Department of Community Medicine and Rehabilitation, 2025

Innovative Exercise for Extrapulmonary Benefits in Chronic Obstructive Pulmonary Disease

Feasibility, Physiological Responses and Methodology

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ISBN: 978-91-8070-839-5 (print)
ISBN: 978-91-8070-840-1 (pdf)
ISSN: 0346-6612
Umeå University Medical Dissertations New Series no. 2391
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Printed by: Scandinavian Print Group, 2025

"I have approximate answers and possible beliefs and different degrees of uncertainty about different things, but I am not absolutely sure of anything and there are many things I don't know anything about, such as whether it means anything to ask why we're here. I don't have to know an answer. I don't feel frightened not knowing things, by being lost in a mysterious universe without any purpose, which is the way it really is as far as I can tell."

— Richard P. Feynman

To all those living with chronic obstructive pulmonary disease

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Abstract

Background

Chronic obstructive pulmonary disease (COPD) is a leading global health burden and a major cause of morbidity and mortality. Beyond airflow limitation and respiratory symptoms, COPD is associated with multiple extrapulmonary manifestations including cognitive impairment, decreased cardiovascular fitness and muscle dysfunction. These systemic effects contribute to lower physical capacity and increased mortality, independent of lung function. To treat extrapulmonary manifestations among individuals with COPD, exercise training has an important role. However, traditional exercise methods are often difficult for individuals with COPD to tolerate, given their ventilatory limitations and muscle dysfunction, resulting in sub-optimal treatment effects. Short-duration watt-controlled supramaximal high-intensity interval training (HIIT) consisting of 10 × 6 second intervals is promising for individuals with COPD, as it enables high external intensities while allowing for ventilatory relief. Yet, evaluation of its feasibility, physiological response, prescription and long-term effectiveness is lacking. Furthermore, reporting quality in aerobic exercise trials in COPD may be incomplete, hindering reproducibility and the translation of research findings into clinical practice.

The overarching aim of this thesis therefore was to advance the development of effective exercise strategies for COPD by evaluating the feasibility, physiological responses, and methodological aspects of supramaximal HIIT, and by assessing the reporting quality of aerobic exercise interventions in the COPD literature.

Methods

This thesis comprises four papers based on two clinical trials and one systematic review. In a randomised cross-over trial, Paper I examined the feasibility and acute physiological responses to supramaximal HIIT, compared to moderate-intensity continuous training (MICT), in 16 individuals with COPD and 16 matched healthy controls (HCs). Paper II, using data from the same trial, evaluated the feasibility and applicability of the modified Borg Cycle Strength Test (mBCST) for prescribing supramaximal workloads. Paper III presents the study protocol of an ongoing, international multicentre randomised controlled trial (RCT), the COPD-HIIT RCT. The trial compares supramaximal HIIT and MICT over 3 months in individuals with COPD and HC, with continued training for 24 months in the COPD group. Paper IV was a systematic review assessing the

reporting quality and application of exercise training principles in RCTs that included aerobic training in individuals with COPD.

Results

Paper I demonstrated that supramaximal HIIT was feasible and enabled participants with COPD to achieve higher external intensities (245 ± 88 *vs.* 71 ± 22 W) compared to MICT, with reduced ventilatory demand. Both exercise modalities increased plasma brain-derived neurotrophic factor by an average of 59%. Paper II deemed the mBCST feasible and applicable for prescription of supramaximal intensities in COPD. The COPD-HIIT RCT, presented in Paper III, have enrolled 133 participants of which 82 are individuals with COPD. The participants with COPD constitute a representative cohort with a varied disease severity. Compared to matched healthy controls, they exhibit reduced cognitive function, cardiorespiratory fitness and quadriceps function at baseline. Paper IV included 298 trials, in which the quality of reporting was generally poor. This was demonstrated by a mean of 5.4 ± 3.0 reported items (out of a maximum of 19) on the Consensus on Exercise Reporting Template.

Conclusions

This thesis supports the feasibility of short-duration, watt-controlled supramaximal HIIT for individuals with COPD, allowing higher exercise intensities with lower ventilatory demand than MICT. The mBCST appears feasible and applicable for prescribing supramaximal workloads, while further research is warranted for its clinical implementation. Preliminary data from the ongoing COPD-HIIT RCT indicates good adherence to supramaximal HIIT and representative recruitment. Finally, the systematic review revealed suboptimal reporting of aerobic exercise interventions in COPD research, emphasizing the need for improved reporting to strengthen reproducibility and clinical translation.

Sammanfattning på Svenska

Bakgrund

Kroniskt obstruktiv lungsjukdom (KOL) är en av vår tids största folksjukdomar. Globalt lever hundratals miljoner människor med KOL, och sjukdomen är en av de vanligaste dödsorsakerna i världen. Sjukdomen kännetecknas av långvariga symptom från luftvägarna och en begränsning av luftflödet, vilket gör att fysisk aktivitet och träning ofta blir ansträngande.

Utöver påverkan på lungorna leder KOL till en påverkan utanför lungorna – så kallade extrapulmonella manifestationer. Dessa inkluderar bland annat nedsatt kondition, försämrad muskelfunktion och försämrad kognitiv funktion. Dessa konsekvenser är nära kopplade till lägre livskvalitet och ökad dödlighet, oberoende av hur nedsatt lungfunktionen är.

Fysisk träning är en viktig del av behandlingen vid KOL, särskilt avseende förändringar utanför lungorna. Trots god effekt av fysisk träning på gruppnivå är det på individnivå en stor variation och många får endast små effekter av den träning som erbjuds idag. Det beror bland annat på att många med KOL behöver stanna upp, eller till avbryta sin fysiska träning på grund av andfåddhet, detta innan belastningen på exempelvis hjärta och muskulatur är tillräckligt hög. Det finns därför ett behov av nya behandlingsmetoder. En möjlig lösning är supramaximal högintensiv intervallträning (HIIT) – mycket korta och intensiva cykelintervaller på sex sekunder, som kan möjliggöra hög belastning utan att andningen blir alltför påfrestande.

Vidare, trots att träning är en central del av behandlingen vid KOL är beskrivningen av träningsupplägg i tidigare studier ofta bristfällig. Detta gör det svårt att jämföra resultat och att omsätta forskningen i praktiken.

Syftet med avhandlingen var att undersöka om supramaximal HIIT är genomförbart för personer med KOL, hur kroppen reagerar på sådan träning, hur träningen kan individanpassas och vilka metodologiska faktorer som behöver beaktas. Dessutom granskades hur väl tidigare studier om konditionsträning vid KOL har beskrivit sina träningsmetoder.

Metod

Avhandlingen bygger på fyra vetenskapliga artiklar baserade på två kliniska studier och en systematisk litteraturöversikt. I artikel I-III studeras både personer med KOL och en kontrollgrupp med lungfriska deltagare.

Artikel I undersökte genomförbarheten och fysiologisk respons till supramaximal HIIT jämfört med traditionell konditionsträning på måttlig intensitet med konstant belastning. Artikel II använde data från samma studie och undersökte genomförbarheten och användbarheten av ett cykeltest, Borgs cykelstyrketest, för att bestämma lämplig träningsintensitet vid supramaximal HIIT.

Artikel III är ett studieprotokoll som beskriver en pågående internationell randomiserad kontrollerad träningsstudie, där effekterna av supramaximal HIIT och traditionell träning jämförs över tre samt 24 månader. Här studeras effekter på bland annat kognitiv funktion, kondition och lårmuskelkraft.

Artikel IV var en systematisk granskning av tidigare träningsstudier vid KOL, med fokus på hur väl träningsupplägg rapporterats och hur principer för träning har tillämpats.

Resultat

Supramaximal HIIT var genomförbar för personer med KOL och gjorde det möjligt att nå högre belastningar med mindre upplevd andfåddhet än vid traditionell måttligt intensiv träning. Båda träningsformerna ökade nivåerna av brain-derived neurotrophic factor i blodet, vilket kan vara gynnsamt för hjärnans hälsa. Borgs cykelstyrketest visade sig praktiskt genomförbart och användbart för att individanpassa träningsintensitet vid supramaximal HIIT.

I den pågående randomiserade kontrollerade träningsstudien har hittills 133 personer inkluderats, varav 82 med KOL. Deltagarna representerar olika sjukdomsgrader och har överlag god träningsföljsamhet. Preliminära resultat visar att personer med KOL har lägre kognitiv funktion, kondition och lårmuskelfunktion jämfört med friska kontrollpersoner.

Den systematiska granskningen omfattade 298 studier. Resultaten visade på bristfällig beskrivning av träningsmetoder inom KOL-forskning. Viktig information som träningsintensitet samt deltagarnas följsamhet till träningen, saknades ofta.

Slutsatser

Supramaximal HIIT framstår som en lovande och genomförbar träningsform för personer med KOL, eftersom den möjliggör hög träningsintensitet utan att öka den upplevda andfåddheten. Forskningen fortsätter nu med att undersöka hur väl denna typ av träning fungerar på längre sikt och dess effekter på bland annat kognitiv funktion, kondition och muskelfunktion

Eftersom personer med KOL uppnår högre intensitet vid genomförande av Borgs cykelstyrketest än vid ett traditionellt arbetsprov, indikerar resultaten att testet kan vara användbart vid förskrivning av träningsintensitet vid supramaximal HIIT. Borgs cykelstyrketest kan alltså användas för att individanpassa supramaximal HIIT, men mer forskning om testets implementering behövs.

Slutligen visar avhandlingen att forskare behöver vara mer tydliga i hur de beskriver sina träningsupplägg och resultat, för att framtida studier bättre ska kunna tolkas, jämföras och användas inom vården.

Abbreviations and Acronyms

Commonly used abbreviation throughout the thesis. Abbreviations that only are included in tables or figures are defined in that table or figure.

ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
CAT	COPD assessment test
CANTAB	Cambridge Neuropsychological Test Automated Battery
CERT	Consensus on Exercise Reporting Template
CRQ	Chronic respiratory disease questionnaire
COPD	Chronic obstructive pulmonary disease
CONSORT	Consolidated Standards of Reporting Trials
CPET	Cardiopulmonary exercise test
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
FEV_1	Forced expiratory volume in one second
FITT	Frequency, Intensity, Type and Time
FVC	Forced vital capacity
HIIT	High-intensity interval training
IL	Interleukin
MAP	Maximum aerobic power
MVV	Maximal voluntary ventilation
mBCST	Modified Borg cycle strength test
mMRC	Modified medical research council dyspnea scale
MICT	Moderate-intensity continuous training
MoCA	Montreal cognitive assessment
MPO6	Maximum mean power output for six seconds
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomised controlled trial
RPE	Rating of perceived exertion
RPM	Revolutions per minute
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials

TIDieR	Template for Intervention Description and Replication
TMT	Trial making test
VCO_2	Carbon dioxide output (volume of carbon dioxide produced)
VO_2	Oxygen uptake (volume of oxygen)
V_E	Minute ventilation (total volume of air expired per minute)

Glossary

Exacerbation	An event characterized by an increased dyspnea and/or cough and sputum that worsens in < 14 days which may be accompanied by tachypnoea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways[1].
Exerkine	Signalling molecules, including hormones, metabolites, proteins, lipids, and nucleic acids, that are released in response to exercise, exerting effects through endocrine, paracrine, and autocrine pathways[2].
Feasibility	Within this thesis, feasibility refers to the extent to which participants can complete an exercise session, intervention or test as intended, and whether it is tolerable and practical. In Paper I, exercise feasibility was determined through exercise fidelity, defined as the need for modifications to the planned exercise protocol (intensity, duration or cadence), as well as completion rate and perceived symptoms. In Paper II, test feasibility was determined by achieved intensity, interpretability, familiarity required, duration, scoring complexity, completion complexity, safety and cost. In Paper III, intervention feasibility is determined by completion rate, attendance rate, adherence to the prescribed exercise, exercise fidelity, occurrence of adverse events and participant satisfaction.
Supramaximal HIIT	Supramaximal high-intensity interval training (HIIT) involves short, repeated work intervals performed at an external intensity that exceeds the maximal aerobic power (MAP)[3].
Maximal aerobic power	The external work rate achieved at the point of maximal oxygen uptake, during an incremental cardiopulmonary exercise test.
Myokine	An exerkine that is mainly produced and released by skeletal muscle[4].
Physiological response	Refers to the acute exercise-changes that occur during or immediately after a bout of physical activity, including changes in oxygen consumption, ventilation, heart rate and circulating exerkines.
W' (W prime)	A parameter in exercise physiology that represents the finite amount of work that can be performed above the critical power before exhaustion[5].

List of Original Papers

This thesis is based on the following four papers which will be referred to by their Roman numerals. In addition, preliminary unpublished data related to Paper III are included in the thesis.

I. **Jakobsson, J***., De Brandt, J*., Hedlund, M., Rullander, A-C., Sandström, T., Nyberg, A. (2025). Feasibility and acute physiological responses to supramaximal high-intensity interval-training in COPD: A randomised crossover trial. *ERJ Open Research, 11(5), 01321-2024. DOI: https://doi.org/10.1183/23120541.01321-2024*

II. De Brandt, J*., **Jakobsson, J***., Hedlund, M., Sandström, T. & Nyberg, A. (2025). The modified Borg cycle strength test (mBCST): Feasibility and physiological response in people with COPD and healthy older adults. *Experimental Physiology*, 1-16. DOI: https://doi.org/10.1113/EP092151

III. **Jakobsson, J**., Burtin, C., Hedlund, M., Boraxbekk, C. J., Westman, J., Karalija, N., Stål, P., Sandström, T., Ruttens, D., Gosker, H. R., De Brandt, J., & Nyberg, A. (2024). Effects and mechanisms of supramaximal high-intensity interval training on extrapulmonary manifestations in people with and without chronic obstructive pulmonary disease (COPD-HIIT): study protocol for a multi-centre, randomized controlled trial. *Trials*, *25*(1), 664. DOI: https://doi.org/10.1186/s13063-024-08481-3

IV. **Jakobsson, J**., Stoffels, A., van Hees, HWH., bij de Vaate, E., Frykholm, E., Girard, F., Van'T Hul, A., Morelli, N., Burtin, C., De Brandt, J., Nyberg, A#., Klein, P#. Quality of reporting and application of exercise training principles in chronic obstructive pulmonary disease: a systematic review of randomised controlled trials. *In manuscript.*

*These authors contributed equally and shared first-authorship.

#These authors contributed equally and shared senior-authorship.

My Contributions

My paper-specific contribution based on the Contributor Roles Taxonomy (CrediT).

Papers I and II: Co-first author, corresponding author (Paper I). Conceptualization; Methodology; Investigation (participant recruitment and screening, data collection); Data curation (data entry and data cleaning); Project administration; Formal analysis; Visualization; Writing – Original draft (Paper I); Writing – Review & Editing (Paper II).

Paper III: First and corresponding author; Conceptualization; Methodology; Investigation (blinded data assessor – cycling assessments, cognitive tests, functional tests); Data curation (data entry and data cleaning); Project administration; Formal analysis; Visualization; Writing – Original draft; Funding acquisition (partial funding for materials).

Paper IV: First and corresponding author; Methodology; Investigation (abstract and full text screening, data extraction); Data curation; Project administration; Formal analysis; Visualization; Writing – Original draft.

Preface

I completed my bachelor's degree in sports medicine in 2015, a subject that had interested me long before I knew where it would lead. At that time, I did not imagine that my research journey would take me into the field of chronic respiratory disease.

Perhaps the first seed of a PhD was planted during my master's studies in sports medicine, when I immersed myself in writing my thesis. Or maybe it began even earlier, during school science projects that allowed me to explore ideas through reading and writing, guided by a few particularly inspiring teachers.

When this doctoral project was announced, I saw it as an opportunity to unite my scientific interests with something that could contribute meaningfully to others. A sense of purpose captured by the Japanese term *ikigai*.

I hope that this work, in some small or large way, contributes to greater understanding and to something of value in the world.

Introduction

As populations age, the burden of chronic diseases is increasing worldwide, driven by a complex interplay of genetic predisposition, environmental exposures, and lifestyle factors. Among these conditions, chronic respiratory diseases are of particular concern, with chronic obstructive pulmonary disease (COPD) representing a major cause of morbidity and mortality worldwide[6].

Chronic obstructive pulmonary disease is currently the fourth leading cause of death[7], affecting 400 million individuals globally with climbing prevalence rates[8,9]. Once considered only a pulmonary disorder, COPD is now recognized for its extensive impact on multiple organ systems, challenging the individual's ability to maintain daily function and overall health[10]. As such, COPD represents a major public health challenge. A hallmark of COPD is impaired pulmonary ventilation and gas exchange, making physical activity particularly challenging for individuals with the disease. Exercise training is a cornerstone in the non-pharmacological treatment of COPD[11]. Yet, many individuals with COPD experience limited benefits from traditional exercise methods, which are often attributed to the ventilatory constraints imposed by the disease[12-14]. This highlights the need for new and effective interventions that address both the pulmonary and extrapulmonary consequences of COPD.

This thesis explores the feasibility and physiological effects of a watt-controlled supramaximal high-intensity interval training (HIIT) protocol, compared to traditional moderate-intensity continuous training (MICT) in individuals with COPD. My aim is that the findings will contribute to a deeper understanding of how exercise interventions can be used to address extrapulmonary manifestations in COPD, ultimately improving outcomes and prognosis for individuals with COPD.

Background

This background outlines an overview of COPD, beginning with its pathogenesis and pathophysiology, and how these contribute to exercise limitation. Next, I will describe the clinical presentation of COPD, followed by an overview of current management strategies. Emphasis will be placed on pulmonary rehabilitation and the role of endurance exercise training within the scope of this thesis.

Chronic Obstructive Pulmonary Disease

The definition of COPD has evolved over time. In their 2025 report[8], the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines COPD as:

"…a heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction".

Individuals diagnosed with COPD commonly experience symptoms such as shortness of breath, wheezing, a sensation of tightness in the chest, fatigue, restricted physical capability, and/or persistent coughing, with or without sputum production[8]. Individuals with COPD are also susceptible to acute respiratory events, exacerbations, which are marked by a sudden increase in respiratory symptoms.

Global Burden of COPD

While prevalence data vary widely, the global prevalence in people aged 30-79 is currently estimated to be 10.3% when using the GOLD definition[15]. Therefore, roughly 400 million people suffer from the disease, causing 3.5 million deaths in 2021, accounting for 6% of all deaths globally[7,8]. Further, COPD is the eighth leading cause of years of life lost[15], and a leading cause of disability-adjusted life years[16,17]. In Sweden, an estimated 400 000 to 700 000 people live with COPD, corresponding to a prevalence of 7-17%, depending on the cohort and age range studied[18,19]. Overall, prevalence increases with age[15,18].

With the aging of the world's population, increased prevalence of smoking in developing countries, urbanization, and continued exposure to other risk factors, it is projected that the global prevalence and annual deaths of COPD will rise over the coming decades and approach 600 million patients with COPD by 2050[20,21]. Historically, COPD has been more prevalent in men than in women, primarily

due to higher rates of cigarette smoking among men[22,23]. However, recent data indicate that the prevalence of COPD is close to equal in males and females, and future trends suggest a continued increase among women and a decline among men[6,8,18,23].

Beyond morbidity and mortality, COPD imposes a significant economic burden worldwide. Its high prevalence, chronic course and high treatment costs, combined with productivity loss, place a substantial strain on our healthcare systems and society[8,17,24]. This financial burden of COPD is related to both itself and its multiple comorbidities.

With this in mind, one can argue that COPD is a highly neglected disease worldwide, by some organizations called a forgotten public disease[25]. As a leading contributor to the global burden of disease, COPD is significantly underfunded compared with other chronic diseases. For example, research expenditure per death is substantially lower for COPD than for cardiovascular disease, diabetes and cancer[17,26]. A possible reason for this disparity might be the social stigma inaccurately portraying COPD as a self-inflicted disease. Such stigma is less prevalent in cardiovascular disease and type 2 diabetes, despite lifestyle factors significantly contributing to these conditions as well[17]. This misalignment is also true for other chronic diseases, such as asthma, which receives 100 times more funding per death compared to COPD in the US[26].

Pathogenesis: Causes and Risk Factors

The development of COPD is more complex than the traditional view of it as a self-inflicted disease caused by tobacco smoking, as initially formulated[27]. Rather, as described in a recent proposal[28,29], COPD is the result of complex, dynamic, cumulative and repeated gene-environment interactions over the lifetime that can damage the lungs and/or alter their normal development and aging processes. Beyond smoking, various risk factors contribute to COPD through distinct pathophysiological mechanisms, influencing diagnosis and treatment[8,17,30]. Understanding these risk factors is crucial for a more comprehensive approach to COPD prevention and management.

Environmental Risk Factors

Environmental factors are the most significant risk factors for COPD. Of these, cigarette smoking remains indeed a key factor[31], but other forms of tobacco exposure, including second-hand smoking[32], pipes, cigars, water pipes[33], marijuana[34], and likely electronic nicotine delivery systems such as vaping[31]—also increase the risk. Yet, about half of all COPD cases worldwide are due to non-tobacco-related risk factors[30]. In low- and middle-income countries, non-

smoking environmental exposures account for most COPD cases. Indoor pollution from biomass fuel combustion, used by three billion people worldwide[35], leads to high household air pollution and is a major cause of COPD in never-smokers, with estimates suggesting up to 70% of cases in low- and middle-income countries occur in non-smokers[30]. Globally, air pollution, including greenhouse gases, ozone, particulate matter and heavy metal, is another major contributor to COPD[8,36]. Notably, the risk of air pollution is dose-dependent with no safe threshold[8]. Additionally, occupational exposure to gases, fumes, chemicals, and dust is a major risk factor for COPD and common in many industries including mining, steelworks, farming, manufacturing and automotive repair[17].

Factors Affecting Lung Function Trajectories

Chronic obstructive pulmonary disease can result from reduced peak lung function early in life, or accelerated lung function decline later in life. Several factors influence our normal trajectory of lung function, which typically peaks in early adulthood[37]. These factors can either reduce peak lung function or hasten its decline, thereby increasing the risk of COPD[38]. These include so-called childhood disadvantage factors or early life events that alter the respiratory and immune system, making the lungs more susceptible to risk factors in adult life[17]. Some important early life events include childhood asthma, repeated respiratory infections, in-utero and early-life exposure to tobacco smoke, prematurity, low birth weight, and malnutrition[38].

Other Risk Factors

Multiple genetic variants associated with increased risk of COPD have been identified[39]. However, the best documented genetic risk factor is mutations in the SERPINA1 gene, which lead to alpha-1 antitrypsin deficiency. This condition is present in 1-2% of individuals with COPD[39,40]. In brief, alpha-1 antitrypsin deficiency impairs the protection of lung tissue, resulting in neutrophil-elastase-mediated development of emphysema[41].

Lower socioeconomic status and poverty are also associated with increased risk for COPD[42,43]. Whether this reflects exposures to environmental risk factors, poor nutrition, infections or other factors related to low socioeconomic status is unclear. Still, almost all risk factors for developing COPD are also associated with low socioeconomic status[17].

Furthermore, a history of chronic bronchial infections[44] or tuberculosis[45], as well as being HIV positive[46,47], are risk factors for COPD. Notably, in lower- and middle-income countries, pulmonary and systemic infections are among the most

important non-smoking risk factors[17] for COPD and other chronic respiratory diseases.

COPD Beyond Tobacco Smoking

Growing recognition of non-smoking-related COPD has led to new taxonomic proposals, based on the different causes contributing to the disease[17,48]. In short, the taxonomy has been expanded to include different types of COPD, capturing the variation in its causes and linking underlying endotypes to distinct pathophysiological mechanisms. By combining two recent proposals[17,48], the following etiotypes of COPD can be categorized[8]: 1) genetically determined COPD; 2) COPD related to early-life events; 3) infection-related COPD; 4) COPD related to smoking or vaping; 5) biomass and pollution exposure-related COPD; 6) COPD and asthma, and 7) COPD of unknown cause. To date, this proposal has little impact on current clinical practice, and further research is needed into these subtypes to advance COPD management[8,17].

Pathophysiology: From Cellular Damage to Systemic Effects

Pathological changes in COPD include both inflammatory and structural changes to the airways, lung parenchyma and the pulmonary vasculature[49]. Inflammation in COPD involves an increased number of macrophages, neutrophils, and lymphocytes, which release inflammatory mediators, leading to tissue damage and remodeling[50,51]. Oxidative stress, driven by both inhaled irritants and immune cell activation, further amplifies inflammation and tissue destruction[50,52].

A key feature of COPD pathobiology is the imbalance between proteases, which degrade connective tissue and antiproteases that counteract this action, leading to alveolar destruction and airway remodeling[53]. Peribronchiolar fibrosis, excess fibrous connective tissue around the bronchi, and altered lung vasculature have also been reported[54,55].

Airflow Obstruction, Hyperinflation and Impaired Gas Exchange: Contributors to Exercise Intolerance

Airflow obstruction in COPD results from pathological changes in the smaller airways (bronchioles) and emphysema. Chronic inflammation narrows and destroys bronchioles, increasing airway resistance[56]. Emphysema is characterized by irreversible destruction of alveolar walls, enlargement of air space, leading to loss of lung elastic recoil and airflow limitation. These processes

may occur independently or at different rates[8], but both impair lung emptying during expiration, leading to gas trapping, the inability to fully exhale[57].

Gas trapping and reduced elastic recoil cause lung hyperinflation, defined as an abnormally increased end-expiratory lung volume[57]. Hyperinflation contributes to dyspnea[58,59], hospitalizations and mortality[60,61]. It may be present at rest (static hyperinflation) or during exercise, when increased ventilatory demand and reduced expiratory times due to higher breathing frequency lead to *dynamic hyperinflation*[62]. In a laboratory setting, dynamic hyperinflation is assessed using an inspiratory capacity manoeuvre during exercise[62,63]. Dynamic hyperinflation has multiple negative effects on exercise tolerance, as it leads to: 1) increased work of breathing; 2) weakened inspiratory muscles due to shortening of the diaphragm muscle fibers[64]; and 3) reduced ability to expand tidal volume, leading to mechanical limitation of ventilation. In turn, this can in some cases lead to carbon dioxide retention and oxygen desaturation[65]. In addition, dynamic hyperinflation can negatively affect cardiac function by reducing preload and increasing afterload[57].

