surviving acute chronic respiratory failure. Results revealed that these patients had lower scores on the Mini-Mental State examination at discharge compared to controls, which were patients with stable COPD with no past admission in the intensive care unit. Furthermore, Kirkil et al. [93] revealed that patients with COPD have weakened information processing and impaired attention and memory during an exacerbation.

4.2.2.4 – Obstructive Sleep Apnea and Cognitive Function

Patients with COPD suffer from daytime sleepiness and have trouble falling asleep [94]. This is problematic since sleep is crucial for learning, memory, and attention [88, 95]. Fletcher [96] states that approximately 20% of patients with COPD have sleep apnea syndrome. In a meta-analysis reviewing the cognitive function of patients with untreated obstructive sleep apnea by Beebe et al. [97], results showed an association of obstructive sleep apnea with vigilance, motor coordination and executive function. A study conducted by Roehrs et al. [98] found that patients with obstructive sleep apnea had a similar level of cognitive impairment to patients with COPD. Patients with obstructive sleep apnea had worse scores on cognitive

assessments in attention, a cognitive function relying on sleep. Patients with COPD had worse scores when tested on motor skills, a cognitive function possibly influenced by hypoxemia [98].

4.2.2.5 – Vascular Risk Factors and Cognitive Function

Vascular comorbidities have been suggested as a possible reason for brain changes in people with COPD [71]. A combination of risk factors for vascular disease (e.g., hypertension, smoking, alcohol intake, serum cholesterol, glucose levels, homocysteine levels, etc.) and peak expiratory flow rate were predictive of impaired processing speed and capacity on cognitive tests [99]. Additionally, elevated blood pressure was associated with a larger decline in logical reasoning, a measure of executive function [100]. The cognition of individuals with COPD could be negatively affected by vascular complications, as more than 50% of individuals with COPD were reported to have concurrent vascular disease [101]. In addition, a study by Villeneuve et al. [76] reported that participants with COPD had more cognitive complaints and vascular comorbidities than healthy control participants.

4.2.2.6 – Inflammatory Mediators and Cognitive Function

Several studies propose an association between inflammatory mediators, such as C-reactive protein, interleukin-6, interleukin-1b, and tumor necrosis factor-a, and cognitive impairment [102-105]. Increases in inflammatory mediators have been well documented in COPD [89, 90, 102]. As mentioned previously, Ranieri et al. [89] found that inflammatory indicators, such as C-reactive protein and erythrocyte sedimentation rate, were significantly higher in patients with acute exacerbation of COPD than in patients with other illnesses. Borson et al. [102] discovered a significantly higher amount of soluble tumor necrosis factor receptor 1(TNFR1) in patients with COPD compared to healthy controls. A high amount of TNFR1 is representative of chronic systemic inflammation [102]. Inflammation plays a vital role in acute exacerbation of COPD as exacerbations are thought to represent symptoms of increased inflammation [90].

4.2.2.7 – Smoking and Cognitive Function

Smoking status appears to relate to cognitive performance in individuals with COPD and is associated with a higher risk of Alzheimer's disease [106]. In a meta-analysis investigating the association of smoking with dementia and cognitive impairment, results showed that people who smoke had a larger annual decline in Mini-Mental State Exam scores than non-smokers [106]. Grant et al. [107] suggest that cigarette smoke worsens cerebral hypoxia by raising carbon monoxide levels, and as a result impairs cognition. In addition, smoking is associated with

impaired processing speed, verbal memory and Mini-Mental State Examination scores [71]. However, studies report associations between reduced lung function and cognitive function that are independent of smoking status [108, 109].

4.2.3 Consequences of Cognitive Impairment

Cognitive impairment can lead to functional disability and memory loss leading to a reduced quality of life even when the impairment is mild [110]. Tabert et al. [110] reported that functional deficits were greater in participants with MCI compared to healthy age-, sex-, and education-matched controls. Antonelli-Incalzi et al. [111] and Martinez et al. [73] found that COPD and cognitive impairment are both independently associated with prevalent disability. Furthermore, patients with COPD and MCI are at a greater risk of disability than patients with COPD or MCI alone [73]. In addition, dependency in instrumental activities of daily living in patients with COPD were correlated with cognitive impairment and older age [111].

Mild cognitive impairment is a known risk factor for dementia and has been associated with reduced adherence to treatment and increased mortality in COPD patients [111-113]. Antonelli-Incalzi et al. [112] investigated elderly patients with stable COPD and found that drawing impairment is a potential risk factor for mortality. Recently, Cleutjens et al. [113] conducted a cross-sectional observational study comparing the pulmonary rehabilitation dropouts and outcomes between patients with COPD with or without cognitive impairment. Results showed that 15.3% of all patients dropped out of the pulmonary rehabilitation program, 23.3% of which had cognitive impairment compared to 10.3% without cognitive impairment. The authors concluded that individuals with COPD and cognitive impairment are at more of a risk of not complying to and/or dropping out of a pulmonary rehabilitation program.

Early detection and management of this comorbidity could thus have an important impact on COPD treatment outcome. PR, particularly the exercise training component, has been proposed as a promising approach to mitigate cognitive declines in patients with COPD [114-120] and will be discussed in further details later.

4.3 Clinical Management of COPD

Management of COPD is aimed at alleviating symptoms, preserving functional capacity, increasing exercise tolerance and health status, and decreasing the intensity and incidence of disease exacerbations [1, 121]. Pharmacologic treatment of COPD should be tailored to the individual needs of the patient by considering the patient's priorities, comorbidities, severity of

symptoms, and risk of exacerbations [1]. The pharmacologic treatments of COPD include the use of bronchodilators, such as inhaled B_2-adrenergic agonists and anticholinergic agents, and steroids, such as inhaled corticosteroids [1]. Antibiotics are prescribed to treat the complications that come with COPD, such as bacterial infections [1].

Bronchodilators, such as inhaled B_2-adrenergic agonists, anticholinergic drugs or their combination, produce bronchodilation by stimulating adrenergic receptors or by hindering parasympathetic cholinergic receptors [1]. Adrenergic receptors initiate relaxation of bronchial smooth muscle and therefore relax the smooth muscle of airways when stimulated [1]. Cholinergic receptors initiate contraction of bronchial smooth muscle and therefore blocking them relaxes the smooth muscle of the airways [1]. Overall, bronchodilators help improve FEV_1 and decrease dynamic hyperinflation at rest and during exercise [122, 123]. In addition, raising the dose of an anticholinergic or a B_2-adrenergic agonist is helpful for increasing mean daily peak flow rates in those with COPD[124], but is not as beneficial in stable COPD [125]. Therefore, bronchodilators are crucial for the management of symptoms and should be prescribed on a regular basis to control symptoms [1].

Anti-inflammatory agents, such as inhaled corticosteroids, are used to treat COPD to reduce airway activity and respiratory symptoms [121]. Corticosteroids are termed anti-inflammatory immunosuppressant because of their ability to suppress the immune system by preventing the release of inflammatory mediators [22]. A clinical trial involving corticosteroid therapy reported a modest improvement in medical outcomes, such as increases in FEV_1 and shorter hospital stays [126]. However, many studies have reported that regular treatment with inhaled corticosteroids does not improve FEV_1 long-term or reduce mortality in people with COPD [127]. Inhaled corticosteroids are more helpful in increasing lung function, decreasing exacerbations and improving health status when combined with B_2-adrenergic agonists in moderate to very severe COPD [128, 129]. Asthma and COPD have different inflammatory mediators and cells involved in their pattern of inflammation [1]. For this reason, inhaled corticosteroids have a limited effect on COPD patients but work well with asthma patients.

Antibiotics are reported to have a positive but small effect on patients with emphysema and bronchitis [130]. Recent studies have reported that antibiotics can lower the rate of exacerbations when used regularly [131, 132]. The most common bacteria encountered during bronchitis and emphysema are *S. pneumoniae, H. influenza,* and *M. catarrhalis*. Specific

antibiotics are given according to the severity of the exacerbations the patient is experiencing [121].

Non-pharmacological management of COPD includes smoking cessation, immunization to influenza and pneumococcal infections, oxygen therapy and pulmonary rehabilitation. Smoking cessation is an important method that slows down the progression of COPD [41] and is considered the most crucial factor to prevent or slow down COPD [116]. Respiratory tract infections can be fatal to individuals with COPD and therefore measures to avoid infections should be taken [22]. People with COPD are encouraged to get vaccines, such as influenza and pneumococcal vaccinations [41]. Influenza vaccinations can decrease the incidence of lower respiratory tract infections [133] and mortality in individuals with COPD [134]. Oxygen therapy is prescribed for individuals with severe hypoxemia with an oxygen saturation of less than or equal to 88% while sleeping [121] or with a PaO_2 of 55 mm Hg or less [121, 135]. The goal of oxygen therapy is to administer oxygen to maintain an oxygen saturation of at least 90% [22]. Long-term administration of oxygen has been shown to improve the survival rates of individuals with severe resting hypoxemia [136]. Lastly, pulmonary rehabilitation is crucial to the management of COPD as it is the most efficient therapeutic approach to improve shortness of breath, health status and exercise tolerance in individuals with COPD [137]. Furthermore, pulmonary rehabilitation is suitable for individuals with all levels of COPD severity. Figure 2 illustrates the recommended approach to manage COPD according to disease severity [138].

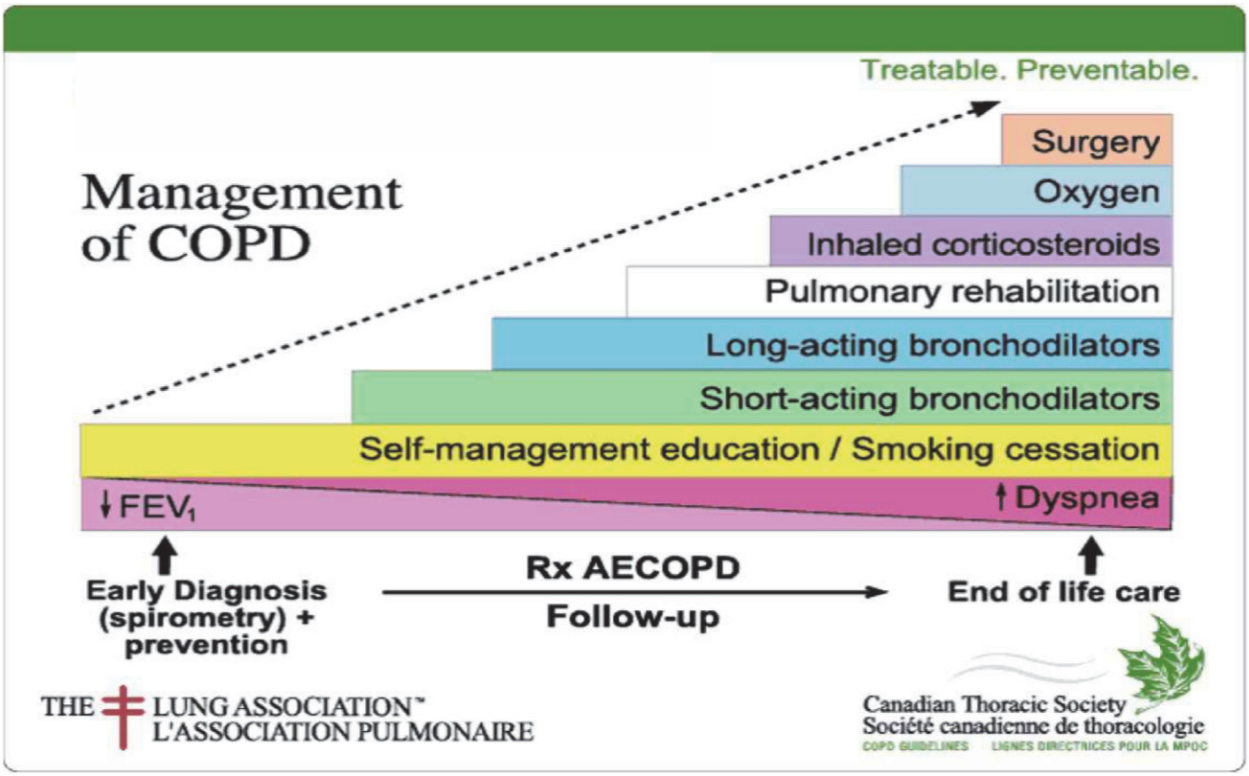

Figure 2 – A comprehensive approach to the management of chronic obstructive pulmonary disease (COPD). AECOPD: Acute exacerbation of COPD; RX: Treatment.
Taken from CTS COPD Recommendations [138]

4.4 Pulmonary Rehabilitation (PR)

4.4.1 Description of PR

The American Thoracic Society and European Respiratory Society define PR as 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-adherence to health-enhancing behaviors" [139]. It is an individualized intervention targeting the unique needs of the patient based on disease severity, complexity, and comorbidities [139]. There is extensive evidence that PR reduces symptoms, improves exercise tolerance, and enhances health-related quality of life in people with COPD [137]. Additionally, PR stimulates long-term health-enhancing behavior change and promotes autonomy [139]. As a result, PR is now widely recognized as a core component in the management of COPD [1, 140].

4.4.2 Documented Effects of the Exercise Component of PR

Exercise training is considered key to successful PR and the best way to improve muscle function in patients with COPD [141-143]. Muscle adaptions that have been documented in response to exercise training in patients with COPD include significant improvements in cellular bioenergetics, such as a decrease in half-time of phosphocreatine recovery, and a decrease of inorganic phosphate to phosphocreatine ratio and intracellular pH at a submaximal work rate [141]. In addition, an increase in skeletal muscle oxidative capacity and reduction in exercise-induced lactic acidosis were reported in patients with moderate-to-severe COPD after endurance training [143]. Furthermore, significant increases in muscle strength and mass were seen in patients with COPD after combined aerobic and strength training [142]. Improvements in muscle function lead to a lower ventilatory requirement for a given work rate [144]. In turn, this leads to a reduction in dyspnea for a given workload [144, 145], and an increase in exercise tolerance [144-146]. Other beneficial effects of exercise training include reduced symptoms of anxiety and depression [117], lower respiratory symptom burden [147], and improved cardiovascular function [148, 149].

4.4.3 Optimal Training Intensity for People With COPD

Present guidelines for PR support the use of continuous training at high intensity (CTHI) for patients with COPD [139, 150]. However, complying to this training intensity is difficult for patients and results in low adherence rates [151]. In 1997, Maltais et al.[151] conducted a study investigating the feasibility and efficacy of high-intensity training in 42 participants with COPD. Participants trained for 30 minutes a day, three times a week for 12 weeks on cycle ergometers, with a training intensity of 80% of their baseline maximal power output. Although a significant improvement in exercise tolerance was observed after training, the target intensity was attained in only zero, three, five, and five patients at the second, fourth, tenth, and twelfth week, respectively. In addition, participants had difficulty sustaining the high-intensity exercise for the entire exercise duration [151].

In 2006, Probst et al.[152] conducted a study investigating 11 participants with COPD who each performed circuit training in cycling, walking and leg press resistance training, stair climbing and arm cranking . Participants trained three times a week for 12 weeks. For ergometer cycling, the training intensity was targeted at 60% of the maximal work rate achieved on the baseline incremental exercise test. Results revealed that cycling, walking and stair climbing led to more cardiopulmonary stress, such as oxygen consumption, minute ventilation and heart rate compared to resistance training and arm cranking. Furthermore, cycling resulted

in more symptoms of dyspnea, as measured by the Borg scale, compared to resistance training. Authors concluded that high-intensity endurance training resulted in higher cardiopulmonary stress and more symptoms [152].

More tolerable exercise interventions, such as continuous training at the ventilatory threshold (CTVT) and high intensity interval training (HIIT), have therefore been recommended as alternative methods for people with COPD, with the rationale that they may be associated with higher adherence rates and thereby potentially be more effective in the long run [153-155].

The ventilatory threshold is defined as the point during incremental exercise where ventilation increases at a faster rate than oxygen consumption [156]. In 1994, Vallet et al.[156] conducted a study investigating 20 patients with COPD who were randomized into a training group and a control group. The training group walked four times a week for 2 months at a heart rate equivalent to their metabolic level at the ventilatory threshold. Results revealed that the training group had an increase in symptom-limited oxygen consumption, maximal ventilation, and ventilatory threshold. Furthermore, the training group had a decrease in ventilation and breathing frequency at 50% and 75% of VO_2. Authors concluded that training at the ventilatory threshold could improve exercise tolerance in patients with COPD while providing tolerable levels of ventilation [156].

In a subsequent study[154], the same group compared two methods of training, an individualized training program and a standardized training program. Twenty-four participants with chronic airway limitation were randomized into either the individualized or standardized training program. The target intensity for the individualized program was based on the heart rate measured at the ventilatory threshold. The target intensity for the standardized training program was based on the heart rate corresponding to 50% heart rate reserve. The ventilatory threshold was determined by analyzing the participant's carbon dioxide output as a function of oxygen uptake during the baseline incremental exercise test. The 50% of maximal heart rate reserve was calculated by a formula provided by the American College of Sports Medicine [158]. Both groups trained five times a week for 4 weeks on cycle ergometers. Results revealed that training at the ventilatory threshold was associated with an increase in symptom limited oxygen consumption and maximal oxygen pulse. Furthermore, the participants training at the ventilatory threshold had a decrease in minute ventilation, carbon dioxide production, and venous lactate concentration at a given workload, while the standardize training group had no significant

changes in these outcomes. Even though both groups had a similar absolute training intensity, the individualized program led to better physiological outcomes compared to the standardized program [154]. This study supports earlier findings that continuous training at the ventilatory threshold is associated with lower levels of dyspnea and ventilation, and is potentially more tolerable than continuous training at a high intensity for individuals with COPD [154, 156, 157].

Interval training is considered a good alternative for patients who have difficulty reaching their target duration or intensity of continuous training due to disease-related shortness of breath or fatigue [151, 152]. Interval training consists of alternating short intervals of exercise at a certain intensity with intervals of rest or active recovery (e.g., unloaded pedaling). In 2002, Vogiatzis et al.[159] conducted a randomized controlled parallel group study investigating the effectiveness of interval training compared to continuous training in 36 patients with COPD. Participants in the continuous training group trained on cycle ergometers at 50% of their baseline peak work rate (measured previously) for 40 minutes per day, 2 days a week for 12 weeks. Participants in the interval-training group trained for the same length of time, frequency and duration as the continuous training group. However, they were instructed to train at 100% of their baseline peak work rate for 30-second intervals interspersed with 30-second rest intervals. The total training time and amount of work performed per session for the interval-training group was devised to equate to the work that these participants would have performed if they were assigned to the continuous training group. Results revealed that exercise tolerance, measured as peak work rate on a symptom-limited incremental cycling test, significantly increased in both training groups. Continuous and interval training also resulted in a significant improvement in total quality-of-life score on the Chronic Respiratory Disease Questionnaire. Furthermore, both groups presented significant reductions in minute ventilation at a given work rate after the training program. Authors concluded that interval training produces similar exercising-training adaptations to those produced by continuous training [159].

In a subsequent randomized controlled parallel group study[160], the same group investigated skeletal muscle adaptations to interval training compared to continuous exercise training in 19 patients with advanced stable COPD. All participants trained 3 days a week for 10 weeks. Participants in the continuous training group trained at an average intensity of 75 +/- 5% of their baseline peak work rate for 30 minutes per day. Participants in the interval training group trained at an average intensity of 124 +/- 15% of their baseline peak work rate for 30-second intervals interspersed with 30-second rest intervals for 45 minutes a day. After interval training,

results revealed a significant increase in cross-sectional areas of type 1 and 2a fibers, and a substantial capillary-to-fiber ratio enlargement in the vastus lateralis muscle. Furthermore, interval training also resulted in a significant improvement in peak work rate and lactate threshold. However, these skeletal muscle adaptations were not significantly different than those elicited after constant-load exercise training. Interestingly, interval training resulted in significantly lower scores of dyspnea and leg discomfort compared to constant-load exercise training. Therefore, these results support the group's earlier findings that interval training produces equal exercise-training adaptations as moderately intense continuous training, but with less training symptoms [160].

Previous studies, including Vogiatzis et al.'s studies, report similar exercise-training adaptations in continuous and interval training protocols [159-161]. Even though continuous training and interval training have similar effects, interval training is beneficial to patients with COPD who are limited by their symptoms and thus incapable of complying to continuous training at high intensity [139].