Structural changes in the airways, alveoli, and pulmonary vasculature may disrupt the normal balance between air supply (ventilation) and blood flow (perfusion). This ventilation-perfusion mismatch contributes to inefficient gas exchange and exercise intolerance[66], as some lung regions are well perfused but poorly ventilated, and others are well ventilated but underperfused[67]. Emphysematous changes further reduce the available surface area for gas exchange, leading to decreased lung diffusing capacity[56]. Together, these mechanisms increase the ventilatory demand during exercise in COPD.

Exacerbations

An exacerbation is defined as an event characterized by an increased dyspnea and/or cough and sputum that worsens in < 14 days which may be accompanied by tachypnoea and/or tachycardia and is often associated with increased local and systemic inflammation caused by infection, pollution, or other insult to the airways[1]. Exacerbations are often caused by viral or bacterial respiratory infections or pollutants, and are significant events in the trajectory of COPD[68]. Exacerbations increase gas trapping, hyperinflation, expiratory flow and therefore increase dyspna[69]. They contribute to COPD progression by means of airway inflammation[70] and long-term decline in lung function[71].

Symptoms and Diagnosis

A diagnosis of COPD should be considered in individuals who are presenting symptoms related to the lungs, such as dyspnea, chronic cough, sputum production, or recurrent lower respiratory tract infections, and/or a history of exposure to risk factors[8,72]. Chronic dyspnea is a cardinal symptom of COPD and one of the major causes of the disability and anxiety associated with the disease[73]. It is prevalent across all stages of the disease and particularly occurs during physical activity and exercise[74]. Further, a cough with or without sputum production is present in many individuals with COPD[8]. Importantly, these symptoms can precede a measurable airflow obstruction by multiple years. Fatigue, the subjective feeling of tiredness or exhaustion, is also a common and distressing symptom in COPD that impacts the ability to perform daily life activities and impacts the patient's quality of life[75,76]. Chest tightness and inspiratory or expiratory wheezes are also common symptoms that might vary between and within days[8].

To confirm a diagnosis of COPD, spirometry is required to demonstrate a persistent, non-fully reversible limitation of expiratory airflow[8,72]. This is defined by a post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) of less than 0.7. Currently, this represents the gold standard for diagnosing COPD and offers a simple, non-invasive, low-cost, reproducible and readily available test[8,17]. In Sweden, the diagnosis of COPD is based on a triad comprising evidence of airway obstruction, the presence of relevant risk factors, and respiratory symptoms[77].

However, this approach has recently been challenged, as it precludes the detection of early disease, oversimplifies COPD and fails to capture the heterogeneity of the disease[17,78]. Notably, airway and parenchymal changes can be present even in individuals without spirometric evidence of expiratory airflow limitation[79]. Consequently, there are suggestions to explore alternative diagnostic methods with greater sensitivity, including methods that show lung destruction or airway remodelling (directly or indirectly), either using chest computer-tomography, diffusion capacity measures or measures of respiratory mechanics[17]. Today, chest computed tomography is not needed to establish a diagnosis of COPD. Yet, it is used to provide insight into the structural and pathophysiological abnormalities present in the lungs, such as emphysema and airway abnormalities[8].

Once confirmed by spirometry, the diagnosis of COPD is further assessed based on the severity of airflow obstruction using GOLD spirometric grades I to IV, based on the predicted FEV_1 depicted in Figure 1[8]. Then, symptoms are evaluated using standardized questionnaires, either using the COPD assessment test[80]

(CAT) for disease-specific symptoms or the modified Medical Research Council dyspnea scale[81] (mMRC) for dyspnea. Additionally, the frequency of moderate and severe exacerbations is considered. This framework provides insight into airflow obstruction severity, symptom burden and exacerbation risk. Individuals with COPD are then classified as A, B or E (Figure 1) which is used to guide treatment[8].

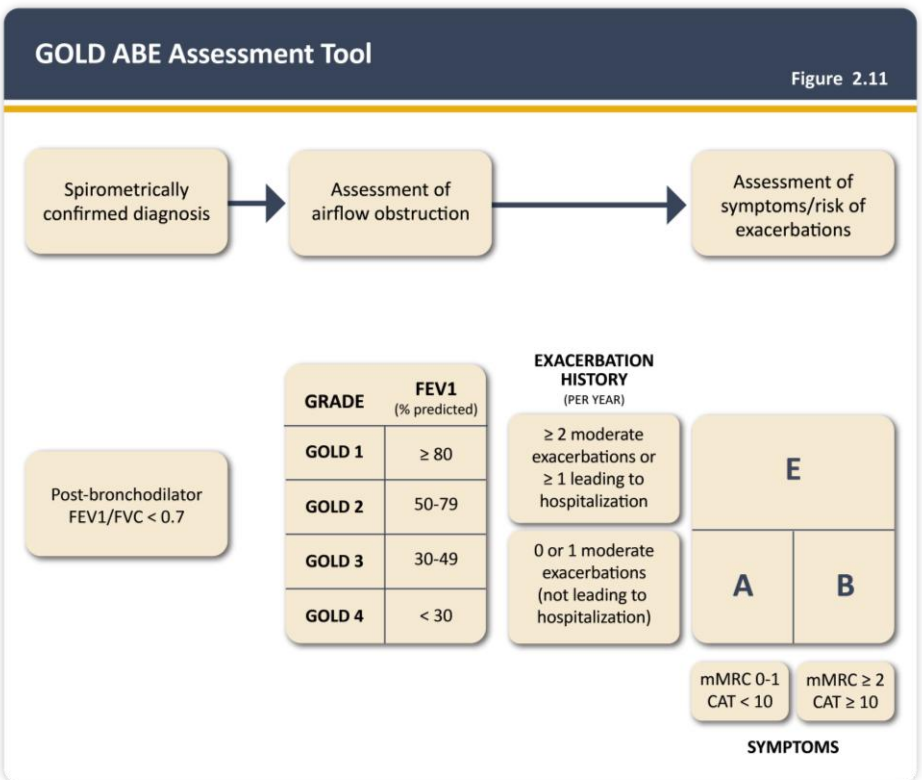

Figure 1. The GOLD ABE Assessment Tool. The assessment of airflow limitation by spirometry is shown on the left side and is one part of the classification. It is combined with the presence of symptoms or dyspnea, and the history of exacerbations. Being categorized into group A means one has a lower risk of exacerbations and less severe symptoms. In group B, one has a lower risk of exacerbations and more severe symptoms. Those with a higher risk of exacerbations are categorized into group E, irrespective of the level of symptoms or dyspnea. Abbreviations: FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; mMRC: modified Medical Research Council dyspnea scale; CAT: Chronic obstructive pulmonary disease assessment test.

While this classification is well-established, additional measures have been proposed. These suggestions are not yet formally integrated into current

guidelines but may provide potential avenues for future refinement. For example, in relation to exercise and cardiorespiratory fitness, a central theme of this thesis, there have been suggestions to incorporate VO_2peak in this assessment tool, with VO_2peak < 14.6 mL·kg^{-1} min^{-1} or <55% predicted as a cut-off for increased mortality[82].

COPD Beyond the Lungs: Extrapulmonary Manifestations

Beyond being a pulmonary disease, COPD presents multiple extrapulmonary manifestations and comorbidities. These include decreased brain health[83,84], cardiovascular disease[85], skeletal muscle dysfunction[86,87], metabolic disorders[88,89], osteoporosis[90], mood disorders[91,92], sarcopenia[93] and cachexia[94], amongst others (Figure 2). Together with the pulmonary symptoms, these extrapulmonary manifestations contribute to reduced exercise tolerance, diminished physical activity levels, overall functional impairment and decreased survival[95-97]. Systemic inflammation is a hallmark of the disease and appears to be a common denominator for many of these manifestations, not least related to cognitive dysfunction[50,98-101]. Furthermore, the presence of one or more comorbidities is associated with increased hospitalizations and higher mortality rates[102,103], in many cases independent of airflow obstruction[104]. Despite their significant impact on key clinical outcomes, extrapulmonary aspects remain an area that has not been optimally addressed in COPD management.

In the following section, I will introduce the extrapulmonary manifestations of COPD most relevant to this thesis (Figure 2).

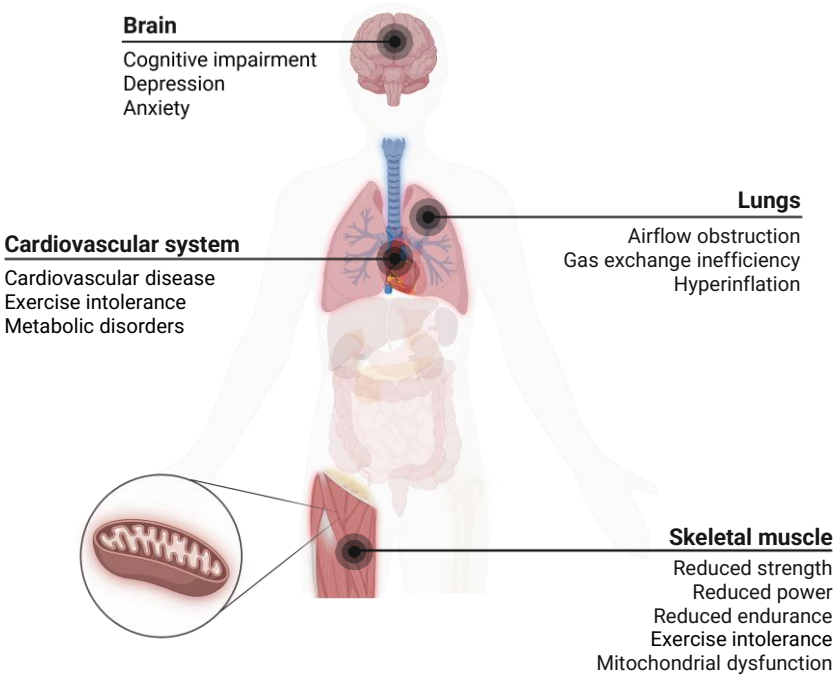

Figure 2. Selected pulmonary and extrapulmonary manifestations in chronic obstructive pulmonary disease[10,84].

Cognitive Impairment

Individuals with COPD exhibit a greater risk of developing cognitive impairment compared to those without the disease[101,105,106]. Reported prevalence rates vary widely, ranging from 5% to 77%[107,108], with an average prevalence of 32%[108]. This wide variation is primarily attributed to differences in assessment methodologies and study populations[109]. Importantly, cognitive impairment is seen across the entire range of airflow obstruction severity[110]. Cognitive impairment can negatively impact medication adherence and proper inhaler technique[111-113], leading to a higher risk of hospitalizations. Further, having coexisting COPD and cognitive impairment increases the mortality risk threefold compared to having either condition alone[103].

Several pathophysiological mechanisms have been proposed to explain the elevated risk of cognitive impairment in COPD. These include hypoxemia, systemic inflammation, and oxidative stress, which are factors inherent to the disease, as well as the presence of comorbidities such as cardiovascular disease, which can further compromise cerebral function[84,109,114,115]. Neuroinflammation has also been suggested as a potential contributor, but this remains insufficiently investigated in the COPD context[115]. The development of cognitive impairment in

COPD is therefore likely multifactorial, and the underlying mechanisms are not yet fully understood[109].

Neuroimaging studies have identified structural brain abnormalities in individuals with COPD, including grey matter atrophy and reduced white matter integrity[116]. Cognitive deficits in this population span multiple domains[83], with impairments most commonly reported in memory and attention[117,118]. Deficits in information processing speed, learning abilities and executive function have also been documented[117,119-121].

Although evidence increasingly supports a link between COPD and cognitive impairment, several research gaps persist. Research indicates benefits from exercise for cognitive abilities[122-124], with the hippocampus being one of the more plastic brain regions, responsive to exercise-induced changes[125-127]. Yet, research on the treatment of cognitive impairment in individuals with COPD is still in its infancy, and the role of exercise should be further investigated[128]. Both general and COPD-specific literature highlight the need for well-designed, longitudinal studies employing standardized, reproducible exercise protocols[123,128]. In particular, the effects of varying exercise intensities, as well as the underlying mechanisms linking exercise to cognitive outcomes in COPD, remain insufficiently addressed.

Cardiovascular Function and Cardiorespiratory Fitness

Cardiorespiratory fitness, commonly quantified as maximal oxygen uptake (VO_2max or VO_2peak), is a fundamental measure in exercise physiology, a measure of respiratory, cardiovascular and muscular performance. It is widely used as an indicator of overall health and disease risk[129,130]. In individuals with COPD, cardiorespiratory fitness is highly reduced compared to healthy individuals of the same age[74,131-133].

The cardiovascular system in COPD is adversely affected in several ways[85]. Concomitant cardiovascular disease is common and individuals with COPD have a higher prevalence of conditions such as heart failure, ischemic heart disease and cardiac arrhytmias[134]. Cardiovascular diseases are not within the scope of this thesis; however, they contribute to reduced cardiovascular fitness and exercise intolerance in COPD. Yet, in the absence of cardiovascular disease, the traditional perspective reasons that ventilatory constraints in COPD prevent individuals from reaching sufficient cardiac stress during exercise, such as maximal cardiac output[62,135]. This, in turn, may restrict the cardiovascular system's ability to adapt to regular exercise.

The cyclical interplay of dyspnea, which leads to reduced physical activity, deconditioning and further declines in cardiovascular fitness, might be further aggravated by cardiovascular comorbidities. Notably, both physical capacity and physical activity levels have repeatedly been identified as important predictors of mortality in COPD, independent of airflow limitation severity[82,136]. Given these considerations, exercise interventions aimed at enhancing cardiorespiratory fitness are essential in the management of COPD[137,138].

Also, COPD is associated with imbalance in autonomic nervous control of cardiac rhytm[139]. Evidence indicates a pattern of sympathetic dominance accompanied by reduced overall parasympathetic tone, yet an enhanced local parasympathetic activity in the airways[139,140]. This autonomic dysfunction represents both a marker and a potential modifiable mechanism of systemic involvement in COPD. By targeting this imbalance through structured exercise it may be possible to improve cardiovascular regulation and overall disease outcomes[141,142], yet more long-term exercise trials in COPD are warranted[143].

Limb Muscle Dysfunction

Limb muscle dysfunction is a major extrapulmonary consequence of COPD. Compared to individuals without COPD, those with COPD often elicit structural and functional abnormalities in muscles[86]. The lower limbs, particularly the quadriceps, are the most studied and will be emphasized herein, although similar alterations can be found in other muscle groups[144]. Reduced lower-limb muscle capacity is associated with clinical outcomes, including exercise intolerance[145,146], increased healthcare use[147] and mortality[148,149].

The pathophysiology underlying muscle dysfunction in COPD overlaps with mechanisms implicated in other comorbidities such as cognitive impairment and cardiovascular disease, namely chronic inflammation, oxidative stress, hypoxemia, hypercapnia[86,150]. Skeletal muscle dysfunction in COPD is characterized by abnormal fibre type distribution, with a shift from oxidative type I to glycolytic type II fibre proportions, in contrast to normal aging[151-154]. Other important alterations include reduced muscle fibre size[153,155], diminished oxidative enzyme activity[154] and impaired capillarization such as reduced capillary density[155,156]. One study has suggested that individuals with COPD fail to co-ordinately activate some cellular pathways related to bioenergetics, inflammation and tissue remodelling, leading to skeletal muscle abnormalities in COPD[157].

In recent years, mitochondrial dysfunction has received growing attention as a key feature of COPD-related muscle dysfunction[86,158]. Several changes have been observed. These include reduced mitochondrial density[159,160], impaired oxidative

phosphorylation[161,162] and increased production of reactive oxygen species[161,163]. In addition, a lower drive for mitochondrial biogenesis, indicated by reduced expression of key mitochondrial transcriptional factors and coactivators has been suggested[164].

A significant proportion of the COPD population shows reduced muscle strength[165,166]. In the quadriceps, strength loss is often attributed to muscle mass reduction[167], with long-term systemic corticosteroid use likely contributing to this process[168,169]. Muscle endurance, the ability to repeat a contraction over time[170], is also markedly reduced in COPD[171,172]. Somewhat counterintuitively, leg fatigue can be as limiting as dyspnea in contributing to exercise intolerance in this population[145,173-175]. Further, muscle power – the product of force and velocity[176] – has been proposed as an important target to enhance physical capacity and preserve independence in later life for the elderly[177]. In COPD, reduced muscle power has recently been linked to declines in functional exercise capacity[178].

Importantly, limb muscle dysfunction in COPD may have prognostic implications. Though causality has not been definitively established, lower limb muscle mass and strength are both associated with increased mortality risk. For instance, a mid-thigh cross-sectional area below 70 cm^2 is associated with a fourfold increase in mortality, even after adjusting for age, sex and airflow obstruction[148]. Similarly, a quadriceps strength measured as maximal voluntary contraction force (kg) to BMI (kg/m^2) ratio less than 120% is associated with increased mortality, and a 10% increment of this ratio is associated with a 9% reduction in mortality[149].

The aetiology of limb muscle dysfunction in COPD remains to be fully elucidated. Ongoing research tries to determine whether it stems from chronic muscle *disuse* and deconditioning due to physical inactivity and sedentarism, from a COPD-related *myopathy* caused by pathophysiological mechanisms and pharmacological treatment, or from a combination of both[86,179,180]. To shed light on this, longitudinal exercise training trials are needed. These should investigate limb muscle function and intramuscular adaptations, ideally including non-COPD control participants matched for physical activity levels[86], to gain insight into the question of disuse versus disease.

Management of COPD

The following section provides a brief overview of key management strategies before introducing pulmonary rehabilitation and exercise-based interventions.

The management of COPD should be based on the assessment of airflow obstruction, symptoms, history of exacerbations, exposure to risk factors and comorbidities[8]. The primary aims of COPD management are to reduce symptoms and risk of future exacerbation, disease progression, and mortality. Evidence-based treatment includes pharmacologic and non-pharmacologic treatments, including pulmonary rehabilitation[8]. Effective COPD management begins with identifying and reducing exposure to risk factors. Smoking, a major and easily identifiable risk factor, is a key target for intervention. Smoking cessation not only improves symptoms[181] and reduces the frequency of exacerbations[182], but can also slow the rate of airflow decline by half[183]. The most effective approach, supported by high-quality evidence, combines behavioural therapy and pharmacotherapy, adapted to the level of nicotine dependence[184,185]. Additionally, legislative smoking bans are effective in increasing quit rates and reducing harms from second-hand smoke[186]. Beyond smoking, minimizing exposure to household and outdoor pollutants, occupational dusts, fumes, and gases should also be addressed[8]. In relation to climate change, people with COPD are at increased risk of death as a consequence of exposure to heat[187,188], and higher outdoor temperatures are associated with increased risk of hospitalizations[187,189]. Therefore, these risks should be considered in patient education.

People with COPD should receive all recommended vaccinations in line with local guidelines. International guidelines suggest vaccinations for influenza, SARS-CoV-2 (based on World Health Organization recommendations), pneumococcal vaccine, respiratory syncytial virus, pertussis and zoster vaccine[8]. Vaccination against influenza and pneumococcal viruses reduces the risk of severe respiratory illness[190,191] and exacerbations in COPD[192].

Pharmacological Interventions

Pharmacotherapy is based on the individual's GOLD class (A, B or E: Figure 1). The most common medications for symptom management and exacerbation reduction include short and long-acting bronchodilators and long-acting muscarinic antagonists[8]. These medications relax airway smooth muscles[193], improve expiratory airflow, reduce dyspnea and enhance quality of life[194]. In advanced COPD, inhaled corticosteroids may be considered if blood eosinophil counts are elevated, the risk of exacerbation is high, or if concomitant asthma is present[8,195]. Inhaled corticosteroids exert an anti-inflammatory effect on the airways and lungs[196]. For severe COPD, an oral phosphodiesterase-4 inhibitor,

targeting systemic inflammation may be added to the treatment regimen[197,198]. During exacerbations, other treatments include systemic corticosteroids[199], antibiotics[200], and methods for respiratory support such as oxygen therapy[201] and non-invasive ventilatory support[202].

Non-pharmacological Interventions

Long-term oxygen therapy is delivered to individuals with COPD who suffer from resting hypoxemia, as it increases survival[203,204]. For individuals with mild or no hypoxemia, supplemental oxygen therapy can relieve breathlessness during exercise but shows no improvements in breathlessness in daily life[204,205]. During exacerbations, in very severe COPD or in those with obstructive sleep apnoea, non-invasive ventilation is considered to decrease hospitalizations and mortality[8,206,207].

Surgical treatment can benefit a small number of individuals with COPD, especially those with severe emphysema[8,208]. One example is lung volume reduction surgery, where the most emphysematous portion of the lungs is removed to reduce hyperinflation. While associated with risks, this can lead to better lung function and health status in selected individuals[209]. Other surgical treatments include lung transplantation or bullectomy, where enlarged alveoli are removed[208].

Pulmonary Rehabilitation

Pulmonary rehabilitation is a structured program based on a thorough patient assessment, incorporating individualised therapies such as exercise training, education, and behaviour modification. It aims to improve the physical and psychological well-being of individuals with chronic respiratory disease while promoting long-term adherence to health-enhancing behaviours[8,11,137]. All individuals with COPD, especially those with high symptom burden and risk of exacerbation (GOLD groups B and E) are recommended to take part in a pulmonary rehabilitation program[8,11]. An initial assessment should identify the individual's needs and expectations, including identifying health status, exercise capacity and limitations[8,210].

A rich body of high-quality evidence demonstrates that pulmonary rehabilitation is effective in increasing exercise capacity, relieving symptoms, and improving overall health status, with improvements being clinically meaningful and substantial[8,11,211]. Additionally, it plays a crucial role in reducing symptoms of anxiety and depression, offering benefits that are considered clinically relevant[212]. The best benefits are seen in programs lasting six to twelve weeks[8,213,214], while some argue that the longest program possible and practical is optimal but that improvements tend to plateau after 12 weeks. Pulmonary rehabilitation is one of

the most cost-effective therapies for individuals with COPD[215]. Troublesome, pulmonary rehabilitation is underutilised worldwide[215,216], including Sweden[217].

Education and Self-management

Education is a part of pulmonary rehabilitation where individuals with COPD are educated about the disease, its medical treatment, strategies to minimize dyspnea, decision-making during exacerbations, exercise and physical activity[8]. The educational component should promote self-management strategies by providing skills and knowledge required to take part in one's healthcare[218]. Education with a single component action plan for exacerbations, reduces hospital utilization and increases treatment with corticosteroids and antibiotics[219]. Yet, one randomised controlled trial (RCT) found no additional benefit of education when added to exercise training, compared to exercise training alone[220].

Exercise Training

Exercise training is a cornerstone in the non-pharmacological treatment of COPD. Its beneficial effects have been well documented, either as a standalone intervention or part of pulmonary rehabilitation[137,211]. People with COPD have reduced exercise capacity due to both pulmonary and extrapulmonary manifestations[221-224]. Nonetheless, the general principles of exercise training do not differ between healthy individuals and those with COPD[137]. To be effective, exercise must be of sufficient dose. The physiological stimulus must exceed habitual levels to drive adaptation, and to maintain adaptations, the training stress must be continually progressed. Without continued stimulus, these adaptations will regress toward baseline[225,226]. National and international treatment guidelines recommend both endurance and resistance training[137,210,211]. Exercise training is also recommended to be delivered posthospital discharge for an exacerbation of COPD, as it reduces hospital readmissions and improves health-related quality of life, dyspnea and exercise capacity[227].

Exercise Physiology in COPD: Key Considerations

An understanding of the physiological limitations underlying exercise intolerance in COPD is important to inform effective exercise prescription.

During exercise, a primary physiological goal is to meet the increased metabolic demand of working muscles through the production of adenosine triphosphate (ATP). This process relies on the efficient uptake (diffusion), transport (convection), and utilization of oxygen. In its journey from the atmosphere to the muscle, oxygen (O_2) is inhaled into the lungs, diffuses across the alveolar-

capillary membrane into the bloodstream, is transported via the circulatory system, and ultimately diffuses into muscle cells where it is used by mitochondria to generate ATP through oxidative phosphorylation[228] (Figure 3). In healthy individuals, this oxygen cascade is finely tuned to support the increased energy demands of physical activity. In the absence of disease, cardiac output is typically the limiting factor for oxygen delivery during intense physical activity[229,230]. In COPD, however, cumulative impairments across the oxygen cascade, including ventilation, gas exchange, circulation, and muscle oxygen utilization limit the efficiency of oxygen transport and ATP production during exercise[231-233]. These deficits contribute to early onset of dyspnea and fatigue during exercise, markedly reducing exercise capacity compared to healthy individuals. As described by O'Donnell (2014)[234], individuals with COPD exhibit increased ventilatory demands, gas trapping, and mechanical constraints on tidal volume even in the early stages of the disease (GOLD I). These abnormalities manifest as a steeper dyspnea–VO_2 slope compared with healthy controls, indicating that breathlessness develops more rapidly in response to increasing workload.

Given these impairments, conventional continuous exercise often leads to an early ventilatory limitation, restricting the ability to sustain sufficient exercise intensity[235-237]. Thus, there is a need for exercise interventions that reduce the burden on the ventilatory system while providing adequate cardiometabolic and limb muscle stimulus. This issue will be addressed in this thesis.

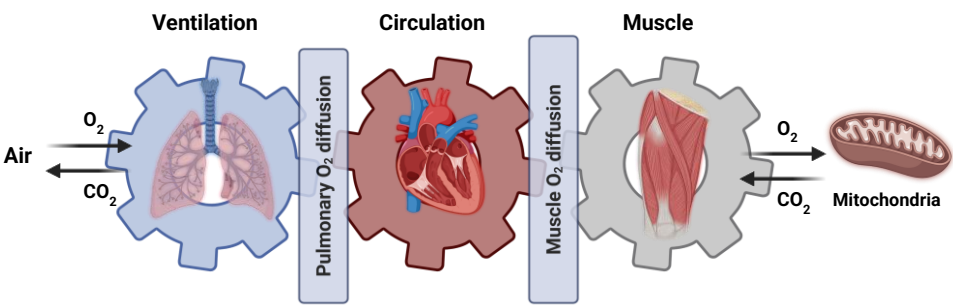

Figure 3. A schematic overview of the oxygen transport cascade. In chronic obstructive pulmonary disease, oxygen transport can be compromised at multiple levels of the cascade. As described in the background , and by others[238], this begins with mechanical restraints on ventilation due to obstruction, causing abnormal breathing and hyperinflation. Next, pulmonary oxygen diffusion might be impaired due to the presence of emphysema and ventilation-perfusion mismatch. Convective oxygen transport through the circulation may be impaired due to lower cardiac output and/or impaired hemodynamic response, potentially worsened by dynamic hyperinflation[239-241]. Muscle diffusion capacity of oxygen might be adapted to the lower muscle oxygen delivery[241], but the skeletal muscle with a low oxidative phenotype and oxidative enzyme abnormalities is less capable of efficiently utilizing the available oxygen[86,154].

Endurance Training

Endurance training is the most used exercise modality in pulmonary rehabilitation, commonly performed as walking or cycling[137,214,215]. Endurance training can improve cardiorespiratory fitness, needed for being more physically active in daily life, which is a primary goal of endurance training in COPD[137]. For example, a six-week cycling intervention improved peak work rate by 36%, and time to exhaustion of 77% in a constant work rate test[242]. Another trial with ten weeks of cycling improved maximal work capacity, six-minute walking distance and health-related quality of life[243]. Endurance exercise can also enhance limb muscle function, quality of life and reduce symptoms, amongst other clinically meaningful benefits[137,211,215,244-246].

Guidelines on endurance exercise training in COPD is generally mirroring the ones by the American College of Sports Medicine[247]. As such, it is recommended that endurance exercise training is performed three to five times a week, at an intensity of ≥60% of maximal work rate to maximize benefits[137,247]. Moderate-intensity continuous or interval training has traditionally been prescribed for people with COPD. However, achieving sufficient exercise intensity, or total exercise dose, to attain physiological adaptations is challenging. As such, the response to exercise training in COPD is heterogeneric[12-14].

Endurance training interventions in COPD have traditionally been based on continuous exercise, in which exercise is performed at a constant intensity for an extended duration[137,214]. Exercise programs including high-intensity training yield superior physiological benefits, compared with low-intensity exercise[242,248,249]. As indicated by a recent network meta-analysis, at least moderate-intensity training is needed for improvements in VO_2peak, while high-intensity tended to result in the greatest improvement[250]. However, high-intensity exercise is often difficult to tolerate for people with COPD, given their ventilatory limitations and muscle dysfunction, resulting in early exercise termination[235], and suboptimal training adaptations. To address these challenges, alternative training modalities have been explored to enable higher intensities without overwhelming ventilatory load[251]. Interval training has gained increasing attention as an approach to achieving high exercise intensities.

Exercise Intensity – From Moderate to Supramaximal.

A few words on exercise intensity are warranted to provide context for how exercise intensity is defined, prescribed and measured in this thesis. These concepts are important for understanding the physiological demands of different exercise training and testing modalities.

The duration of which exercise can be sustained is closely linked to its intensity. This relationship is defined by the power-duration curve, which demonstrates a non-linear decline in sustainable exercise duration as intensity increases[5] (Figure 4). The curve approaches a level (asymptote) known as critical power, the highest sustainable exercise intensity, or rate of ATP regeneration, that can be maintained over a prolonged period[5,252]. Critical power marks the upper boundary of the heavy intensity domain. The lactate threshold, the intensity at which blood lactate begins to rise, defines its lower boundary[253]. Importantly, physiological responses differ significantly to whether constant power exercise is performed above or belove these metabolic thresholds[5], providing the rationale behind the different domains of exercise intensity (Figure 4).

Exercise intensities exceeding critical power (severe intensity or high intensity) have been suggested to rely on a finite pool of energy, termed W' (W prime), which is largely independent of the uptake of atmospheric O_2. This reserve includes stored O_2, high-energy phosphates and energy derived from non-oxidative glycolysis[5,252]. The power-duration concept is well established in healthy humans and different forms of exercise, and is also conserved across the animal kingdom[5]. It is also apparent in people with COPD in which both critical power and W' are reduced[5,254]. Yet, in COPD, reasons for exercise intolerance at intensities close to critical power, partly explained by dyspnea and ventilatory constraints[255], likely differ from healthy individuals.

Exercise intensity is typically prescribed relative to an individual's maximal or submaximal capacity, using a defined anchor[256]. In endurance training, it is common to prescribe intensity as a percentage of maximal heart rate or maximal oxygen consumption. These are ideally determined through an adequate exercise test and are objective measures of *internal intensity*. Intensity can also be assessed subjectively, for instance using the rating of perceived exertion (RPE) scale[257] or as commonly used in COPD, perceived dyspnea on 0-10 scale (Borg CR-10)[258]. In contrast, *external intensity* refers to the actual work performed, such as power output measured in watts (W). One commonly used anchor for external intensity is the peak work rate achieved during an incremental exercise test until exhaustion, namely the maximal aerobic power (MAP). Other commonly used anchors include peak power output and various threshold-based concepts[5,256,259-261]. A more intricate breakdown of exercise intensity terminology and the power-duration relationship is certainly possible[5,253,256,262]. Yet, I am avoiding venturing too deeply into that terrain herein. With regards to critical power, some data indicate that individuals with COPD have their critical power at a relatively higher percentage of MAP, compared to healthy individuals[254,255].

This thesis primarily distinguishes between moderate- and supramaximal training intensities based on external intensity. These are linked to both objective

and subjective measures of internal intensity. Moderate-intensity training typically involves continuous work, lasting from minutes to hours, performed at intensities at a physiologically sustainable intensity within the moderate to heavy domains of exercise (Figure 4). This generally corresponds to external intensities of 40–70% of MAP and occurs below metabolic thresholds such as critical power. Supramaximal intensity refers to external intensities exceeding MAP, commonly performed as short-duration intervals of 30 seconds or less, performed in the very severe or extreme intensity domain (Figure 4). When performed as all-out efforts, this is commonly referred to as sprint-interval training[262], but as further discussed below, supramaximal intensities could also be reached without using all-out efforts.

Lastly, between moderate- and supramaximal intensities lies high intensity exercise, as in traditional HIIT. This typically includes exercise intensities close to 80%-100% MAP, performed at the upper border to the severe intensity domain[3,253,263]. Distinguishing between these intensities, or domains, is central not only to exercise physiology but also to evaluating how different training protocols challenge individuals with COPD in terms of feasibility and physiological response.

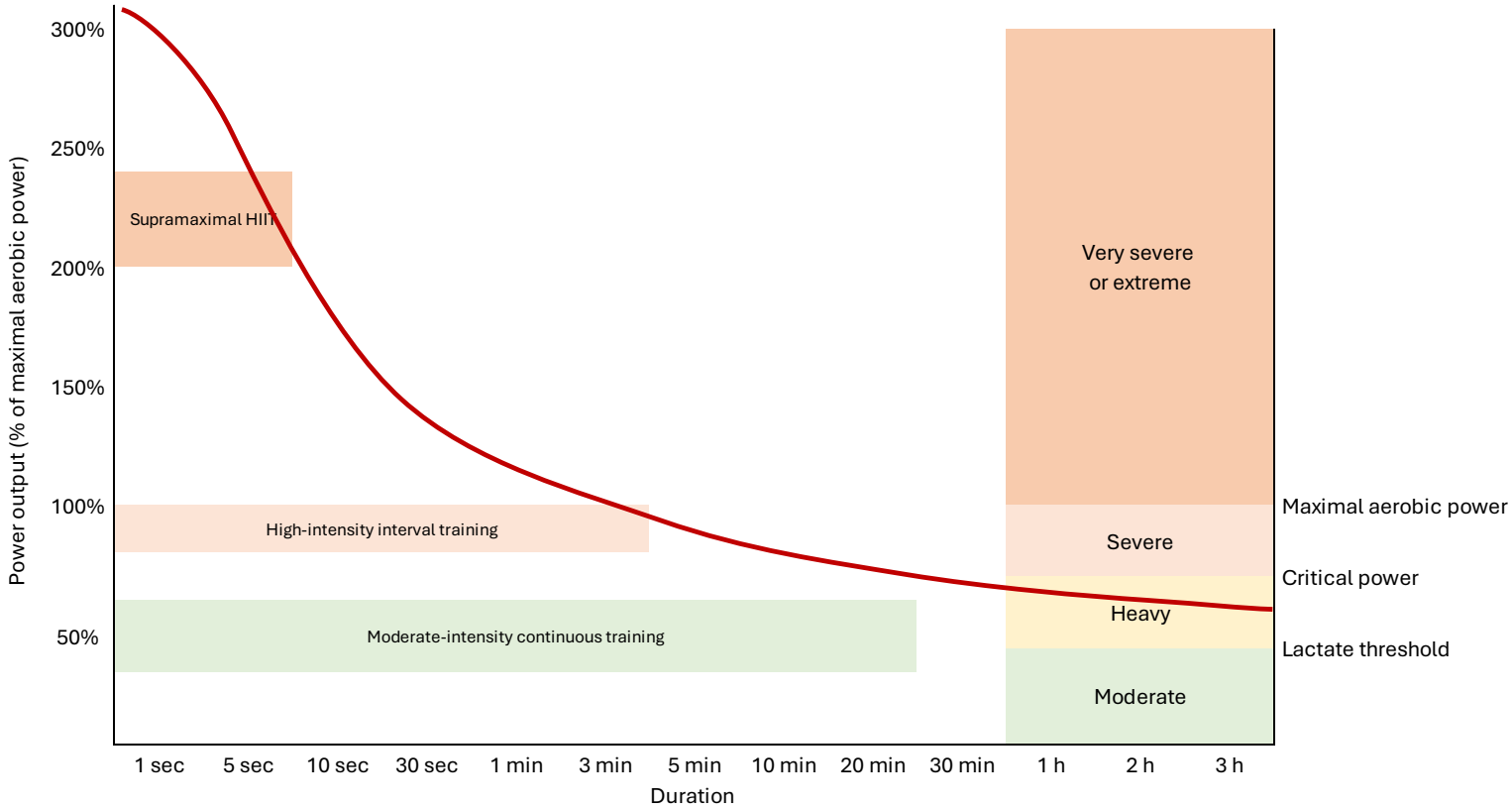

Figure 4. An illustration of the power-duration relationship and exercise intensity domains. The red line illustrates the maximum duration to task failure for a given intensity. In this thesis, supramaximal HIIT is performed as 10 x 6 second intervals, and moderate-intensity continuous training as 20 minutes continuous exercise. HIIT: high-intensity interval training.

Resistance Training

To improve the strength and function of the limb muscles, resistance training is recommended for individuals with COPD in addition to endurance training[137,264]. Resistance training is effective in enhancing muscle mass, muscle strength, endurance capacity[265-267] and potentially muscle power[268]. It can also confer benefits in daily life activities, such as stair climbing and sit-to-stand tasks[269,270]. To improve walking capacity, a higher number of repetitions using a lower load have been shown effective[271]. Resistance training is often used as an adjunct to endurance training[86,264] in which it can increase the achieved benefits in muscle function, but not health status or maximal oxygen uptake[265,272,273]. Thus, a combination of endurance training and resistance training improves outcomes to a greater degree than either modality alone and is recommended in COPD[274 264].

High-Intensity Interval-Training

In HIIT, short periods of high-intensity efforts are combined with periods of lower intensity. In itself, interval-training is nothing new, as it has been studied and practiced for decades by athletes[275], potentially stemming from the Swedish phenomenon "Fartlek training" minted in the 1930's[276]. More recently, HIIT has been increasingly studied beyond young and healthy athletes. Research has expanded to include older adults and clinical populations[277-279] such as individuals with heart failure[280] who share a severely reduced exercise tolerance and experience exercise-induced dyspnea, similar to those with COPD. In general, these studies show that HIIT confers at least similar adaptations compared to MICT on outcomes including cardiorespiratory fitness[279,281] and cardiometabolic health[282]. Some studies also indicates that HIIT is more enjoyable than MICT, although this is not a universal finding[283,284].

In COPD, interval training, not necessarily of high intensity, has traditionally been used as an alternative in individuals who are unable to tolerate continuous exercise, especially for those with severe airflow obstruction[214,264]. Higher intensity interventions have been shown superior or equally effective as low-intensity interventions[137,285,286], enabling increased peak oxygen uptake[242], ability to sustain a given workload[287], reduction in ventilatory requirements[242,288] and increased quality of life[289]. In the strive for effective training stimulus for physiological adaptations in COPD, HIIT has become an attractive strategy in recent years[243,290-293], predominately performed at 80%-100% of MAP.

High-intensity interval training is of particular interest in COPD because it may offer a way to achieve high training intensities without imposing excessive ventilatory demands. Large fluctuations in external workload typically elicits small oscillations in ventilation[294]. Moreover, individuals with COPD exhibit

slower oxygen uptake and ventilatory kinetics compared to healthy individuals[295,296]. As a result, at the onset of high external intensity, the increase in ventilation is both delayed and relatively small[297]. As such, shortening the work-phase duration may allow individuals with COPD to tolerate very high work rates without reaching their ventilatory ceiling. Still, the feasibility and effectiveness of different HIIT modalities in COPD, especially those performed at intensities exceeding MAP — supramaximal HIIT — remains to be investigated. This thesis seeks to address that gap.

Considerations when Prescribing High-Intensity Exercise in COPD

In COPD research, cycling exercise intensities are generally based on results from an incremental cardiopulmonary exercise test (CPET)[290,292,293]. The CPET, described more in the methods chapter, is commonly used in COPD to determine prognosis, determine factors contributing to exercise limitation and to assess response to treatment[82,298]. It allows for the evaluation of physiological responses at submaximal and maximal exercise intensities. It involves the measurement of respiratory gas exchange including oxygen uptake (VO_2), carbon dioxide output (VCO_2) and minute ventilation (V_E)[299]. In brief, it is performed as a progressively increasing work rate protocol, ideally lasting 8-12 minutes until symptom-limitation or exhaustion is reached. The highest workload achieved, MAP, is then commonly used for prescription of MICT and HIIT in COPD[214].

Considering the ventilatory limitations in COPD that may limit performance on a CPET, prescribing high-intensity exercise based on CPET work rates, MAP, might underestimate the metabolic, muscular or cardiovascular capacity for shorter duration work at intensities exceeding MAP[300-303]. For instance, one study showed that individuals with COPD exhibit a much larger evocable power reserve at the limit of tolerance in a CPET, equivalent to 260% of MAP compared to 130% in age-matched controls[304]. Also, it can be argued that exercise at intensities exceeding MAP should preferably be based on exercise tests in this intensity domain[305].

Accordingly, prescription of supramaximal HIIT for individuals with COPD is preferably based upon exercise tests with a shorter duration and higher intensity, accessing supramaximal intensities within the very severe intensity domain, (Figure 4) while circumventing disabling dyspnea. Yet, commonly used tests in this domain, such as the Wingate test[306], often involve all-out efforts characterized by high and uncontrolled pedalling cadence, which may be unsuitable for older individuals with COPD, often naïve to intense exercise[307].

For this purpose, a few studies have investigated alternative tests, such as the steep ramp anaerobic test, initially developed for prescription of HIIT in people

with heart failure[308]. It is a progressive work rate protocol with a markedly faster rate of workload increase compared to a CPET, resulting in about twice the achieved peak workload with a test duration of approximately one minute[307]. Nonetheless, the steep ramp anaerobic test induced similar levels of ventilatory constraint as the CPET[307].

In the context of prescribing supramaximal HIIT, a modified version of the Borg cycle strength test (mBCST) has been developed and used by Hedlund et al. (2019)[309] and Simonsson et al. (2023)[310]. It is a less strenuous alternative to all-out tests, and uses a submaximal, stepwise incremental approach with controlled cadence to estimate maximum mean power output over 30 seconds (MPO30)[311]. In older adults, it is feasible and applicable for prescribing supramaximal HIIT[309,310]. Its relatively short duration of approximately five minutes, and intermittent nature, makes it an interesting test also in COPD but its feasibility and applicability in COPD are yet to be investigated.

Supramaximal HIIT

As introduced above, supramaximal HIIT refers to exercise intensities exceeding MAP. Supramaximal HIIT protocols have been suggested as a time-efficient alternative with health-benefits similar to those achieved in moderate-intensity training in adults[312] and healthy older adults[279,313]. Several different supramaximal HIIT protocols exist, with varying work-rest ratios and intensities. Notably, most of these protocols have been developed and tested in healthy younger populations and are often performed as all-out intervals, commonly ranging from six to 30 seconds[312,314]. However, a recently developed concept of supramaximal HIIT involves regulated, watt-controlled cycling intervals of ten times six seconds[309].

In older inactive adults, Simonsson et al. (2023)[310] and Frykholm et al. (2024)[315] found this type of supramaximal HIIT to be feasible and well-tolerated. A key feature of this protocol is that it includes an individually regulated intensity, based on an individual's capacity for six-second power output and prescribed as a percentage of that. It also utilises standardized pedalling cadence throughout the intervals. As such, excessive perceived exertion and a negative affective state can be reduced compared to an all-out regimen[315-317]. Considering the potential of interval exercise to reduce the ventilatory constraints during exercise in COPD, short-duration supramaximal HIIT like that used by Simonsson et al. and Frykholm et al., may be specifically suitable in this population.

Supramaximal HIIT in COPD: Extrapulmonary Benefits?

In COPD, HIIT protocols using work rates exceeding MAP have rarely been explored. However, it holds the potential to circumvent limitations imposed by continuous exercise in this population. By accessing external intensities well above MAP for short periods, it enables prolonged exposure to high-intensity exercise while potentially keeping ventilatory requirements below limiting thresholds.

In healthy adults, a systematic review including 16 RCTs found sprint interval training it to be equally effective as continuous training in improving cardiorespiratory fitness, despite reduced exercise volume[312]. Studies have further found improvements in endurance capacity and mitochondrial oxidative enzyme content[318,319]. Supramaximal HIIT can improve skeletal muscle function and strength, given the high stress on skeletal muscle[320,321].

Exercising at high-intensities is an important factor for activation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α)[322], an important regulator of mitochondrial biogenesis[323,324]. Some evidence suggests that high intensity is a key factor for PGC-1α upregulation with similar or greater upregulation seen in supramaximal HIIT compared to moderate-intensity training[325,326]. Yet, initiation of mitochondrial biogenesis is complex and investigation of more targets is warranted[327]. Nonetheless, given the reduced expression of PGC-1α in the skeletal muscles of individuals with COPD[164], stimulating its activation via supramaximal HIIT might be a viable option for improving mitochondrial function in this population.

While research on the effects of supramaximal HIIT on cognition is scarce, especially in COPD, exercise can promote cognition and brain health through multiple mechanisms[123,328,329]. One is via exerkines such as brain-derived neurotrophic factor (BDNF), an important mediator for neurocognitive benefits[330,331]. Increased BDNF levels promote neurogenesis, synaptic plasticity, and overall cognitive function[332]. In turn, exercise-induced upregulation of PGC-1α pathways has been suggested as an important mechanism to elevate brain- and circulating levels of BDNF[333,334]. Further, high exercise intensities seem to be most effective in increasing BDNF and other neuroprotective exerkines, such as cathepsin B and irisin[335,336].

Taken together, short duration supramaximal HIIT may be particularly relevant to enable extrapulmonary adaptations in COPD. However, studies investigating the feasibility, acute physiological responses, prescription and long-term adaptations of supramaximal HIIT compared to MICT are yet to be conducted but will be explored in this thesis (Paper I–III).

Quality of Reporting in Exercise Trials for COPD

Regardless of the exercise training modality, the successful implementation of exercise interventions in clinical practice depends on clear and detailed reporting of the prescribed protocols. Without such information, it becomes challenging to interpret outcomes, translate findings to real-world settings, or synthesize evidence across studies to inform best practice[337]. The methodological quality and transparency of exercise training trials are thus critical for advancing evidence-based rehabilitation in COPD. Despite the clear rationale for implementing exercise training in COPD, the quality and consistency of evidence underpinning clinical recommendations remain a concern.

Evidence-based medicine depends on high-quality, well-designed, properly executed and transparently reported RCTs[337]. Yet, evidence suggests that the completeness of reporting of RCTs is often inadequate[338,339], including non-pharmacological interventions[340], leading to wasted time and resources in medical research[341]. To address this, the Consolidated Standards of Reporting Trials (CONSORT) statement was introduced in 1996 to improve transparency and reproducibility in RCTs[342]. Two decades later, the Template for Intervention Description and Replication (TIDieR) checklist was introduced to further strengthen the reporting of interventions[343].

The field of exercise science and respiratory medicine are not exempt from these concerns, but suffer from methodological concerns[344,345], including poorly reported trials[346]. Incomplete reporting of exercise interventions is a widespread problem[347-349]. This is troublesome and led to the development of the Consensus on Exercise Reporting Template (CERT) in 2016[346]. The CERT provides structured guidance on key items considered essential to report in exercise trials to enhance reproducibility and practical implementation.

These challenges must not be underestimated. Obviously, to implement effective exercise interventions, researchers and clinicians must understand what has been prescribed. Only with complete and transparent reporting can interventions be accurately evaluated, findings translated into clinical practice, and data synthesized to inform evidence-based guidelines[337]. Furthermore, effective exercise prescription should adhere to the principles of exercise training, such as progression, overload and specificity[225,226,350]. These should, preferably, be applied and reported together with other key components such as frequency, intensity, time and type of training, i.e. the FITT-components[170,346]. Moreover, understanding who the participants were, through proper reporting of relevant demographic and clinical characteristics is vital for assessing relevance and external validity of the findings[351].

The quality of reporting and exercise prescription in exercise training trials have been systematically investigated across several clinical populations[348,349,352-360]. One systematic review of 136 RCTs in cancer patients found that exercise interventions were often incompletely reported when assessed using the TIDieR checklist; no study adequately reported all items, and on average, 29% of items deemed essential for replication were missing[360]. Another systematic review of 25 RCTs in obesity reported that only 47% of CERT items were sufficiently described[361].

In COPD, this issue has received limited attention to date. A systematic review of 26 trials in COPD exacerbations reported substantial variability and generally poor reporting of exercise prescription details[362]. However, the quality of reporting and exercise prescription in the broader COPD literature remains insufficiently investigated[363,364]. Addressing this limitation is essential to improve transparency, facilitate replication, and enhance the translation of exercise training research into clinical practice. This issue is examined in the present thesis (Paper IV).

Key Messages - Background

- COPD is characterized by airflow obstruction, dyspnea, lung hyperinflation and impaired gas exchange, all of which contribute to exercise intolerance.

- COPD extends beyond the lungs, with multiple extrapulmonary manifestations including, but not limited to cognitive impairment, reduced cardiovascular fitness and muscle dysfunction, contributing to reduced exercise capacity, functional impairment, and mortality.

- Pulmonary rehabilitation, including endurance training, is a cornerstone of COPD management, improving symptoms, functional capacity, and health status, yet remains underutilised globally.

- Achieving high intensities remains a challenge in individuals with COPD. Supramaximal HIIT, characterized by short-duration bouts performed at very high external workloads, may offer a feasible and effective alternative for targeting extrapulmonary manifestations in this population.

- To ensure clinical relevance and reproducibility, exercise training trials must clearly report intervention details and exercise prescription, an area that is yet to be systematically evaluated in COPD literature.

Rationale for This Thesis

Chronic obstructive pulmonary disease is one of the deadliest societal diseases of the 21st century with globally increasing prevalence rates. Accordingly, COPD is a significant public health challenge. In addition to pharmacological treatment, exercise training is a cornerstone in the management of COPD and an essential component of pulmonary rehabilitation programs. Exercise interventions can improve and preserve physical and cognitive function, enhance independence, and promote quality of life in people with COPD.

Current clinical guidelines emphasize pulmonary rehabilitation and endurance exercise as key components in the management of COPD[137,210]. Yet, many individuals with COPD fail to achieve clinically relevant adaptations from endurance exercise. This highlights the need for new and individualised endurance exercise methods that can overcome the ventilatory constraints inherent to the disease.

Supramaximal HIIT has the potential to reduce the impact of the ventilatory limitations for exercise in people with COPD, resulting in increased exercise intensities and potentially extrapulmonary benefits. Yet, the feasibility and acute physiological responses to watt-controlled supramaximal HIIT in COPD remain unexplored. Moreover, how supramaximal HIIT compares to MICT, has not been systematically evaluated in COPD.

Understanding disease-specific exercise limitations and adaptations also requires appropriate reference data. Therefore, inclusion of age-, sex-, and physical activity–matched healthy controls is important to disentangle the specific impact of COPD from that of aging and inactivity. Such comparisons can provide important insights into the extent to which COPD alters the acute response and adaptations to exercise.

Finally, to advance the field of exercise training trials in the COPD literature, the quality of reporting and exercise prescription in the field has to be investigated. A systematic evaluation of reporting practices is therefore warranted to identify gaps and guide future research toward higher methodological standards. As such, recommendations to enhance the quality of exercise prescription and study reporting practices can be addressed.

Aims of the Thesis

The overarching aim of this doctoral thesis was to contribute to the development of effective exercise strategies for the management of COPD. It sought to advance the understanding of the feasibility, physiological responses and methodological considerations of supramaximal HIIT in people with COPD and to evaluate the reporting quality in aerobic exercise interventions in the COPD literature.