In a study conducted in our laboratory[157], Rizk et al. investigated 35 patients with COPD who were randomized to either a continuous training at high intensity group (CTHI), a continuous training at ventilatory threshold group (CTVT), or a high-intensity interval training group (HIIT). All groups trained three times a week for 12 weeks on cycle ergometers. Participants training at the ventilatory threshold had a target intensity of the heart rate reached at the ventilatory threshold on their baseline incremental exercise test. Results revealed that training at the ventilatory threshold produced a decrease in respiratory exchange ratio, respiratory rate and heart rate compared to CTHI. Interval training was associated with a decrease in pulse oxygen saturation and an increase in respiratory rate, minute ventilation and minute ventilation/maximal voluntary ventilation compared to CTHI. Authors concluded that training at the ventilatory threshold was more physiologically tolerable for patients with COPD than continuous training at a standardized intensity, thereby supporting Vallet et al.'s findings [154,156]. Authors also concluded that, compared to CTHI and CTVT, interval training was associated with more physiological strain, lower post-exercise alertness, and reduced 12-week adherence.

4.5 Effects of Exercise-Training on Cognition

4.5.1 Exercise and Cognition in Healthy Older Adults

Exercise can have beneficial effects on cognitive function in healthy older adults [162-166]. In a systematic review by Angevaren et al. [162], eight out of the 11 studies reported improvements in cardiorespiratory fitness in the aerobic exercise interventions groups. These improvements coincided with increases in cognitive function, specifically in motor function, auditory attention, cognitive speed and visual attention. A systematic review by Tseng et al. [163] reported that an exercise intervention of 6 weeks with a frequency of three times per week for 60 minutes had a beneficial effect on cognitive function in healthy older adults. In a systematic review by van Uffelen et al. [164], significant positive exercise effects were seen in information processing, memory, and executive function in healthy older adults. Several studies report an improvement in cognitive functions as a result of short-term [165], and long-term exercise training in healthy older adults [166]. Nouchi et al. (2014) investigated the effects of a four-week combined aerobic, strength, and stretching exercise intervention in healthy older adults. The authors found that the combination exercise intervention improved executive functions, episodic memory, and processing speed versus the control group that did not partake in the exercise intervention [165]. Therefore, exercise can have beneficial effects on cognitive function resulting from psychological and physiological modifications occurring during exercise interventions, which are discussed in further details below.

Nouchi et al. [165] observed the pathway of improvement of cognition after exercise from a cognitive and neuroscience viewpoint [165]. From a cognitive science view, the authors refer to the overlapping hypothesis. The overlapping hypothesis suggests that improvements of cognition by an exercise would occur if the cognitive processes during the exercise tasks and non-exercise tasks (cognitive measures) are overlapped and share similar cognitive processes. In this study, participants used their processing speed, executive functions, and episodic memory when performing the exercise intervention. Processing speed and executive functions are required to switch between exercises, perform exercises at a fixed rhythm, plan actions, and complete movements as many times as possible. Episodic memory is required to remember an order of movements in exercises, and remember how to properly use machines. The participants recruited these cognitive processes to perform the exercises. The exercises and measures of cognition shared the same cognitive processes, and as a result the exercise intervention further improved the cognitive processes [165].

From a neuroscience viewpoint, the improvements in the cognitive processes are a result of modifications occurring directly in the brain, such as brain structure, function and plasticity [165]. Past studies using MRI have reported that specific types of exercise selectively modify brain structure, brain function, and brain plasticity in older adults [167, 168]. A study by Erickson et al. (2011) reported an increase in brain volume of the hippocampus, which is involved in the storage of memory, after 1 year of a walking exercise intervention [167]. In addition, Colcombe et al. (2004) reported an increase in activity in the middle frontal gyrus, which has a role in executive functions and processing speed, after 6 months of an aerobic exercise intervention [168].

From a physiological viewpoint, improvements in cognition are possibly a result of cerebrovascular benefits from regular involvement in physical activity [169]. A study by Guiney et al. [169] explored the possibility that cerebral blood-flow regulation efficiency supports exercise and cognition associations in healthy young adults. Multiple regression analyses showed that increased physical activity and aerobic fitness predicted higher cerebral blood-flow regulation and cognitive inhibitory control. Interestingly, better cerebral blood-flow also predicted improved cognitive inhibitory control. In addition, mediation analyses revealed that increased physical activity could improve cognitive inhibitory control via better cerebral blood-flow regulation [169]. Therefore, cerebral blood-flow regulation could be a possible physiological mechanism that explains exercise-related cognitive benefits.

4.5.2 Exercise and Cognition in COPD

In COPD, seven published studies have reported on the documented effects of six exercise interventions on cognition [114-120]. Emery et al. [115, 116] investigated the effects of a 1-month pulmonary rehabilitation program on the psychological, physiologic, and cognitive function in 64 participants with COPD. Participants trained 5 days a week, 4 hours a day, for 1 month. Exercise sessions involved 45 minutes of aerobic exercise, such as rapid walking, riding on a stationary bicycle, and arm ergometry, however intensity was not specified in the study. In addition, participants completed upper body strengthening exercises each session, and pool exercises twice a week. Results showed a significant improvement in the Trail Making B, which measures an individual's attention and executive functions, and Digit Symbol test, which measures an individual's processing speed. In addition, a significant improvement was observed in the Finger Tapping test with the dominant hand. Overall, the results suggest that

exercise-based rehabilitation could improve cognitive functioning in patients with COPD [115, 116].

In a subsequent study[117], the same group conducted a randomized controlled trial comparing the effects of a combination of exercise, education, and stress management (exercise intervention) to those of education and stress management (attention control) to those of no treatment (control) in 79 participants with COPD. The intervention was 10 weeks, with the active intervention and attention control groups both partaking in 16 educational classes and 10 stress management classes. The exercise group completed a total of 37 training sessions. During the first 5 weeks of the program, the exercise group trained five times a week, which included 45 minutes of aerobic and strength training. During the last 5 weeks, the exercise group trained three times a week for 60-90 minutes. Results showed significant improvement in verbal fluency in the exercise group only [117].

Kozora et al. [119] investigated the effects of a 3-week rehabilitation program on the psychological, physical, and cognitive function in 30 participants with COPD. The 30 participants were compared to 29 participants with COPD that were not involved in the rehabilitation program, and to 21 healthy controls. Participants trained four times a week for 3 weeks. Exercise intervention variables, such as the type and intensity of exercise were not reported. Participants with COPD were divided into 2 groups, those who had impaired and nonimpaired performances on neuropsychological tests before and after the intervention. Results showed significant improvements, from baseline to post-intervention, in verbal memory, visuospatial functions and visual attention in those who had an impairment at baseline and underwent the rehabilitation. The results emphasize a potential cognitive benefit to 3 weeks of rehabilitation in patients with COPD [119].

Aquino et al. [114] investigated the comparative effectiveness of high-intensity aerobic training to high-intensity aerobic training combined with resistance training on cognition in 28 participants with COPD. All participants trained twice a day, five times a week for 4 weeks. Participants in the aerobic training group completed two 30-minute sessions a day of aerobic exercise on a treadmill at 70-90% of their heart rate maximum. Participants in the combined training group completed a similar 30-minute session of aerobic exercise and one 30-minute session of resistance exercise. Participants performed 3 sets of 4-10 repetitions at 70-90% of their one repetition-maximum. Overall, results showed improvement in long-term memory,

verbal fluency, attentional capacity, apraxia, and reasoning skills in both groups. However, the combined training group had significantly higher improvements in long-term memory, apraxia, and reasoning skills compared to the aerobic training group [114].

Pereira et al. [120] conducted a study investigating the effects of a 3-month pulmonary rehabilitation program on cognition in 34 participants with COPD. Participants trained three times a week for 3 months. The exercise intervention included aerobic and resistance training, however intensity was not specified in the study. Results showed a significant improvement in the Rey Auditory Verbal Learning Test, which assessed verbal learning and memory, after the rehabilitation program [120].

Etnier et al. (2001) conducted a study investigating fluid intelligence after a short-term and long-term exercise intervention in older patients with COPD [118]. Fluid intelligence represents an individual's performance in abstractions and relations [170], and reflects reasoning and problem-solving skills [118]. Fluid intelligence was assessed by forms A and B of Scale 3 of the Culture Fair Intelligence Test. Participants were randomized into either a 3-month exercise intervention or an 18-month intervention. The exercise intervention included aerobic exercise (walking), upper body strength training, and stretching exercises. Participants trained 3 times a week, and intensity was prescribed based on ratings of perceived dyspnea. Results revealed that at 3-months there was a significant increase in fluid intelligence in both groups. In the short-term group (3-month intervention), there was no change in fluid intelligence from 3 months to 18 months, but a modest increase was seen in the long-term group (18-month intervention) [118].

The previous studies support a positive effect of exercise interventions, such as aerobic and resistance training, on cognition in COPD. However, among the seven previously discussed articles [114-120], there are inconsistencies in the study design, exercise-training protocols, and measures of cognition. Current literature lacks sufficient reporting of intervention variables, such as type of exercise, session duration, and intensity, to apply beneficial exercise interventions to patients with COPD. Furthermore, the comparative impact of CTHI, CTVT, and HIIT on cognitive function in individuals with COPD has yet to be investigated. The general aim of the proposed study was thus to compare the effects of these three different exercise-training protocols on cognition in people with COPD.

5. RATIONALE

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by chronic obstruction in the airways. Patients with COPD are often caught in a downward spiral that goes from chronic airflow limitation to shortness of breath, activity limitation, deconditioning, and eventually invalidity and poor quality of life. Although COPD cannot currently be cured, it is possible to slow down disease progression with pulmonary rehabilitation (PR). PR, which combines exercise training, self-management education, and psychosocial support, has become widely recognized as a core component in the management of COPD [1, 140]. Exercise training is considered key to successful PR. Current PR guidelines advocate continuous high-intensity training (CTHI) [139]. However, complying to this training intensity is difficult for patients and results in low adherence rates [151]. More tolerable exercise interventions, such as continuous training at the ventilatory threshold (CTVT) and high-intensity interval training (HIIT), are recommended as alternative methods with higher adherence rates and potentially greater long-term effectiveness [154-157, 159-161]. The general goal of this study was to compare the effects of these three different exercise-training approaches (CTHI, CTVT, and HIIT) on key health parameters in people with COPD. One of these key health parameters was cognitive function. Cognitive impairment was detected three times more often in patients with COPD compared to healthy controls in a study using validated diagnostic criteria [76]. Mild cognitive impairment (MCI) is a known risk factor for dementia and has been associated with reduced adherence to treatment and increased mortality in COPD patients [111-113]. Early detection and management of this comorbidity could thus have an important impact on COPD treatment outcome. PR, particularly the exercise training component, has been proposed as a promising approach to mitigate cognitive declines in COPD patients [114-120]. However, the comparative effects of CTHI, CTVT, and HIIT on cognitive function in individuals with COPD has yet to be investigated. The aim of the proposed study was thus to compare the effects of these three different exercise-training protocols on cognition in people with COPD.

6. OBJECTIVES and HYPOTHESES

Objectives

To compare, in people with COPD:

i) The effects of 12 weeks of CTHI, CTVT, and HIIT on cognition in domains that are typically affected in COPD and previously shown to respond to exercise training such as, attention and executive functions, verbal learning and memory, visuospatial abilities, and processing speed.

ii) The maintenance of these effects at a 1-year follow-up.

Hypotheses

Based on the current literature, we hypothesized that:

i) **Short-term changes:**

   a. **Within-subjects:** Cognitive scores would improve significantly in all groups combined after 12 weeks of exercise training for all the domains measured, namely attention and executive functions, verbal learning and memory, and processing speed. This hypothesis was based on the current literature documenting improvements in these domains after exercise training interventions in people with COPD [114-120].

   b. **Between-subjects:** Cognitive scores would improve similarly between all three groups after 12 weeks of exercise training. This hypothesis was based on earlier findings from our group[157], showing similar short-term gains in exercise tolerance from pre- to post-intervention between CTHI, CTVT and HIIT. Therefore, we expected similar results for cognition, as exercise capacity and cognition have been shown to be positively associated in several studies [114-120].

ii) **Long-term changes:**

   a. **Within-subjects:** Cognitive scores would decrease in all groups combined from 12 weeks (post-rehab) to 1 year. This hypothesis was based on earlier findings by Emery et al. (2003) showing a decrease in cognitive performance, in executive functions and processing speed, from week 10 (post-rehab) to 1 year [171].

   b. **Between-subjects:** Gains in cognition would be better maintained at 1 year in the CTHI and CTVT groups than in the HIIT group. This hypothesis was based

on earlier findings by Emery et al.'s (2003) 1-year follow-up showing that participants who adhered to their exercise-training program maintained their improvements in cognition [171]. Additionally, Etnier et al. [118] reported a modest increase in fluid intelligence in the long-term training group from 3 months to 18 months. Earlier results from our trial showed a lower adherence rate in the HIIT group [157]. Therefore, we expected the HIIT group to maintain cognitive gains less than CTHI and CTVT.

7. ARTICLE: Short- and Long-Term Changes in Cognitive Function After Exercise-Based Rehabilitation in People with COPD

Primary Author:

Brent Rosenstein[1,2], brent.rosenstein@icloud.com

Co-Authors:

Anna Smyrnova[3], annaperkova@gmail.com

Amanda Rizk[4], amanda.rizk@concordia.ca

Frédérique Escudier[5,6], frederique.escudier@gmail.com

Jean-François Gagnon[5,6], gagnonjf@hotmail.com

Véronique Pepin[1,2,4], veronique.pepin@concordia.ca

Institution

Department of Health, Kinesiology, and Applied Physiology, Concordia University

Affiliations:

[1]Department of Health, Kinesiology, and Applied Physiology (HKAP), Concordia University

[2]Axe Maladies Chroniques, Centre de recherche du CIUSSS du Nord de l'Ile de Montréal (CR-CIUSSS-NIM)

[3]Department of Mathematics and Statistics, Concordia University

[4]PERFORM Centre, Concordia University

[5]Centre d'Études Avancées en Médecine du Sommeil, CR-CIUSSS-NIM

[6]Département de psychologie, Université du Québec à Montréal (UQAM)

7.1 Abstract

Objective: To compare the 12-week effects of continuous high-intensity training (**CTHI**), continuous training at the ventilatory threshold (**CTVT**) and high-intensity interval training (**HIIT**) on cognition, and the 1-year maintenance of these effects in people with COPD.

Methods: Participants were randomized to **CTHI, CTVT,** or **HIIT** and underwent 12 weeks of three times weekly training on cycle ergometers. The intensity phase included 25 minutes of pedaling at 80% of peak wattage (W_{peak}) for **CTHI**. For **CTVT**, the intensity was set at the ventilatory threshold, while **HIIT** consisted of 30-second intervals at 100% of W_{peak} alternated with unloaded pedaling. Session duration for **CTVT** and **HIIT** was calculated to ensure comparable total work as for **CTHI**. Assessments were made at baseline (**week 0**), program completion (**week 12**) and 1 year after baseline (**year 1**). Cognition was assessed with a neuropsychological testing battery. Global cognitive function was assessed using the Montreal Cognitive Assessment (MoCA).

Results: Thirty-six participants (64% women, mean age: 67.5±9 years) with moderate COPD were randomized. The 12-week effects of exercise training on cognition were small or very small, except for visuospatial abilities, which detected larger effects especially in participants with mild cognitive impairment at baseline. There was considerable heterogeneity between intervention groups. **CTHI** was the only group with medium-to-large effects in each cognitive domain assessed. At year 1, gains and losses in cognition were seen in all groups.

Conclusion: In COPD, 12 weeks of training led to small changes in cognition, with notable heterogeneity between exercise protocols and across cognitive domains.

Keywords: COPD, pulmonary rehabilitation, exercise training, cognitive function

7.2 Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterized by chronic obstruction in the airways. Patients with COPD are often caught in a downward spiral that goes from chronic airflow limitation to shortness of breath, activity limitation, deconditioning, and eventually a poor quality of life. Although COPD cannot currently be cured, it is possible to slow down disease progression with pulmonary rehabilitation (PR).

PR, which combines exercise training, self-management education, and psychosocial support, has become widely recognized as a core component in the management of COPD [1, 140]. Exercise training is considered key to successful PR. Current PR guidelines advocate continuous high-intensity training (CTHI) [139]. However, complying with this training intensity can be difficult for patients and can result in lower adherence rates [151]. More tolerable exercise interventions, such as continuous training at the ventilatory threshold (CTVT) and high-intensity interval training (HIIT), have thus been recommended as alternative methods with potentially higher adherence rates and better long-term effectiveness [154-157, 159-161].

Cognitive impairment is a frequent comorbidity in people with COPD [71], with past studies demonstrating a higher rate of cognitive impairment in individuals with COPD overall [72-75], and versus age-matched healthy controls [76]. Cognitive impairment is generally defined as the decline of intellectual functions of impactful severity with daily functional influences [77], while mild cognitive impairment (MCI) is defined as significant cognitive decline without notable functional influences on activities of daily living [78, 79]. A systematic review by Yohannes et al. [72] found a pooled prevalence of 25% for MCI and 32% for any cognitive impairment in those with COPD. In another study using validated diagnostic criteria, MCI was detected three times more often in patients with COPD (36%) compared to age-, sex- and education-matched healthy controls (12%) [76]. MCI is a known risk factor for dementia and has been associated with reduced adherence to treatment and increased mortality in COPD patients [111-113]. Early detection and management of this comorbidity could thus have an important impact on COPD treatment outcome. PR, particularly the exercise training component, has been proposed as a promising approach to mitigate cognitive declines in COPD patients [114-120]. However, the comparative effects of CTHI, CTVT, and HIIT on cognitive function in individuals with COPD has yet to be investigated.

The general aim of the proposed study was thus to compare the effects of these three different exercise-training protocols on cognition in people with moderate to severe COPD. More specifically, the study objectives were to compare, in people with COPD: 1) the effects of 12 weeks of CTHI, CTVT, and HIIT on cognition in domains that are typically affected in COPD and previously shown to respond to exercise training such as, attention and executive functions, verbal learning and memory, visuospatial abilities, and processing speed; and 2) the maintenance of these effects at a 1-year follow-up.

Improvements in cognitive domains, such as attention and executive functions, verbal learning and memory, and processing speed after exercise-training interventions in people with COPD are well documented [114-117, 120]. Therefore, we hypothesized that, for all groups combined, cognitive scores would improve after 12 weeks of exercise training in these domains Additionally, earlier findings from our team, driven from the same trial as the present study [157], showed similar short-term gains in exercise tolerance from pre- to post-intervention between CTHI, CTVT and HIIT. Therefore, we expected similar results for cognition, since exercise capacity and cognition have been shown to be positively associated in several studies [114-120]. . As such, between the three intervention groups, we hypothesized similar short-term improvements in cognitive scores after 12 weeks of exercise training.

Earlier findings by Emery et al. (2003) showed a decrease in cognitive performance, namely processing speed, from week 10 (post-rehab) to 1 year [171] when no maintenance component was offered to participants. Therefore, at the 1-year follow-up, we hypothesized that, for all groups combined, cognitive scores would decrease from 12 weeks (post-rehab) to 1 year. Additionally, earlier results from our team using data from this trial showed a lower adherence rate in the HIIT group [157]. Therefore, we expected the HIIT group to show poorer maintenance of cognitive gains than CTHI and CTVT at the 1-year follow-up. As such, between the three groups, we hypothesized that long-term gains in cognition would be better maintained at 1 year in the CTHI and CTVT groups than in the HIIT group.

7.3 Methodology

7.3.1 Study Design

The present study stems from a larger trial [157], which aimed to compare the effects of different exercise-training protocols on several health parameters in people with COPD. Cognition, a secondary outcome in the larger trial, was the main outcome of the current study. The trial followed a prospective, randomized, parallel-group design with blinding of outcome assessors. Individuals who met the eligibility criteria and agreed to participate were randomly assigned to one of three exercise-training groups: the continuous high-intensity training (CTHI) group, the continuous training at the ventilatory threshold (CTVT) group, or the high-intensity interval training (HIIT) group. All groups received standardized comprehensive self-management education from the same health care practitioners. Assessments were made at baseline (week 0), program completion (week 12), and 1 year after program initiation (year 1).

7.3.2 Participants

The present study used data collected in 36 individuals with COPD. Participants were recruited at the Hôpital du Sacré-Coeur de Montréal according to the following criteria: Inclusion: 1) clinically stable COPD; 2) age ≥ 40 years; 3) smoking history ≥ 10 American pack-years (20 cigarettes per pack); 4) post-bronchodilation forced expiratory volume in one second (FEV_1) less than 80% of the predicted normal value; 5) FEV_1 to forced vital capacity ratio less than 0.7. Exclusion: 1) exacerbation of respiratory symptoms in the preceding 4 weeks; 2) contraindication to exercise testing based on guidelines from the American Thoracic Society [172]; 3) active condition other than COPD that can influence exercise tolerance; 4) oxygen therapy; 5) participation in a pulmonary rehabilitation program in the preceding year; 6) inability to complete baseline evaluations. Ethical approval was obtained from the Hôpital du Sacré-Coeur de Montréal's ethics committee, and all participants gave their written informed consent according to the Helsinki Declaration.

Flow of Participants

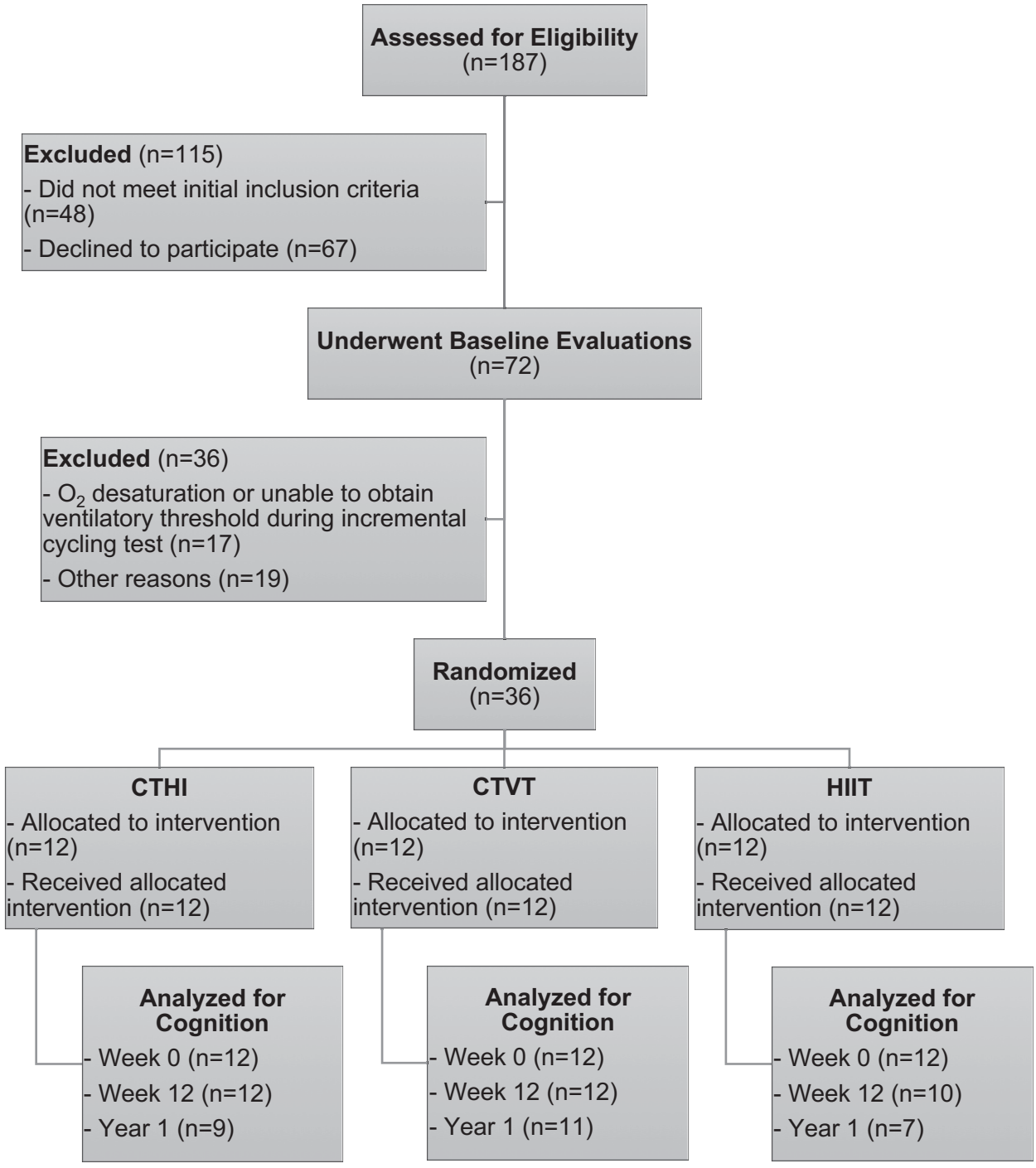

Figure 3 – Flow of Participants

7.3.3 Assessments

7.3.3.1 Pulmonary Function Testing

Spirometry, lung volumes, and lung diffusion capacity for carbon monoxide (D_LCO) were measured at baseline and at follow-up evaluations according to recommended techniques [173]. Values were compared to predicted normal values from the European Community for Coal and Steel/European Respiratory Society [174].

7.3.3.2 Cardiopulmonary Exercise Testing

A symptom-limited incremental cycling exercise test was completed to measure wattage at peak effort (Wpeak) and at the ventilatory threshold at baseline. Peak effort is defined as the highest wattage maintained at 50 revolutions per minute or more, for a duration of 30 seconds. The ventilatory threshold was established using the V-slope method [175], which identifies the breakpoint in the VCO_2-VO_2 relationship. Participants used an electromagnetically braked cycle ergometer (Quinton Corival 400; A-H Robins, Seattle, WA), and were connected to an electrocardiogram and respiratory circuit through a mouth piece. The respiratory circuit included a pneumotachograph, O_2 and CO_2 analyzers, and a mixing chamber. After five minutes of rest and three minutes of unloaded pedalling, the workload was increased in a stepwise manner up to the participant's maximal capacity. Each step lasted a minute, with increments of 5-10 watts. Five-watt increments were used for participants that had a predicted work rate of < 50 watt, and 10-watt increments were used for participants that had a predicted work rate of > 50 watt. Gas exchange parameters (minute ventilation O_2 uptake, CO_2 excretion) and heart rate were evaluated at rest and during exercise on a breath-by-breath analysis. Ratings of dyspnea and leg fatigue were assessed at rest and every other minute during the test with the modified 10-point Borg scale [176]. A constant-load cycling test was completed at baseline and after 12 weeks to assess change in exercise tolerance.

7.3.3.3 Neuropsychological Testing

For the assessment of cognitive function, participants completed a battery of neuropsychological tests administered by a trained neuropsychologist and scored according to standard procedures [177]. Domains that were assessed included attention and executive functions, verbal learning and memory, visuospatial abilities, and processing speed. In addition, the Montreal Cognitive Assessment (MoCA) was used to assess global cognitive functioning. The selected neuropsychological tests measure cognitive domains that are typically affected in COPD and that are sensitive to exercise interventions in that population [114-120]. The cognitive domains measured and the specific test used to assess them are listed in Table 1.

Alternative versions were used at follow-up, when applicable, to avoid test-retest effect. Each test is described with additional information about the measurement procedures below.

Table 1. Cognitive domains and their respective neuropsychological tests

Neuropsychological Tests	***Cognitive Domains***
Montreal Cognitive Assessment (MoCA)	**Global Cognitive Function**
Digit Span test	**Attention and Executive Functions**
Trail Making test (Part B)	
Stroop Color Word test	
Semantic and Letter Verbal Fluency tests	
Rey Auditory-Verbal Learning test	**Verbal Learning and Memory**
Copy of the Rey-O Figure test	**Visuospatial Abilities**
Block Design test	
WAIS Digit Symbol Coding test	**Processing Speed**
Trail Making test (Part A)	
Stroop Color Word test	

Definitions of Cognitive Domains:
Executive Functions: An individual's ability to concentrate and pay attention, using inhibition, working memory and cognitive flexibility [178]
Verbal Learning and Memory: An individual's ability to acquire, store and recall verbal information in different phases of memory [179].
Visuospatial Abilities: An individual's ability to identify visual and spatial relationships between objects. Ability to encode, maintain, and process visual structures [180].
Processing Speed: An individual's ability to easily and quickly do simple mental tasks with a reasonable amount of accuracy [181].

Montreal Cognitive Assessment (MoCA):

The MoCA test assessed an individual's global cognitive functioning. The MoCA test is a 5- to 10- minute screening tool designed to identify cognitive impairments [182] and has been shown to be superior to the Mini-Mental State Examination in detecting MCI in various populations [182-184] and in individuals with COPD [76].

The Digit Span Test:

The Digit Span test assesses short-term memory and includes two parts. In the first part, the examiner reads a list of numbers, and the participant is instructed to repeat the numbers in the same order. This sequence begins with 2 digits but progressively increases to 9 digits. In the second part of the test, the participant is instructed to repeat a new sequence of digits in the reverse order. This trial also begins with 2 digits and progressively increases to 9 digits. For both parts of the test, there are two trials for each sequence length. The test is stopped when both trials of a sequence length are unsuccessful. In the forward Digit Span test, there are 8 different sequence lengths and therefore 16 trials total. One point is assigned for each correct trial for a maximum score of 16 points. In the backward Digit Span test, there are 7 different sequence lengths and therefore 14 trials total. One point is assigned for each correct trial for a maximum score of 14 points. The scores of the forward and backward Digit Span sections will be summed up for a total score. The final test outcome is the score out of a maximum of 30 points. For clinical interpretation, the raw scores are converted to age-scaled scores in the 3rd edition of the Wechsler Adult Intelligence Scale (WAIS) [185].

The Trail Making Test (part A):

Part A of The Trail Making test measures an individual's processing speed. The participant is given a paper that consists of numbers. The examiner instructs the participant to begin at number 1 and to draw a line from 1 to 2, from 2 to 3 and so on until they reach the final number. The goal is to complete the task as fast and as accurate as possible, while not lifting the pencil from the paper. The first attempt is a sample trial with the final number being 8. The second attempt is the test trial with the final number being 25. The examiner instructs the participant to begin at number 1 and to draw a line from 1 to 2, from 2 to 3 and so on until they reach number 25. The amount of time it takes to complete the task in seconds and the number of errors is recorded. Therefore, higher scores indicate greater impairment. The final test outcome is time in seconds. For clinical interpretation, test results are compared to age-, sex-, and education-specific normative values driven from community-dwelling individuals aged 18 to 89 years [186].

The Trail Making Test (part B):

Part B of the Trail Making test integrates mechanisms of perceptual motor speed and sequencing, and measures an individual's attention and executive functions. The participant is given a paper that consists of numbers and letters. The examiner instructs the participant to

begin at number 1 and to draw a line from 1 to “A”, from “A” to 2, from 2 to “B” and so on until they reach the final number and letter combination. The goal is to complete the task as fast and as accurately as possible, while not lifting the pencil from the paper. The first attempt is a sample trial with the final number being number 4 and the final letter being “D”. The second attempt is the test trial with the final number being number 13. The time it takes to complete the task and the number of errors is recorded. The final test outcome is time in seconds. For clinical interpretation, test results are compared to age-, sex-, and education-specific normative values from community-dwelling individuals aged 18 to 89 years [186].

The Stroop Color Word Test (SCWT):

The SCWT measures an individual’s attention and executive functions, and processing speed. This test is composed of four trials consisting of colour denomination, word reading, inhibition and inhibition/switching sections. The colour denomination section displays marks of colours, such as red, green and blue, which have to be named out loud. The word section displays names of colours, such as “red,” “green,” and blue, printed in black that have to be read out loud. The inhibition section displays names of these colours, printed incompatibly in different coloured ink, and participants are instructed to name the colour of the ink on the words. The inhibition/switching section displays names of these colours printed incompatibly in different coloured ink as in the third trial. However, half of the words are enclosed within squares. The participant is instructed to read the word and not the name of the ink colour only when a word is enclosed within a square. The goal is to perform each of these tasks as quickly and as accurately as possible. Both errors that are self-corrected and not corrected, and the time of completion are noted for each trial. The final test outcome is time in seconds and number of errors. For clinical interpretation, test results are compared to age-, sex-, race-, geographic- and education-specific normative values in The Delis-Kaplan Executive Function System: Technical Manual [187].

Semantic Verbal Fluency Test:

The Semantic Verbal Fluency test measures an individual’s capacity for verbal processing. Participants are given 1 minute to state as many words as possible that are part of a specific category, such as animals, fruits or vegetables…etc. One point is awarded for each correct word named. The higher the score the better the performance. The final test outcome is the amount of words stated in under a minute. For clinical interpretation, test results are

compared to age- and education-adjusted normative values [188], and age-, sex-, race-, geographic and education-specific normative values [187].

Letter Verbal Fluency Test:

The Letter Verbal Fluency test measures an individual's capacity for verbal processing. Participants are given 1 minute to state as many words as possible that start with a specified letter. One point is awarded for each correct word named. The higher the score the better the performance. The final test outcome is the amount of words stated in under a minute. For clinical interpretation, test results are compared to age-, sex-, and education-specific normative values [189], and sex-, race-, and geographic-specific normative values driven from healthy children and adults aged 8 to 89 years [187].

Rey Auditory-Verbal Learning Test (RAVLT):

The RAVLT measures verbal learning and memory. The first part of the RAVL test assesses an individual's immediate recall. The assessor states that they will read 15 words, and the participant is instructed to remember all the words in any order. The assessor reads the 15 words, and the participant is required to say all the words that they remember. This procedure is completed five times, and one point is given for each word remembered for a maximum score of 15 points per trial. Trials 1-5 can be summed up for a total maximum score out of 75. After the last trial, the assessor reads a new list of 15 words for the participant to remember. The participant is asked to say all the words they remember from the new list. Immediately after the new list trial, the assessor asks the participant to recall as many words from the original list of words. After a 20-minute delay, the assessor then instructs the participant to say all the words that they remember from the original list of words. The last trial is performed to assess the participant's delayed recall and long-term memory. Words cited correctly, words cited twice, and words cited falsely are recorded. The final test outcome is the amount of words repeated correctly out of a maximum of 15 points per trial. For clinical interpretation, test results are compared to age-specific normative values [190].

Copy of the Rey-Osterrieth Figure Test:

The Rey-Osterrieth Figure test measures an individual's visuospatial abilities. In this test, the participant is given a paper and pencil, and is instructed to copy a complex figure as accurate as possible. The total score and figure are separated into 18 sections with each section worth between 0.5 to 2 points. The amount of points granted depends on accuracy, distortion, and location of the participant's reproduction of the figure. Two points are granted if

the section is correct and placed properly, 1 point is granted if it is correct but placed poorly or if it is distorted but placed correctly, 0.5 points is granted if it is distorted and placed poorly, and no points are granted if a section is missing or not identifiable. The total score ranges from 0-36, with higher scores demonstrating better performance. In addition, the time needed to complete the task is recorded. The final test outcome is the score out of a maximum of 36 points. For clinical interpretation, test results are compared to age- and education-adjusted normative values [191, 192].

The Block Design Test:

The Block Design Test measures an individual's visuospatial abilities. In this test, the participant rearranges blocks with their hands. The blocks have colour patterns on different sides, such as red, white and half red and half white. The examiner presents a pattern design and instructs the participant to reproduce the same pattern with the blocks as quickly as possible. The number of blocks required to match the presented patterns increases over trials, making the patterns more difficult to reproduce. The final test outcome is based on accuracy of matching the patterns and the amount of time to complete each task. The final test outcome is the score out of a maximum of 68 points. For clinical interpretation, the raw scores are converted to age-scaled scores in the 3rd edition of the WAIS [185].

The WAIS Digit Symbol Coding Test:

The Wechsler Adult Intelligence Scale (WAIS) Digit Symbol Coding Test measures an individual's processing speed. The examiner presents a code to the participant at the top of the test page. The code is a list of numbers ranging from 1-9 that have corresponding symbols. The participant is then presented, on the same page, a list of numbers and below them empty boxes. The examiner instructs the participant to use the code key to put the symbol that matches the number in each of the empty boxes. The first attempt is a trial consisting of 7 numbers for the participant to practice. The second attempt is the test trial. The examiner instructs the participant to fill in as many symbols that match their respective numbers until they are told to stop. The participant is instructed to complete the task as quickly and as accurate as possible in the allotted time. The final test outcome is the number of correct symbols in the allotted time. For clinical interpretation, the raw scores are converted to age-scaled scores in the 3rd edition of the WAIS [185].

7.3.4 Criteria for MCI Diagnosis

All of the below criteria needed to be met for a diagnosis of MCI [79, 193, 194]: 1) a complaint of cognitive change by the patient or informant on a structured interview or the Cognitive Failures Questionnaire [195] (based on a total score > 24, or, on at least one item, the response 3: quite often or 4: very often); 2) evidence of cognitive decline defined as at least two scores in the same cognitive domain ≥ 1.5 standard deviations below the standardized mean, adjusted for age and education; 3) conserved activities of daily living; and 4) cognitive deficits not better justified by other medical or psychiatric disorders, or use of medication.

7.3.5 Exercise Intervention

The exercise-training program consisted primarily of cycling on a cycle ergometer at the prescribed intensity and duration, at a frequency of three sessions per week for a total of 12 weeks. The prescribed intensity was determined based on the previously conducted symptom-limited incremental cycling test. The cycling program consisted of a 10-minute warm-up, an intensity phase at the target intensity and duration, and a 5-minute cool-down. During the 10-minute warm-up, participants performed 5 minutes of unloaded pedaling and 5 minutes of pedaling with a gradually increasing load. The intensity phase for CTHI included pedaling for 25 minutes at the heart rate reached at 80% W_{peak} on the baseline incremental test. The intensity phase for CTVT included pedaling at the heart rate reached at the ventilatory threshold on the incremental test. HIIT included pedaling for 30-second periods at the heart rate reached at 100% W_{peak} on the incremental test, alternated with 30-second periods of unloaded pedaling. For CTVT and HIIT, exercise duration was adjusted for each participant using metabolic equations to equal the total amount of work that would have been performed with 25 minutes of CTHI. Participants were instructed to pedal within ± 5 beats/minute of their target heart rate. All participants trained in groups of 6, with the same intervention for a given group. Exercise sessions were administered by two trained exercise physiologists. At program completion, all participants were given the same standardized exercise recommendations from the exercise supervisors.

In addition to the aerobic exercise-training program, the pulmonary rehabilitation program encompassed resistance training (upper back, shoulders, chest, biceps, triceps, abdominals, quadriceps, buttocks, abductors of the thigh, and calves), stretching (upper back, shoulders, chest, biceps, triceps, abdominals, quadriceps, buttocks, calves), relaxation and self-management education. The relaxation portion of the sessions included participants sitting or

lying down for 20 minutes in a comfortable position while listening to a CD produced for the relaxation of people with COPD. The self-management education portion was based on *Living Well with COPD* [196]. The only component of the pulmonary rehabilitation program that differed between the groups was the exercise-training intensity of the aerobic exercise-training protocols on the cycle ergometer.

7.3.6 Attendance and Adherence to the Exercise Intervention

Attendance was defined as the percentage of sessions attended out of the possible maximum of 36 sessions. Adherence was defined as the percent of time spent within the target heart rate range (± 5 beats/minute) during the 12-week intervention. Adherence was only calculated for the attended sessions, and was measured using continuous data tracking technology (Bike Excite Med 700, Technogym, Italy; T31 transmitter, Polar, Finland; CardioMemory, Technogym, Italy)[197].

7.3.7 Statistical Analysis

Descriptive statistics (mean, median, standard deviation, minimum and maximum scores, and frequencies) were obtained and reported for participants' baseline demographic and clinical characteristics and cognitive scores (for all groups combined and for each intervention group separately). The distribution of cognitive scores were assessed for normality. Multicollinearity between cognitive scores of the same cognitive domain were assessed with correlation analyses for each time point (week 0, week 12, and year 1) and for the change (delta) in cognitive scores between time 1 (Week 0) and time 2 (Week 12). Variables with correlation coefficients of ± 0.7 or greater were considered collinear. If multicollinearity was seen between two variables of the same cognitive domain, one was selected to represent the domain.

Changes in cognitive scores of the remaining cognitive variables (after assessing for multicollinearity) were assessed from week 0 to week 12 to year 1 for all groups combined and for each intervention group separately. Based on the effect size calculated from pre-post rehabilitation changes in RAVLT delayed recall score reported by Aquino et al. [114] on (Cohen's d = 0.1637, i.e. "small" effect), approximately 75 participants would be needed to detect a similar effect from week 0 to week 12 in all groups combined, at an alpha of 0.05 and a power of 0.8. As mentioned previously, the present study is using data collected in 36

individuals with COPD. Given this information, the number of intervention groups and the number of cognitive outcomes measured in the present study, the statistical power to detect a time effect similar to the one obtained by Aquino et al. [114] was estimated to be approximately 0.5. As such, the analysis strategy for the present study was largely descriptive, along with calculations of effect sizes because of the awareness that the trial is underpowered. Effect sizes of exercise training on cognition were calculated for all participants combined and for each intervention group using Cohen's d_z.

In an exploratory manner, changes in cognitive scores from baseline (week 0) to program completion (week 12) were further examined in relation to cognitive status [76] at baseline, and exercise-adherence and attendance rate [157,197].