The specific aims of this thesis were to, in people with COPD and matched healthy controls:

- Evaluate the feasibility[a] and acute physiological responses[b] of supramaximal HIIT compared to MICT (Paper I)
- Assess the feasibility[a] of the mBCST and its applicability in enabling supramaximal external exercise intensities (Paper II)

And to:

- Describe the study design of the COPD-HIIT RCT investigating the effects and mechanisms of supramaximal HIIT and MICT in people with COPD compared to matched healthy controls on clinical outcomes (Paper III)
- Present the current trial status and preliminary baseline characteristics of enrolled participants in the COPD-HIIT RCT
- Systematically review the reporting quality and application of training principles in aerobic exercise interventions for people with COPD (Paper IV)

[a] In Paper I, exercise feasibility was determined through exercise fidelity, defined as the need for modifications to the planned exercise protocol (intensity, duration or cadence), as well as completion rate and perceived symptoms. In Paper II, test feasibility was determined by achieved intensity, interpretability, familiarity required, duration, scoring complexity, completion, cost and safety. In Paper III, intervention feasibility is determined by completion rate, attendance rate, adherence to the prescribed exercise, exercise feasibility, occurrence of adverse events and participant satisfaction.

[b] Refers to the acute exercise-changes that occur during or immediately after a bout of physical activity, including changes in oxygen consumption, ventilation, heart rate and circulating exerkines, with brain-derived neurotrophic factor specifically targeted.

Materials and Methods

Overview

This thesis comprises four scientific papers, summarized in Table 1. Papers I-III are based on trials conducted within the COPD-HIIT project.

Papers I and II utilise data from a randomised crossover trial, the COPD-HIIT acute study. Paper I investigate the feasibility and acute physiological responses to supramaximal HIIT compared with MICT, whereas Paper II evaluates the feasibility of the mBCST and its applicability for prescribing supramaximal HIIT.

Paper III presents the study protocol for the ongoing COPD-HIIT RCT, hereafter called *the RCT*, detailing its design and methodology. In addition to the published protocol, the thesis includes preliminary trial data, providing an overview of trial status and baseline characteristics of enrolled participants. To preserve blinding and prevent bias among investigators, no post-intervention outcome data has been analysed. Instead, the enrolled participants are characterized, and the groups are compared on selected outcomes. Paper III is presented in the methods while preliminary data from the ongoing RCT is presented in the results.

Lastly, Paper IV is a systematic review evaluating the quality of exercise prescription and completeness of reporting in aerobic training trials within the COPD literature.

Recruitment and Participants in Paper I-III

Individuals with COPD were recruited via four main pathways: 1) referrals by a COPD/asthma nurse or pulmonologist; 2) previous study participators who had consented to being contacted for future studies; 3) advertisement and 4) referrals by primary care health care professionals who had been informed about the trial (Paper III only). Healthy controls were recruited via advertisement. Sample sizes for the respective papers are presented in Table 1.

Table 1. An overview of the trials and papers included in the thesis

	Paper I	Paper II	Paper III	Paper IV
Project	COPD-HIIT Acute study		COPD-HIIT RCT	Quality of reporting
Study design	Randomised cross-over trial		Study protocol, RCT	Systematic review
Location	Umeå		Umeå, Belgium	NA
Registration	ClinicalTrials.gov: NCT05874999		ClinicalTrials.gov: NCT06068322	PROSPERO: CRD42021247343
Ethical approval	2020-03199, 2020-06883, 2021-05408-02		2023-007471-01, Z-2022078	NA
Participants	COPD: N = 16 HC: N = 16	COPD: N = 18 HC: N = 16	COPD: N = 138 HC: N = 70	N = 298 trials, 28 568 participants
Period data collection	March 2022 – December 2022		November 2023 - ongoing	2007 – 2025*
Primary outcomes	Exercise intensity (W) and change in BDNF	Feasibility	Cognitive and cardiorespiratory function, quadriceps power	Reporting quality
Main analytical methods	Repeated measures analysis of variance	Pairwise comparisons	Analysis of covariance	Systematic synthesis, descriptive statistics
Guidelines	CERT, CONSORT		SPIRIT, CERT, TIDieR, CONSORT	PRISMA-P, PRISMA, SWiM
International collaboration	None		Belgium, Netherlands, Denmark	Belgium, Netherlands, Canada

*Trials published between 2007 and 2025 were included in the systematic review. COPD: Chronic obstructive pulmonary disease; HIIT: High-intensity interval training; HC: Healthy controls; RCT: Randomised controlled trial, BDNF: Brain derived neurotrophic factor; CERT: Consensus on Exercise Reporting Template; CONSORT: Consolidated Standards of Reporting Trials; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; TIDieR: template for intervention description and replication; PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses; SWiM: Synthesis-without meta-analysis; NA: Not applicable

Table 2 outlines the criteria used to determine eligibility for participation in Papers I-III. In general, we aimed to include a broad range of participants in terms of COPD severity and a balanced sex distribution. All stages of the disease were eligible, and most comorbidities were not reasons for exclusion, provided that the participant met the other eligibility criteria.

Table 2. Eligibility criteria in Paper I, II and III

Inclusion criteria		Details	Papers
1)	Age	60 years or older	I, II, III
2)	COPD diagnosis and lung function	COPD: Diagnosis of COPD based on post-bronchodilator spirometry (forced expiratory volume in one second/forced vital capacity < 0.70) Healthy control: Normal lung function	I, II, III
3)	Symptoms	Symptomatic (COPD assessment test ≥ 10 or modified Medical Research Council dyspnea questionnaire ≥ 2), and/or meeting inclusion criteria 4).	III
4)	Physical activity	Not regularly physically active at moderate or high intensity over the past year (i.e., not meeting World Health Organization physical activity guidelines) and/or meeting inclusion criteria 3).	III
5)	Physical activity	A step count too low or too high to allow physical activity matching (Healthy controls only)	I, II, III
6)	mBCST	Completed at least three steps in the mBCST at intended cadence	I
7)	Independence	Independent in activities of daily living	III
Exclusion criteria			
1)	Comorbidities	Unstable movement-related, cardiovascular, neuromuscular, metabolic, skeletal, or rheumatic conditions that prohibit exercise or testing based on physician screening.	I, II, III
2)	Comorbidities COPD	Comorbidities that limit exercise capacity more than COPD itself, based on screening by physician	I, II, III
3)	Lung conditions	Including but not limited to severe asthma, interstitial lung disease, pulmonary fibrosis and pulmonary hypertension, diagnosis and treatment of lung cancer in the last five years	I, II, III
4)	Exacerbation	Acute exacerbation of COPD within the last six weeks	I, II, III
5)	Rehabilitation	Current participation in pulmonary rehabilitation or have been involved in pulmonary rehabilitation in the last 12 months	III
6)	MRI and PET/CT specific criteria	MRI-incompatible factors, such as metal implants and pacemakers	III

COPD: Chronic obstructive pulmonary disease; mBCST: modified Borg cycle strength test; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography

The COPD-HIIT Acute Study

A single centre randomised controlled crossover trial was conducted between 1st of March and 22nd of December 2022. The trial design is outlined in Figure 5. Participants attended the facility four times on separate days within 14 days (Figure 5). The first visit included two parts. Part A included pulmonary function tests and a CPET conducted at the Unit of Clinical Physiology at University Hospital of Umeå. Then, after 1.5 hours of recovery, Part B was conducted at the Umeå Movement and Exercise laboratory at Umeå University. Here, participants performed the mBCST[311]. Additional participant characteristics assessments, including body composition, were also performed. The second and third visit encompassed either supramaximal HIIT or MICT in a randomised order. Lastly, the fourth visit consisted of a second session of the supramaximal HIIT protocol but at a higher intensity than the first session of supramaximal HIIT. To investigate the feasibility and physiological response of the exercise modalities (Paper I) and the mBCST (Paper II), several physiological parameters and subjective ratings were measured during the exercise, detailed in the Assessments and Outcomes section.

Reporting of Paper I follows applicable items from the CONSORT extension for crossover trials[365] and CERT[346], while Paper II is reported following applicable items from The Strengthening the Reporting of Observational Studies in Epidemiology statement[366].

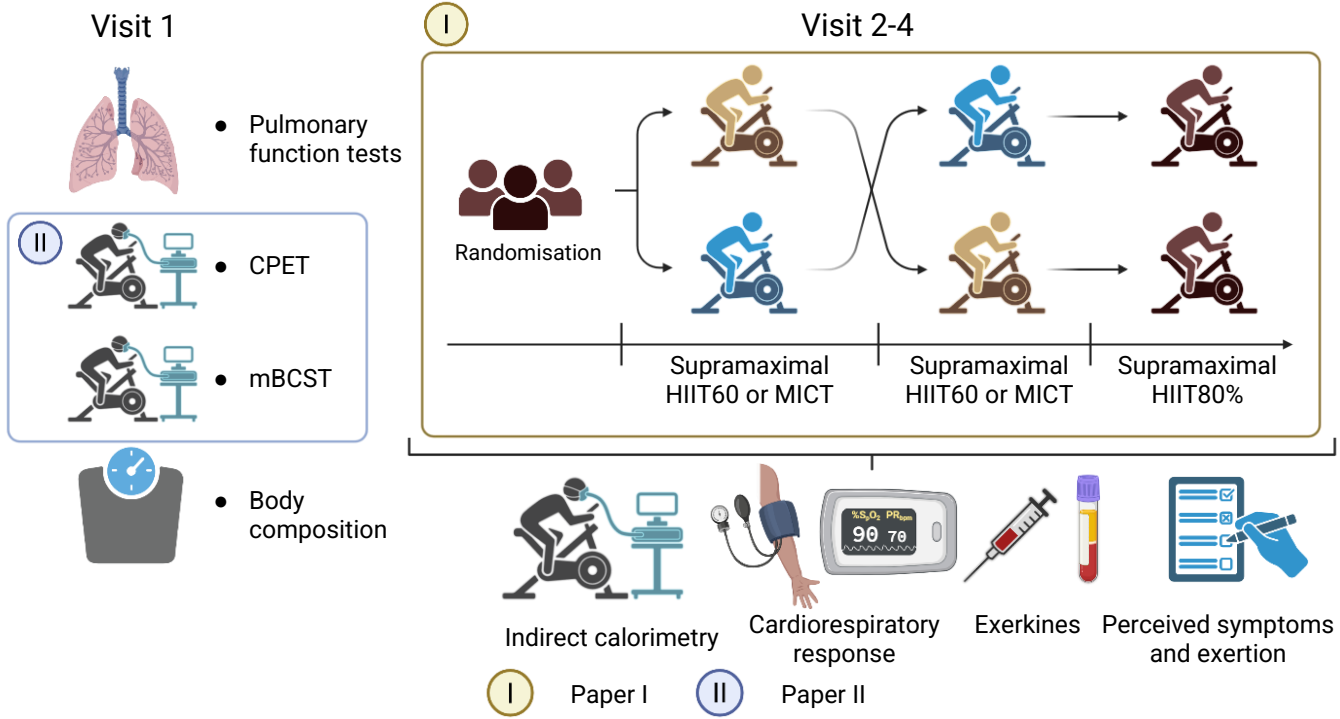

Figure 5. Overall design of the randomised cross-over trial (Paper I and Paper II). Adapted from Paper I, Jakobsson (2025)[367]. CPET: cardiopulmonary exercise test; mBCST: modified Borg cycle strength test; HIIT: High-intensity interval-training; MICT: moderate-intensity continuous training. HIIT60 and HIIT80 refers to supramaximal HIIT performed at 60% or 80% of maximum mean power output for six seconds, estimated from the mBCST.

Exercise Modalities

In Paper I, we investigated the feasibility and acute physiological response of a single session of supramaximal HIIT and MICT. This section describes the exercise protocols and how they were designed in Paper I. The modalities are also used in the RCT, with study-specific considerations in its own section.

Both supramaximal HIIT and MICT were conducted on stationary cycle ergometer (Monark LC6, Monark, Vansbro, Sweden). By using RPM-independent ergometers, the power output was kept constant regardless of the user's pedalling cadence. This was achieved through automatic adjustments to the torque applied to the pedals.

Both supramaximal HIIT and MICT began with a three-minute resting phase in which baseline (oxygen consumption, ventilation, heart rate etc.) data were collected. Then, protocols continued with a five-minute warm-up and ended with a five-minute cool-down, both performed at 30% of MAP, with a self-selected cadence of 50-70 RPM. Characteristics of the interventions used in Paper I and the RCT are described below and summarized in Table 3. Each exercise session was performed individually in a laboratory-setting, supervised by a physiotherapist or exercise physiologist.

Supramaximal HIIT

Following the warm-up, supramaximal HIIT was performed as ten intervals of six seconds at a cadence of 80-90 RPM, interspersed with a 54-second recovery. The recovery period was separated into 24 seconds of passive rest followed by 30 seconds of active recovery at 30% of MAP, with a cadence of 50-70 RPM (Figure 6A, Table 3).

Interval intensity was individually prescribed. This was anchored to a short-duration power metric, namely the estimated maximum mean power output for six seconds (MPO6). The MPO6 is estimated from the mBCST (further described in the *Assessments and Outcomes section*), by multiplying the achieved power output at the last stage of the test by 1.75. Then, interval intensity corresponded to 60% and 80% of MPO6, referred to as HIIT60 and HIIT80, respectively. Including warm-up and cool-down, the total session duration was 20-minutes (Figure 6A). The HIIT80 session was predetermined as the last session to ensure an unbiased comparison between HIIT60 and MICT, not knowing the feasibility a priori.

The supramaximal HIIT protocol followed the methods developed by Hedlund et al.[309] and Simonsson et al.[310] with modifications tailored to the current cycle ergometer setup.

Due to the delay in resistance adjustment on cycle ergometers, the programmed interval durations were set to eight seconds in Paper I and twelve seconds in the RCT. Pilot testing and analysis of power output data showed that approximately two seconds (Paper I) and six seconds (the RCT) were required to ramp up to the target intensity, resulting in a six-second segment performed at, or close to, the intended power output. However, these measurements do not account for the additional power required to accelerate the flywheel as cadence increased from 50-70 RPM during active recovery, to 80-90 RPM during the intervals.

Moderate-Intensity Continuous Training

Following the warm-up, MICT was performed as 20 minutes of constant workload of 60% of MAP, with a target pedalling cadence of 60-70 RPM. Including warm-up and cool-down, the total session duration was 30-minutes (Figure 6B, Table 3). The MICT was designed following current guidelines[137] and common practice[214] for moderate-intensity continuous exercise in people with COPD, which suggests an intensity of ≥60% of MAP for 20 to 60 minutes, to maximise benefits.

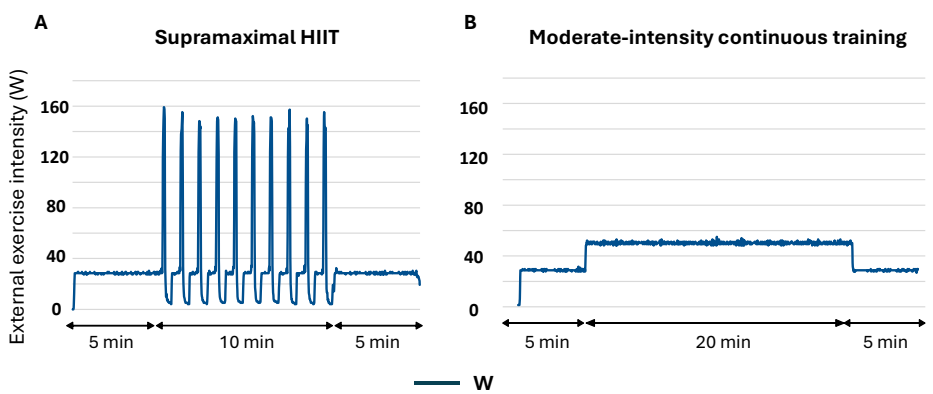

Figure 6. An overview of the exercise protocols for a representative participant. Power output during a **(A)** supramaximal high-intensity interval-training session performed at 80% of maximum mean power output for 6-seconds and **(B)** moderate-intensity continuous session, performed at 60% of maximal aerobic power achieved during a cardiopulmonary exercise test. HIIT: high-intensity interval training.

Table 3. Overview of interventions characteristics in Paper I and Paper III

General characteristics	**Supramaximal HIIT**	**MICT**
Duration[a]	20 min	30 min
of which warm-up and cool-down	5 min each	5 min each
of which main work-phase	10 min	20 min
Number of intervals x duration[a]	10 x 6 seconds	Continuous
Recovery between intervals[b]	54 seconds	NA
of which passive	24 seconds	NA
of which active	30 seconds	NA
Maximal duration at end of phase 1	25 min (15 intervals)	48 min
Maximal duration at end of phase 2	30 min (20 intervals)	60 min
Target pedalling cadence, RPM		
Warm-up, active recovery and cool-down	50-70	50-70
Intervals or main work-phase[c]	80-90	60-70
External intensity		
Warm-up, active recovery and cool-down	30 % of MAP	30% of MAP
Intervals or main work-phase[d]	60%-80% of MPO6	50%-60% of MAP
Progression criteria for external intensity and duration in the RCT		
Able to maintain cadence during the last interval or minute	80	60
Rating of perceived exertion (6–20 points)	≤ 17	≤ 13
Regress if	≥ 19	≥ 15
Dyspnea (0-10 points)	≤ 7	≤ 5
Regress if	≥ 9	≥ 7
Possible progression or regression in the RCT (Phase 1)		
Workload (from second session)	± 2.5-10%	± 2.5 -10%
Duration (week of first extension)	+ 1 interval (week 8)	+ 2 min (week 3)
Frequency (phase 1), from week seven	+ 1 session / week	+ 1 session / week

[a] In the RCT, duration for both interventions is progressed throughout the trial. For supramaximal HIIT, this is done by adding one interval at a time, for a maximum of 15 intervals in phase 1 and 20 in phase 2. For MICT, duration is extended by adding two to four minutes at a time, for a maximum of 38 minutes in phase 1 and 50 minutes in phase 2. [b] Due to small delay in the cycle ergometers in adjusting the resistance to achieve the target power output, the interval duration was programmed as 8 seconds in Paper I and 12 seconds in the RCT. [c] If needed, 60-70 RPM is allowed in supramaximal HIIT. [d] In Paper I, supramaximal HIIT was performed at 60% and 80% of MPO6, respectively, while MICT was conducted at 60% of MAP. In the RCT, supramaximal HIIT starts at 60% of MPO6, with the goal to increase to 80% during the first few sessions, and MICT starts at 50% of MAP, aiming to reach 60% in the same period. HIIT: High-intensity interval training; MICT: moderate-intensity continuous training; RPM: revolutions per minute; MAP: maximum aerobic power; MPO6: maximum mean power output for six seconds; NA: not applicable

The COPD-HIIT Randomised Controlled Trial

Trial Design

The COPD-HIIT RCT is a prospective, multi-centre, randomised, controlled, parallel-group superiority trial with assessor and statistician blinding. The trial is performed at two centres: in Umeå, Sweden and Hasselt, Belgium. While the aim of Paper III is to describe the study design of the RCT, the RCT comprises of two phases with the following primary objectives:

- To determine and compare the effect of 12 weeks of supramaximal HIIT and MICT on cognitive function, cardiorespiratory fitness, and quadriceps power in individuals with COPD compared to matched healthy controls (phase 1).
- To determine and compare the effect of 24 months of supramaximal HIIT, MICT, and usual care on cognitive function, cardiorespiratory fitness, and quadriceps power in individuals with COPD (phase 2).

As such, phase 1 of the trial spans 12 weeks and includes both individuals with COPD and healthy controls. After completing the 12-week intervention and follow-up assessments, people with COPD, but not healthy controls, will proceed to phase 2 of the trial. Phase 2 comprises a 21-month maintenance exercise program until a 24-month follow-up. In addition, a separate passive control group of individuals with COPD, receiving usual care only, will undergo assessments at baseline and 24 months. This arm is not included in the randomisation; thus, phase 2 is a partially randomised controlled trial. Separate recruitment will be conducted specifically for this group. However, participants who are unable to take part in the exercise interventions arms, for example due to medical contraindications or long travel distance to the training facility, can also be considered for inclusion in this group.

The RCT started to enrol participants in November 2023. Phase 1 is expected to be completed by the end of 2026 and phase 2 at the end of 2028. Two thirds of the participants (n = 138) is planned to be enrolled in Umeå, and the remaining third (n = 70) in Hasselt. Figure 7 outlines the general design of the trial and Figure 14 in the results outlines the participant flow of the trial.

Paper III entails the study protocol for the RCT and describes the rationale, design, interventions, assessments, and analysis plan for the trial. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[368,369], Template for Intervention Description and Replication[343] and CERT[346].

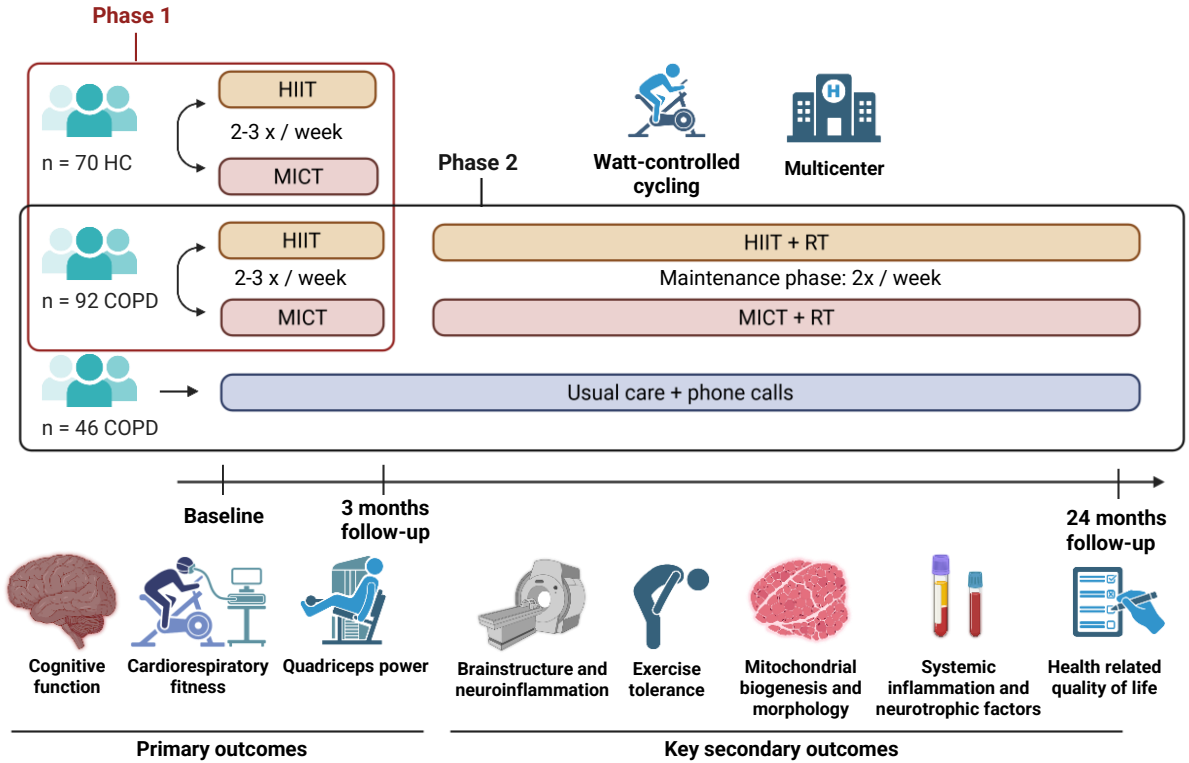

Figure 7. Overall design of the COPD-HIIT randomised controlled trial. In phase 1, supervised exercise training (supramaximal HIIT or MICT) will be performed two to three times per week. In phase 2, participants with COPD will continue to exercise until a 24-month follow-up. HC: healthy controls; COPD: chronic obstructive pulmonary disease; HIIT: supramaximal high-intensity interval training; MICT: moderate intensity continuous training; RT: resistance training.

Interventions: Phase 1

Training was performed for two (first six weeks) to three times (last six weeks) per week for a total of 30 sessions. Both intervention arms performed supervised group training with groups of up to eight participants at the same time (Picture 1).

Picture 1. Picture from a group training session in the COPD-HIIT RCT.

Eligible participants were randomised to either supramaximal HIIT (intervention arm) or MICT (active control arm) on a stationary bicycle (Smart Zbike, Zycle, Valencia, Spain). Each bicycle is coupled with a tablet showing visual supporting information including remaining time, RPM, target power and current power output (Picture 2). For this, the exercise training application Kinomap (Kinomap, Douai, Nord-Pas-de-Calais, France) is used.

The starting point for both exercise protocols followed the design described in Paper I (Figure 6, Table 3), with some adaptations for the RCT. Because different cycle ergometers used, requiring a longer time to apply breaking resistance, the intervals in supramaximal HIIT were programmed to last 12 seconds, yielding six seconds at the target output of 60% of MPO6. To maintain session duration, the recovery period was set to 48 seconds, comprising 20 seconds of passive and 28 seconds of active recovery. In addition, MICT was initiated at a slightly lower intensity, starting at 50% of MAP.

Both protocols allow controlled adjustments of training intensity, duration, and frequency using standardized criteria to achieve progressive overload, ensure consistency across centres, and facilitate replication in clinical settings. Progression or regression of intensity and duration was guided by three criteria (Table 3): 1) Able to maintain the target RPM the last interval or last minute of exercise in a controlled manner; 2) RPE and 3) perceived dyspnea. For 2) and 3), these ratings were collected by the training instructor at the end of exercise. Notably, the instructor can override the suggested progression criteria if deemed necessary, though this option is used with caution. The detailed-oriented reader finds further details on the interventions in the study protocol (Paper III, Table 1-3).

Picture 2. The tablet with visual information for the ongoing exercise sessions, placed on the handlebar of the stationary bicycle. It shows the remaining duration of the whole session, remaining duration of the current block, such as warm-up or interval, target power output, current power output and cadence.

Interim Assessments

During week six of the intervention, one training session was replaced by an interim assessment consisting of a CPET and a mBCST. These provide updated MAP and MPO6 values to optimize exercise intensities for supramaximal HIIT and MICT in the following six weeks. Would a participant already be exercising

at or above the intensity estimated from the interim assessment, the higher training intensity load was kept.