7.4 RESULTS

7.4.1 Participants

Baseline demographic and clinical characteristics of the 36 participants are summarized in Table 2. The sample included mostly women (64%), with a mean age of 67.5 ± 9 years, a slightly elevated BMI (mean±SD: 27.6 ± 5.1 kg/m^2), and moderate airflow obstruction (FEV_1: 59 ± 17% of the normal predicted value) corresponding to GOLD stage Ⅱ COPD [1]. One third of participants were smoking at baseline and the mean smoking history was 42 ± 13 American pack-years. Age, education and BMI were evenly distributed across intervention groups, as projected by the study design. The mean FEV_1 value, expressed both in liters and percentage of the normal predicted value, was highest in the CTVT group and lowest in the HIIT, but not significantly different. In contrast, mean D_LCO was lowest in the CTVT group. When looking at the FEV_1/FVC ratio, lung volumes, and blood oxygenation levels, the groups were similar.

In terms of cognitive function, the mean MoCA score for the entire sample was 25.7 ± 3.3 (range 20-30), which is very close to the screening cutoff of 26 that was previously established as optimal for people with COPD (≤ 25 indicates impairment) [76]. More specifically, 16 participants (44%) had a MoCA score of ≤ 25. In parallel, 14 participants (40%) were diagnosed with MCI from the complete neuropsychological assessment at baseline with 50%, 33%, and 36% of participants having MCI in CTHI, CTVT, and HIIT, respectively.

For the response to the symptom-limited incremental exercise test, participants had a mean peak VO_2 of 14.0 $\pm$ 3.2 mL/kg/min and 1.05 $\pm$ 0.33 L/min. A reduced VO_2 peak is expected in people with COPD [198], but compared to reports from previous studies of exercise training and cognition in COPD, participants in our sample had a relatively good exercise capacity [114-118].

Table 2. Participant baseline characteristics

	All (n = 36)	**CTHI** (n = 12)	**CTVT** (n = 12)	**HIIT** (n = 12)
Female, n (%)	23 (64)	9 (75)	6 (50)	8 (67)
Age, years	68 ± 9	66 ± 7	69 ± 9	67 ± 10
Education, years	12 ± 4	11 ± 2	13 ± 5	13 ± 4
BMI, kg/m^2	27.6 ± 5.1	28.3 ± 5.1	27.1 ± 5.4	27.5 ± 5.3
Current smokers, n (%)	12 (33)	4 (33)	2 (17)	6 (50)
Pack-years	42 ± 13	45 ± 14	44 ± 12	37 ± 12
Pulmonary Function				
FEV_1, L	1.41 ± 0.42	1.37±0.30	1.61±0.42	1.25±0.48
FEV_1, % predicted	59 ± 17	60 ± 15	66 ± 17	50 ± 17
FEV_1/FVC, %	50 ± 9	52 ± 12	50 ± 9	47 ± 7
TLC, % predicted	111 ± 20	108 ± 23	113 ± 19	112 ± 21
FRC, % predicted	135 ± 30	131 ± 36	136 ± 27	139 ± 27
RV, % predicted	139 ± 39	135 ± 44	136 ± 41	146 ± 36
D_LCO CorrVA, % predicted	77 ± 17	80 ± 13	71 ± 20	80 ± 18
SaO_2, %	97 ± 2	96 ± 2	96 ± 1	95 ± 2
$PaCO_2$, mmHg	41.6±3.4	41.8±3.6	41.6±3.8	41.4±3.2
Cognitive Function				
MoCA score	25.7±3.3	27.1±3.0	25.7±3.0	24.3±3.4
MoCA score ≤ 25, n (%)	16 (44)	3 (25)	6 (50)	7 (58)
MCI diagnosis♯, n (%)	14* (40)	6 (50)	4 (33)	4** (36)
Psychological Symptoms				
BDI score	9.4±6.6	9.8±5.4	8.3±5.9	10.2±8.6
BDI score ≥ 14, n (%)	5 (14)	2 (17)	2/12 (17)	1/12 (8)
ASI score	17.9±9.6	17.3±6.7	18.1±10.8	18.5±11.5
Comorbidities				
Charlson Index	1.5±0.8	1.6±0.9	1.4±0.9	1.5±0.8
Exercise Tests				
Peak VO_2 (mL/kg/min)	14.0 ± 3.2	13.4 ± 3.0	14.0 ± 3.8	14.7 ± 3.0
Endurance cycling test (s)	285 ± 118	299 ± 135	301 ± 120	255 ± 103

Values are presented as means ± sd unless otherwise specified.

BMI: Body mass index; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; TLC: Total lung capacity; FRC: Functional residual capacity; RV: Residual volume; D_LCO CorrVA: Lung diffusion capacity for carbon monoxide corrected for alveolar volume; SaO_2: Oxygen saturation; $PaCO_2$: Partial pressure of carbon dioxide in arterial blood; MoCA: Montreal Cognitive Assessment; MCI: Mild cognitive impairment; BDI: Beck Depression Inventory; VO_2: Oxygen uptake

*N = 35 for this variable

**N = 11 for this variable

#based on complete neuropsychological test

7.4.2 Multicollinearity

Originally, a total of 18 cognitive variables were measured with the neuropsychological battery. Using the Pearson correlation coefficients of ± 0.7 or greater, the total number of cognitive variables was reduced to 15. More specifically, the cognitive domain of attention and executive functions had nine cognitive variables, which was reduced to six. Multicollinearity was found between the forward part of the Digit Span Test and the total score of the Digit Span Test ($r = 0.911$), and between the backward part of the Digit Span Test and the total score of the Digit Span Test ($r = 0.902$). Therefore, the total score of the Digit Span Test was selected to represent this subdomain. Multicollinearity was also found between part B of the Trail Making Test and part B of the Trail Making Test minus part A of the Trail Making Test ($r = 0.974$). Therefore, part B of the Trail Making Test was selected to represent this subdomain. The cognitive domain of verbal learning and memory had four cognitive variables, which remained unchanged. The cognitive domain of visuospatial abilities had two cognitive variables, which remained unchanged. Finally, the cognitive domain of processing speed had three cognitive variables, which remained unchanged. Multicollinearity was not found between any variables in these domains.

7.4.3 Changes in Cognitive Scores

7.4.3.1 Descriptive Statistics

Table 3 shows raw cognitive scores (mean and standard deviation) for all participants at baseline, week 12, and year 1. Table 4 shows the raw cognitive scores (mean and standard deviation) for each intervention group at baseline, week 12, and year 1.

Table 3. Raw cognitive scores (M ± SD) for all participants

	All Participants		
Test	**Baseline** (n = 36)	**Week 12** (n = 34)	**Year 1** (n = 27)
MoCA Score	25.7±3.3	25.6±3.6	26.3±3.2
Digit Span Test	14.8±4.6	15.9±5.1	16.4±4.9
Trail Making Test (Part B)	125.5±79.0	124.2±70.8	128.3±72.4
Stroop Color Word Test (Part 3-1)	-0.15±2.56	-0.50±2.83	0.15±2.43
Stroop Color Word Test (Part 4-3)	0.47±2.83	0.45±2.44	0.27±2.63
Semantic Verbal Fluency	32.7±9.1	34.7±8.9	31.6±8.3
Letter Verbal Fluency	31.8±9.6	33.7±11.6	34.6±10.8
RAVLT Total 1 to 5	41.1±9.7	40.2±9.9	40.5±11.6
RAVLT List B	4.1±1.6	4.6±1.7	4.0±1.8
RAVLT Immediate Recall	8.2±2.8	8.3±2.7	8.2±3.3
RAVLT Delayed Recall	8.1±3.3	8.1±3.0	8.1±3.2
Copy of the Rey-O Figure	29.1±3.9	30.8±3.2	30.0±4.2
Block Design Test	28.0±11.4	28.6±12.5	29.6±12.0
Trail Making Test (Part A)	45.6±19.5	43.1±18.9	47.2±19.9
WAIS Digit Symbol Coding Test	53.3±14.5	54.1±15.8	51.3±17.9
Stroop Color Word Test (Part 2)	25.3±15.5	22.6±4.6	22.7±4.1

Values are presented as means ± sd unless otherwise specified. Higher scores indicate better cognitive performance with the exception of Trail Making Test (Part B), Trail Making Test (Part A), Stroop Color Word Test (Part 2), Stroop Color Word Test (Part 3-1) and Stroop Color Word Test (Part 4-3).

Table 4. Raw cognitive scores (M ± SD) for each intervention group

	CTHI			CTVT			HIIT		
Test	**Baseline** (n = 12)	**Week 12** (n = 12)	**Year 1** (n = 9)	**Baseline** (n = 12)	**Week 12** (n = 12)	**Year 1** (n = 11)	**Baseline** (n = 12)	**Week 12** (n = 10)	**Year 1** (n = 7)
MoCa Score	27.1±3.0	26.1±3.1	27.8±2.1	25.7±3.0	25.3±3.9	25.0±3.6	24.3±3.4	25.2±4.1	26.3±3.5[a]
Digit Span	13.9±3.9	16.3±5.3	14.6±4.3	16.8±6.0	15.8±5.0	17.3±5.0	13.8±3.2	15.3±5.4	17.6±5.5
TMT (B)	99.3±44.8	101.5±55.6	98.7±58.0	139.8±95.5	145.7±86.1	147.9±81.6	137.5±87.3	125.8±65.2	135.4±71.0
SCWT (3-1)	-0.67±3.17	-0.83±2.55	-1.22±3.19	0.20±1.69**	0.25±1.96	1.00±1.41	0.09±2.63***	-1.00±3.94	0.57±2.07
SCWT (4-3)	0.58±2.97	0.67±1.61	0.63±1.41*	-0.90±2.60**	-0.33±3.17	-0.91±3.36	1.50±2.61	1.22±2.17♯	1.71±1.60
Semantic VF	35.1±10.5	36.3±8.5	35.1±7.7	30.8±6.9	34.4±8.2	30.4±5.8	32.1±9.6	33.2±11.0	29.0±11.7
Letter VF	31.6±9.4	34.1±10.9	33.6±8.8	32.1±8.3	30.7±10.5	35.1±10.9**	31.8±11.7	36.9±13.7	35.3±14.2
RAVLTSum	42.8±10.6	41.1±11.0	42.2±10.2	38.8±7.6	40.4±8.7	38.7±9.5	41.6±11.2	38.8±10.8	41.1±16.8
RAVLT(B)	4.2±1.4	5.5±2.2	4.3±1.9	4.1±2.1	4.2±1.2	3.7±2.0	4.0±1.4	3.9±0.9	4.1±1.2
RAVLT(IR)	8.4±2.5	8.6±3.1	8.3±2.7	7.8±2.9	8.2±2.1	7.8±3.3	8.5±3.1	8.1±2.9	8.4±4.2
RAVLT(DR)	8.7±2.4	8.4±3.6	8.7±2.1	7.5±3.8	8.2±2.2	7.6±2.8	8.0±3.8	7.7±3.5	8.1±5.1
Copy Rey-O	28.3±3.6	30.3±3.2	29.9±4.1	28.5±4.6	31.4±2.6	29.6±4.5	30.6±3.5	30.6±3.9	30.6±4.4
Block Design	28.3±10.5	29.3±9.9	28.1±9.7	29.8±10.4	29.9±15.3	29.7±14.5**	25.8±13.7	26.3±12.5	31.3±12.6
TMT (A)	40.6±13.9	39.3±16.3	39.3±18.7	51.0±25.4	48.0±21.6	51.1±24.4	45.1±17.4	41.9±19.0	51.0±10.7
Digit Coding	57.8±15.9	60.1±15.5	56.9±15.4	50.9±14.2	49.1±17.1	48.4±22.0	51.3±13.5	52.8±13.6	48.7±13.6
SCWT-2	20.2±3.6	20.9±4.2	20.7±3.8	33.7±24.4	23.1±3.4	23.9±4.4	22.1±6.2	23.9±5.9	23.4±3.3

Values are presented as means ± sd unless otherwise specified.

MoCA: Montreal Cognitive Assessment; TMT: Trail Making Test; SCWT: Stroop Color Word Test; VF: Verbal Fluency; RAVLT: Rey Auditory-Verbal Learning Test; IR: Immediate Recall; DR: Delayed Recall; Copy Rey-O: Copy of the Rey-O Figure; Digit Coding: WAIS Digit Symbol Coding Test.

Higher scores indicate better cognitive performance with the exception of TMT (B), TMT (A), SCWT-2, SCWT (3-1) and SCWT (4-3).

* N = 8 for this variable

** N = 10 for this variable

*** N = 11 for this variable

♯ N = 9 for this variable

a N = 6 for this variable

7.4.3.2 Effect Sizes

Table 5 shows the effect sizes of exercise training on cognitive scores (Z scores) for all groups combined and each group separately.

In all intervention groups combined, effect sizes for short-term changes from baseline (week 0) to program completion (week 12) in cognitive scores were generally small with the exception of visuospatial abilities, where there was a medium effect size (Cohen's d_z = 0.464) for the Copy of the Rey-O Figure test.

Between intervention groups, patterns of short-term change were heterogeneous across and within cognitive domains from baseline (week 0) to program completion (week 12). Large effect sizes were seen in CTHI for the Digit Span test (Cohen's d_z = 0.830) and the Copy of the Rey-O Figure test (Cohen's d_z = 0.963). Medium effect sizes were seen in CTHI for the RAVLT test (List B) (Cohen's d_z = 0.672) and the WAIS Digit Symbol Coding test (Cohen's d_z = 0.649), in CTVT for the Semantic Verbal Fluency test (Cohen's d_z = 0.609) and the Copy of the Rey-O Figure test (Cohen's d_z = 0.659), and in HIIT for the Letter Verbal Fluency test (Cohen's d_z = 0.584).

In all intervention groups combined, effect sizes for long-term changes from program completion (week 12) to 1 year after program initiation (year 1) in cognitive scores were small.

Between intervention groups, patterns of change were heterogeneous across and within cognitive domains from program completion (week 12) to 1 year after program initiation (year 1). Large effect sizes were seen in CTHI for the MoCa test (Cohen's d_z = 0.932) and in HIIT for the Stroop Color Word test (Part 4 – 3) (Cohen's d_z = 0.849). Medium effect sizes were seen in CTHI for the RAVLT test (List B) (Cohen's d_z = -0.483) and for the Block Design test (Cohen's d_z = -0.715). Medium effect sizes were seen in CTVT for the Stroop Color Word test (Part 3 – 1) (d_z = 0.472), the Semantic (Cohen's d_z = -0.561) and Letter Verbal Fluency (Cohen's d_z = 0.671) tests, the RAVLT test (List B) (Cohen's d_z = -0.539), and the Copy of the Rey-O Figure test (Cohen's d_z = -0.493). Medium effect sizes were seen in HIIT for the Digit Span test (Cohen's d_z = 0.707), the Semantic Verbal Fluency test (Cohen's d_z = -0.460) and the Stroop Color Word test (Part 2) (Cohen's d_z = -0.700).

Overall, in all intervention groups combined, effect sizes for short and long-term changes in cognitive scores were small. Between intervention groups, patterns of change were heterogeneous across and within cognitive domains.

Table 5. Effect sizes of exercise training on cognitive scores (Z scores) for all groups combined and for each intervention group

No Effect (<0.2), **Small** (0.2), **Medium** (0.5), **Large** (0.8)

Attention and Executive Functions

Test	Group	Baseline to Week 12	Week 12 to Year 1
Digit Span Test	All	0.3	0.1
	CTHI	0.8	-0.4
	CTVT	-0.3	0.4
	HIIT	0.4	0.7
Trail Making Test (Part B)	All	0.0	0.0
	CTHI	0.1	-0.3
	CTVT	-0.1	0.1
	HIIT	0.0	0.3
Stroop Color Word Test (Part 3 – 1)	All	0.0	0.3
	CTHI	-0.1	-0.2
	CTVT	-0.1	0.5
	HIIT	0.2	0.4
Stroop Color Word Test (Part 4 – 3)	All	0.0	0.1
	CTHI	0.1	0.1
	CTVT	0.0	-0.4
	HIIT	0.0	0.8
Semantic Verbal Fluency Test	All	0.4	-0.3
	CTHI	0.3	0.2
	CTVT	0.6	-0.6
	HIIT	0.4	-0.5
Letter Verbal Fluency Test	All	0.2	0.2
	CTHI	0.3	-0.3
	CTVT	-0.2	0.7
	HIIT	0.6	-0.1

Verbal Learning and Memory

Test	Group	Baseline to Week 12	Week 12 to Year 1
RAVLT Total 1 to 5	All	-0.0	-0.1
	CTHI	-0.2	-0.0
	CTVT	0.3	-0.1
	HIIT	-0.1	-0.1
RAVLT List B	All	0.4	-0.4
	CTHI	0.7	-0.5
	CTVT	0.1	-0.5
	HIIT	0.2	-0.2
RAVLT Immediate Recall	All	0.1	-0.1
	CTHI	0.1	-0.2
	CTVT	0.2	0.0
	HIIT	0.1	-0.1
RAVLT Delayed Recall	All	0.1	0.0
	CTHI	-0.1	-0.1
	CTVT	0.2	0.1
	HIIT	0.0	-0.1

Visuospatial Abilities

Test	Group	Baseline to Week 12	Week 12 to Year 1
Copy of the Rey-O Figure	All	0.5	-0.3
	CTHI	1.0	-0.3
	CTVT	0.7	-0.5
	HIIT	0.0	-0.1
Block Design Test	All	0.1	-0.1
	CTHI	0.1	-0.7
	CTVT	-0.0	-0.2
	HIIT	0.2	0.4

Processing Speed

Test	Group	Baseline to Week 12	Week 12 to Year 1
WAIS Digit Symbol Coding Test	All	0.2	-0.1
	CTHI	0.6	-0.0
	CTVT	-0.1	-0.1
	HIIT	0.2	-0.4
Trail Making Test (Part A)	All	0.2	-0.0
	CTHI	0.1	0.1
	CTVT	0.1	-0.1
	HIIT	0.4	-0.1
Stroop Color Word Test (Part 2)	All	-0.1	-0.1
	CTHI	-0.3	0.4
	CTVT	0.2	-0.3
	HIIT	-0.3	-0.7

MoCA (RAW)

Test	Group	Baseline to Week 12	Week 12 to Year 1
MoCA (RAW)	All	-0.1	0.2
	CTHI	-0.4	0.9
	CTVT	0.2	0.0
	HIIT	0.3	-0.2

7.4.4 Cognitive Status

In an exploratory manner, changes in cognitive scores from baseline (week 0) to program completion (week 12) were further examined in relation to cognitive status at baseline. Table 6 shows the effect sizes of exercise training on cognitive scores (Z scores) from baseline (week 0) to program completion (week 12) for participants with MCI and those without MCI at baseline.

We also looked at the change in cognitive status across time points. At baseline, 21 participants (60%) had no MCI, 11 participants (31.4%) had single domain MCI, and 3 participants (8.6%) had multiple domain MCI. At week 12, 22 participants (66.7%) had no MCI, 8 participants (24.2%) had single domain MCI, and 3 participants (9.1%) had multiple domain MCI. At year 1, 16 participants (61.5%) had no MCI, 7 participants (26.9%) had single domain MCI, and 3 participants (11.5%) had multiple domain MCI.

From baseline to week 12, 24/33 had no change in cognitive status, 5 participants' cognitive status improved (2 from single domain MCI to no MCI, 2 from multiple domains to single domain MCI, and 1 from multiple domain MCI to no MCI), and 4 participants' cognitive status worsened. From week 12 to year 1, 21/26 participants had no change in cognitive status, 2 participants improved from single domain MCI to no MCI, and 3 participants' cognitive status worsened. Lastly, from baseline to year 1, 15/26 participants had no change in cognitive status, 6 participants' cognitive status improved (3 from single domain MCI to no MCI, 3 from multiple domain to single domain MCI), and 5 participants' cognitive status worsened.

Table 6. Effect sizes of exercise training on cognitive scores (Z scores) for participants with and without MCI at baseline

No Effect (<0.2), **Small** (0.2), **Medium** (0.5), **Large** (0.8)

Attention and Executive Functions

Test	Group	Baseline to Week 12
Digit Span Test	MCI	0.4
	No MCI	0.3
Trail Making Test (Part B)	MCI	0.3
	No MCI	-0.3
Stroop Color Word Test (Part 3 – 1)	MCI	-0.5
	No MCI	0.2
Stroop Color Word Test (Part 4 – 3)	MCI	0.2
	No MCI	-0.1
Semantic Verbal Fluency Test	MCI	0.8
	No MCI	0.4
Letter Verbal Fluency Test	MCI	-0.0
	No MCI	0.5

Verbal Learning and Memory

Test	Group	Baseline to Week 12
RAVLT Total 1 to 5	MCI	-0.2
	No MCI	0.1
RAVLT List B	MCI	0.4
	No MCI	0.3
RAVLT Immediate Recall	MCI	0.3
	No MCI	-0.1
RAVLT Delayed Recall	MCI	0.3
	No MCI	-0.2

Visuospatial Abilities

Test	Group	Baseline to Week 12
Copy of the Rey-O Figure	MCI	1.1
	No MCI	0.2
Block Design Test	MCI	0.1
	No MCI	0.0

Processing Speed

Test	Group	Baseline to Week 12
Code WAIS-3	MCI	0.4
	No MCI	0.1
Trail Making Test (Part A)	MCI	0.3
	No MCI	0.0
Stroop Color Word Test (Part 2)	MCI	-0.3
	No MCI	0.1

MoCA (RAW)

Test	Group	Baseline to Week 12
MoCA (RAW)	MCI	-0.3
	No MCI	0.1

7.4.5 Attendance and Adherence to the Exercise Intervention

Table 7 shows attendance and adherence rates for all participants and for each intervention group. CTVT had the highest attendance rate and HIIT had the lowest one. With respect to adherence rates, values were high and similar for participants from the CTHI and CTVT groups, while substantially lower for participants in HIIT group.

Table 8 shows attendance and adherence rates for participants with and without MCI. Attendance rates were highest in participants with MCI, while adherences rates were exactly the same between both subgroups.

Table 7. Attendance and adherence (M ± SD) for all participants and for each intervention group

	All (n = 36)	**CTHI** (n = 12)	**CTVT** (n = 12)	**HIIT** (n = 12)
Attendance (%)				
M±SD	71.8 ± 29.7	70.1 ± 32.8	81.9 ± 17.2	63.4 ± 35.2
Median	83.3	80.6	90.3	77.8
Min-Max	0.0-100.0	2.8-100.0	44.4-97.2	0.0-100.0
Adherence (%)				
M±SD	76.3 ± 34.0	88.3 ± 16.9	91.0 ± 16.9	49.6 ± 44.0
Median	93.6	95.0	98.4	48.9
Min-Max	0.0-100.0	43.3-100.0	40.4-100.0	0.0-100.0

Table 8. Attendance and adherence (M ± SD) all participants and for participants with and without MCI at baseline

	MCI (n = 14)	**No MCI** (n = 21)
Attendance (%)		
M±SD	77.8 ± 27.6	68.1 ± 31.7
Median	91.7	77.8
Min-Max	11.1-100.0	0.0-100.0
Adherence (%)		
M±SD	78.5 ± 30.1	78.5 ± 33.7
Median	91.1	96.4
Min-Max	0.1-100.0	0.0-100.0

7.5 DISCUSSION

Summary of Main Findings

To our knowledge, this is the first study to report on the comparative effects of three different exercise-training protocols on cognitive function in people with COPD. In a sample of 36 participants with moderately-severe COPD and stable global cognitive functioning (based on MoCA scores), the effects of 12 weeks of exercise training on cognition were small or very small, except for one test of visuospatial abilities, the Copy of the Rey-O Figure. This test detected a medium effect size in all participants combined, and a large effect size in the subgroup of participants with MCI at baseline. The effects of exercise training on cognition were very heterogeneous between the three intervention groups. CTHI was the only group in which medium to large effects were detected in each of the four cognitive domains assessed. At the 1-year follow-up, gains and losses in cognitive scores were seen in all three intervention groups. Both continuous training groups (CTHI and CTVT) had medium-sized decreases in verbal learning and memory, and in visuospatial abilities over the maintenance phase.

Short-Term Changes in Cognitive Function

Within-Groups

We hypothesized that, for all groups combined, cognitive scores would improve after 12 weeks of exercise training for all the domains measured, namely attention and executive functions, verbal learning and memory, and processing speed. This hypothesis was largely based on the current literature documenting improvements in these domains after exercise-training interventions in people with COPD [114-117, 120]. Our results do not support this hypothesis since we found no or small effects of exercise training on all measures related to these cognitive domains when results from the three interventions groups were combined. One exception to this was the Copy of the Rey-O Figure test, which measures visuospatial abilities, in which we found a medium effect size.

The absence of substantial improvements in attention and executive functions, verbal learning and memory, and processing speed obtained in our study is surprising, as it goes against the literature in healthy older adults [163-165] and in COPD [114-117, 120]. Inconsistencies between our results and previous findings could stem from differences in exercise interventions. Many of the earlier studies reporting on the impact of exercise training on cognition in people with COPD used exercise interventions of higher weekly frequency but shorter total intervention length compared to the one used in our study [114-117]. The higher

exercise training frequency may have allowed participants to achieve higher levels of overall physical activity. A dose-response relationship between physical activity levels and cognition – more specifically verbal learning and memory (Delayed Word Recall test) – has been reported in healthy older adults [199] and older adults with cognitive impairments [200]. Therefore, it is possible that the higher weekly frequency of exercise training in the previous studies led to higher gains in cognition. As for program length, evidence in healthy older adults suggests that exercise-training programs lasting 6 months or more elicit greater effects on cognition than shorter programs, while short (1-3 months) and intermediate-length (4-6 months) programs induce similar gains [201]. It thus seems unlikely that program length explains the discrepancies between our results and earlier ones in COPD. Target training intensity is another factor known to influence the cognitive gains obtained from exercise training [202, 203]. Unfortunately, target training intensity was not specified in most of the earlier studies of exercise training and cognition in COPD [115-117, 120], making it difficult to determine whether or not this factor could explain discrepancies observed. Adding a resistance training component to the exercise intervention can increase the cognitive gains obtained through aerobic training. Indeed, Aquino et al. [114] investigated the effects of aerobic training compared to aerobic training combined with resistance training in 28 males with COPD (mean age: 68.4 ± 9.6 years). They showed that the group randomized to combined aerobic and resistance training had significantly higher improvements in attention and executive functions and long-term memory compared to the group randomized to aerobic training alone. In our study, all three intervention groups had the same resistance training component added to their aerobic training intervention. Therefore, it seems unlikely that this aspect of the intervention would explain the minimal effect of the training interventions on cognition observed in the present study.

Differences in participant baseline characteristics, such as age, male/female ratio, pulmonary function, and baseline cognitive function could also explain gaps between our study and previous ones [114-117, 120]. Our sample included mostly women (64%), with a mean age of 67.5 ± 9 years, and moderate airflow obstruction corresponding to GOLD stage Ⅱ COPD [1]. All of the previous studies [114-117, 120] included participants that were of a very similar age distribution as ours, but had a majority of males. Emery and colleagues [115] showed that males generally performed better than females in attention and executive functions, and processing speed (Trail Making Test Part B, Finger Trapping and WAIS Digit Symbol Coding) [115]. However, exercise-induced gains in cognition were similar between both subgroups, so the male/female split unlikely explains differences in findings between your study and earlier ones.

Most of the previous studies [115-117, 120] included participants with more severe airflow obstruction and COPD than those who completed our study. People with more advanced COPD are generally more prone to acute exacerbations [1]. The deleterious effects of COPD exacerbations on inflammation, comorbidities, lung functions, health-related quality of life, exercise fitness and mortality are well documented [204-206]. Exacerbation risk has also been shown to predict cognitive scores, even after controlling for non-COPD predictors of cognitive function [207]. The higher the number of COPD exacerbations a person experiences, the worse the total cognitive score. It is thus possible that participants included in previous studies [115-117, 120], which had more severe COPD, also had lower baseline cognitive scores. Our study and previous ones reported similar baseline scores in tests of verbal learning and memory. In contrast, some of these earlier trials recorded slightly worse baseline scores in attention and executive functions (on the Trail Making Test (Part B) and Letter Verbal Fluency) [117, 120] and in processing speed (on the WAIS Digit Symbol Coding) [115]. Participants included in these earlier trials therefore had more room for improvement in cognition – particularly in the domains of attention and executive function and processing speed – than those included in our study. Kozora et al. [119] also found significant improvements, from baseline to post-intervention, in visual attention, verbal memory and visuospatial abilities in those who had an impairment at baseline. This supports the notion that perhaps COPD patients with impaired cognition at baseline would be more responsive to the effects of exercise than those with preserved cognition.

Lastly, inconsistencies between our findings and earlier ones could be due to differences in the cognitive assessments used [114-117, 120]. The testing battery used in the present study was substantially more comprehensive than the one used in former trials. These past studies [114-117, 120] reported on significant improvements in attention and executive functions, verbal learning and memory and processing speed using 4-6 cognitive tests. In contrast, our cognitive testing battery reported on these domains using 13 tests. Having more tests increased the number of signals obtained in our study, perhaps increasing the likelihood of heterogeneous findings and, more generally, the risk of error, especially in the context of an underpowered study. Focusing on domains and tests that seem particularly responsive to exercise training in COPD may be warranted for future trials.

We did observe medium-sized positive effects of exercise training on visuospatial abilities (Copy of the Rey-O Figure) in all participants in our study. This is in line with Aquino

and colleagues' findings [114] showing significant improvements in visuospatial abilities in both of their exercise-training groups. Of note, larger gains in this domain were seen in the combined aerobic-resistance training group compared to the aerobic only training group. The combined group in Aquino et al.'s study is most similar to the CTHI group from our study, in which we found a large effect size on visuospatial abilities (Copy of the Rey-O Figure). Interestingly, the largest effect of exercise training on cognition obtained in our study was for visuospatial abilities (Copy of the Rey-O Figure) in the subgroup of participants with MCI at baseline. Kozora et al. [119] reported a similar finding with a different test (Clock Drawing), noting significant gains in this domain after exercise training only for the subgroup of participants considered "impaired" at baseline. To our knowledge, several of the former studies reporting on the effects of exercise-training on cognition in COPD did not assess visuospatial abilities [115-118, 120]. Our results add to those from Kozora et al. [119] and suggest that perhaps visuospatial abilities are responsive to the effects of exercise in people with COPD and MCI, and should be included in future trials of pulmonary rehabilitation and cognition.

Between-Groups

Between the three intervention groups, we hypothesized similar short-term improvements in cognitive scores after 12 weeks of exercise training. This hypothesis was largely based on earlier findings from our team, driven from the same trial as the present study [157], showing similar short-term gains in exercise tolerance from pre- to post-intervention between CTHI, CTVT and HIIT. Therefore, we expected similar results for cognition, since exercise capacity and cognition have been shown to be positively associated in several studies [114-120]. Our results do not support this hypothesis since effect sizes of exercise training on cognitive outcomes were very heterogeneous between the three intervention groups across and within cognitive domains. CTHI induced medium to large effects on one test from each of the four cognitive domains assessed. Indeed, large effects were seen in CTHI for attention and executive functions (Digit Span) and visuospatial abilities (Copy of the Rey-O Figure), while medium effects were found for verbal learning and memory (RAVLT (List B)) and processing speed (WAIS Digit Symbol Coding). CTVT induced medium effects for attention and executive functions (Semantic Verbal Fluency) and visuospatial abilities (Copy of the Rey-O Figure). Lastly, HIIT induced a medium effect for attention and executive functions only (Letter Verbal Fluency).

Current PR guidelines advocate continuous high-intensity training (CTHI) [139]. However, in the literature, complying to this training intensity has been shown to be difficult for many patients with COPD and to result in lower adherence rates [151]. More tolerable exercise interventions, such as continuous training at the ventilatory threshold (CTVT) and high-intensity interval training (HIIT), have therefore been proposed as alternatives to CTHI with the hope of leading to higher adherence rates and better long-term effectiveness [154-157, 159-161]. In contrast to these beliefs and earlier findings, the observed attendance (70.1 ± 32.8%) and adherence (88.3 ± 16.9%) rates to CTHI were very good in our study; this may explain why this exercise protocol was the most effective at eliciting cognitive gains across domains. CTHI is also likely the protocol most similar to exercise interventions used in earlier studies showing cognitive gains in these domains in COPD [114-120]. This is not surprising since the international guidelines for pulmonary rehabilitation have recommended CTHI for years [139]. CTVT is less popular in COPD and was probably not used in any of the previous studies on cognition. However, this exercise intervention reflects, on average, a moderate intensity level of exercise training, which could be similar to Emery's et al.'s studies [115-117]. Unfortunately, because the intensity was not reported in Emery's trial, we cannot confirm this information. In previous findings from our team, CTVT had the highest attendance (81.9 ± 17.2) and adherence (91.0 ± 16.9) rates. Therefore, perhaps CTVT should continue to be included in future trials of pulmonary rehabilitation in people with COPD, especially since we did see beneficial cognitive effects in this group in attention and executive functions and visuospatial abilities. Lastly, to our knowledge, HIIT has not been used in studies investigating the effects of exercise-training on cognition in COPD [114-120]. The specific protocol used in our study led to the lowest attendance (63.4 ± 35.2) and adherence (49.6 ± 44.0) rates, in contrast to our expectations. It is difficult to say, at this stage, whether our findings about HIIT are protocol- or sample-specific, or whether they are indeed generalizable to the larger COPD population.

Long-Term Changes in Cognitive Function

Within-Groups

We hypothesized that, for all groups combined, cognitive scores would decrease from 12 weeks (post-rehab) to 1 year. This hypothesis was largely based on earlier findings by Emery et al. [171] showing a decrease in cognitive performance, namely processing speed, from week 10 (post-rehab) to 1 year [171] when no maintenance component was offered to participants. Likewise, our study did not include an active maintenance intervention from week 12 to year 1. At program completion, participants were given standardized exercise recommendations, but

were left to exercise on their own. Our results are not in line with our hypothesis, since effect sizes for long-term changes in cognitive scores – including processing speed – from program completion (week 12) to year 1 were either small or very small in all groups combined. Nevertheless, our results are in line with Etnier et al.'s findings [118], which showed no change from 3-months (week 12) to 18-months in participants randomized to receive no maintenance intervention in the follow-up phase.

Possible explanations for why our study resulted in findings more similar to Etnier et al.'s [118] than Emery et al.'s [171] include, once again, exercise interventions, participant baseline characteristics, and baseline cognitive function. Our study had a similar program length (12 weeks) and training frequency (3 times per week) as Etnier et al. [118], and included participants of similar disease severity. In contrast, Emery et al. [171] had a shorter program length (10 weeks) and higher training frequency (3-5 times per week). Therefore, their study had more exercise sessions than our study in a shorter period/time frame. A possible explanation to why Emery et al. found decreases in cognitive performance while we found small to very small effects could be the fact that their exercise intervention was more demanding than ours, leading participants to adhere less to their exercise regimen during the follow-up phase.

Another explanation for the inconsistencies between our results and Emery et al.'s [171] could be the fact that their sample had severe airflow obstruction, corresponding to GOLD stage Ⅲ COPD, while our sample had moderate airflow obstruction, corresponding to GOLD stage Ⅱ COPD [1]. As mentioned previously, there may be a link between increased disease severity, high risk for acute exacerbations, and cognitive impairment in COPD [91, 207]. Therefore, this could be another factor that possibly led their participants to having more trouble maintaining a regular exercise regimen than ours during the follow-up phase. In addition, a study investigating the role of disease related factors on adherence to PR in people with COPD showed that adherence to PR was associated with higher FEV_1 values [208]. Therefore, our participants' higher FEV_1 values could have led to a higher long-term exercise adherence than Emery et al.'s participants, leading to a better maintenance of cognitive gains. Although we do not have a measure of adherence during the follow-up phase in this study, we do know that our participants had a good overall adherence rate (76.3 ± 34.0) during the active phase. This high adherence rate could have continued on throughout the follow-up phase, additionally contributing to the maintenance of cognitive gains from the active phase.

Another explanation could be due to differences in cognitive scores at program completion and at the 1-year follow-up. Our sample had higher scores at program completion (week 12) and at year 1 in processing speed than Emery et al.'s sample at program completion (week 10) and at year 1 on the same test (WAIS Digit Symbol Coding). Therefore, it is possible that our sample was more cognitively preserved than theirs, resulting in a less loss in cognitive performance in the follow-up phase.

Several studies have reported on cognitive declines over the years in people with COPD while not participating in an exercise program [209-211]. Incalzi et al. [209] investigated the cognitive function using the Mini Mental State Exam (MMSE) in 84 people with COPD (mean age: 64 years) who were on oxygen therapy over two years. Results showed a slight decline of cognition from baseline to year 1, and a significant decline in cognition from baseline to year 2. Another longitudinal study [210] investigated the cognitive function of 110 elderly men with COPD (mean age: 81 years) compared to 110 age- and education-matched controls over three years. Results showed that the participants with COPD had a faster rate of cognitive decline in the MMSE, word list recall, delayed recall, animal category fluency and symbol digit tests compared to the control group. Lastly, another study [211] investigated the cognitive function of older adults with COPD (mean age: 63 years) over 6 years in the Health and Retirement Study. Results showed that cognition, which was assessed by a validated 35-point scale [212], declined 0.7 points in participants without COPD and 1.0 point in participants with COPD over the 6 years. These findings all indicate that, within a year, people with COPD commonly experience cognitive decline. Therefore, seeing no change in cognition at the 1-year follow-up in our study participant may in fact reflect an improved situation.

Incalzi et al. [209] reported that participants who experienced a decline in cognition from baseline to year 1 and to year 2 had lower percent predicted FVC and FEV_1 values, and higher scores on the Geriatric Depression Scale (GDS), which assesses affective status. In addition, a significant inverse correlation was found between 2-year changes in MMSE and GDS scores. Therefore, participants experiencing cognitive declines were characterized by more severe airflow obstruction and depressive symptoms. The authors concluded that cognitive decline is more rapid with more severe airflow obstruction and parallels the decline of the affective status in people with COPD. In addition, Hung et al. [211] found that cognition declined 0.9 points in those with non-severe COPD and 1.1 points in those with severe COPD. Of note, the Beck Depression Inventory was used in our trial to assess the presence and severity of depressive

symptoms. A cut-off score of 14 is the threshold for “mild” clinical depression in the general population [213], in which 13.9% of our sample met. Earlier findings from our study also found that subclinical levels of depression predicted poor pulmonary rehabilitation exercise attendance and low exercise levels after pulmonary rehabilitation. Additionally, affect, which was defined as the degree of pleasure a person experiences during exercise, was also assessed in our trial using the Positive and Negative Affect Schedule (PANAS) and the global vigor and affect (GVA) instrument. Earlier findings from our study found that affect generally improved from rest to post-exercise across groups [157]. Therefore, it is possible that the decline in cognition seen in some of our participants could be explained by airflow obstruction and depressive symptoms, which could have led to low levels of exercise maintenance during the follow-up phase. Low levels of exercise maintenance during the follow-up phase combined with the absence of an exercise intervention, which showed to improve affect, could explain the losses in cognitive scores found in some of our participants.

Between-Groups

Between the three groups, we hypothesized that long-term gains in cognition would be better maintained at 1 year in the CTHI and CTVT groups than in the HIIT group. This hypothesis was largely based on earlier findings by Emery et al. showing that participants who adhered to their exercise-training program maintained their improvements in cognition [171]. Additionally, Etnier et al. [118] reported a modest increase in fluid intelligence in the active maintenance intervention group from 3 months to 18 months. Earlier results from our team using data from this trial showed a lower adherence rate in the HIIT group [157]. Therefore, we expected the HIIT group to show poorer maintenance of cognitive gains than CTHI and CTVT at the 1-year follow-up. Our results do not support this hypothesis since patterns of effect sizes of exercise training were heterogenous between the groups across and within cognitive domains. CTHI induced a positive large effect for global cognitive functioning (MoCa) and negative medium effects in verbal learning and memory (RAVLT (List B)) and visuospatial abilities (Block Design). CTVT induced positive medium effects in tests of attention and executive functions (Stroop Color Word Test (Part 3 – 1) and Letter Verbal Fluency), but also induced negative medium effects in another test of attention and executive functions (Semantic Verbal Fluency), verbal learning and memory (RAVLT (List B)), and visuospatial abilities (Copy of the Rey-O Figure). HIIT induced a positive medium and large effect in tests of attention and executive functions (Digit Span and Stroop Color Word Test (Part 4 – 3), respectively), but also induced negative medium effects in other tests of attention and executive functions (Semantic Verbal

Fluency) and processing speed (Stroop Color Word Test (Part 2)). Overall, in all three intervention groups, there were some gains and some losses in cognitive performance over the follow-up phase.

Another interesting finding in our study is that both continuous training groups, CTHI and CTVT, had medium-sized decreases in verbal learning and memory in the same test (RAVLT (List B)), and in visuospatial abilities in two different tests (Block Design and Copy of the Rey-O Figure). It is difficult to compare these findings with past studies because, to our knowledge, there are only two studies reporting on the changes in cognition from post-rehabilitation to a 1-year follow-up in COPD [118, 171]. These studies did not include cognitive assessments on verbal learning and memory, and visuospatial abilities. Therefore, perhaps these domains are sensitive to cognitive changes in COPD over time and worth including in future trials of pulmonary rehabilitation and cognition. Additionally, these studies did not thoroughly describe the intensity of their exercise intervention. Therefore, clear reports of the frequency, intensity, duration, and type of exercise training intervention(s) should be included in future trials as well.