Interventions: Phase 2

Supramaximal HIIT and MICT

For participants in phase 1, the subsequent phase 2 includes a 21-month maintenance phase. After two weeks with outcome assessments and one or two weeks of rest, participants with COPD continues to exercise using the same training modality as during phase 1, for two times per week. Now, participants can select to perform their training either at *home*, *outpatient*, or a *mix* setting. In the *home* setting, participants are provided with a cycle ergometer for unsupervised training at home. Would a participant like to continue at home but does not want to receive a cycle ergometer, they can continue with walking-based HIIT or MICT. In the *outpatient* setting, participants continue with supervised group training. In *mix*, participants combine home-based sessions with one supervised outpatient session every two weeks. Irrespective of the setting a participant chooses to continue in, data analysis will be conducted per allocated trial arm.

Resistance Training

Irrespective of the original arm and chosen setting, all participants also perform an adjunct resistance training regime in phase 2. The regime consists of an exercise battery of ten exercises, including exercises for both the upper- and lower body. The participants were instructed to choose and perform four exercises in each exercise session, with two sets per exercise. Of these, a sit-to-stand exercise should always be included (if performed in an outpatient setting, a leg press or knee extension should always be included), but the participant should select three additional exercises each session. The goal of the resistance training regime changed monthly and focused on either strength, endurance or power. All exercises will be performed using body weight of the participant and/or with elastic bands (Thera-Bands®, The Hygienic Corporation, Akron, OH, USA). If performed in an outpatient setting, available resistance training equipment at the facility will be used.

Passive Control Group: Usual care

The passive control group receives usual care alone and a standardized phone call every three months including assessment of symptoms of exacerbations. Participants in the usual care group will also receive the CAT and CRQ questionnaire via the post to self-administer. Participants in the usual care group

were matched to those randomised to supramaximal HIIT or MICT by age, sex, disease severity (GOLD A/B/E classification), years of education, and objectively measured physical activity levels (steps per day).

In Sweden, usual care for COPD could (and should) include: 1) support for smoking cessation; 2) assessment of physical capacity with a six-minute walk test; 3) supervised aerobic and resistance training to individuals with stable COPD and decreased physical capacity and those with an exacerbation; 4) nutritional treatment for those with BMI <22 and 5) patient education and support for self-treatment. However, despite these guidelines, availability and utilization of proper pulmonary rehabilitation is far from optimal[217,370,371]. For most, treatment is limited to pharmacological interventions. In Belgium, there are no national guidelines for COPD management and like Sweden, most patients receive only pharmacological intervention. Centre based pulmonary rehabilitation is provided in many hospitals in Belgium, but access remains poor. While there is no official data, it is said to be around 2%.

Standardized Phone calls and Follow-ups

All participants in the supramaximal HIIT and MICT arms received a phone call once every 14 days during phase 2. Using a standardized protocol, we gathered the necessary information to progress the exercise and information about attendance and adherence to the intervention. Every third month, information about symptoms of exacerbations were gathered as well. Additionally, questions on the impact of COPD using the CAT, and disease-specific quality of life, using the CRQ were collected every third month via self-administered questionnaires.

Intervention Adherence, Modifications and Discontinuation

In phase 1, attendance was recorded by the instructor at each centre. Missing sessions without notice prompted a follow-up call. If needed due to missed sessions, the intervention period may be extended by up to two weeks to reach a minimum attendance rate of 75% or 22 sessions, would a participant consent. Adherence to prescribed exercise training in terms of duration, intensity, and RPM were tracked by the instructors and via the Kinomap training app.

In phase 2, participants chose their preferred training environment (home, outpatient, or mixed) to support adherence. Those training at home or in a mixed setting received an initial home visit to deliver equipment, instructions on exercises, including a booklet related to the bike and the training application. Instructors are available to provide support during office hours. Adherence were monitored via the training app, providing data on actual training dose undertaken and not only attendance, addressing a common limitation in similar

maintenance programs[372-375]. Objective data from the application, participant reported ratings, and follow-up calls guided exercise load adjustments. The duration of Phase 2 will not be extended to compensate for missed sessions.

Assessments and Outcomes in Paper I-III

Table 4 provides an overview of the assessments and outcomes included in this thesis. While covering every procedure in detail would be enough to overwhelm even the most dedicated reader of a doctoral thesis, the following section focuses on some of the key assessments and outcomes most central to the papers and this thesis. Yet, the full COPD-HIIT project expands beyond this thesis including additional outcomes in the RCT such as brain magnetic resonance imaging, positron emission tomography, muscle-biopsy related outcomes and heart rate variability, amongst others. Those interested can find further details in Paper III.

Pulmonary Functions Tests

Pulmonary function testing was conducted at baseline to confirm the COPD diagnosis, assess eligibility and characterize participants. Testing was done with each test site's standard routine equipment (Vyntus or Masterscreen; Vyaire Medical, Mettawa, USA). Pulmonary function was assessed using spirometry[376], body plethysmography[377] and single-breath diffusion capacity for carbon monoxide[378] following American Thoracic Society/European Respiratory Society guidelines. In the RCT, spirometry is performed at 3- and 24-month follow-ups for up-to-date pulmonary function data during cycling tests.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed as the maximum oxygen uptake (VO_2peak, mL $O_2 \cdot kg^{-1}$ min^{-1}) during a standardized ramp-protocol CPET[298] on a RPM-independent cycle ergometer using electro-magnetic braking (Lode Corival CPET, Lode, Groningen, The Netherlands). The maximum work rate achieved during the test is defined as the MAP, used as a secondary outcome and to prescribe exercise intensities in the RCT. Within this thesis, the MAP is used as an outcome from the CPET.

In the RCT, VO_2peak is selected as a primary outcome as it is clinically relevant, an adaptation in cardiorespiratory fitness following an exercise intervention is a key objective in international guidelines[137]. A CPET provides an assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle system, provides quantification of the level of impairment, and measures the effects of an intervention[137,298].

Table 4. Overview of the assessments and outcomes in Paper I-III

	Paper I	Paper II	Paper III
Baseline assessments			
Spirometry	X	X	X
Whole-body plethysmography	X	X	X
Diffusion capacity for carbon monoxide	X	X	X
Physical activity	X	X	X
COPD assessment test	X	X	X
Modified Medical Research Council dyspnea scale	X	X	X
Montreal Cognitive Assessment			X
Self-Mini Nutritional Assessment			X
Outcomes			
Cardiorespiratory fitness[1]	X	X	**X**
Cognitive function			**X**
Quadriceps power			**X**
Borg cycle strength test		X	X
Exercise intensity during exercise	**X**		X
Exercise modality preference	X		
Constant workload test			X
Quadriceps strength			X
Quadriceps endurance			X
Five-time sit-to-stand			X
Stair-climb power test			X
Blood samples[2]	**X**		X
Muscle biopsy			X
Brain MRI			X
Positron emission tomography			X
Heart rate variability			X
Chronic respiratory disease questionnaire			X
Health-related quality of life: EQ-5D-5L			X
Hospital anxiety and depression scale			X
Body composition[3]	X	X	X
Feasibility[4]	X	**X**	X
Safety (adverse events, serious adverse events)	X	X	X
Exacerbations, hospitalizations, mortality			X

Primary outcomes are indicated by bold text. [1]Medical assessment and characterizing assessment in Paper I. [2] Brain-derived neurotrophic factor being a primary outcome in Paper I. [3]Only baseline assessment for Paper I-II. [4]Feasibility of the modified Borg cycle strength test being a primary outcome in Paper II. See text for further information on measures of feasibility. MRI: magnetic resonance imaging.

In brief, the CPET started with a three-minute resting phase prior to a three-minute warm-up phase with a minimal load (0-10 W). Next, the ramp-phase starts at 10-20 W with a continuous increase of 5 to 20 W per minute until exhaustion, followed by a three-minute unloaded recovery phase.

Instruments

During cycle test assessments, fractions of inspired and expired gas (O_2 and CO_2), respiratory rate and tidal volume were measured using indirect calorimetry with breath-by-breath data collection. For this, the Metamax-3B (Cortex BioPhysik GmbH, Leipzig, Germany[379]) was used in Paper I and II (mBCST), and the Vyntus CPX[380] (Vyaire Medical) was used in the RCT, as well as the CPET in Paper II.

During CPET, except for the interim assessment in the RCT, participants were equipped with standard 12-lead electrocardiography for medical monitoring (Cardiolex EC Sense, Cardiolex Medical, Solna, Sweden; Vyntus ECG). Blood pressure was measured with a manual (AB Henry Eriksson, Bandhagen, Sweden) or automatic sphygmomanometer (Tango M2, Suntech Medical, Morrisville, USA), heart rate was measured with electrocardiography or chest strap (Polar H9 or H10, Polar Electro, Kempele, Finland) and oxygen saturation with pulse oximetry on forehead or earlobe (Vyntus SpO_2) or fingertip (Nonin 3150, Nonin Medical, Plymouth, MN, USA). Additional paper-specific details are found in the papers and their supplementary materials.

Cognitive Function

Global Cognitive Function

Global cognitive function was assessed as the z-score determined by the performance of five tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB), and the trail making test (TMT) part A and B.

A global cognitive score constitutes the primary outcome, as recommended by recent meta-analysis on the effects of exercise on cognition[124]. In addition to the global cognitive score, each separate test score is assessed as a secondary outcome. In the thesis, you will find baseline data on some of these separate test's scores.

Cognitive function is selected as a primary outcome as the research on cognitive function and brain health in people with COPD is scarce[128], and the pathogenesis of cognitive impairment is not fully understood. The test battery is fully described in Paper III[381].

Mild Cognitive Impairment

Baseline cognitive function and prevalence of mild cognitive impairment were assessed using the Montreal Cognitive Assessment (MoCA, 0-30 points), frequently used as a screening tool for cognitive function and mild cognitive

impairment in various populations[382-384]. The MoCA takes approximately 10 minutes to perform and evaluates multiple domains of cognition[384].

The original recommended cut-off score to distinguish healthy individuals from those with mild cognitive impairment is ≥26[384], yet lower cut-offs have been suggested for higher diagnostic accuracy. Herein, the number of participants scoring ≤23 and ≤21 points is reported, which corresponds to approximately 1.5 and 2.0 standard deviations below the normative mean for Swedish adults aged 70-80 years with secondary school education[385].

Quadriceps Power, Strength and Endurance

Quadriceps power was assessed as peak power (W) during a single repetition seated single leg extension on a computerized dynamometer using isotonic mode against a fixed resistance of 0.5 Nm (Biodex System 3 or 4, Biodex Medical Systems Inc., Shirley, NY, USA), further detailed in Paper III. Within this thesis, the secondary outcome peak velocity (°/s) from the same assessment is presented.

Quadriceps power is chosen as a primary outcome because it is associated to functional capacity and physical activity levels[178,386]. After the quadriceps power assessment, quadriceps strength was determined as the one-repetition maximum defined as the maximum torque (Nm) able to be lifted through the full range of motion during seated leg extension in isotonic mode. Then, quadriceps endurance was assessed as the maximal number of repetitions at an intensity of 45% of one-repetition maximum[381,387].

Modified Borg Cycle Strength Test

This thesis evaluated the feasibility and acute physiological response of the mBCST (Paper II). The test was also used to assess anaerobic exercise capacity in Paper III and to prescribe supramaximal HIIT in Paper I and the RCT.

The mBCST[311], fully described in Paper II[388] and III[381], is a submaximal cycle ergometer test used to estimate maximum mean power output for 30 seconds without an all-out effort. The mBCST consists of 30-second bouts with increasing intensity, interspersed with 30-seconds passive recovery between each bout. With an externally paced target pedalling cadence of 80-90 RPM, participants cycled until they scored an RPE of ≥17, or until they could not keep the target cadence.

To tailor the test to our population, we modified the initial load (15-50 W) and the rate of increase (15-50 W) from the original BCST[311]. The initial load and increment were determined on the participant's previously determined MAP,

with the goal of reaching an RPE of 17 after 4-6 stages. For MPO6 calculation, incomplete 30-second stages lasting ≥10 seconds were considered by adding a proportional load based on the completed duration (e.g., completing 15 seconds of a 50-W increment would add 25 W to the last fully completed stage). The MPO6 was then estimated by multiplying power during the last completed stage by 1.75 as previously described[309].

Anaerobic Exercise Capacity

Anaerobic exercise capacity was assessed as external intensity expressed as W and % of MAP, at the final stage of the mBCST. From this, the estimated MPO6 was calculated. The mBCST was performed on a Monark LC6 (Paper II) or Lode Corival CPET (Paper III).

Feasibility

Feasibility of the mBCST was assessed by participants reaching a supramaximal intensity (> 100% MAP) and using Robertson et al.'s[389] test quality framework, including the following feasibility criteria: *interpretability, familiarity required, duration, scoring complexity, completion complexity* and *cost*. Also, adverse events were reported as a safety criterion. How these criteria are defined is further detailed in the results section Table 8.

Blood Sampling and Analysis

Non-fasted venous blood samples were collected in conjunction with exercise in Paper I to assess the acute response of certain exerkines to the different exercise modalities. These were collected at rest; directly after the main work-phase (10 min supramaximal HIIT or 20 min MICT); and 30 minutes after exercise. In addition, an iso-time sample was collected after 10 minutes of MICT. In the RCT, fasted venous blood samples were collected at baseline, 3-months and 24-months.

Venous blood was collected into dipotassium ethylenediaminetetraacetic acid, serum separator, lithium-heparin and sodium-citrate tubes and kept at room temperature for 15-30 minutes before centrifugation for 15 minutes at 1500 × g. Aliquots of plasma, serum, buffy coat, erythrocytes or whole blood (the latter separated prior centrifugation) were put in -80°C immediately or analysed within an analyte-appropriate timeframe.

In Paper I, haemoglobin (Hb 201+, HemoCue, Ängelholm, Sweden) and haematocrit (Hematocrit 200, Andreas Hettich GmbH, Tuttligen, Germany) were

determined in whole blood for correction of exercise-induced changes in plasma volume following the method by Dill and Costill[390].

Circulating levels of exerkines and inflammatory markers were measured in plasma and serum samples using immunoassay techniques. Analytes were assessed using single- or multiplex bead-based immunoassays (Luminex methodology, Luminex Corp. Austin, TX, USA) or enzyme-linked immunosorbent assays, using commercially available kits with a Bio-Rad Bioplex 200 (Bio-rad Laboratories Inc., CA, USA [Luminex]) or Synergy HT plate reader (Agilent Technologies Inc. CA, USA). A technician blinded for group allocation performed all analyses in duplicate. Allocation of participant's samples to 96-plates was randomised, though all within-participant samples were put on the sample plate.

Brain-Derived Neurotrophic Factor

In Paper I, change-from-baseline in plasma BDNF ($pg \cdot mL^{-1}$) during exercise was a primary outcome. It was also expressed as relative change (%) and normalized to duration at target intensity. Brain-derived neurotrophic factor is an established exerkine believed to in part mediate some potential benefits of exercise on brain function, being involved in neuronal differentiation, synapse function and cognitive development[330,331,391]. Specifically, we were primarily interested in plasma BDNF, as it is likely of greater physiological importance than serum BDNF. Serum levels capture both BDNF stored in platelets and the free, unbound fraction. Free, unbound plasma BDNF, however, is thought to cross the blood-brain barrier bidirectionally[392,393].

Neurotrophic Factors, Exerkines and Markers of Inflammation

In Paper I, additional neurotrophic factors and exerkines including lactate, irisin, cathepsin B, and interleukins were assessed to examine the acute effects of the different exercise modalities. Inflammatory markers such as tumour necrosis factor-alpha and interleukins were also evaluated. In the RCT, change from baseline in resting levels of various neurotrophic factors and systemic inflammation markers, including high-sensitivity C-reactive protein, fibrinogen, and eosinophils are investigated.

Physiological Responses and Cardiorespiratory Demand

The acute physiological response to exercise (Paper I) and exercise tests (Paper II-III) was measured by means of indirect calorimetry, monitoring of heart rate (beats per minute), blood pressure (mmHg), peripheral blood oxygen saturation (%) and subjective ratings of dyspnea and leg fatigue (0-10 points) and RPE (6-

20 points). These variables were analysed as means during exercise or tests, and at end of exercise.

In addition to rate of oxygen consumption (VO_2, $mL \cdot kg^{-1} \cdot min^{-1}$), outcomes providing information on the ventilatory demand including minute ventilation (V_E, $L \cdot min^{-1}$), V_E to maximal voluntary ventilation (V_E/MVV), respiratory rate ($breaths \cdot min^{-1}$) were of interest. Related variables, such as respiratory exchange ratio and ventilatory efficiency (V_E/VO_2; V_E/VCO_2) were also analysed. In addition, inspiratory capacity manoeuvres were performed to measure dynamic hyperinflation, but only data from the mBCST was of enough quality for further analysis. For CPET and mBCST, ventilatory limitation was assessed based on V_E/MVV ≥ 85% and having at least one other positive ventilatory limitation criteria: drop in SpO_2 ≥ 5% or Borg Dyspnea > upper limit of normal, or V_E/VCO_2 nadir > 34.

Patient Reported Outcomes

The mMRC[81] and CAT[80] questionnaires are used in Paper I-III for characterising the symptom burden in individuals with COPD. In the RCT, the CAT and CRQ are used to investigate change-from-baseline impact of COPD and disease-specific quality of life. Further, health-related quality of life is assessed with the EQ-5D-5L[394], a valid and responsive tool in COPD[395]. Symptoms of depression and anxiety were assessed using the Hospital Anxiety and Depression Scale[396].

Feasibility of Interventions

In Paper I, feasibility was determined by exercise fidelity defined as exercise sessions needing modifications; adherence to prescribed cadence, intensity, and duration; session completion; symptoms including RPE, dyspnea, and leg fatigue.

In the RCT, feasibility of the interventions is measured as attendance rate (%), adherence to exercise duration and intensity, exercise fidelity i.e. incidence of exercise sessions requiring modifications, occurrence of adverse events and participant satisfaction based on a questionnaire previously used in COPD[397]. Reasons for dropouts and non-adherence will be obtained. In addition, individual interviews will be used to explore participants' experiences after both phase 1 and phase 2.

Assignment of Interventions, Blinding and Bias

In Paper I, eligible participants were randomised in a 1:1 ratio to one of the sequences for the experimental conditions (starting with either supramaximal HIIT or MICT). The randomisation was stratified by sex and computer-generated using a dedicated tool (randomization.com). Due to the nature of the

experiments, blinding of assessors was not feasible, and allocation concealment was therefore not possible. To ensure an unbiased comparison between supramaximal HIIT at 60% of MPO6 and MICT, supramaximal HIIT at 80% of MPO6 was excluded from the randomisation sequence. In Paper II, randomisation of test order (mBCST and CPET) was not possible, as CPET served as an initial medical assessment and eligibility screening.

In the RCT participants were randomised in a 1:1 ratio to the intervention or control arm using a computer-generated blocked randomisation schedule (Sealed Envelope Ltd., London, UK) with variable block sizes of two or four, stratified by sex and centre. The usual care arm in phase 2 is not included in the randomisation. A delegated person independent from recruitment, assessments, and training generated the allocation sequence. Group allocation occured after baseline assessments and eligibility confirmation. The allocation sequence is stored in an opaque, tamper-proof, sealed, and stapled envelope that is concealed until the outcome assessment is completed. Outcome assessors and data analysts were blinded for group allocations. Thus, participants were requested not to disclose any aspect of their intervention to the blinded outcome assessor at any stage during the post-intervention assessment. Would unblinding of an assessor occur, there was a change of assessors. Given the nature of the interventions, neither participants nor instructors of the training sessions can be blinded during the intervention. Participants were informed of the study's general purpose but not its hypotheses.

Systematic Review of Aerobic Training Trials in COPD

Paper IV is a systematic review that assessed the quality of reporting and application of exercise training principles in RCTs including aerobic training in people with COPD. The published study protocol is available in the Appendix[363]. A summary of the methodology for Paper IV is provided herein. Notably, the protocol for paper IV includes two objectives; however, only the first objective-evaluation of reporting quality and application of training principles, is relevant to this thesis. Consequently, the second objective, related to efficacy of the interventions, that will risk of bias assessment, assessment of the certainty of the evidence and meta-analyses, is not described herein.

The paper is reported following the Preferred reporting items for systematic reviews and meta-analyses statement (PRISMA)[398] and the review was prospectively registered in the International prospective register of systematic reviews (PROSPERO: CRD42021247343).

Study Eligibility

Studies including individuals with a diagnosis of COPD being ≥90% of the participants were considered. There were no eligibility criteria for sex, age, body composition, comorbidities or ethnicity. Any type of training intervention independent of duration or number of sessions that was aerobically demanding for the lower limbs was eligible. This included cycling and walking, water-based movements and aerobics, but excluded Tai Chi and Qigong. There were no eligibility criteria for comparators. If there was one group with an eligible aerobic training intervention, it was included independent of type of, or the existence of, a control group. Further, studies were excluded if they did not measure any outcome related to aerobic fitness. Only RCTs written in English were included. Since our unit of analysis was the trial rather than individual publications, only the primary publication was included when multiple reports of the same RCT were identified.

Search Methods for Identification of Studies

Two systematic searches were performed. Studies published from the 1st of January 2007 until 21st of February 2025, the date for the second search, were included. The cutoff for 2007 was chosen because that would include RCTs published after the first joint statement on pulmonary rehabilitation by American Thoracic Society and the European Respiratory Society in 2006[399].

Studies were identified using electronic searches in the databases MEDLINE, Embase, CINAHL, Cochrane Central Register of Controlled Trials, and PEDro. The search strategy was developed by the authors together with an experienced librarian. Comprehensive searches were constructed of both index terming (medical subject headings term), free-text terms and synonyms.

Selection and Data Collection Process

The selection process of potentially relevant studies occurred in two steps: screening of title and abstracts, and full texts. Title and abstracts were screened by one (first search) or two authors (second search), while full texts were reviewed by two authors independently. A third reviewer assessed agreement and resolved disagreements on eligibility using a majority rule.

Data extraction was performed by authors in duplicate independently using a standardized and pilot-tested data extraction form in Microsoft Excel. To assess the quality of reporting and application on exercise training principles, extensive data extraction was conducted, encompassing up to 77 variables (see appendix A or Paper IV). These included study details such as study design; eligibility criteria; participant characteristics including pulmonary function, body composition; aerobic training intervention details such as exercise type, supervision, and

setting; training principles: progression, overload, specificity, individuality, initial values, periodization and reversibility; and training variables such as duration, frequency, and intensity.

Each variable was independently rated by two reviewers as "1" (reported), "0" (not reported), "not clear", "insufficient" or "not applicable".

Analyses and Statistical Methods

Software

Statistical analyses for Paper I, IV and findings specifically presented in this thesis were performed using JMP Pro version 17 or 18 (JMP Statistical Discovery LLC, Cary, NC, USA), while analyses for Paper II were performed using the Statistical Package for the Social Sciences version 30 (IBM, Armonk, NY, USA). Microsoft Excel has been used for data curation and data conditioning (Paper I and II) partly by using Visual Basic Application macros. Standard curve fitting for blood analyses (Paper I) was performed using manufacturer guidelines using GraphPad Prism 10.0. Records identified in the literature searches in Paper IV were uploaded to Rayyan (Rayyan Systems Inc., Cambridge, MA, USA), a web-tool for collaborative systematic reviews that facilitates the management of records, including deduplication and abstract screening[400].

Statistical Analysis

This thesis employs null hypothesis significance testing as the primary statistical approach, drawing on the frameworks established by Fisher[401] and by Neyman and Pearson[402].

Continuous variables were reported as mean (SD) for normally distributed data, as determined by normal Q-Q plots and histograms. Non-normally distributed variables were presented as median (quartile 1 [Q1] – quartile 3 [Q3]). Ordinal variables were presented as median (Q1 – Q3) or as *n* (%), and categorical variables as *n* (%).

Pairwise Comparisons in Paper I-III and Within the Thesis

Pairwise group comparisons for continuous, normally distributed data were conducted using independent t-tests or Welch's t-tests, depending on variance homogeneity as assessed by Levene's test. For non-normally distributed data, the Mann–Whitney U test was used. Categorical variables were compared using the Chi-square test for homogeneity or Fisher's exact test. Analysis of covariance was applied to assess between-group differences in cognitive function (MoCA score), with adjustment for years of education.

Group comparisons were performed at baseline to evaluate cohort differences and assess the success of matching, as well as at different time points to assess differences between individuals with COPD and healthy controls, including analyses of change scores. Within-group comparisons (Paper II) were carried out using paired t-tests or Wilcoxon signed-rank tests, based on data distribution. In Paper II, within- and between-group differences are reported with mean or median differences with 95% confidence intervals.

Linear Mixed Models in Paper I

In Paper I, linear mixed-effects models were used to analyse differences in external exercise intensity, cardiorespiratory outcomes, symptom ratings, and exerkine concentrations. To assess within-group changes over time, separate models were fitted for each group (COPD and healthy controls), with time as a fixed effect and participant as a random effect. Models were estimated using restricted maximum likelihood approach. To meet model assumptions, including normality of residuals and homoscedasticity, log transformations were applied where appropriate to improve model fit. Following significant main effects, post hoc comparisons of estimated marginal means were performed using Tukey's test with adjustments for multiple comparisons.

Correlation Analysis in Paper I-II

Non-predefined exploratory correlation analyses using Pearson's and Spearman's correlation coefficients were used to measure the strength and direction of associations between; 1) baseline characteristics to selected outcomes, such as airflow obstruction (FEV_1%pred) and symptoms (CAT and mMRC) to change in plasma BDNF during exercise (Paper I) and 2) relative mBCST workload in individuals with COPD (Paper II). The strength of the correlation coefficients was categorized as, for Pearson's r: low (0–0.25), moderate (> 0.25–0.50), strong (> 0.50–0.75) and very strong (> 0.75); For Spearman's Rho: trivial (<0.1), low (0.1–0.3), moderate (0.3–0.5), strong (0.5–0.7), very strong (0.7-0.9) and extremely strong (>0.9)[403].

Statistical Considerations and Methods in Paper III

A preliminary plan for statistical methods can be found in Paper III as summarised herein. Yet, for the RCT, a detailed statistical analysis plan with further details will be published before the study is completed. A statistical analysis plan enhances transparency and reproducibility, and might be updated in response to new methods, emerging evidence and challenges encountered during a trial that spans over several years[404,405]. It will include details on the method to handle family-wise error rate for the multiple primary outcomes.

Analyses will, as recommended[351], employ the intention-to-treat principle when applicable, meaning that all participants randomised, whether they receive their allocated intervention or withdrew from the trial, will be included in the analysis. In addition, a per-protocol analysis (defined as ≥ 75% attendance rate as well as no exacerbations during the last 2 weeks prior to follow-up assessment), and a complete case analysis (including participants with complete outcome measurements independent of attendance rate) will be reported. Missing data will be imputed using multiple imputations by chained equations.

The primary analysis approach for outcomes with continuous data in the final dataset will be analysis of covariance. Treatment effects will be estimated using post-intervention values as the dependent variable and baseline values, age, sex, trial centre, and VO_2peak as covariates. Age, sex and VO_2peak are used as covariates given that there are deemed to have prognostic value for the primary outcomes[406]. Also, the variables used for stratifications (trial centre and age) are also recommended to use as covariates[337,407]. Mean change-from-baseline (Δ) with 95% confidence intervals and effect size will be reported.

Assumptions of linearity, normality of residuals, and homogenous variance will be checked using residual plots, normal quantile plots, and histograms. Violations of assumptions will be dealt with by transformations of the dependent variable or non-linear modelling of the independent variables. Outliers will not be removed unless there is a methodological reason for it.

Mortality, hospitalizations, and exacerbations will be summarized with descriptive statistics and analysed using Kaplan–Meier curves and Cox proportional hazard models. In addition, longitudinal mediation analyses will be performed on the entire magnetic resonance imaging and positron emission tomography sample between changes in VO_2peak and neurodegenerative measures, such as cognitive function and hippocampal volume and inflammation levels between baseline and 24 months.

Statistics and Synthesis in Paper IV

Given the descriptive objective of Paper IV, no meta-analysis was performed. The sum scores of applied training principles and number of items reported concerning participant characteristics, intervention characteristics and training variables including the FITT-components, were calculated for each study and presented using descriptive statistics. The number and percentage of studies complying with all training principles, FITT-components, and all relevant training variables were calculated.

Using data collected, included studies were also appraised using the CERT checklist. Studies were provided with 0-19 points on CERT-compliance. The number and percentage of studies complying for each CERT item was calculated, and an average CERT compliance (%) adjusted for non-applicable items were calculated. In addition to descriptive statistics a narrative synthesis was presented.

Sample Size

A priori sample size calculations were performed with a two-sided alpha level of 0.05 and beta of 0.20, corresponding to a power of 80%.

Sample Size in Paper I and II

For this trial, a sample size was calculated to detect a within-group mean difference in external exercise intensity between supramaximal HIIT and MICT of 50 ± 30 W, considered the smallest difference of interest. This revealed a minimum sample size of six. For plasma BDNF, a sample size of 16 was based on meta-analyses[408,409] examining the acute response of exercise on BDNF, with effect sizes around 1.0, revealing a sample size of 10. Considering the uncertainty and high variability in these measures, a sample size of 16, able to detect an effect size of 0.80, was determined. This sample size was also judged reasonable to investigate our feasibility aims in Paper I as well as sufficient for Paper II[410].

Paper III

Sample size calculations were made to ensure a sufficient sample size to detect between-group differences in change in the three primary outcomes.

For cognitive function, a sample size of 60 (n = 30 per arm) is needed to detect a clinically relevant mean difference of 0.27 (SD: 0.40) in a global cognition z-scored measured using a cognitive test battery[127]. A decrease in global cognition of this magnitude is associated with increased all-cause and cardiovascular mortality[411]. This sample size is sufficient to detect a mean difference of 3.5 (4.6) mL $O_2 \cdot kg^{-1}$ min^{-1} measured during a CPET (n = 26 per group). This increase is associated with a 15% decrease in risk for cardiovascular disease[129]. Further, a sample size of 30 per arm is also sufficient to detect a difference of 19.4% (26.8%) in quadriceps power[412]. While there is no minimal clinically relevant difference in this outcome, a difference of 19.4% is the minimal detectable change. To account for an assumed drop-out rate of approximately 15% at three months follow-up, a total of 70 participants (35 per arm) are needed for these outcomes.

In phase 2, the sample size is increased to 46 participants in each arm, including usual care, to account for an additional 30% drop-out rate at 24-month follow-up. However, an interim blinded sample size re-estimation will be performed after half of the participants have completed 24-month follow-up, using recommended procedures for non-comparative data preserving allocation concealment[413].

The multicentre trial utilises individual randomisation at each centre. Unlike cluster randomised designs, which typically reduce statistical power due to intra-cluster correlation, this approach enhances statistical power by avoiding such correlation[414,415]. Additionally, incorporating predictive covariates is also associated with a gain in statistical power[406,416,417]. Nonetheless, the potential gains in statistical power have not been considered in the sample size calculations.

Ethical Considerations

As with all clinical trials, research on exercise training in older individuals with and without COPD necessitates ethical considerations. The trials have been approved by the Swedish Ethical Review Authority (Table 1) and the Comité Medische Ethiek at Ziekenhuis Oost-Limburg (Belgium, Paper III). The studies are conducted according to the World Medical Association's Declaration of Helsinki's ethical principles for conducting research with human subjects[418]. All participants received verbal and written information about the trials' aims and methods, prior to study participation. Written informed consent was obtained from all participants before study entry. Participants were compensated for costs related to study participation and were given economic compensation according to the respective Universities guidelines.

Participants in the trials are covered by insurance via the Swedish Legal, Financial and Administrative Services Agency (Kammarkollegiet) and, for visits at the Umeå University Hospital, a patient injury insurance. Participants in Belgium are covered by an insurance for clinical experiments (Allianz).

Strenuous exercise entails certain risks, temporary fatigue and discomfort. To mitigate these, several measures were implemented throughout the studies. A medically responsible physician screened the medical records of potentially eligible participants. The first assessment was a CPET with ECG, overseen by a medical doctor. During assessments with high cardiorespiratory stress, participants were monitored with indirect calorimetry, blood pressure and oxygen saturation by medically trained personnel, with defibrillators close by. Although supramaximal HIIT is a novel procedure not used in COPD, it is proven

to be feasible and safe for older non-exercising adults[309,310]. Other types of HIIT have been previously used, and proven to be safe in people with COPD[235].

Some procedures, such as blood sampling is invasive. This is commonly used in exercise training trials and are performed by experienced registered personnel with adequate medical education.

If cases of incidental findings of potential clinical relevance, the participant was referred to the appropriate specialized care. All personal data is processed in accordance with the EU General Data Protection Regulation (GDPR) and Umeå University regulations. Paper records are stored in locked file cabinets, and electronic data is stored on local servers utilizing two-factor authentication that are backed up daily.

In summary, COPD is one of our most common and most serious chronic diseases. The potential benefits, knowledge gained and clinical insights from the project are considered to outweigh the associated risks.

Results

This results section is divided into three parts. The first part presents results from Paper I and II. The second part includes preliminary data from the ongoing RCT (Paper III). Lastly, the third part presents results from the systematic review (Paper IV).

Participants in Paper I and Paper II

Figure 8 depicts the flow of participants from screening to analysis.

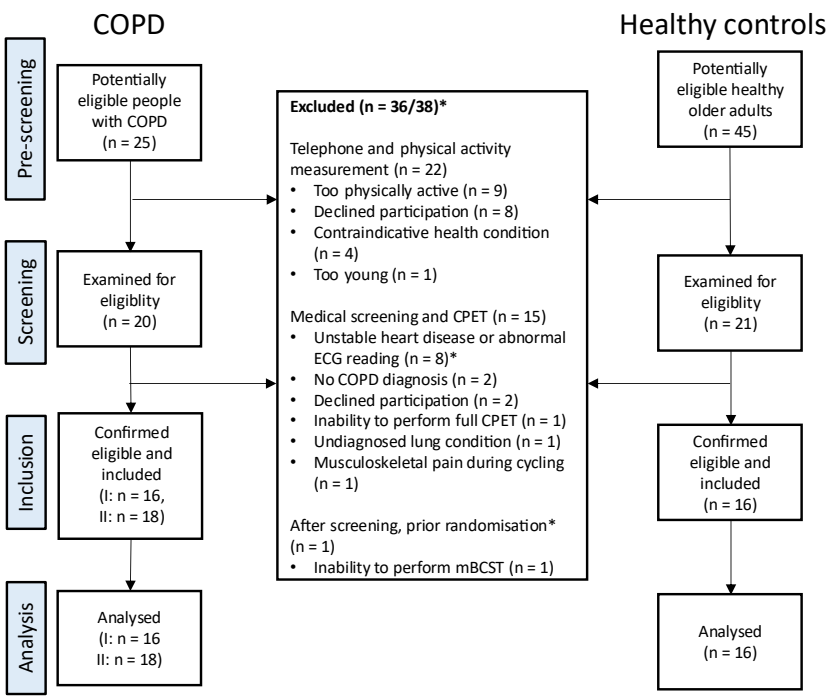

Figure 8. Participant flow chart in Paper I and Paper II. *Two individuals with COPD were eligible for Paper II but not Paper I based on pre-defined criteria. One participant was excluded from exercise training due to incomplete performance on the mBCST. Another participant completed the mBCST but was excluded from exercise training following abnormal ECG findings during CPET. COPD: chronic obstructive pulmonary disease; ECG: electrocardiogram; mBCST: modified Borg cycle strength test.

Baseline characteristics of the included participants are presented in Table 5. Individuals with COPD and healthy controls were well matched for age and sex and had comparable body composition. Although physical activity levels were not statistically different between groups, the difference in average daily step count is considered clinically meaningful[419]. Participants with COPD had mild to severe airflow limitations, a higher number of prescribed medications, and more comorbidities compared to the matched healthy controls.

Table 5. Baseline characteristics of included participants in Paper I and II

	COPD (n=16)	COPD (n=18)	HC (n=16)	P[a]
	Paper I	**Paper II**	**Paper I & II**	
Anthropometrics and demographics				
Age, years	74.8 (6.1)	74.8 (5.9)	74.2 (4.5)	0.746
Female sex, n (%)	8 (50)	10 (56)	8 (50)	
Body mass index, $kg \cdot m^{-2}$	24.9 (3.8)	24.8 (3.6)	25.2 (2.1)	0.782
Fat-free mass index, $kg \cdot m^{-2}$	17.4 (2.6)	17.2 (2.5)	17.9 (1.6)	0.511
Cardiorespiratory fitness and physical activity				
MAP, W	119 (37)	111 (42)	164 (38)	0.002
MAP, % predicted[b]	85 (20)	81 (23)	116 (22)	<0.001
VO_2peak, mL $O_2 \cdot kg \cdot min^{-1}$	21.8 (5.2)	21.1 (5.1)	25.4 (3.8)	0.003
VO_2peak %pred[c]	95 (18)	93 (18)	113 (19)	0.012
mBCST Wpeak, W	175 (63)	175 (63)	256 (55)	<0.001
Steps/day, n[d]	6727 (3212)	6727 (3212)	8450 (2520)	0.069
Clinical characteristics				
CAT score, 0–40	14.2 (5.7)	14.7 (6.4)	-	-
mMRC score, 0–4, n	2/7/5/1/1	2/7/6/2/1	6/10/0/0/0	0.022
GOLD stage, I/II/III/IV, n	5/10/1/0	6/10/2/0	-	-
GOLD stage A/B/E, n	4/12/0	4/12/2	-	-
Exacerbations and hospitalizations last 12 months, n, 0/1/≥2				
Exacerbations	15/1/0	15/2/1	-	-
Hospitalizations	13/1/2	14/2/2	16/0/0	0.226
Emergency visits	10/4/2	10/5/3	13/2/1	0.528
Smoking				
Smoking status, n (%)				0.006
Current	1 (6)	1 (6)	0 (0)	
Ex-smoker	14 (88)	16 (89)	7 (44)	
Never-smoker	1 (6)	1 (6)	9 (56)	
Pack years	24.2 (16.6)	26.0 (16.9)	5.4 (9.8)	<0.001
Medications				
Non-inhaler medications, n	4.4 (2.7)	4.4 (2.5)	1.6 (1.5)	0.002
Inhaled medications, n	2 (1–3)	2 (1-3)	0 (0–0)	<0.001
ICS use, n (%)	6 (38)	8 (44)	1 (6)	
LABA + LAMA, n (%)	12 (75)	14 (78)	0 (0)	
Triple therapy, n (%)	5 (31)	6 (33)	0 (0)	
Cholesterol-lowering, n (%)	5 (31)	6 (33)	5 (31)	1.000
Betablockers, n (%)	7 (44)	7 (39)	2 (13)	0.113

Table 5. Baseline characteristics of included participants in Paper I and II

	COPD (n=16)	COPD (n=18)	HC (n=16)	P[a]
Other heart medication, n (%)	12 (75)	14 (78)	8 (50)	0.273
Anti-thrombotic, n (%)	6 (38)	7 (39)	2 (13)	0.220
Spirometry, diffusion capacity and lung volumes				
FEV_1, L	1.8 (0.3)	1.7 (0.4)	2.8 (0.5)	<0.001
FEV_1, % predicted	73 (13)	72 (16)	106 (13)	<0.001
FVC, % predicted	98 (16)	98 (16)	108 (12)	0.044
FEV_1/FVC	0.56 (0.08)	0.54 (0.09)	0.73 (0.04)	<0.001
Inspiratory capacity, L	2.5 (0.5)	2.4 (0.6)	2.8 (0.5)	0.096
MVV, $L \cdot min^{-1}$	69.6 (14.1)	65.6 (17.6)	92.9 (21.4)	0.001
D_{LCO}, $mmol \cdot min^{-1} \cdot kPa^{-1}$	5.2 (1.5)	5.0 (1.5)	6.8 (1.3)	0.004
D_{LCO}, % predicted	72 (16)	71 (15)	90 (16)	0.003
TLC, % predicted	97 (11)	99 (13)	97 (7)	0.922
FRC, % predicted	105 (27)	109 (28)	93 (12)	0.103
FRC/TLC, %	65 (6)	66 (7)	58 (7)	0.006
RV, % predicted	98 (26)	102 (29)	84 (14)	0.078
RV/TLC, %	43 (4)	44 (7)	37 (5)	0.002
Blood markers[e]				
Plasma BDNF, $pg \cdot mL^{-1}$	3638 (1762)		3246 (1745)	0.786
Cathepsin B, $ng \cdot mL^{-1}$[f]	157 (79)		181 (94)	0.476
Interleukin-6, $pg \cdot mL^{-1}$	1.05 (0.77-1.24)		0.60 (0.46-1.08)	0.021
TNF-α, $pg \cdot mL^{-1}$	8.52 (2.26)		8.29 (3.31)	0.819

Data is presented as mean (SD) or median (Q1-Q3) if not otherwise stated. [a] P-values refer to comparisons between groups in Paper I. Notes: [b] Using Brudin 2014 equation. [c]: Using Gläser 2013 equation. [d] Same sample size (n=16) for step count assessment. [e] Mean of three resting samples on different days. [f] n=14 for both groups. COPD: chronic obstructive pulmonary disease; HC: healthy controls; FFMI: fat-free mass index; MAP: Max aerobic power; mBCST: modified Borg cycle strength test; CAT: COPD assessment test; mMRC: modified medical research council; GOLD: global initiative for chronic obstructive lung disease; ICS: inhaled corticosteroid; LAMA: Long-acting muscarinic antagonist; LABA: long-acting beta-agonist; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MVV: maximum voluntary ventilation; TLC: total lung capacity; FRC: functional residual capacity; RV: residual volume; D_{LCO}: diffusion capacity of the lung for carbon monoxide; BDNF: brain-derived neurotrophic factor; TNF-α: tumour-necrosis factor alpha.

Feasibility of Supramaximal HIIT in COPD

Completion Rates and Preference

Supramaximal HIIT was feasible with a 100% completion rate in both individuals with COPD and healthy controls, without requiring modifications to intensity, cadence or duration. Five out of 16 individuals with COPD were unable to complete the 20 minutes of MICT, stopping due to voluntarily exhaustion after 5 to 15 minutes. In addition, a majority preferred supramaximal HIIT over MICT: 13 of 16 individuals with COPD ($\chi^2 = 6.7$, $P = 0.009$) and 14 of 16 healthy controls ($\chi^2 = 10.1$, $P = 0.002$).

Exercise Intensity

External exercise intensity was significantly higher during supramaximal HIIT compared with MICT in both groups (COPD: $F[2,30] = 102.9$, $P < 0.001$; healthy controls: $F[2,30] = 283.6$, $P < 0.001$; Figure 9).

In individuals with COPD, mean (SD) workloads were 184 ± 66 W in HIIT60 and 245 ± 88 W in HIIT80, compared with 71 ± 22 W during MICT, which represents a 2- to 3.5-fold increase. Healthy controls showed a similar pattern, exercising at 269 ± 58 W (HIIT60), 358 ± 77 W (HIIT80), and 98 ± 23 W (MICT). At HIIT80, COPD participants exercised at 204 ± 33% of MAP, while healthy controls reached 220 ± 23 %.

Across all three protocols, participants with COPD consistently exercised at lower intensities than healthy controls (all P < 0.01). Exploratory analyses revealed no significant correlations between FEV_1 % predicted (r[16] = 0.16, P = 0.567) or MAP % predicted (r[16] = 0.33, P = 0.218) and the increase in exercise intensity from MICT to supramaximal HIIT among COPD participants (Paper I, Figure 3b-c).

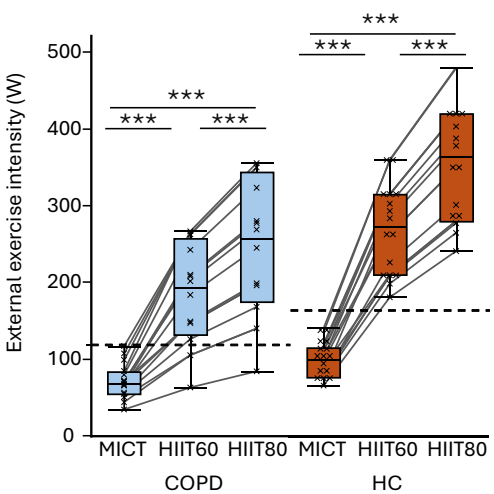

Figure 9. Boxplots of external exercise intensity (W) during each modality in COPD (left) and healthy controls (right). Supramaximal high-intensity interval training (HIIT60 and HIIT80) enabled a 2–3.5-fold increase in exercise intensity compared with moderate-intensity continuous training (MICT). Dashed line indicates the mean maximum aerobic power for each group. *** = significant difference between modalities, Tukey's post hoc comparison (P < 0.001). COPD: chronic obstructive pulmonary disease; HC: healthy controls.

Adverse Events and Safety

No serious adverse event occurred during supramaximal HIIT or MICT. One participant with COPD experienced moderate tachycardia during cool-down in a HIIT80 session. This participant, on inhaler treatment and dual antiarrhythmic therapy with known persistent atrial fibrillation, remained asymptomatic and had a stable blood pressure. Supramaximal HIIT had a comparable cardiopulmonary response as MICT, yet slightly lower blood pressure response (Table 6). Peripheral oxygen saturation was maintained during both supramaximal HIIT and MICT, with slightly higher levels during supramaximal HIIT than MICT, though not of clinical relevance.

Acute Responses to Supramaximal HIIT in COPD

Cardiorespiratory Demand and Symptoms

The ventilatory demand in supramaximal HIIT was reduced compared to MICT, as seen in the V_E, V_E/MVV ratio, and breathing frequency (Table 6). During supramaximal HIIT, individuals with COPD had a mean %VO_2peak of 68 ± 11% and 75 ± 11% (HIIT60 and HIIT80, respectively), reaching 77 ± 14% and 85 ± 13% at end-of-exercise (Paper I, Table S5). Regarding heart rate, they exercised at 72 ± 8% and 74 ± 7%, peaking at 77 ± 8% and 80 ± 7% of % peak heart rate, respectively. Similar values were seen in healthy controls. In both groups, MICT induced a significantly higher VO_2 and heart rate (Table 6).

Peripheral oxygen saturation maintained at slightly higher levels during supramaximal HIIT (94-95%) compared to MICT (93%), for individuals with COPD. Yet, the decrease in saturation during MICT was modest. In both groups, systolic blood pressure was higher during MICT compared supramaximal HIIT (Table 6).

Those with COPD had a lower VO_2 compared to healthy controls. In relation to VO_2peak and peak heart rate, the groups exercised at a similar relative intensity while the SpO_2 and blood pressure response were similar across all sessions. While the groups had similar levels of ventilation ($L \cdot min^{-1}$), those with COPD utilised a higher percentage of their MVV during all sessions (Table 6) and displayed a lower ventilatory efficiency as seen in the V_E/VO_2 and V_E/VCO_2 ratios.

Dyspnea, leg fatigue and RPE were generally lower in supramaximal HIIT compared to MICT when analysed as mean during session (Table 6) and at end of exercise (Table 7). Among individuals with COPD, clinically relevant reductions in dyspnea, leg fatigue and RPE were seen in HIIT60 compared to MICT (Table 7). Still, they experienced higher dyspnea and leg fatigue compared to healthy controls (Table 6-7).

Table 6. Cardiorespiratory variables, perceived exertion and symptoms during supramaximal HIIT and MICT

	HIIT60			HIIT80			MICT		
	COPD	**HC**	**P-group**	**COPD**	**HC**	**P-group**	**COPD**	**HC**	**P-group**
Cardiorespiratory parameters									
VO_2, mL $O_2 \cdot kg^{-1} \cdot min^{-1}$	14.5 (2.7)[#¶]	17.7 (2.2)[#¶]	**0.001**	16.1 (3.3)[#]	18.8 (3.2)[#]	**0.027**	18.6 (3.5)	21.8 (3.3)	**0.012**
VO_2, % peak	68 (11)[#¶]	70 (6)[#¶]	0.641	75 (11)[#]	74 (14)[#]	0.930	87 (11)	86 (10)	0.914
Heart rate, % peak	72 (8)[#]	71 (5)[#¶]	0.610	74 (7)[#]	77 (7)	0.163	80 (9)	85 (5)	0.054
RER, ratio	0.90 (0.02)[#]	0.91 (0.04)[¶]	0.443	0.92 (0.04)	0.94 (0.03)	0.154	0.93 (0.04)	0.93 (0.02)	0.812
V_E, L	38.5 (8.6)[#]	37.8 (8.2)[#¶]	0.819	41.7 (9.6)[#]	43.7 (8.2)[#]	0.546	47.4 (13.1)	48.6 (10)	0.774
V_E/MVV, %	56 (14)[#]	38 (9)[#¶]	**<0.001**	61 (15)[#]	44 (7)[#]	**<0.001**	70 (17)	49 (10)	**<0.001**
V_E/VO_2	33.1 (5.4)	26.1 (3.4)[¶]	**<0.001**	33.2 (5.6)	29 (4.3)[#]	**0.026**	32.9 (5.7)	27.8 (4.5)	**0.009**
V_E/VCO_2	36.9 (5.8)	28.9 (3.8)[¶]	**<0.001**	36.0 (6.8)	30.8 (4.2)	**0.014**	35.4 (6)	30.0 (4.5)	**0.007**
BF, min^{-1}	28.3 (4.6)[#]	24.5 (3)[#¶]	**0.011**	28.5 (3.8)[#]	26.3 (3.3)	0.089	30.5 (5.5)	27.4 (4.3)	0.090
V_T, L	1.4 (0.3)[#¶]	1.6 (0.2)[#¶]	0.117	1.5 (0.4)	1.7 (0.3)[#]	0.132	1.6 (0.4)	1.8 (0.3)	0.117
SpO_2, %	95 (2)[#]	95 (1)[#]	0.568	94 (2)[#]	95 (2)	0.449	93 (2)	94 (1)	0.181
Systolic BP, mmHg	160 (29)[#]	156 (29)[#]	0.678	152 (37)[#]	155 (27)[#]	0.819	182 (32)	187 (23)	0.637
Perceived exertion and symptoms, mean during exercise									
RPE, points	13.5 (2.4)[#]	12.5 (2.6)	0.267	14.3 (2.0)	13.3 (2.2)	0.170	15.1 (2.3)	13.1 (2.0)	**0.014**
Dyspnea, points	4.3 (1.8)[#]	3.0 (1.5)[#]	**0.034**	5.0 (1.5)	3.6 (1.3)	**0.006**	5.5 (1.7)	3.7 (1.3)	**0.002**
Leg fatigue, points	4.1 (1.7)[#]	3.0 (1.5)[#]	**0.044**	4.9 (1.5)	3.4 (1.7)	**0.014**	5.4 (1.8)	3.7 (1.5)	**0.008**
Session RPE, points	3.9 (1.6)[#]	3.2 (1.3)[#]	0.149	4.6 (1.8)	3.6 (1.4)[#]	0.117	5.3 (1.9)	4.9 (2.1)	0.595

Data is shown as mean (SD). Indirect calorimetry data, blood pressure and perceived exertion/symptoms are averages over the whole exercise session (10 minutes of supramaximal HIIT, up to 20 minutes of MICT), excluding warm-up and cool down. Notes: n=16 for all except HC at HIIT60 where n=14 for VO_2/VCO_2-related variables and n=15 for VE-related variables due to technical issues. Supramaximal HIIT at 60% (HIIT60) and 80% (HIIT80) are performed at 60% and 80%, respectively, of maximum mean power output for six seconds. MICT is performed at 60% of maximal aerobic power. Tukey's *post hoc* comparisons were made after a significant main effect: [#]: significantly different from MICT ($p<0.05$), [¶]: significantly different from HIIT80 ($p<0.05$). p-group indicates p-value for pairwise comparison with independent t-test or Mann–Whitney U-test. COPD: chronic obstructive pulmonary disease, HC: healthy control; VO_2: oxygen consumption; RER: respiratory exchange ratio; VE: minute ventilation; MVV: maximal voluntary ventilation; BF: breathing frequency; V_T: tidal volume; SpO_2: peripheral oxygen saturation; BP: blood pressure; RPE: rating of perceived exertion.