Strengths and Limitations

There are several limitations that should be considered in the interpretation of the findings from this study. The present study included a small sample size (36 participants), three intervention groups, and 16 cognitive outcomes, which limited the statistical power to detect group differences. Therefore, the analysis strategy for the study was largely descriptive, along with calculations of effect sizes, because of the awareness that the trial was underpowered. The small sample size also prevented the ability to control for covariates and affects the generalizability of the findings to the COPD population. In addition, the lack of a non-exercising control group limits the study's internal validity. Indeed, the addition of such a group would have provided a better understanding of the specific influence of exercise training on cognition in COPD.

Despite some limitations, this study also has several notable strengths. To our knowledge, this is the first trial to compare the effects of three different aerobic exercise protocols that are commonly used in COPD (CTHI, CTVT, and HIIT) on cognition. Exercise protocols are also thoroughly described and attendance and adherence to them is reported [214]. This is especially important since many of the past studies reporting on the effects of exercise training on cognition in people with COPD did not specify the intensity of their exercise

protocols, making it difficult to inform future trials [115-117, 119, 120]. In addition, there was an effort to equalize the total dose of training between the three exercise protocols so that the analyses could focus on the impact of the protocol and not total exercise volume. For our cognitive assessment, our study used a comprehensive battery of validated tests administered and interpreted by neuropsychologists, which was not the case in most former trials [114-117, 119, 120]. Lastly, this study had a randomized design and a 1-year follow-up, which many of the past studies did not have. The randomized design further helps focus the analysis on the impact of the exercise protocol. The 1-year follow-up allowed the analysis of the long-term changes in cognition without a maintenance intervention.

Future Directions

In the present study, we observed medium- and large-sized positive effects of exercise training on visuospatial abilities (Copy of the Rey-O Figure) in all participants, those in the CTHI group, and those with MCI at baseline. These findings suggest that this cognitive domain may be particularly responsive to the effects of exercise in people with COPD, and those with combined COPD and MCI, and should therefore be measured in future trials of pulmonary rehabilitation and cognition. Future studies should assess larger samples than the one included in our trial for statistical power to be high enough to detect significant changes in cognition from exercise training, similar to those reported in past studies and to allow for covariates to be included in the analysis model. Future trials should also clearly report the frequency, intensity, duration, and type of exercise training intervention(s) used and, ideally, gather precise exercise adherence data. Lastly, future trials should include a non-exercising control group to provide a better understanding of the specific influence of exercise training on cognition in COPD.

7.6 CONCLUSION

In conclusion, results from the present study support the idea that pulmonary rehabilitation, particularly the exercise-training component, can help mitigate cognitive declines in people with COPD. Our results add to earlier ones suggesting that visuospatial abilities may be particularly responsive to the effects of exercise in people with combined COPD and cognitive impairment. This should be considered in future trials of pulmonary rehabilitation and cognition. Continuous high-intensity training may be the safest option to choose to elicit cognitive gains across domains in people with COPD, provided that they are able to adhere to

this approach. Over time, losses in cognitive performance are likely to occur if no active maintenance intervention is offered.

8. REFERENCES

1. Global Initiative for Chronic Obstructive Pulmonary Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2018 Report: p. 1-142.
2. Rabe, K. F., Hurd, S., Anzueto, A., Barnes, P. J., Buist, S. A., Calverley, P., . . . Global Initiative for Chronic Obstructive Lung Disease. (2007). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine, 176*(6), 532-555. doi:200703-456SO [pii]
3. Murray, C. J., & Lopez, A. D. (1997). Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study. *Lancet (London, England), 349*(9064), 1498-1504. doi:S0140-6736(96)07492-2 [pii]
4. Evans, J., Chen, Y., Camp, P. G., Bowie, D. M., & McRae, L. (2014). Estimating the prevalence of COPD in canada: Reported diagnosis versus measured airflow obstruction. *Health Reports, 25*(3), 3-11. doi:82-003-X201400311908 [pii]
5. Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine, 3*(11), e442. doi:06-PLME-RA-0071R2 [pii]
6. Rycroft, C. E., Heyes, A., Lanza, L., & Becker, K. (2012). Epidemiology of chronic obstructive pulmonary disease: A literature review. *International Journal of Chronic Obstructive Pulmonary Disease, 7*, 457-494. doi:10.2147/COPD.S32330 [doi]
7. Halbert, R. J., Natoli, J. L., Gano, A., Badamgarav, E., Buist, A. S., & Mannino, D. M. (2006). Global burden of COPD: Systematic review and meta-analysis. *The European Respiratory Journal, 28*(3), 523-532. doi:09031936.06.00124605 [pii]
8. Garcia Rodriguez, L. A., Wallander, M. A., Tolosa, L. B., & Johansson, S. (2009). Chronic obstructive pulmonary disease in UK primary care: Incidence and risk factors. *Copd, 6*(5), 369-379. doi:10.1080/15412550903156325 [pii]
9. Mannino, D. M., Homa, D. M., Akinbami, L. J., Ford, E. S., & Redd, S. C. (2002). Chronic obstructive pulmonary disease surveillance--united states, 1971-2000. *Morbidity and Mortality Weekly Report.Surveillance Summaries (Washington, D.C.: 2002), 51*(6), 1-16.
10. Gershon, A. S., Wang, C., Wilton, A. S., Raut, R., & To, T. (2010). Trends in chronic obstructive pulmonary disease prevalence, incidence, and mortality in ontario, canada, 1996 to 2007: A population-based study. *Archives of Internal Medicine, 170*(6), 560-565. doi:10.1001/archinternmed.2010.17 [doi]

11. Camp, P. G., Chaudhry, M., Platt, H., Roch, M., Road, J., Sin, D., & Levy, R. D. (2008). The sex factor: Epidemiology and management of chronic obstructive pulmonary disease in british columbia. *Canadian Respiratory Journal, 15*(8), 417-422.
12. Nie, J. X., Wang, L., & Upshur, R. E. (2007). Mortality of elderly patients in ontario after hospital admission for chronic obstructive pulmonary disease. *Canadian Respiratory Journal, 14*(8), 485-489.
13. Hansell, A. L., Walk, J. A., & Soriano, J. B. (2003). What do chronic obstructive pulmonary disease patients die from? A multiple cause coding analysis. *The European Respiratory Journal, 22*(5), 809-814.
14. Janssen, F., Kunst, A. E., & Netherlands Epidemiology and Demography Compression of Morbidity research group. (2005). Cohort patterns in mortality trends among the elderly in seven european countries, 1950-99. *International Journal of Epidemiology, 34*(5), 1149-1159. doi:dyi123 [pii]
15. Janssen, F., Nusselder, W. J., Looman, C. W., Mackenbach, J. P., & Kunst, A. E. (2003). Stagnation in mortality decline among elders in the netherlands. *The Gerontologist, 43*(5), 722-734.
16. Wilson, D. H., Tucker, G., Frith, P., Appleton, S., Ruffin, R. E., & Adams, R. J. (2007). Trends in hospital admissions and mortality from asthma and chronic obstructive pulmonary disease in australia, 1993-2003. *The Medical Journal of Australia, 186*(8), 408-411. doi:wil10877_fm [pii]
17. de Marco, R., Accordini, S., Cerveri, I., Corsico, A., Anto, J. M., Kunzli, N., . . . Burney, P. (2007). Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. *American Journal of Respiratory and Critical Care Medicine, 175*(1), 32-39. doi:200603-381OC [pii]
18. Kojima, S., Sakakibara, H., Motani, S., Hirose, K., Mizuno, F., Ochiai, M., & Hashimoto, S. (2007). Incidence of chronic obstructive pulmonary disease, and the relationship between age and smoking in a japanese population. *Journal of Epidemiology, 17*(2), 54-60. doi:JST.JSTAGE/jea/17.54 [pii]
19. Lindberg, A., Jonsson, A. C., Ronmark, E., Lundgren, R., Larsson, L. G., & Lundback, B. (2005). Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. *Chest, 127*(5), 1544-1552. doi:S0012-3692(15)34717-6 [pii]
20. Lindberg, A., Eriksson, B., Larsson, L. G., Ronmark, E., Sandstrom, T., & Lundback, B. (2006). Seven-year cumulative incidence of COPD in an age-stratified general population sample. *Chest, 129*(4), 879-885. doi:S0012-3692(15)38800-0 [pii]

21. Blair, K. A., & Evelo, A. J. (2014). Risk factors for COPD: What do NPs know? *Journal of the American Association of Nurse Practitioners, 26*(3), 123-130. doi:10.1002/2327-6924.12032 [doi]
22. Porth, Carol, et al. *Essentials of Pathophysiology: Concepts of Altered Health States.* 8th ed. Philaedlphia: Wolter Kluwers Health, 2009. Print.
23. Kawane, H. (1999). Smoking as a risk factor for COPD and prognosis after smoking cessation. *Nihon Rinsho.Japanese Journal of Clinical Medicine, 57*(9), 1959-1964.
24. Salvi, S. S., & Barnes, P. J. (2009). Chronic obstructive pulmonary disease in non-smokers. *Lancet (London, England), 374*(9691), 733-743. doi:10.1016/S0140-6736(09)61303-9 [doi]
25. Forbes, L. J., Kapetanakis, V., Rudnicka, A. R., Cook, D. G., Bush, T., Stedman, J. R., . . . Anderson, H. R. (2009). Chronic exposure to outdoor air pollution and lung function in adults. *Thorax, 64*(8), 657-663. doi:10.1136/thx.2008.109389 [doi]
26. Balmes, J., Becklake, M., Blanc, P., Henneberger, P., Kreiss, K., Mapp, C., . . . Environmental and Occupational Health Assembly, American Thoracic Society. (2003). American thoracic society statement: Occupational contribution to the burden of airway disease. *American Journal of Respiratory and Critical Care Medicine, 167*(5), 787-797. doi:10.1164/rccm.167.5.787 [doi]
27. Blanc, P. D., Eisner, M. D., Earnest, G., Trupin, L., Balmes, J. R., Yelin, E. H., . . . Katz, P. P. (2009). Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. *Journal of Occupational and Environmental Medicine, 51*(7), 804-810. doi:10.1097/JOM.0b013e3181a7dd4e [doi]
28. Liu, Y., Lee, K., Perez-Padilla, R., Hudson, N. L., & Mannino, D. M. (2008). Outdoor and indoor air pollution and COPD-related diseases in high- and low-income countries. *The International Journal of Tuberculosis and Lung Disease : The Official Journal of the International Union Against Tuberculosis and Lung Disease, 12*(2), 115-127.
29. Stephens, M. B., & Yew, K. S. (2008). Diagnosis of chronic obstructive pulmonary disease. *American Family Physician, 78*(1), 87-92.
30. Weinmann, S., Vollmer, W. M., Breen, V., Heumann, M., Hnizdo, E., Villnave, J., . . . Buist, A. S. (2008). COPD and occupational exposures: A case-control study. *Journal of Occupational and Environmental Medicine, 50*(5), 561-569. doi:10.1097/JOM.0b013e3181651556 [doi]
31. de Marco, R., Accordini, S., Marcon, A., Cerveri, I., Anto, J. M., Gislason, T., . . . European Community Respiratory Health Survey (ECRHS). (2011). Risk factors for

chronic obstructive pulmonary disease in a european cohort of young adults. *American Journal of Respiratory and Critical Care Medicine, 183*(7), 891-897. doi:10.1164/rccm.201007-1125OC [doi]

32. Dharmage, S. C., Erbas, B., Jarvis, D., Wjst, M., Raherison, C., Norback, D., . . . Svanes, C. (2009). Do childhood respiratory infections continue to influence adult respiratory morbidity? *The European Respiratory Journal, 33*(2), 237-244. doi:10.1183/09031936.00062907 [doi]
33. MacNee, W. (2005). Pathogenesis of chronic obstructive pulmonary disease. *Proceedings of the American Thoracic Society, 2*(4), 258-266. doi:procats24258 [pii]
34. The definition of emphysema. report of a national heart, lung, and blood institute, division of lung diseases workshop. (1985). *The American Review of Respiratory Disease, 132*(1), 182-185. doi:10.1164/arrd.1985.132.1.182 [doi]
35. MacNee, W. (2006). Pathology, pathogenesis, and pathophysiology. *BMJ : British Medical Journal, 332*(7551), 1202-1204. doi:1202 [pii]
36. Sakao, S., Voelkel, N. F., & Tatsumi, K. (2014). The vascular bed in COPD: Pulmonary hypertension and pulmonary vascular alterations. *European Respiratory Review : An Official Journal of the European Respiratory Society, 23*(133), 350-355. doi:10.1183/09059180.00007913 [doi]
37. Gjerde, B., Bakke, P. S., Ueland, T., Hardie, J. A., & Eagan, T. M. (2012). The prevalence of undiagnosed renal failure in a cohort of COPD patients in western norway. *Respiratory Medicine, 106*(3), 361-366. doi:10.1016/j.rmed.2011.10.004 [doi]
38. Mirrakhimov, A. E. (2012). Chronic obstructive pulmonary disease and glucose metabolism: A bitter sweet symphony. *Cardiovascular Diabetology, 11*, 132-2840-11-132. doi:10.1186/1475-2840-11-132 [doi]
39. Barnes, P. J., & Celli, B. R. (2009). Systemic manifestations and comorbidities of COPD. *The European Respiratory Journal, 33*(5), 1165-1185. doi:10.1183/09031936.00128008 [doi]
40. Cooper, C. B., & Dransfield, M. (2008). Primary care of the patient with chronic obstructive pulmonary disease-part 4: Understanding the clinical manifestations of a progressive disease. *The American Journal of Medicine, 121*(7 Suppl), S33-45. doi:10.1016/j.amjmed.2008.04.005 [doi]
41. Hillas, G., Perlikos, F., Tsiligianni, I., & Tzanakis, N. (2015). Managing comorbidities in COPD. *International Journal of Chronic Obstructive Pulmonary Disease, 10*, 95-109. doi:10.2147/COPD.S54473 [doi]

42. Schonhofer, B., Wenzel, M., Geibel, M., & Kohler, D. (1998). Blood transfusion and lung function in chronically anemic patients with severe chronic obstructive pulmonary disease. *Critical Care Medicine, 26*(11), 1824-1828.
43. Miller, J., Edwards, L. D., Agusti, A., Bakke, P., Calverley, P. M., Celli, B., . . . Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. (2013). Comorbidity, systemic inflammation and outcomes in the ECLIPSE cohort. *Respiratory Medicine, 107*(9), 1376-1384. doi:10.1016/j.rmed.2013.05.001 [doi]
44. Sidney, S., Sorel, M., Quesenberry, C. P.,Jr, DeLuise, C., Lanes, S., & Eisner, M. D. (2005). COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser permanente medical care program. *Chest, 128*(4), 2068-2075. doi:S0012-3692(15)52604-4 [pii]
45. Rutten, F. H., Cramer, M. J., Lammers, J. W., Grobbee, D. E., & Hoes, A. W. (2006). Heart failure and chronic obstructive pulmonary disease: An ignored combination? *European Journal of Heart Failure, 8*(7), 706-711. doi:S1388-9842(06)00011-0 [pii]
46. Le Jemtel, T. H., Padeletti, M., & Jelic, S. (2007). Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *Journal of the American College of Cardiology, 49*(2), 171-180. doi:S0735-1097(06)02500-9 [pii]
47. Undas, A., Kaczmarek, P., Sladek, K., Stepien, E., Skucha, W., Rzeszutko, M., . . . Tracz, W. (2009). Fibrin clot properties are altered in patients with chronic obstructive pulmonary disease. beneficial effects of simvastatin treatment. *Thrombosis and Haemostasis, 102*(6), 1176-1182. doi:10.1160/TH09-02-0118 [doi]
48. Doehner, W., Haeusler, K. G., Endres, M., Anker, S. D., MacNee, W., & Lainscak, M. (2011). Neurological and endocrinological disorders: Orphans in chronic obstructive pulmonary disease. *Respiratory Medicine, 105 Suppl 1*, S12-9. doi:10.1016/S0954-6111(11)70005-1 [doi]
49. Vaidyula, V. R., Criner, G. J., Grabianowski, C., & Rao, A. K. (2009). Circulating tissue factor procoagulant activity is elevated in stable moderate to severe chronic obstructive pulmonary disease. *Thrombosis Research, 124*(3), 259-261. doi:10.1016/j.thromres.2008.12.030 [doi]
50. Finkelstein, J., Cha, E., & Scharf, S. M. (2009). Chronic obstructive pulmonary disease as an independent risk factor for cardiovascular morbidity. *International Journal of Chronic Obstructive Pulmonary Disease, 4*, 337-349.

51. Huang, B., Yang, Y., Zhu, J., Liang, Y., Zhang, H., Tian, L., . . . Wang, J. (2014). Clinical characteristics and prognostic significance of chronic obstructive pulmonary disease in patients with atrial fibrillation: Results from a multicenter atrial fibrillation registry study. *Journal of the American Medical Directors Association, 15*(8), 576-581. doi:10.1016/j.jamda.2014.04.009 [doi]
52. Tillie-Leblond, I., Marquette, C. H., Perez, T., Scherpereel, A., Zanetti, C., Tonnel, A. B., & Remy-Jardin, M. (2006). Pulmonary embolism in patients with unexplained exacerbation of chronic obstructive pulmonary disease: Prevalence and risk factors. *Annals of Internal Medicine, 144*(6), 390-396. doi:144/6/390 [pii]
53. Weitzenblum, E., Sautegeau, A., Ehrhart, M., Mammosser, M., & Pelletier, A. (1985). Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *The American Review of Respiratory Disease, 131*(4), 493-498. doi:10.1164/arrd.1985.131.4.493 [doi]
54. Cazzola, M., Bettoncelli, G., Sessa, E., Cricelli, C., & Biscione, G. (2010). Prevalence of comorbidities in patients with chronic obstructive pulmonary disease. *Respiration; International Review of Thoracic Diseases, 80*(2), 112-119. doi:10.1159/000281880 [doi]
55. Mannino, D. M., Thorn, D., Swensen, A., & Holguin, F. (2008). Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *The European Respiratory Journal, 32*(4), 962-969. doi:10.1183/09031936.00012408 [doi]
56. Song, Y., Klevak, A., Manson, J. E., Buring, J. E., & Liu, S. (2010). Asthma, chronic obstructive pulmonary disease, and type 2 diabetes in the women's health study. *Diabetes Research and Clinical Practice, 90*(3), 365-371. doi:10.1016/j.diabres.2010.09.010 [doi]
57. Ehrlich, S. F., Quesenberry, C. P.,Jr, Van Den Eeden, S. K., Shan, J., & Ferrara, A. (2010). Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. *Diabetes Care, 33*(1), 55-60. doi:10.2337/dc09-0880 [doi]
58. Feary, J. R., Rodrigues, L. C., Smith, C. J., Hubbard, R. B., & Gibson, J. E. (2010). Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: A comprehensive analysis using data from primary care. *Thorax, 65*(11), 956-962. doi:10.1136/thx.2009.128082 [doi]
59. Ferguson, G. T., Calverley, P. M. A., Anderson, J. A., Jenkins, C. R., Jones, P. W., Willits, L. R., . . . Celli, B. (2009). Prevalence and progression of osteoporosis in patients

with COPD: Results from the TOwards a revolution in COPD health study. *Chest, 136*(6), 1456-1465. doi:S0012-3692(09)60724-8 [pii]