Table 7. Perceived symptoms and exertion at end of exercise

					Effect of session	
		COPD (n = 16)	HC (n = 16)	P-group	COPD	HC
Dyspnea, points	HIIT60	5.1 (2.3)[#¶]	3.6 (1.5)[#]	0.036	F = 10.6, P <0.001	F = 7.0, P = 0.003
	HIIT80	6.3 (1.9)	4.3 (1.8)	0.004		
	MICT	7.1 (1.9)	5.1 (2.3)	0.009		
Leg fatigue, points	HIIT60	4.7 (1.9)[#¶]	3.3 (1.7)[#]	0.027	F = 13.5, P < 0.001	F = 11.1, P < 0.001
	HIIT80	6.1 (1.7)	4.3 (2.2)	0.012		
	MICT	6.8 (1.6)	5.0 (2.5)	0.022		
RPE, points	HIIT60	14.8 (2.4)[#]	13.7 (2.5)	0.233	F = 8.4, P = 0.001	F = 11.8, P < 0.001
	HIIT80	15.8 (1.9)[#]	14.2 (2.3)	0.034		
	MICT	17.0 (2.1)	15.1 (2.4)	0.021		

Supramaximal HIIT at 60% (HIIT60) and 80% (HIIT80) are performed at 60% and 80%, respectively, of maximum mean power output for six seconds. MICT is performed at 60% of maximum aerobic power. Tukey's *post hoc* comparisons were made after a significant main effect. [#]:significantly different from MICT; [¶]: significantly different from HIIT80. p-group indicates p-value for pairwise comparison with independent t-test or Mann–Whitney U-test. COPD: chronic obstructive pulmonary disease, HC: healthy control

Plasma BDNF

Circulating levels of plasma BDNF increased during all sessions in both groups, depicted in Figure 10. The change from baseline was not different between exercise sessions in any group (COPD: $F[3, 40.0] = 1.1$, $P = 0.345$; healthy control: $F[3, 43.5] = 1.3$, $P = 0.299$) or between those with COPD and healthy controls for any modality ($P > 0.05$ for all sessions). The average relative increase from baseline in plasma BDNF was 59% (range: 30% to 87%) across modalities and groups (Paper I, Table S3, Figure S2).

Exploratory correlation analyses in individuals with COPD showed that symptoms, dyspnea and MAP % predicted were associated with the change in plasma BDNF during MICT, but not during supramaximal HIIT, depicted in Figure 11.

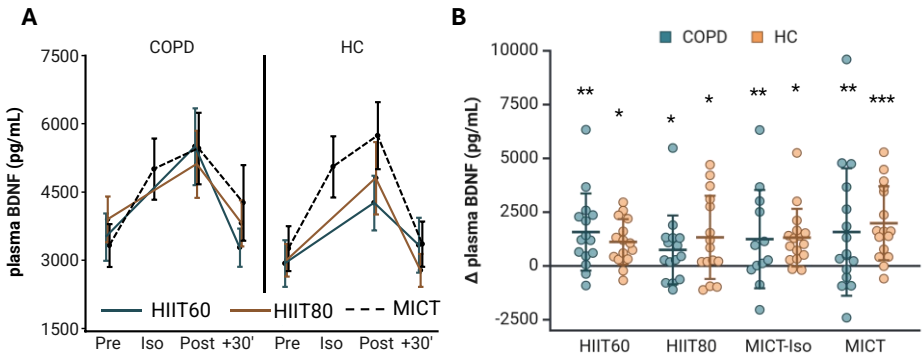

Figure 10. Exercise-induced change in plasma brain-derived neurotrophic factor (BDNF). **A)** Change in plasma BDNF during and after exercise. **B)** Change from baseline in plasma BDNF for each session depicting a significant increase from baseline to post-exercise, as well as to MICT-Iso (10 minutes of MICT). * P < 0.05, ** P < 0.01, *** P < 0.001. COPD: chronic obstructive pulmonary disease, HC: healthy control

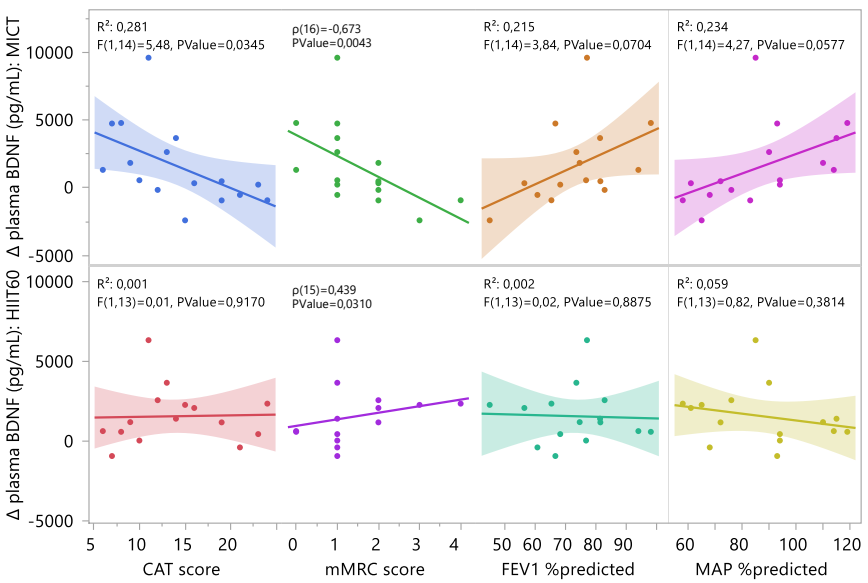

Figure 11. Linear associations between change in plasma brain-derived neurotrophic factor (pBDNF) during moderate-intensity continuous training (MICT; upper panel) and supramaximal high-intensity interval training (HIIT; lower panel) at 60% of maximum mean power output for six seconds (HIIT60), and CAT score, mMRC score, FEV1 % predicted and MAP % predicted for individuals with chronic obstructive pulmonary disease. For mMRC, the lines illustrate a linear trend for visualization while statistical analysis was performed using Spearman's rank correlation. CAT: COPD assessment test; mMRC: modified medical research council dyspnea scale; FEV1: forced expiratory volume in one second; MAP: maximum aerobic power.

Exerkines and Inflammatory Markers

Markers generally responded similarly to exercise in those with COPD and healthy controls. As shown in Figure 12, exercise induced changes in clusterin, IL-6, hepatocyte growth factor, and lactate, all of which were responsive to the intervention. No noteworthy changes were observed in cathepsin B, irisin, IL-10, IL-15, tumour necrosis factor-α or vascular endothelial growth factor-A during any session (Paper I, Table S12-S19).

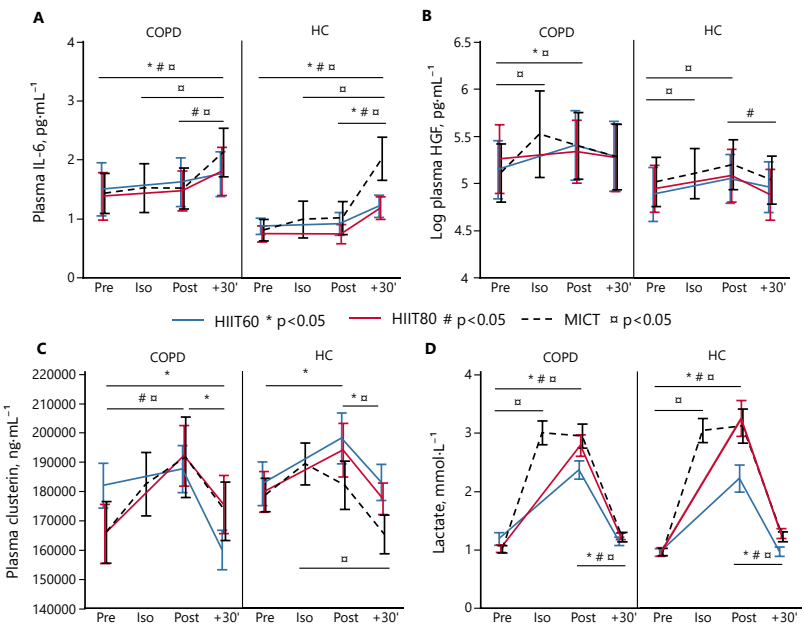

Figure 12. Exercise induced change in **A)** plasma interleukin 6 (IL-6), **B)** plasma hepatocyte growth factor (HGF), **C)** plasma clusterin and **D)** lactate during supramaximal high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) in people with chronic obstructive pulmonary disease (COPD) and matched healthy controls (HC). *: significant difference ($p < 0.05$) between timepoints for HIIT60: #: significant difference ($p < 0.05$) between timepoints for HIIT80; ¤: significant difference ($p < 0.05$) between timepoints for MICT.

Modified Borg Cycle Strength Test

Feasibility

All participants in both groups with a valid test reached supramaximal intensities during the mBCST (COPD: 145 (125–168) %MAP; healthy control: 154 (148–163) %MAP). Feasibility of the mBCST, evaluated using the test feasibility framework, is presented in Table 8 (see Paper II for additional details). The test duration was

approximately five minutes (Table 8), significantly shorter than the CPET which lasted approximately ten minutes, namely 523 ± 162 sec in individuals with COPD, and 642 ± 73 in healthy controls. In terms of applicability, the extrapolated MPO6 values provided appropriate external workloads for supramaximal HIIT, as evaluated in Paper I.

External Intensity and Physiological Response

The external intensity achieved during the mBCST was significantly higher than MAP in both groups. Although individuals with COPD demonstrated a smaller absolute increase in external intensity ($\Delta W_{mBCST-CPET}$) compared to healthy controls, the mBCST workload expressed relative to MAP did not differ between groups (Figure 13).

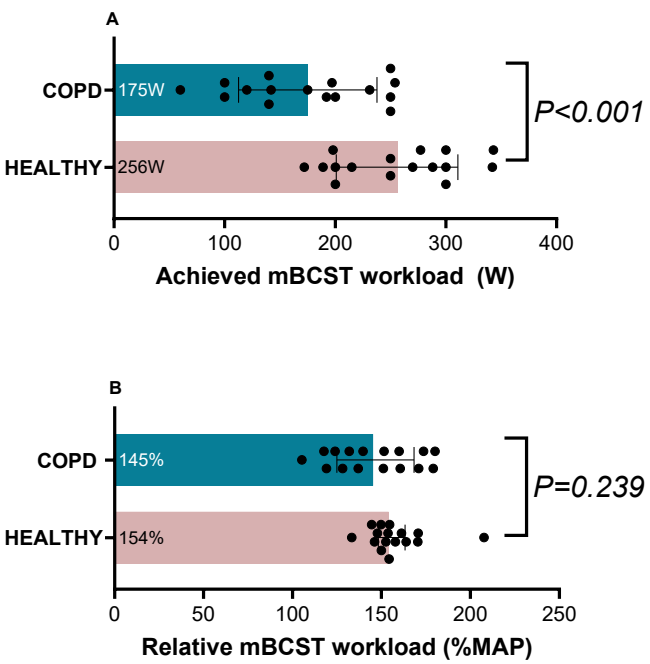

Figure 13. A) Achieved mBCST workload and **B)** relative mBCST workload for people with COPD (n = 16; blue bar) and healthy older adults (n = 16; pink bar) are depicted in panel A and B respectively. In panel A mean ± SD are indicated by bar height and error bars, and the mean is provided on the left side of the bar. In panel B median and interquartile range are indicated by bar height and error bars, and the median is provided on the left side of the bar. Abbreviations: COPD: chronic obstructive pulmonary disease; mBCST: modified Borg cycle strength test; MAP: maximal aerobic power.

Table 8. Feasibility of the modified Borg cycle strength test

Feasibility criteria	Measure during mBCST	Results	
		COPD (n = 18)	Healthy adults (n = 16)
Reaching supramaximal intensity	Achieved mBCST workload in W[a]	175 ± 63 W	256 ± 55 W
	Percentage of participants that achieve a mBCST workload exceeding MAP[a]	100%	100%
Interpretability	Description of the practical meaning of mBCST achieved workload	The highest power output someone can maintain for 30 seconds with an RPE ≤ 17. We used the achieved workload for estimation of maximum mean power output for six seconds.	
Familiarity required	Percentage of participants that successfully completed the familiarization	94%	100%
	Reasons for failing the familiarization	Not reaching target RPM (n = 1)	-
	Description of familiarization with RPE scale	All participants were familiar with the RPE scale as the scale was used during CPET. The RPE scale was explained again to the participants prior to the mBCST.	
Duration	Test duration, excluding rest and recovery	274 ± 32 sec	324 ± 44 sec
	Test duration, including rest and recovery	634 ± 32 sec	684 ± 44 sec
Scoring complexity	Percentage of test conduction problems	12%	0%
	Reasons for test conduction problems	- Misinterpreted encouragement (n = 1) - Technical problem with bike (n = 1)	-
	Percentage with RPE stop-criteria[a]	69%	44%
	Percentage with RPM stop-criteria[a]	31%	56%
Completion complexity	Percentage that completed the test[b]	94%	100%
	Reason for non-completion of test/non-valid test[b]	Not able to reach at least 3 steps (n = 1)	-
Cost	Description of the equipment needed, monitoring equipment, and expertise of test administrator	- Equipment: a cycle ergometer able to quickly (2-3 sec) adjust the resistance, RPE scale - Optional equipment: HR sensor, blood pressure device, pulse oximeter, Borg CR 10 scale Test administrator's expertise (in our study): - Master's degree in Sport Sciences or alike, expertise in exercise testing	
Safety	Frequency and type of adverse events	n = 1 (6%); saddle pain	n = 1 (6%); high HR during cool-down

[a] non-completers and people that could not do the familiarization session were excluded (n = 2); [b] = persons that were not able to do the familiarization session are excluded (n = 1). mBCST: Modified Borg cycle strength test; CPET: Cardiopulmonary exercise test; MAP: maximal aerobic power; RPM: revolutions per minute; RPE: rating of perceived exertion; HR: heart rate.

As shown in Figure 13, individuals with COPD displayed greater heterogeneity in mBCST workload relative to MAP. Higher relative mBCST workload was moderately to strongly associated with lower mMRC dyspnea score (ρ = -0.618; P = 0.011), higher diffusion capacity (D_{LCO}; ρ = 0.575; P = 0.025). Subgroup analysis further showed that those with an abnormal exercise response characterized by ventilatory limitation had lower relative mBCST workloads than participants with a normal response; 25 [95% CI; 2–47] %MAP; Paper II, Figure 6).

Peak VO_2 during the mBCST was comparable to that achieved during the CPET in both groups. However, ventilatory demand and heart rate were lower during the mBCST (Table 9). Further, the mBCST elicited lower ratings of RPE, dyspnea and leg fatigue, except for leg fatigue in healthy controls (Table 9). At iso-MAP (the mBCST workload corresponding to peak CPET work rate), all cardiorespiratory variables and symptom ratings were significantly lower compared to end-CPET in both groups. The only exceptions were V_E/VCO_2 in participants with COPD and oxygen pulse in healthy controls (Paper II, Table S5).

Dynamic hyperinflation data were available for 12 participants. The mean reduction in inspiratory capacity from baseline to end-mBCST was -0.50 L (95% CI, -0.82 to -0.19; P = 0.005). This indicates dynamic hyperinflation; however, the change was not significantly different (P = 0.094) from that in healthy controls (-0.15 L; 95% CI, -0.46 to 0.16; P = 0.301)

No significant group differences were observed in the mean changes between mBCST and CPET, or in the relative expression of cardiovascular, ventilatory, gas exchange, metabolic parameters, and symptom ratings (Table 9). However, at iso-MAP, healthy controls demonstrated greater mean difference (ΔmBCST-CPET) than COPD participants in gas exchange efficiency, respiratory exchange ratio and absolute ventilation (P < 0.05; Paper II, Table S5).

Table 9. Physiological response at end-exercise modified Borg cycle strength test and CPET

	COPD (n = 16)				Healthy controls (n = 16)				COPD vs. HC
	mBCST	**CPET**	**ΔmBCST-CPET (95% CI)**	**P-value**	**mBCST**	**CPET**	**ΔmBCST-CPET (95% CI)**	**P-value**	**ΔmBCST-CPET P-value**
Workload (W)	175 (63)	119 (37)	56 (39 to 74)	**<0.001**	256 (55)	164 (38)	92 (79 to 105)	**<0.001**	**0.002**
VO_2, mL · kg^{-1} · min^{-1}	20.9 (4.5)	21.8 (5.0)	-0.9 (-1.8 to 0.1)	0.068	25.7 (3.5)	25.4 (3.8)	0.3 (-1.2 to 1.7)	0.709	0.173
HR, b · min^{-1}[a]	120 (104 – 130)	135 (123 – 145)	-16 (-25 to -12)	**<0.001**	135 (122 – 151)	148 (138 – 156)	-14 (-17 to -10)	**<0.001**	0.520
V_E, L · min^{-1}	56 (47 – 68)	60 (52 – 82)	-8 (-15 to -4)	**0.002**	69 (54 – 84)	82 (58 – 98)	-11 (-16 to -4)	**0.013**	0.445
V_E, %MVV[b]	82 (78 – 89)	97 (85 – 111)	-13 (-20 to -7)	**0.001**	76 (62 – 87)	87 (70 – 98)	-13 (-16 to -3)	**0.015**	0.892
BF, b · min^{-1}	35 (31 – 43)	41 (36 – 49)	-6 (-10 to -3)	**0.002**	36 (31 – 40)	39 (30 – 46)	-4 (-6 to 0)	**0.034**	0.086
SpO_2, %	95 (93 – 97)	98 (95 – 98)	-2 (-4 to -1)	**0.004**	95 (94 – 96)	98 (95 – 99)	-3 (-4 to -2)	**0.011**	0.520
V_E/VO_2, ratio	35.7 (5.2)	39.2 (4.8)	-3.4 (-5.6 to -1.3)	**<0.004**	33.4 (5.4)	38.3 (7.0)	-4.9 (-7.2 to -2.6)	**<0.001**	0.323
V_E/VCO_2, ratio	35.6 (5.1)	36.5 (4.1)	-0.9 (-2.6 to 0.8)	0.275	31.1 (4.6)	33.1 (5.3)	-1.9 (-3.0 to -0.9)	**0.002**	0.276
RER, ratio	1.01 (0.08)	1.07 (0.08)	-0.07 (-0.11 to -0.03)	**0.003**	1.07 (0.05)	1.16 (0.09)	-0.09 (-0.13 to -0.04)	**0.002**	0.573
SBP, mmHg	164 (27)	212 (24)	-49 (-61 to -36)	**<0.001**	170 (29)	215 (22)	-45 (-58 to -33)	**<0.001**	0.688
RPE, points	17 (17 – 17)	20 (18 – 20)	-2 (-3 to -1)*	**0.016**	17 (15 – 17)	17 (16 – 19)	-1 (-2 to -1)	**0.003**	0.423
Dyspnea, points	7 (7 – 9)	9 (7 – 10)	-2 (-3 to 0)*	**0.029**	6 (4 – 7)	7 (4 – 9)	-1 (-2 to 0)	**0.028**	0.669
Leg Fatigue, points	7 (5 – 8)	9 (7 – 10)	-2 (-3 to 0)*	**0.035**	7 (4 – 7)	7 (4 – 9)	-1 (-2 to 0)	0.070	0.149

Data is reported as mean (SD), median (Q1-Q3) or for ΔmBCST-CPET as mean difference (95% confidence interval [CI]) or median Hodges-Lehman median difference (95% confidence interval). [a]: altered sample size (COPD: n = 15) due to technical failure HR equipment; [b]: altered sample size (COPD: n = 15) due to MVV value not being available. CPET: Cardiopulmonary exercise test; mBCST: Modified Borg cycle strength test; VO_2: oxygen consumption; HR: heart rate; RER: respiratory exchange ratio; V_E: minute ventilation; MVV: maximal voluntary ventilation; BF: breathing frequency; SpO_2: peripheral oxygen saturation; VCO_2: carbon dioxide production; SBP: systolic blood pressure; RPE: rating of perceived exertion.

The COPD-HIIT RCT

Trial status

The trial started enrolling participants on the 9 of November 2023 in Umeå and the 16 of September 2024 in Hasselt. As of 11 November 2025, 133 participants had been enrolled in the trial: 82 with COPD (29 in the usual care arm) and 51 healthy controls (Figure 14). Recruitment included 98 participants in Umeå and 35 in Hasselt. The first five participants are scheduled to complete their 24-month follow-up in November 2025.

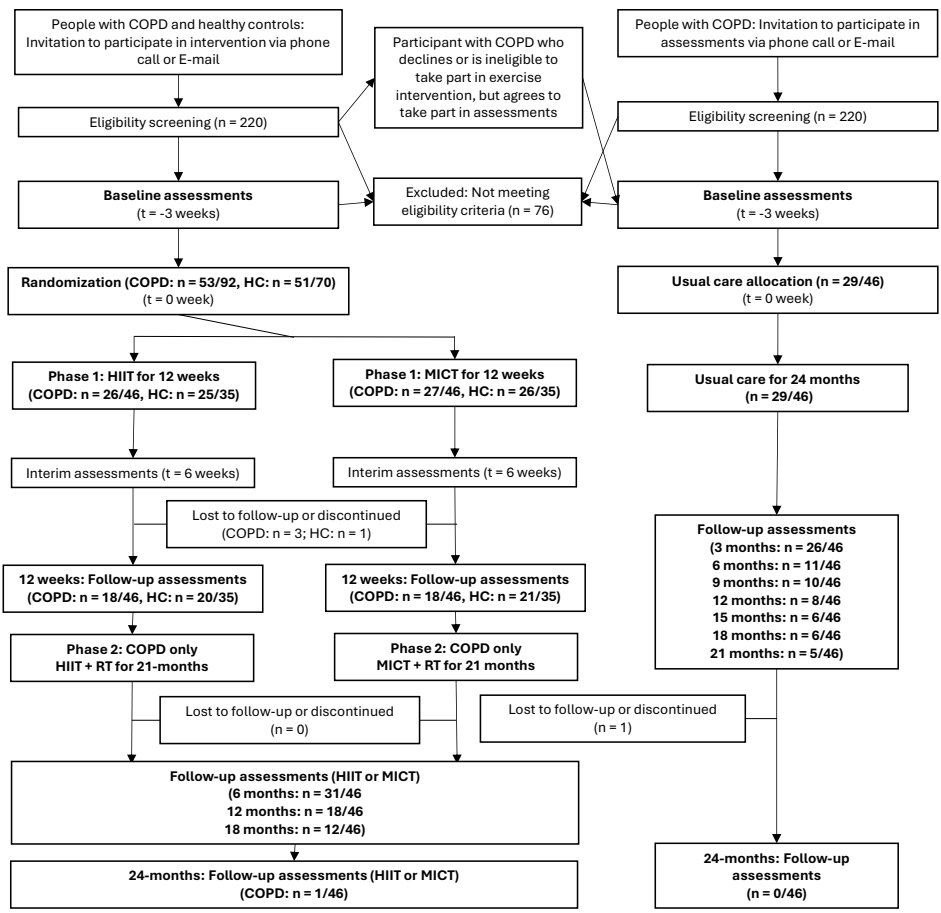

Figure 14. Study timeline of the COPD-HIIT RCT and participant flowchart as of 2025-11-12. COPD: chronic obstructive pulmonary disease; HC: healthy control; HIIT: supramaximal high-intensity interval-training; MICT: moderate-intensity continuous training; RT: resistance training.

Participant Characteristics

Table 10 presents the characteristics of the participants including participants to date. For brevity, and given that recruitment is still ongoing, individuals with COPD are presented as a single group rather than separated by intervention and usual care.

In those with COPD, airflow obstruction ranged from mild to very severe (FEV_1 % predicted range: 26–115%), with most participants classified as having moderate airflow obstruction. The COPD group was well matched to healthy controls in terms of age and sex. As in Papers I-II, the healthy controls exhibited a clinically relevant higher step count.

Participants enrolled in the usual care arm did not differ from those with COPD in the intervention arms on characteristics such as age, body mass index, FEV_1, CAT score, smoking habits or step count ($P > 0.05$, data not shown). In terms of the different centres, COPD participants in Hasselt exhibit a higher degree of airflow limitation (FEV_1 %predicted: 52 [18]; vs. Umeå: 69 [19], lower exercise capacity (MAP: 81 [28]; vs. 99 [35]) and greater history of smoking (pack years: 51 [30]; vs: 26 [16]) to name a few characteristics (all $P<0.05$).