60. Jaramillo, J. D., Wilson, C., Stinson, D. S., Lynch, D. A., Bowler, R. P., Lutz, S., . . . COPDGene Investigators. (2015). Reduced bone density and vertebral fractures in smokers. men and COPD patients at increased risk. *Annals of the American Thoracic Society, 12*(5), 648-656. doi:10.1513/AnnalsATS.201412-591OC [doi]
61. Scanlon, P. D., Connett, J. E., Wise, R. A., Tashkin, D. P., Madhok, T., Skeans, M., . . . Lung Health Study Research Group. (2004). Loss of bone density with inhaled triamcinolone in lung health study II. *American Journal of Respiratory and Critical Care Medicine, 170*(12), 1302-1309. doi:10.1164/rccm.200310-1349OC [doi]
62. Seymour, J. M., Spruit, M. A., Hopkinson, N. S., Natanek, S. A., Man, W. D., Jackson, A., . . . Wouters, E. F. (2010). The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *The European Respiratory Journal, 36*(1), 81-88. doi:10.1183/09031936.00104909 [doi]
63. Kunik, M. E., Roundy, K., Veazey, C., Souchek, J., Richardson, P., Wray, N. P., & Stanley, M. A. (2005). Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. *Chest, 127*(4), 1205-1211. doi:S0012-3692(15)34468-8 [pii]
64. Paz-Diaz, H., Montes de Oca, M., Lopez, J. M., & Celli, B. R. (2007). Pulmonary rehabilitation improves depression, anxiety, dyspnea and health status in patients with COPD. *American Journal of Physical Medicine & Rehabilitation, 86*(1), 30-36.
65. Maurer, J., Rebbapragada, V., Borson, S., Goldstein, R., Kunik, M. E., Yohannes, A. M., . . . ACCP Workshop Panel on Anxiety and Depression in COPD. (2008). Anxiety and depression in COPD: Current understanding, unanswered questions, and research needs. *Chest, 134*(4 Suppl), 43S-56S. doi:10.1378/chest.08-0342 [doi]
66. Regvat, J., Zmitek, A., Vegnuti, M., Kosnik, M., & Suskovic, S. (2011). Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. *The Journal of International Medical Research, 39*(3), 1028-1038. doi:10.1177/147323001103900338 [doi]
67. Al-shair, K., Dockry, R., Mallia-Milanes, B., Kolsum, U., Singh, D., & Vestbo, J. (2009). Depression and its relationship with poor exercise capacity, BODE index and muscle wasting in COPD. *Respiratory Medicine, 103*(10), 1572-1579. doi:10.1016/j.rmed.2008.11.021 [doi]
68. Omachi, T. A., Katz, P. P., Yelin, E. H., Gregorich, S. E., Iribarren, C., Blanc, P. D., & Eisner, M. D. (2009). Depression and health-related quality of life in chronic obstructive

pulmonary disease. *The American Journal of Medicine, 122*(8), 778.e9-778.15. doi:10.1016/j.amjmed.2009.01.036 [doi]

69. Schneider, C., Jick, S. S., Bothner, U., & Meier, C. R. (2010). COPD and the risk of depression. *Chest, 137*(2), 341-347. doi:10.1378/chest.09-0614 [doi]
70. Xu, W., Collet, J. P., Shapiro, S., Lin, Y., Yang, T., Platt, R. W., . . . Bourbeau, J. (2008). Independent effect of depression and anxiety on chronic obstructive pulmonary disease exacerbations and hospitalizations. *American Journal of Respiratory and Critical Care Medicine, 178*(9), 913-920. doi:10.1164/rccm.200804-619OC [doi]
71. Dodd, J. W., Getov, S. V., & Jones, P. W. (2010). Cognitive function in COPD. *The European Respiratory Journal, 35*(4), 913-922. doi:10.1183/09031936.00125109 [doi]
72. Yohannes, A. M., Chen, W., Moga, A. M., Leroi, I., & Connolly, M. J. (2017). Cognitive impairment in chronic obstructive pulmonary disease and chronic heart failure: A systematic review and meta-analysis of observational studies. *Journal of the American Medical Directors Association, 18*(5), 451.e1-451.e11. doi:S1525-8610(17)30061-0 [pii]
73. Martinez, C. H., Richardson, C. R., Han, M. K., & Cigolle, C. T. (2014). Chronic obstructive pulmonary disease, cognitive impairment, and development of disability: The health and retirement study. *Annals of the American Thoracic Society, 11*(9), 1362-1370. doi:10.1513/AnnalsATS.201405-187OC [doi]
74. Singh, B., Parsaik, A. K., Mielke, M. M., Roberts, R. O., Scanlon, P. D., Geda, Y. E., . . . Petersen, R. C. (2013). Chronic obstructive pulmonary disease and association with mild cognitive impairment: The mayo clinic study of aging. *Mayo Clinic Proceedings, 88*(11), 1222-1230. doi:10.1016/j.mayocp.2013.08.012 [doi]
75. Lima, O. M., Oliveira-Souza, R., Santos Oda, R., Moraes, P. A., Sa, L. F., & Nascimento, O. J. (2007). Subclinical encephalopathy in chronic obstructive pulmonary disease. *Arquivos De Neuro-Psiquiatria, 65*(4B), 1154-1157. doi:S0004-282X2007000700012 [pii]
76. Villeneuve, S., Pepin, V., Rahayel, S., Bertrand, J. A., de Lorimier, M., Rizk, A., . . . Gagnon, J. F. (2012). Mild cognitive impairment in moderate to severe COPD: A preliminary study. *Chest, 142*(6), 1516-1523. doi:S0012-3692(12)60685-0 [pii]
77. CDC – Alzheimer's Disease and Healthy Aging. https://www.cdc.gov/aging/healthybrain/index.htm. November 6, 2015
78. Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., . . . International Psychogeriatric Association Expert Conference on mild cognitive impairment. (2006). Mild cognitive impairment. *Lancet (London, England), 367*(9518), 1262-1270. doi:S0140-6736(06)68542-5 [pii]

79. Petersen, R. C., & Morris, J. C. (2005). Mild cognitive impairment as a clinical entity and treatment target. *Archives of Neurology, 62*(7), 1160-3; discussion 1167. doi:62/7/1160 [pii]
80. APA Work Group on Alzheimer's Disease and other Dementias, Rabins, P. V., Blacker, D., Rovner, B. W., Rummans, T., Schneider, L. S., . . . Fochtmann, L. J. (2007). American psychiatric association practice guideline for the treatment of patients with alzheimer's disease and other dementias. second edition. *The American Journal of Psychiatry, 164*(12 Suppl), 5-56.
81. Thakur, N., Blanc, P. D., Julian, L. J., Yelin, E. H., Katz, P. P., Sidney, S., . . . Eisner, M. D. (2010). COPD and cognitive impairment: The role of hypoxemia and oxygen therapy. *International Journal of Chronic Obstructive Pulmonary Disease, 5*, 263-269.
82. Grant, I., Heaton, R. K., McSweeny, A. J., Adams, K. M., & Timms, R. M. (1982). Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Archives of Internal Medicine, 142*(8), 1470-1476.
83. Prigatano, G. P., Parsons, O., Wright, E., Levin, D. C., & Hawryluk, G. (1983). Neuropsychological test performance in mildly hypoxemic patients with chronic obstructive pulmonary disease. *Journal of Consulting and Clinical Psychology, 51*(1), 108-116.
84. Incalzi, R. A., Gemma, A., Marra, C., Capparella, O., Fuso, L., & Carbonin, P. (1997). Verbal memory impairment in COPD: Its mechanisms and clinical relevance. *Chest, 112*(6), 1506-1513. doi:S0012-3692(15)47357-X [pii]
85. Incalzi, R. A., Gemma, A., Marra, C., Muzzolon, R., Capparella, O., & Carbonin, P. (1993). Chronic obstructive pulmonary disease. an original model of cognitive decline. *The American Review of Respiratory Disease, 148*(2), 418-424. doi:10.1164/ajrccm/148.2.418 [doi]
86. Cleutjens, F. A., Janssen, D. J., Ponds, R. W., Dijkstra, J. B., & Wouters, E. F. (2014). COgnitive-pulmonary disease. *BioMed Research International, 2014*, 697825. doi:10.1155/2014/697825 [doi]
87. Fix, A. J., Golden, C. J., Daughton, D., Kass, I., & Bell, C. W. (1982). Neuropsychological deficits among patients with chronic obstructive pulmonary disease. *The International Journal of Neuroscience, 16*(2), 99-105.
88. Grant, I., Prigatano, G. P., Heaton, R. K., McSweeny, A. J., Wright, E. C., & Adams, K. M. (1987). Progressive neuropsychologic impairment and hypoxemia. relationship in

chronic obstructive pulmonary disease. *Archives of General Psychiatry, 44*(11), 999-1006

89. Ranieri, P., Bianchetti, A., Margiotta, A., Virgillo, A., Clini, E. M., & Trabucchi, M. (2008). Predictors of 6-month mortality in elderly patients with mild chronic obstructive pulmonary disease discharged from a medical ward after acute nonacidotic exacerbation. *Journal of the American Geriatrics Society, 56*(5), 909-913. doi:10.1111/j.1532-5415.2008.01683.x [doi]
90. Celli, B. R., & Barnes, P. J. (2007). Exacerbations of chronic obstructive pulmonary disease. *The European Respiratory Journal, 29*(6), 1224-1238. 29/6/1224 [pii]
91. Donaldson, G. C., Seemungal, T. A., Patel, I. S., Lloyd-Owen, S. J., Wilkinson, T. M., & Wedzicha, J. A. (2003). Longitudinal changes in the nature, severity and frequency of COPD exacerbations. *The European Respiratory Journal, 22*(6), 931-936.
92. Ambrosino, N., Bruletti, G., Scala, V., Porta, R., & Vitacca, M. (2002). Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: A controlled study. *Intensive Care Medicine, 28*(2), 170-177. doi:10.1007/s00134-001-1165-6 [doi]
93. Kirkil, G., Tug, T., Ozel, E., Bulut, S., Tekatas, A., & Muz, M. H. (2007). The evaluation of cognitive functions with P300 test for chronic obstructive pulmonary disease patients in attack and stable period. *Clinical Neurology and Neurosurgery, 109*(7), 553-560. doi:S0303-8467(07)00089-3 [pii]
94. Urbano, F., & Mohsenin, V. (2006). Chronic obstructive pulmonary disease and sleep: The interaction. *Panminerva Medica, 48*(4), 223-230.
95. Walker, M. P. (2008). Sleep-dependent memory processing. *Harvard Review of Psychiatry, 16*(5), 287-298. doi:10.1080/10673220802432517 [doi]
96. Fletcher, E. C. (1990). Chronic lung disease in the sleep apnea syndrome. *Lung, 168 Suppl*, 751-761.
97. Beebe, D. W., Groesz, L., Wells, C., Nichols, A., & McGee, K. (2003). The neuropsychological effects of obstructive sleep apnea: A meta-analysis of norm-referenced and case-controlled data. *Sleep, 26*(3), 298-307.
98. Roehrs, T., Merrion, M., Pedrosi, B., Stepanski, E., Zorick, F., & Roth, T. (1995). Neuropsychological function in obstructive sleep apnea syndrome (OSAS) compared to chronic obstructive pulmonary disease (COPD). *Sleep, 18*(5), 382-388.

99. Aleman, A., Muller, M., de Haan, E. H., & van der Schouw, Y. T. (2005). Vascular risk factors and cognitive function in a sample of independently living men. *Neurobiology of Aging, 26*(4), 485-490. doi:S0197458004002015 [pii]

100. Kuo, H. K., Jones, R. N., Milberg, W. P., Tennstedt, S., Talbot, L., Morris, J. N., & Lipsitz, L. A. (2005). Effect of blood pressure and diabetes mellitus on cognitive and physical functions in older adults: A longitudinal analysis of the advanced cognitive training for independent and vital elderly cohort. *Journal of the American Geriatrics Society, 53*(7), 1154-1161. doi:JGS53368 [pii]

101. Report of the National Chronic Obstructive Pulmonary Disease Audit 2008: clinical audit of COPD exacerbations admitte to acute NHS units across the UK. Royal College of Physicians London British Thoracic Society, British Lung Foundation. 2008. Available from: www.rcplondon.ac.uk/clinical-standards/ceeu/ Current-work/ncrop/Documents/Report-of-The-National-COPD- Audit-2008-clinical-audit-of-COPD-exacerbations-admitted-to- acute-NHS-units-across-the-UK.pdf

102. Borson, S., Scanlan, J., Friedman, S., Zuhr, E., Fields, J., Aylward, E., . . . Yeh, S. (2008). Modeling the impact of COPD on the brain. *International Journal of Chronic Obstructive Pulmonary Disease, 3*(3), 429-434.

103. Duong, T., Acton, P. J., & Johnson, R. A. (1998). The in vitro neuronal toxicity of pentraxins associated with alzheimer's disease brain lesions. *Brain Research, 813*(2), 303-312. doi:S0006-8993(98)00966-4 [pii]

104. Engelhart, M. J., Geerlings, M. I., Meijer, J., Kiliaan, A., Ruitenberg, A., van Swieten, J. C., . . . Breteler, M. M. (2004). Inflammatory proteins in plasma and the risk of dementia: The rotterdam study. *Archives of Neurology, 61*(5), 668-672. doi:10.1001/archneur.61.5.668 [doi]

105. Warnberg, J., Gomez-Martinez, S., Romeo, J., Diaz, L. E., & Marcos, A. (2009). Nutrition, inflammation, and cognitive function. *Annals of the New York Academy of Sciences, 1153*, 164-175. doi:10.1111/j.1749-6632.2008.03985.x [doi]

106. Anstey, K. J., von Sanden, C., Salim, A., & O'Kearney, R. (2007). Smoking as a risk factor for dementia and cognitive decline: A meta-analysis of prospective studies. *American Journal of Epidemiology, 166*(4), 367-378. doi:kwm116 [pii]

107. Grant, I., Heaton, R. K., McSweeny, A. J., Adams, K. M., & Timms, R. M. (1982). Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Archives of Internal Medicine, 142*(8), 1470-1476.

108. Richards, M., Strachan, D., Hardy, R., Kuh, D., & Wadsworth, M. (2005). Lung

function and cognitive ability in a longitudinal birth cohort study. *Psychosomatic Medicine, 67*(4), 602-608. doi:67/4/602 [pii]

109. Sachdev, P. S., Anstey, K. J., Parslow, R. A., Wen, W., Maller, J., Kumar, R., . . . Jorm, A. F. (2006). Pulmonary function, cognitive impairment and brain atrophy in a middle-aged community sample. *Dementia and Geriatric Cognitive Disorders, 21*(5-6), 300-308. doi:91438 [pii]

110. Tabert, M. H., Albert, S. M., Borukhova-Milov, L., Camacho, Y., Pelton, G., Liu, X., . . . Devanand, D. P. (2002). Functional deficits in patients with mild cognitive impairment: Prediction of AD. *Neurology, 58*(5), 758-764.

111. Incalzi, R. A., Corsonello, A., Pedone, C., Corica, F., Carbonin, P., Bernabei, R., & GIFA Investigators. (2005). Construct validity of activities of daily living scale: A clue to distinguish the disabling effects of COPD and congestive heart failure. *Chest, 127*(3), 830-838. doi:S0012-3692(15)31091-6 [pii]

112. Antonelli-Incalzi, R., Corsonello, A., Pedone, C., Trojano, L., Acanfora, D., Spada, A., . . . Rengo, F. (2006). Drawing impairment predicts mortality in severe COPD. *Chest, 130*(6), 1687-1694. doi:S0012-3692(15)50888-X [pii]

113. Cleutjens, F. A. H. M., Spruit, M. A., Ponds, R. W. H. M., Vanfleteren, L. E. G. W., Franssen, F. M. E., Dijkstra, J. B., . . . Janssen, D. J. A. (2017). The impact of cognitive impairment on efficacy of pulmonary rehabilitation in patients with COPD. *Journal of the American Medical Directors Association, 18*(5), 420-426. doi:S1525-8610(16)30548-5 [pii]

114. Aquino, G., Iuliano, E., di Cagno, A., Vardaro, A., Fiorilli, G., Moffa, S., . . . Calcagno, G. (2016). Effects of combined training vs aerobic training on cognitive functions in COPD: A randomized controlled trial. *International Journal of Chronic Obstructive Pulmonary Disease, 11*, 711-718. doi:10.2147/COPD.S96663 [doi]

115. Emery, C. F., Leatherman, N. E., Burker, E. J., & MacIntyre, N. R. (1991). Psychological outcomes of a pulmonary rehabilitation program. *Chest, 100*(3), 613-617. S0012-3692(16)32776-3 [pii]

116. Emery, C. F. (1994). Effects of age on physiological and psychological functioning among COPD patients in an exercise program. *Journal of Aging and Health, 6*(1), 3-16. 10.1177/089826439400600101 [doi]

117. Emery, C. F., Schein, R. L., Hauck, E. R., & MacIntyre, N. R. (1998). Psychological and cognitive outcomes of a randomized trial of exercise among patients

with chronic obstructive pulmonary disease. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association, 17*(3), 232-240.

118. Etnier, J. L., & Berry, M. (2001). Fluid intelligence in an older COPD sample after short- or long-term exercise. *Medicine and Science in Sports and Exercise, 33*(10), 1620-1628.

119. Kozora, E., Tran, Z. V., & Make, B. (2002). Neurobehavioral improvement after brief rehabilitation in patients with chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation, 22*(6), 426-430.

120. Pereira, E. D., Viana, C. S., Taunay, T. C., Sales, P. U., Lima, J. W., & Holanda, M. A. (2011). Improvement of cognitive function after a three-month pulmonary rehabilitation program for COPD patients. *Lung, 189*(4), 279-285. doi:10.1007/s00408-011-9303-6 [doi]

121. Hunter, M. H., & King, D. E. (2001). COPD: Management of acute exacerbations and chronic stable disease. *American Family Physician, 64*(4), 603-612.

122. O'Donnell, D. E., Fluge, T., Gerken, F., Hamilton, A., Webb, K., Aguilaniu, B., . . . Magnussen, H. (2004). Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *The European Respiratory Journal, 23*(6), 832-840.

123. O'Donnell, D. E., Sciurba, F., Celli, B., Mahler, D. A., Webb, K. A., Kalberg, C. J., & Knobil, K. (2006). Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest, 130*(3), 647-656. doi:S0012-3692(15)52774-8 [pii]

124. O'Driscoll, B. R., Kay, E. A., Taylor, R. J., Weatherby, H., Chetty, M. C., & Bernstein, A. (1992). A long-term prospective assessment of home nebulizer treatment. *Respiratory Medicine, 86*(4), 317-325.

125. Jenkins, S. C., Heaton, R. W., Fulton, T. J., & Moxham, J. (1987). Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest, 91*(6), 804-807. doi:S0012-3692(15)43155-1 [pii]

126. Niewoehner, D. E., Erbland, M. L., Deupree, R. H., Collins, D., Gross, N. J., Light, R. W., . . . Morgan, N. A. (1999). Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. department of veterans affairs cooperative study group. *The New England Journal of Medicine, 340*(25), 1941-1947. doi:10.1056/NEJM199906243402502 [doi]

127. Yang, I. A., Clarke, M. S., Sim, E. H., & Fong, K. M. (2012). Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (7):CD002991. doi*(7), CD002991. doi:10.1002/14651858.CD002991.pub3 [doi]

128. Nannini, L. J., Lasserson, T. J., & Poole, P. (2012). Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (9):CD006829. doi*(9), CD006829. doi:10.1002/14651858.CD006829.pub2 [doi]

129. Nannini, L. J., Poole, P., Milan, S. J., & Kesterton, A. (2013). Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (8):CD006826. doi*(8), CD006826. doi:10.1002/14651858.CD006826.pub2 [doi]

130. Balter, M. S., La Forge, J., Low, D. E., Mandell, L., Grossman, R. F., Chronic Bronchitis Working Group, . . . Canadian Infectious Disease Society. (2003). Canadian guidelines for the management of acute exacerbations of chronic bronchitis: Executive summary. *Canadian Respiratory Journal, 10*(5), 248-258.

131. Herath, S. C., & Poole, P. (2013). Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *The Cochrane Database of Systematic Reviews, (11):CD009764. doi*(11), CD009764. doi:10.1002/14651858.CD009764.pub2 [doi]

132. Ni, W., Shao, X., Cai, X., Wei, C., Cui, J., Wang, R., & Liu, Y. (2015). Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: A meta-analysis. *PloS One, 10*(3), e0121257. doi:10.1371/journal.pone.0121257 [doi]

133. Wongsurakiat, P., Maranetra, K. N., Wasi, C., Kositanont, U., Dejsomritrutai, W., & Charoenratanakul, S. (2004). Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: A randomized controlled study. *Chest, 125*(6), 2011-2020. doi:S0012-3692(16)58970-3 [pii]

134. Poole, P. J., Chacko, E., Wood-Baker, R. W., & Cates, C. J. (2006). Influenza vaccine for patients with chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (1):CD002733. doi*(1), CD002733. doi:10.1002/14651858.CD002733.pub2 [doi]

135. O'Donnell, D. E., Aaron, S., Bourbeau, J., Hernandez, P., Marciniuk, D. D., Balter, M., . . . Voduc, N. (2007). Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Canadian Respiratory Journal, 14 Suppl B*, 5B-32B. doi:10.1155/2007/830570 [doi]

136. Cranston, J. M., Crockett, A. J., Moss, J. R., & Alpers, J. H. (2005). Domiciliary oxygen for chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (4):CD001744. doi*(4), CD001744. doi:10.1002/14651858.CD001744.pub2 [doi]

137. McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *The Cochrane Database of Systematic Reviews, (2):CD003793. doi*(2), CD003793. doi:10.1002/14651858.CD003793.pub3 [doi]

138. O'Donnell, D. E., Hernandez, P., Kaplan, A., Aaron, S., Bourbeau, J., Marciniuk, D., . . . Voduc, N. (2008). Canadian thoracic society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Canadian Respiratory Journal, 15 Suppl A*, 1A-8A. doi:10.1155/2008/641965 [doi]

139. Spruit, M. A., Singh, S. J., Garvey, C., ZuWallack, R., Nici, L., Rochester, C., . . . ATS/ERS Task Force on Pulmonary Rehabilitation. (2013). An official american thoracic Society/European respiratory society statement: Key concepts and advances in pulmonary rehabilitation. *American Journal of Respiratory and Critical Care Medicine, 188*(8), e13-64. doi:10.1164/rccm.201309-1634ST [doi]

140. Marciniuk, D. D., Brooks, D., Butcher, S., Debigare, R., Dechman, G., Ford, G., . . . Canadian Thoracic Society COPD Committee Expert Working Group. (2010). Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease--practical issues: A canadian thoracic society clinical practice guideline. *Canadian Respiratory Journal, 17*(4), 159-168.

141. Sala, E., Roca, J., Marrades, R. M., Alonso, J., Gonzalez De Suso, J. M., Moreno, A., . . . Wagner, P. D. (1999). Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 159*(6), 1726-1734. doi:10.1164/ajrccm.159.6.9804136 [doi]

142. Bernard, S., Whittom, F., Leblanc, P., Jobin, J., Belleau, R., Berube, C., . . . Maltais, F. (1999). Aerobic and strength training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 159*(3), 896-901. doi:10.1164/ajrccm.159.3.9807034 [doi]

143. Maltais, F., LeBlanc, P., Simard, C., Jobin, J., Berube, C., Bruneau, J., . . . Belleau, R. (1996). Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 154*(2 Pt 1), 442-447. doi:10.1164/ajrccm.154.2.8756820 [doi]

144. Spruit, M. A., Gosselink, R., Troosters, T., De Paepe, K., & Decramer, M. (2002). Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *The European Respiratory Journal, 19*(6), 1072-1078.

145. O'Donnell, D. E., McGuire, M., Samis, L., & Webb, K. A. (1998). General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. *American Journal of Respiratory and Critical Care Medicine, 157*(5 Pt 1), 1489-1497. doi:10.1164/ajrccm.157.5.9708010 [doi]

146. Franssen, F. M., Broekhuizen, R., Janssen, P. P., Wouters, E. F., & Schols, A. M. (2004). Effects of whole-body exercise training on body composition and functional capacity in normal-weight patients with COPD. *Chest, 125*(6), 2021-2028. doi:S0012-3692(16)58971-5 [pii]

147. O'Donnell, D. E., McGuire, M., Samis, L., & Webb, K. A. (1995). The impact of exercise reconditioning on breathlessness in severe chronic airflow limitation. *American Journal of Respiratory and Critical Care Medicine, 152*(6 Pt 1), 2005-2013. doi:10.1164/ajrccm.152.6.8520769 [doi]

148. Camillo, C. A., Laburu Vde, M., Goncalves, N. S., Cavalheri, V., Tomasi, F. P., Hernandes, N. A., . . . Pitta, F. (2011). Improvement of heart rate variability after exercise training and its predictors in COPD. *Respiratory Medicine, 105*(7), 1054-1062. doi:10.1016/j.rmed.2011.01.014 [doi]

149. Gale, N. S., Duckers, J. M., Enright, S., Cockcroft, J. R., Shale, D. J., & Bolton, C. E. (2011). Does pulmonary rehabilitation address cardiovascular risk factors in patients with COPD? *BMC Pulmonary Medicine, 11*, 20-2466-11-20. doi:10.1186/1471-2466-11-20 [doi]

150. Pescatello, Linda S.,, Arena, Ross,, Riebe, Deborah,, Thompson, Paul D.,,American College of Sports Medicine.,. (2014). *ACSM's guidelines for exercise testing and prescription*. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins Health.

151. Maltais, F., LeBlanc, P., Jobin, J., Berube, C., Bruneau, J., Carrier, L., . . . Belleau, R. (1997). Intensity of training and physiologic adaptation in patients with

chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 155*(2), 555-561. doi:10.1164/ajrccm.155.2.9032194 [doi]

152. Probst, V. S., Troosters, T., Pitta, F., Decramer, M., & Gosselink, R. (2006). Cardiopulmonary stress during exercise training in patients with COPD. *The European Respiratory Journal, 27*(6), 1110-1118. doi:09031936.06.00110605 [pii]

153. Sabapathy, S., Kingsley, R. A., Schneider, D. A., Adams, L., & Morris, N. R. (2004). Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax, 59*(12), 1026-1031. doi:59/12/1026 [pii]

154. Vallet, G., Ahmaidi, S., Serres, I., Fabre, C., Bourgouin, D., Desplan, J., . . . Prefaut, C. (1997). Comparison of two training programmes in chronic airway limitation patients: Standardized versus individualized protocols. *The European Respiratory Journal, 10*(1), 114-122.

155. Vogiatzis, I., Nanas, S., Kastanakis, E., Georgiadou, O., Papazahou, O., & Roussos, C. (2004). Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *The European Respiratory Journal, 24*(3), 385-390. doi:10.1183/09031936.04.00128903 [doi]

156. Vallet, G., Varray, A., Fontaine, J. L., & Prefaut, C. (1994). Value of individualized rehabilitation at the ventilatory threshold level in moderately severe chronic obstructive pulmonary disease. [Interet du reentrainement a l'effort individualise, au niveau du seuil ventilatoire, au cours de la bronchopneumopathie chronique obstructive de severite moderee] *Revue Des Maladies Respiratoires, 11*(5), 493-501.

157. Rizk, A. K., Wardini, R., Chan-Thim, E., Bacon, S. L., Lavoie, K. L., & Pepin, V. (2015). Acute responses to exercise training and relationship with exercise adherence in moderate chronic obstructive pulmonary disease. *Chronic Respiratory Disease, 12*(4), 329-339. doi:10.1177/1479972315598691 [doi]

158. Pollock ML, Wilmore JH. Prescribing exercise for the apparently healthy. Guidelines and preliminary con- siderations. *In*: Pollock ML, Wilmore JH, eds. Exercise in Health and Disease. WB. Saunders Co., 2rd, 1990; 7: pp. 371–484.

159. Vogiatzis, I., Nanas, S., & Roussos, C. (2002). Interval training as an alternative modality to continuous exercise in patients with COPD. *The European Respiratory Journal, 20*(1), 12-19.

160. Vogiatzis, I., Terzis, G., Nanas, S., Stratakos, G., Simoes, D. C., Georgiadou, O., . . . Roussos, C. (2005). Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest, 128*(6), 3838-3845. doi:S0012-3692(15)49625-4 [pii]

161. Coppoolse, R., Schols, A. M., Baarends, E. M., Mostert, R., Akkermans, M. A., Janssen, P. P., & Wouters, E. F. (1999). Interval versus continuous training in patients with severe COPD: A randomized clinical trial. *The European Respiratory Journal, 14*(2), 258-263.

162. Angevaren, M., Aufdemkampe, G., Verhaar, H. J., Aleman, A., & Vanhees, L. (2008). Physical activity and enhanced fitness to improve cognitive function in older people without known cognitive impairment. *The Cochrane Database of Systematic Reviews, (3):CD005381. doi*(3), CD005381. doi:10.1002/14651858.CD005381.pub3 [doi]

163. Tseng, C. N., Gau, B. S., & Lou, M. F. (2011). The effectiveness of exercise on improving cognitive function in older people: A systematic review. *The Journal of Nursing Research : JNR, 19*(2), 119-131. 10.1097/JNR.0b013e3182198837 [doi]

164. van Uffelen, J. G., Chin A Paw, M. J., Hopman-Rock, M., & van Mechelen, W. (2008). The effects of exercise on cognition in older adults with and without cognitive decline: A systematic review. *Clinical Journal of Sport Medicine : Official Journal of the Canadian Academy of Sport Medicine, 18*(6), 486-500. 10.1097/JSM.0b013e3181845f0b [doi]

165. Nouchi, R., Taki, Y., Takeuchi, H., Sekiguchi, A., Hashizume, H., Nozawa, T., . . . Kawashima, R. (2014). Four weeks of combination exercise training improved executive functions, episodic memory, and processing speed in healthy elderly people: Evidence from a randomized controlled trial. *Age (Dordrecht, Netherlands), 36*(2), 787-799. doi:10.1007/s11357-013-9588-x [doi]

166. Williams, P., & Lord, S. R. (1997). Effects of group exercise on cognitive functioning and mood in older women. *Australian and New Zealand Journal of Public Health, 21*(1), 45-52.

167. Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., . . . Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences of the United States of America, 108*(7), 3017-3022. doi:10.1073/pnas.1015950108 [doi]

168. Colcombe, S. J., Kramer, A. F., Erickson, K. I., Scalf, P., McAuley, E., Cohen, N. J., . . . Elavsky, S. (2004). Cardiovascular fitness, cortical plasticity, and aging. *Proceedings of the National Academy of Sciences of the United States of America, 101*(9), 3316-3321. doi:10.1073/pnas.0400266101 [doi]

169. Guiney, H., Lucas, S. J., Cotter, J. D., & Machado, L. (2015). Evidence cerebral blood-flow regulation mediates exercise-cognition links in healthy young adults. *Neuropsychology, 29*(1), 1-9. doi:10.1037/neu0000124 [doi]

170. Horn, J. L., & Cattell, R. B. (1967). Age differences in fluid and crystallized intelligence. *Acta Psychologica, 26*(2), 107-129.

171. Emery, C. F., Shermer, R. L., Hauck, E. R., Hsiao, E. T., & MacIntyre, N. R. (2003). Cognitive and psychological outcomes of exercise in a 1-year follow-up study of patients with chronic obstructive pulmonary disease. *Health Psychology : Official Journal of the Division of Health Psychology, American Psychological Association, 22*(6), 598-604. 10.1037/0278-6133.22.6.598 [doi]

172. ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med, 2003. 167(2): p. 211-77*.*

173. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Thoracic Society. (1995). *American Journal of Respiratory and Critical Care Medicine, 152*(5 Pt 2), S77-121.

174. Quanjer, P. H., Tammeling, G. J., Cotes, J. E., Pedersen, O. F., Peslin, R., & Yernault, J. C. (1993). Lung volumes and forced ventilatory flows. report working party standardization of lung function tests, european community for steel and coal. official statement of the european respiratory society. *The European Respiratory Journal.Supplement, 16*, 5-40.

175. Beaver, W. L., Wasserman, K., & Whipp, B. J. (1986). A new method for detecting anaerobic threshold by gas exchange. *Journal of Applied Physiology (Bethesda, Md.: 1985), 60*(6), 2020-2027. 10.1152/jappl.1986.60.6.2020 [doi]

176. Borg GA, Psychophysical Bases of Perceived Exertion. Med Psy Sports Exerc, 1982. **14**(5): p. 377-381.

177. Strauss, Esther., Sherman, Elisabeth M. S., Spreen, Otfried.,Spreen, Otfried.,. A compendium of neuropsychological tests: administration, norms, and commentary. Oxford; New York: Oxford University Press; 2006.

178. Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*, 135-168. doi:10.1146/annurev-psych-113011-143750 [doi]

179. Khosravi Fard, E., L Keelor, J., Akbarzadeh Bagheban, A., & W Keith, R. (2016). Comparison of the rey auditory verbal learning test (RAVLT) and digit test among typically achieving and gifted students. *Iranian Journal of Child Neurology, 10*(2), 26-37.

180. Trojano, L., Siciliano, M., Cristinzio, C., & Grossi, D. (2018). Exploring visuospatial abilities and their contribution to constructional abilities and nonverbal intelligence. *Applied Neuropsychology.Adult, 25*(2), 166-173. doi:10.1080/23279095.2016.1269009 [doi]

181. Groth-Marnat, G. (2009). *Handbook of psychological assessment, 5th ed*. Hoboken, NJ, US: John Wiley & Sons Inc.

182. Nasreddine, Z. S., Phillips, N. A., Bedirian, V., Charbonneau, S., Whitehead, V., Collin, I., . . . Chertkow, H. (2005). The montreal cognitive assessment, MoCA: A brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society, 53*(4), 695-699. doi:JGS53221 [pii]

183. Dalrymple-Alford, J. C., MacAskill, M. R., Nakas, C. T., Livingston, L., Graham, C., Crucian, G. P., . . . Anderson, T. J. (2010). The MoCA: Well-suited screen for cognitive impairment in parkinson disease. *Neurology, 75*(19), 1717-1725. doi:10.1212/WNL.0b013e3181fc29c9 [doi]

184. Gagnon, J. F., Postuma, R. B., Joncas, S., Desjardins, C., & Latreille, V. (2010). The montreal cognitive assessment: A screening tool for mild cognitive impairment in REM sleep behavior disorder. *Movement Disorders : Official Journal of the Movement Disorder Society, 25*(7), 936-940. doi:10.1002/mds.23079 [doi]

185. Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd ed. San Antonio, TX: Harcourt Brace & Company; 1997.

186. Tombaugh, T. N. (2004). Trail making test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists, 19*(2), 203-214. 10.1016/S0887-6177(03)00039-8 [doi]

187. Delis DC, Kaplan E, Kramer JH. *The Delis-Kaplan Executive Function System: Technical Manual*. San Antonio, TX: The Psychological Corporation; 2001

188. Lucas, J. A., Ivnik, R. J., Smith, G. E., Bohac, D. L., Tangalos, E. G., Graff-Radford, N. R., & Petersen, R. C. (1998). Mayo's older americans normative studies: Category fluency norms. *Journal of Clinical and Experimental Neuropsychology, 20*(2), 194-200. 10.1076/jcen.20.2.194.1173 [doi]

189. Tombaugh, T. N., Kozak, J., & Rees, L. (1999). Normative data stratified by age and education for two measures of verbal fluency: FAS and animal naming. *Archives of*

Clinical Neuropsychology : The Official Journal of the National Academy of Neuropsychologists, 14(2), 167-177. S0887617797000954 [pii]

190. Schmidt M. *Rey Auditory-Verbal Learning Test*. Los Angeles, CA: Western Psychological Services; 1996.

191. Spreen O, Strauss E. *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York, NY: Oxford University Press; 1991

192. Machulda, M. M., Ivnik, R. J., Smith, G. E., Ferman, T. J., Boeve, B. F., Knopman, D., . . . Tangalos, E. G. (2007). Mayo's older americans normative studies: Visual form discrimination and copy trial of the rey-osterrieth complex figure. *Journal of Clinical and Experimental Neuropsychology, 29*(4), 377-384. 778610719 [pii]

193. Villeneuve, S., Rodrigues-Brazete, J., Joncas, S., Postuma, R. B., Latreille, V., & Gagnon, J. F. (2011). Validity of the mattis dementia rating scale to detect mild cognitive impairment in parkinson's disease and REM sleep behavior disorder. *Dementia and Geriatric Cognitive Disorders, 31*(3), 210-217. doi:10.1159/000326212 [doi]

194. Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., . . . Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to alzheimer's disease: Recommendations from the national institute on aging-alzheimer's association workgroups on diagnostic guidelines for alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 7*(3), 270-279. doi:10.1016/j.jalz.2011.03.008 [doi]

195. Broadbent, D. E., Cooper, P. F., FitzGerald, P., & Parkes, K. R. (1982). The cognitive failures questionnaire (CFQ) and its correlates. *The British Journal of Clinical Psychology, 21 (Pt 1)*(Pt 1), 1-16.

196. Bourbeau, J., Nault, D., Sedeno, M., Lebel, M., Drouin, I., Joubert, A., . . . Frennete, J. (2006). *Living well with COPD: A plan of action for life.* Retrieved from http://www.livingwellwithcopd.com/

197. Rizk, A. K., Wardini, R., Chan-Thim, E., Trutschnigg, B., Forget, A., & Pepin, V. (2013). Using continuous data tracking technology to study exercise adherence in pulmonary rehabilitation. *Journal of Visualized Experiments : JoVE, (81):e50643. doi*(81), e50643. 10.3791/50643 [doi]

198. Ganju, A. A., Fuladi, A. B., Tayade, B. O., & Ganju, N. A. (2011). Cardiopulmonary exercise testing in evaluation of patients of chronic obstructive pulmonary disease. *The Indian Journal of Chest Diseases & Allied Sciences, 53*(2), 87-91.

199. Xu, L., Jiang, C. Q., Lam, T. H., Zhang, W. S., Thomas, G. N., & Cheng, K. K. (2011). Dose-response relation between physical activity and cognitive function: Guangzhou biobank cohort study. *Annals of Epidemiology, 21*(11), 857-863. doi:10.1016/j.annepidem.2011.06.002 [doi]

200. Sanders, L. M. J., Hortobagyi, T., la Bastide-van Gemert, S., van der Zee, E. A., & van Heuvelen, M. J. G. (2019). Dose-response relationship between exercise and cognitive function in older adults with and without cognitive impairment: A systematic review and meta-analysis. *PloS One, 14*(1), e0210036. doi:10.1371/journal.pone.0210036 [doi]

201. Colcombe, S., & Kramer, A. F. (2003). Fitness effects on the cognitive function of older adults: A meta-analytic study. *Psychological Science, 14*(2), 125-130. doi:10.1111/1467-9280.t01-1-01430 [doi]

202. Kimhy, D., Lauriola, V., Bartels, M. N., Armstrong, H. F., Vakhrusheva, J., Ballon, J. S., & Sloan, R. P. (2016). Aerobic exercise for cognitive deficits in schizophrenia - the impact of frequency, duration, and fidelity with target training intensity. *Schizophrenia Research, 172*(1-3), 213-215. doi:10.1016/j.schres.2016.01.055 [doi]

203. Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in adults older than 50: A systematic review with meta-analysis. *British Journal of Sports Medicine, 52*(3), 154-160. doi:10.1136/bjsports-2016-096587 [doi]

204. Anzueto, A. (2010). Impact of exacerbations on COPD. *European Respiratory Review : An Official Journal of the European Respiratory Society, 19*(116), 113-118. doi:10.1183/09059180.00002610 [doi]

205. Wedzicha, J. A., Brill, S. E., Allinson, J. P., & Donaldson, G. C. (2013). Mechanisms and impact of the frequent exacerbator phenotype in chronic obstructive pulmonary disease. *BMC Medicine, 11*, 181-7015-11-181. doi:10.1186/1741-7015-11-181 [doi]

206. Ambrosino, N., Bruletti, G., Scala, V., Porta, R., & Vitacca, M. (2002). Cognitive and perceived health status in patient with chronic obstructive pulmonary disease surviving acute on chronic respiratory failure: A controlled study. *Intensive Care Medicine, 28*(2), 170-177. doi:10.1007/s00134-001-1165-6 [doi]

207. Tulek, B., Atalay, N. B., Yildirim, G., Kanat, F., & Suerdem, M. (2014). Cognitive function in chronic obstructive pulmonary disease: Relationship to global initiative for

chronic obstructive lung disease 2011 categories. *Respirology (Carlton, Vic.), 19*(6), 873-880. doi:10.1111/resp.12333 [doi]

208. Hayton, C., Clark, A., Olive, S., Browne, P., Galey, P., Knights, E., . . . Wilson, A. M. (2013). Barriers to pulmonary rehabilitation: Characteristics that predict patient attendance and adherence. *Respiratory Medicine, 107*(3), 401-407. doi:10.1016/j.rmed.2012.11.016 [doi]

209. Incalzi, R. A., Chiappini, F., Fuso, L., Torrice, M. P., Gemma, A., & Pistelli, R. (1998). Predicting cognitive decline in patients with hypoxaemic COPD. *Respiratory Medicine, 92*(3), 527-533. doi:S0954-6111(98)90303-1 [pii]

210. Zhou, G., Liu, J., Sun, F., Xin, X., Duan, L., Zhu, X., & Shi, Z. (2012). Association of chronic obstructive pulmonary disease with cognitive decline in very elderly men. *Dementia and Geriatric Cognitive Disorders Extra, 2*, 219-228. doi:10.1159/000338378 [doi]

211. Hung, W. W., Wisnivesky, J. P., Siu, A. L., & Ross, J. S. (2009). Cognitive decline among patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 180*(2), 134-137. doi:10.1164/rccm.200902-0276OC [doi]

212. Herzog, A. R., & Wallace, R. B. (1997). Measures of cognitive functioning in the AHEAD study. *The Journals of Gerontology.Series B, Psychological Sciences and Social Sciences, 52 Spec No*, 37-48. doi:10.1093/geronb/52b.special_issue.37 [doi]

213. Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory_II*. San Antonio, TX: Psychological Corporation.

214. Desveaux, L., Harrison, S. L., Gagnon, J. F., Goldstein, R. S., Brooks, D., & Pepin, V. (2018). Effects of exercise training on cognition in chronic obstructive pulmonary disease: A systematic review. *Respiratory Medicine, 139*, 110-116. doi:S0954-6111(18)30154-9 [pii]