Table 10. Participant characteristics of enrolled participants in the COPD-HIIT RCT

	COPD	N	HC	N	P
Anthropometrics and demographics					
Age, years	74 (7)	74	72 (7)	49	0.085
Female sex, n (%)	39 (53)	74	25 (51)	49	0.855
Body mass index, $kg \cdot m^{-2}$	27 (5)	69	29 (4)	47	0.116
Fat mass, %	36 (8)	69	37 (8)	47	0.882
Lean mass, %	63 (8)	69	63 (8)	47	0.827
Years of education	12.0 (3.8)	73	14.4 (3.6)	48	< 0.001
Highest education level, Primary/secondary/tertiary, n (%)	16/31/27	74	2/16/31	49	0.002
Physical activity					
Mean steps/day, n	5649 (3253)	53	6436 (2561)	32	0.247
Median steps/day, n	5631 (3467)	53	6119 (2603)	32	0.494
Clinical characteristics					
COPD assessment test, score, 0–40	14.9 (7.3)	71	NA		
mMRC dyspnea score, 0/1/2/3/4, n	9/20/31/5/9	74	11/31/5/0/0	49	< 0.001
GOLD I/II/III/IV, n	13/28/14/3	58	NA		
GOLD A/B/E, n	10/49/11	70	NA		
CRQ Dyspnea domain score, 0-7	5.3 (1.2)	69	NA		
CRQ Fatigue domain score, 0-7	4.4 (1.1)	65	NA		
CRQ Emotion domain score, 0-7	5.3 (1.1)	65	NA		
CRQ Mastery domain score, 0-7	5.6 (1.2)	65	NA		
CRQ Overall score, 0-7	5.1 (1.0)	65	NA		

Table 10. Participant characteristics of enrolled participants in the COPD-HIIT RCT

	COPD	N	HC	N	P
Fibrinogen, $g \cdot L^{-1}$	3.3 (0.5)	57	3.3 (0.5)	44	0.789
Lung function[a]					
FEV_1, L	1.7 (0.5)	61	2.8 (0.6)	42	< 0.001
FEV_1, % predicted	63 (21)	61	101 (15)	42	< 0.001
FVC, L	3.1 (0.8)	61	3.7 (0.7)	42	< 0.001
FVC, % predicted	88 (19)	61	101 (13)	42	< 0.001
FEV_1/FVC	54 (11)	61	76 (7)	42	< 0.001
Inspiratory capacity, L	2.6 (0.6)	27	2.9 (0.7)	28	0.059
MVV, L	62 (16)	27	93 (22)	28	< 0.001
D_{LCO}, $mmol \cdot min^{-1} \cdot kPa^{-1}$	4.8 (1.9)	19	7.7 (1.6)	9	< 0.001
D_{LCO}, % predicted	63 (19)	19	100 (13)	9	< 0.001
RV, % predicted	176 (36)	19	102 (17)	9	< 0.001
RV/TLC, %	58 (7)	19	38 (4)	9	< 0.001
Exacerbations and hospitalizations last 12 months, n, 0/1/≥2					
Exacerbations	53/10/11	74	NA		
Hospitalizations	55/13/6	74	43/3/0	46	0.002
Emergency visits	52/15/7	74	35/9/2	46	0.821
Smoking and exposure					
Smoking status, n (%)		74		49	< 0.001
Current smoker	8 (11)		1 (2)		
Ex-smoker	60 (81)		22 (45)		
Never-smoker	6 (8)		26 (53)		
Pack years[b]	32 (23)	57	11 (13)	16	< 0.001
Passive smoking early life, n (%)	52 (70)	74	31 (67)	49	0.777
Passive smoking adult life, n (%)	53 (73)	74	15 (31)	49	< 0.001
Occupational exposure, n (%)	30 (41)	74	7 (14)	49	0.001
Early-life event risk factors, n (%)	9 (12)	74	3 (6)	49	0.313
Infection-related risk factors, n (%)	9 (12)	74	4 (8)	49	0.561
Medications and comorbidities					
Self-MNA,	13 (12-14)	70	14 (12-14)	43	0.008
Self-MNA ≤11, n (%)	16 (23)	70	2 (5)	43	0.015
HADS-Depression	3 (1-6)	72	2 (1-3)	47	0.002
HADS-Anxiety	4 (2-8)	72	3 (1-5)	47	0.009
EQ-5D-Visual analogue scale	69 (19)	72	81 (13)	47	< 0.001

Data is presented as mean (SD) or median (Q1-Q3) if not otherwise stated.
[a]Data on diffusion capacity and lung volumes are only available from the Hasselt centre at the time.
[b]Pack years calculated for current and ex-smokers who primarily smoked cigarettes.
COPD: chronic obstructive pulmonary disease; HC: healthy control; mMRC: modified Medical Research Council Dyspnea Scale; GOLD: Global Initiative for Chronic Obstructive Lung Disease; CRQ: Chronic Respiratory Disease Questionnaire; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IC: inspiratory capacity; RV: residual volume; TLC: total lung capacity; D_{LCO}: diffusion capacity of the lung for carbon monoxide; MNA: Mini-Nutritional Assessment; HADS: Hospital anxiety and depression scale

Systematic analyses of medication use and comorbidities are pending. Participants with COPD showed lower nutritional status (Self-MNA) and higher HADS anxiety/depression scores; however, group medians remained below clinical cut-offs.

Group Comparisons of Selected Outcomes

Table 11 summarizes cycle test performance in the preliminary RCT cohort. As expected, MAP was lower in COPD than in healthy controls, both in absolute terms and when normalized to body mass (both P<0.001). Likewise, peak workload during mBCST was lower in COPD in absolute and relative terms (both P<0.001). However, when expressed relative to MAP, the mBCST peak workload (%MAP) was similar between groups (mean 146% in both; P=0.814), but with a greater range in COPD.

Table 11. Baseline data in cycle test performance

	COPD	N	HC	N	P
Maximum aerobic power, W	94 (34)	73	154 (48)	48	< 0.001
Maximum aerobic power, W·kg^{-1}	1.3 (0.5)	73	1.8 (0.5)	48	< 0.001
mBCST peak workload, W	137 (58)	70	222 (70)	48	< 0.001
mBCST peak workload, W·kg^{-1}	1.9 (0.8)	70	2.6 (0.8)	48	< 0.001
mBCST peak workload, %MAP					
Mean SD	146 (29)	70	145 (22)	48	0.814
Median (Q1-Q3)	146 (130–166)	70	146 (127– 61)	48	
Minimum - maximum	52 - 217	70	99 - 183	48	

Data is presented as mean (SD) if not otherwise stated. COPD: chronic obstructive pulmonary disease; HC: healthy control; mBCST: modified Borg cycle strength test; MAP: maximum aerobic power

Table 12 presents cognitive performance in the preliminary cohort across selected outcomes, including the MoCA and one representative sub measure from each CANTAB test. In addition to the unadjusted MoCA scores, an analysis of covariance adjusted for years of education confirmed that the between-group difference remained statistically significant in favor of healthy controls (adjusted mean difference = 1.3, 95% CI: 0.1–2.4). The groups also differed in executive function, as assessed in the trail making tests depicted in Figure 15.

Table 12. Baseline data of cognitive assessments

	COPD	N	HC	N	P
Multi-domain cognitive screening					
MoCA, points*	23.0 (3.6)	72	25.2 (2.4)	48	< 0.001
MoCA, ≤ 23 points, n (%)	36 (50)	72	11 (23)	48	0.003
MoCA, ≤ 21 points, n (%)	21 (29)	72	5 (10)	48	0.015
Attention and psychomotor speed					
Reaction time, simple, milliseconds#	375 (53)	71	362 (57)	48	0.189
Visual processing, sensitivity to signal (0-1)*	0.83 (0.06)	71	0.87 (0.06)	48	0.002
Memory					
Paired associates learning, n correct on first attempt*	8.9 (3.7)	71	10.8 (3.7)	48	0.006
Word recall, immediate, n correct words and rejected distractors*	15 (13-16)	71	16 (15-17)	48	0.005
Spatial working memory, n incorrect revisits#	20.6 (6.7)	71	19.9 (9.5)	48	0.630

Data is presented as mean (SD) or median (Q1-Q3).
*Higher score indicates better performance; # Lower score indicates better performance.
A MoCA score ≤ 23 and ≤ 21 respectively, correspond to approximately 1.5 and 2.0 standard deviations below the normative mean, for Swedish adults aged 70-80 years with secondary school education[385]. COPD: chronic obstructive pulmonary disease; HC: healthy control; MoCA: Montreal Cognitive Assessment

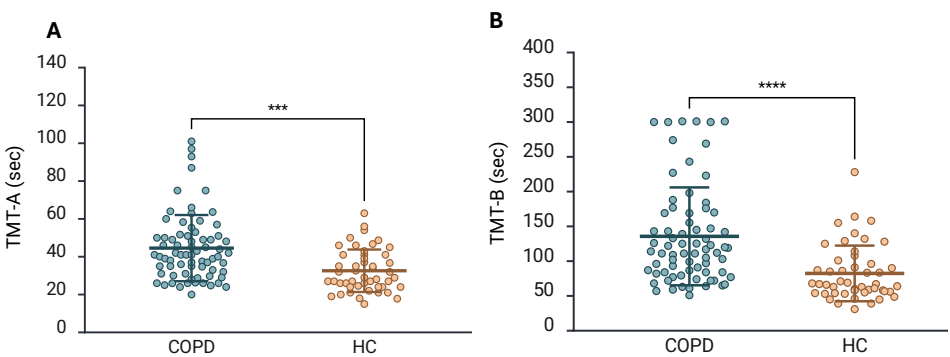

Figure 15. Performance (time to completion) on the **(A)** trail making test (TMT) part A and (COPD: mean [SD] 45 [17] sec; HC: 33 [11] sec) **(B)** TMT-B (COPD: median [Q1Q3] 117 [84–169]; HC: 67 [55–100]). In TMT-B, 300 seconds was the upper limit of test duration. TMT-A is analysed using unpaired t-test, while TMT-B analysed with Mann-Whitney U-test. *** = significantly different between groups (P < 0.001); **** significantly different between groups (P < 0.0001). COPD: chronic obstructive pulmonary disease; HC: healthy control.

Next, Table 13 displays assessment of quadriceps function, as well as the functional performance tests. Notably, quadriceps power, as well as quadriceps endurance, but not quadriceps strength is lower among individuals with COPD, compared to our healthy age, sex and activity matched controls.

Table 13. Baseline quadriceps power, strength, endurance and functional performance

	COPD	N	HC	N	P
Isotonic power, peak velocity, °/s	368 (47)	42	395 (35)	31	0.009
Isotonic 1-repetition maximum, Nm	67 (29)	67	71 (27)	48	0.345
Isotonic endurance, n repetitions	36 (22)	67	51 (23)	48	< 0.001
Isotonic endurance, Nm × n	1031 (685)	51	1653 (881)	35	0.002
5-time sit-to-stand test, sec	13.4 (9.2)	73	9.7 (3.1)	47	0.009
Stair climb power test, sec	5.6 (2.4)	72	4.3 (1.3)	47	0.002

Data is presented as mean (SD). COPD: chronic obstructive pulmonary disease; HC: healthy control

Exercise Progression and Attendance in Phase 1

Table 14 provides an overview of the external exercise intensities and number of intervals recorded in a subset of participants enrolled in Umeå during their first and last training sessions in Phase 1. The table also presents attendance and drop-out rates for the first 80 randomised participants across both study centres.

Table 14. Exercise progression and attendance in phase 1 of the COPD-HIIT RCT

	Supramaximal HIIT		MICT	
Interval intensity	COPD (n = 10)	HC (n = 17)	COPD (n = 12)	HC (n = 18)
First session				
W	168 (137–201)	236 (181–263)	51 (45–58)	75 (51–101)
%MPO6	60	60	-	-
%MAP	149 (116–196)	153 (136–184)	50	50
Last session				
W	325 (241–399)	432 (367–510)	70 (59–84)	101 (79–135)
%MPO6	127 (101–143)	113 (108–124)	-	-
%MAP	294 (200–433)	280 (263–353)	72 (62–77)	69 (63–82)
% 1st session	211 (168–238)	189 (180–206)	143 (123–153)	137 (124–164)
Intervals (n) / duration (min)*				
First session	10	10	20	20
Last session	13 (11–14)	13 (12–14)	25 (22–27)	26 (22–30)
Attendance	**Supramaximal HIIT**		**MICT**	
	COPD (n = 19)	HC (n = 20)	COPD (n = 20)	HC (n = 21)
Session attendance, n	25 (19–28)	26 (24–28)	26 (24–28)	27 (25–28)
Drop-outs, n	2	1	1	0

Data is presented as median (Q1-Q3) or n.
* Number of intervals in supramaximal HIIT; minutes of main work-phase duration in MICT.
COPD: chronic obstructive pulmonary disease; HC: healthy control; MPO6: maximum mean power output for six seconds; MAP: maximum aerobic power; HIIT: high-intensity interval training; MICT: moderate-intensity continuous training

The most commons reasons for non-attendance were illness and pre-announced absence due to travel. The reasons for drop-out were medical events that did not occur during the training sessions (n = 3; shoulder injury, cancer diagnosis and cardiac incident) or dissatisfaction with reimbursement (n = 1). Thus, the current drop-out rate in the intervention arms in phase 1 is 8% (n = 3) in COPD and 2% (n = 1) in healthy controls. In the usual care arm, one participant died during the study period.

Quality of Reporting in COPD Trials

Search Results

Two literature searches identified 13 467 potentially eligible records, of which 298 met eligibility criteria after full-text screening. The flowchart of search results and study selection process is shown in Figure 16.

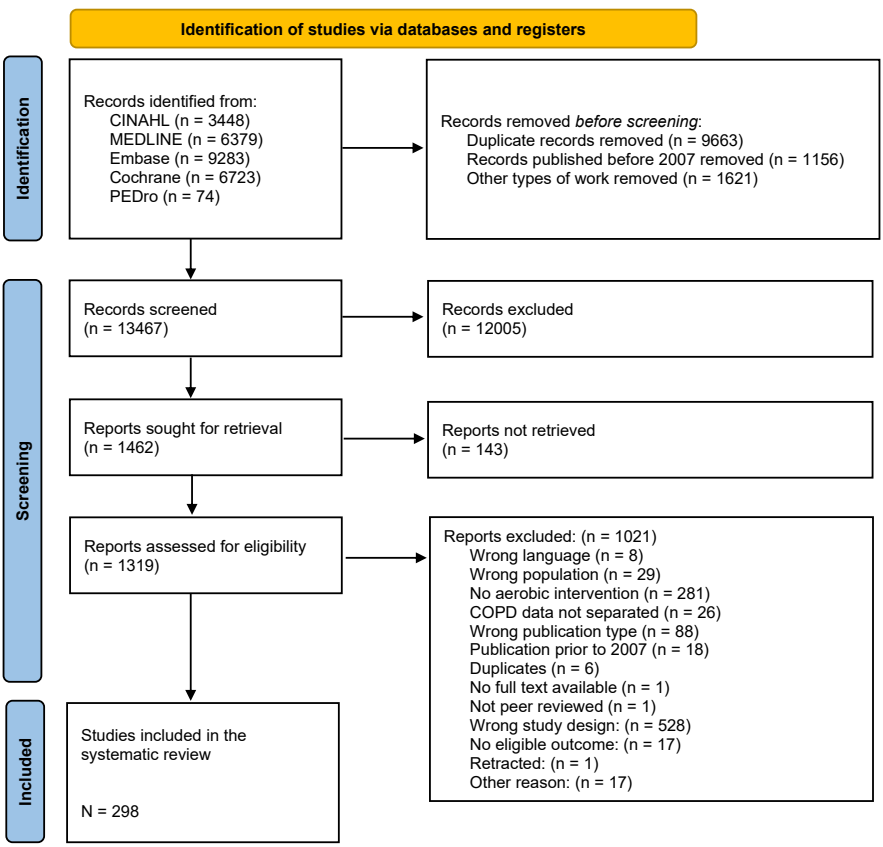

Figure 16. PRISMA[398] flowchart detailing the selection of studies from the two searches.

Characteristics of the Included Trials

The 298 trials were RCTs published between 2007 and 2025. Trials from 44 countries published across 125 different journals were included. Brazil was the most common country across analysed trials (n = 29, 10%), followed by China (n = 29, 10%) and Australia (n = 18, 6%).

Most trials had an aerobic training intervention as part of pulmonary rehabilitation (n = 202, 68%) or as a standalone intervention (n = 83, 28%). Walking was the most common mode of exercise (n = 103, 35%), followed by a combination of walking and cycling (n = 78, 26%) and cycling (n = 59, 20%) while 27 trials (9%) did not define their mode of aerobic exercise.

The included trials comprised of 636 intervention arms with a total of 28 568 participants of which 60% were male. The median (Q1–Q3) of the mean participant age across trials was 66 (63 – 69) years; mean FEV_1 % predicted was 47 (40–54), and BMI was 25 (23–27) $kg \cdot m^{-2}$. The median (Q1–Q3) intervention length was 8 (7–12) weeks, ranging from half a week to two years, and the aerobic training frequency was 3 (2.5–4) sessions per week.

Quality of Reporting

The quality of reporting in the included studies showed great variability. A summary of the findings is provided below, with more details in Paper IV. In text, the number of adequately reported items is described as n (%).

Reporting of Participant Characteristics and Intervention Details

The reporting of participant characteristics (Paper IV, Figure 2) was, for most details well reported. Yet, some studies failed to adequately report the sex[420,421], or, strikingly in this context, any measure of lung function[420,422,423] of their participants. Only 9% of trials adequately reported smoking status of participants.

The mean number of FITT components reported was 3.0 (0.8) and 88 (30%) trials adequately reported all four components. While frequency and type of exercise were relatively well-reported (reported in 279 [94%] and 249 [84%] of trials, respectively), time (duration) and intensity of the aerobic exercise only adequately reported in 161 (54%) and 136 (46%), respectively.

Reporting of other intervention details also varied (Paper IV, Figure 3 and 4). While the context of the aerobic training (i.e. stand-alone, part of pulmonary rehabilitation or other) was well-reported (295 [99%]), training device (78

[26%]), mode of delivery (e.g. individual or group; 209 [21%], adverse events (79 [27%]) and adherence to the intervention (22 [7%]) were poorly reported.

CERT Compliance

In general, the compliance with CERT was low as depicted in Figure 17. Out of 19 items, the mean number of items adequately reported was 5.4 (3.0), ranging from 0 to 16. Adjusted for non-applicable items (e.g. describing an intervention home-component is not-applicable for those not having one), CERT compliance was 29% (16%). Reporting per CERT item (Figure 17B) shows that information regarding qualifications of supervisors (item 2); detailed description of the exercise (item 8); and adherence to the intervention (items 16a and 16b) were poorly reported.

The reporting quality, expressed as the average number of CERT items reported across all trials originating from each country, varied between countries, as illustrated in Figure 18.

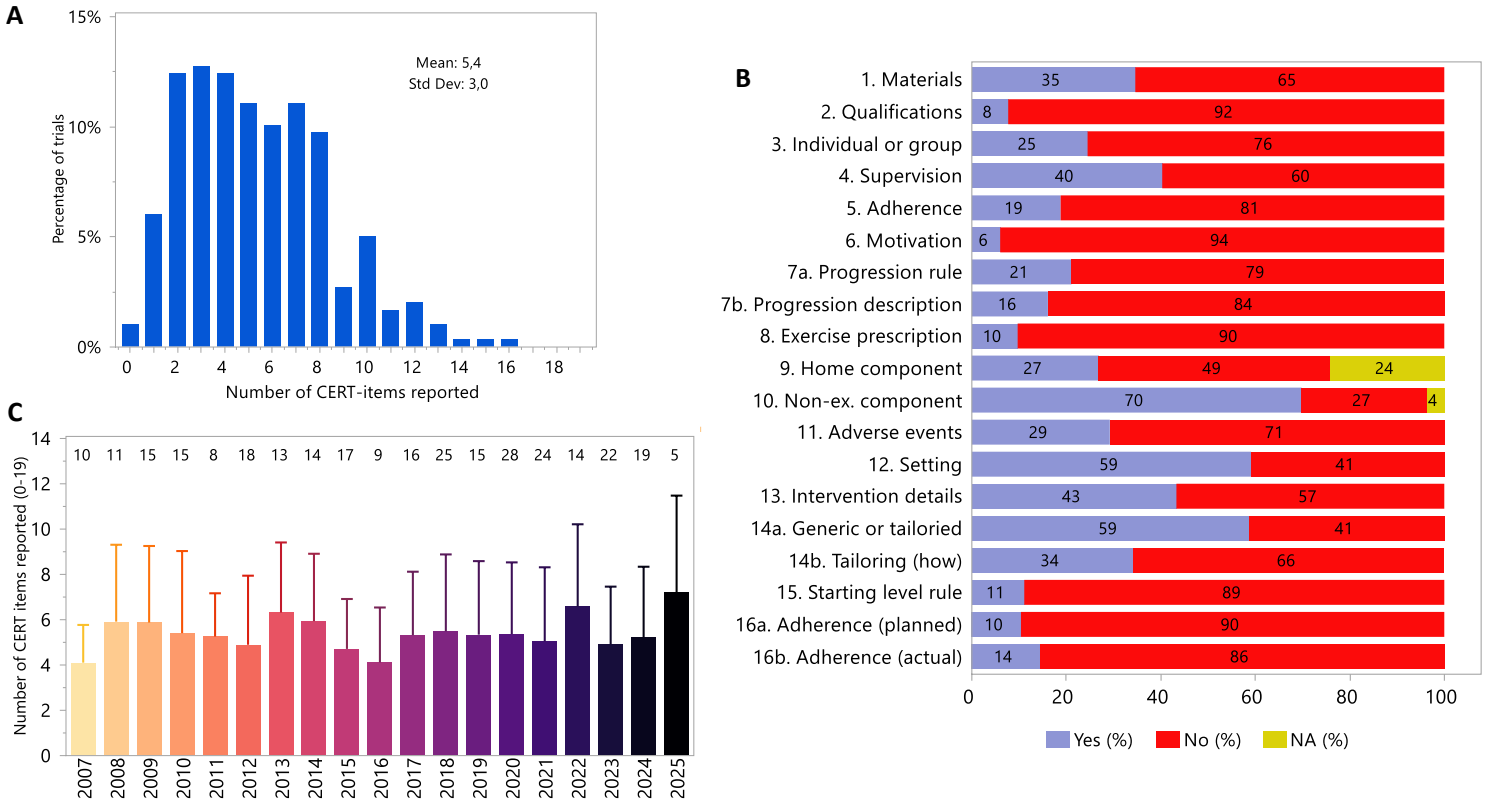

Figure 17. Reporting of aerobic training interventions in randomised controlled trials of COPD (n = 298 trials). (A) Distribution of CERT (Consensus on Exercise Reporting Template) scores across all trials. **(B)** Percentage of trials adequately reporting each CERT item: "Yes": The variable is adequately reported; "No": The variable is not reported; "NA" the items were not applicable for the specific trial. **(C)** Temporal trend in overall reporting quality. Bars represent mean CERT summary scores (0–19) per publication year ± SD; numbers above bars indicate the number of included trials per year

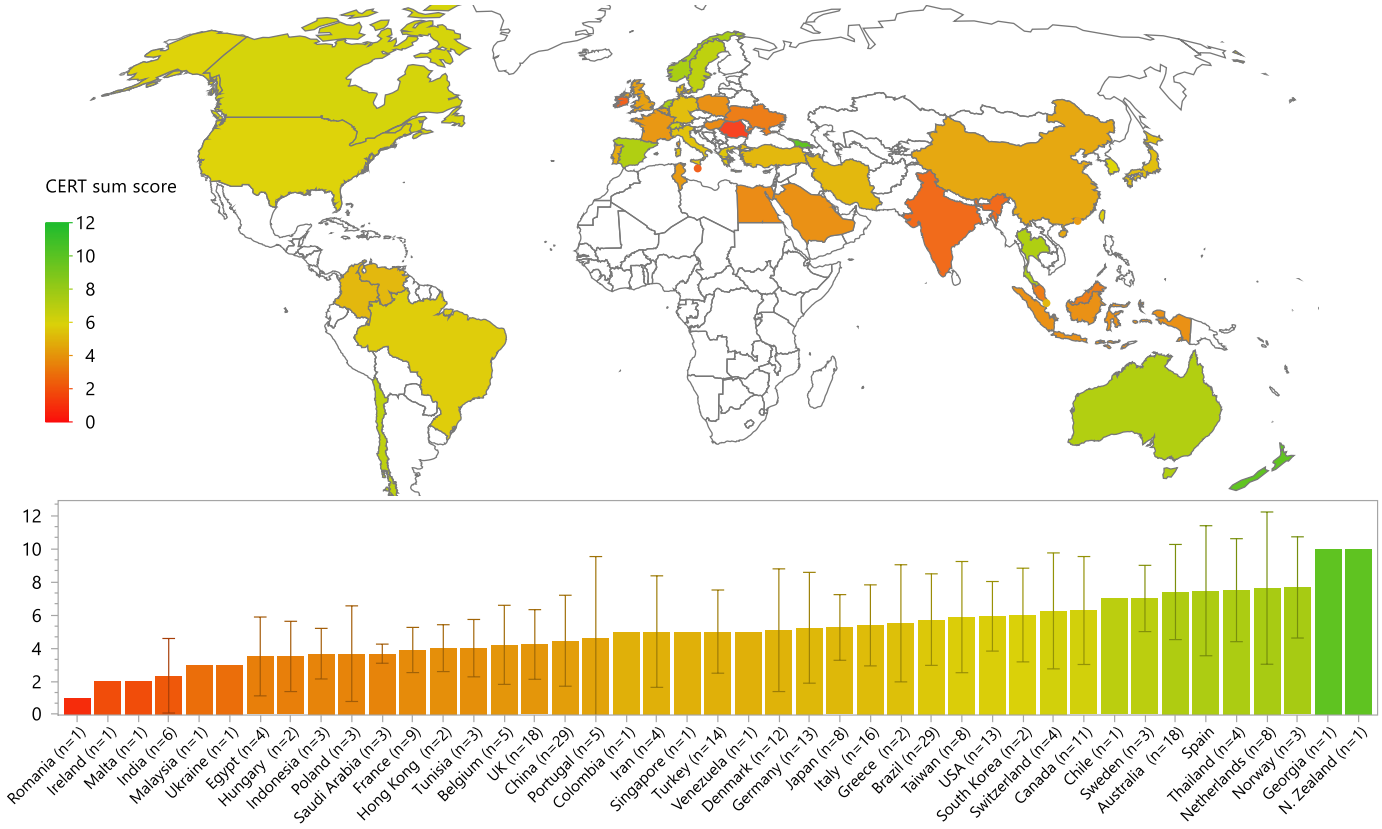

Figure 18. Geographic distribution of CERT reporting quality among included trials (n = 298). Mean number of CERT (Consensus on Exercise Reporting Template) items reported per country. Colours represent the average number of reported CERT items, with higher values indicating better reporting compliance (green) and lower values poorer reporting (red). Countries with no included trials are shown in white, multi-national trials are excluded

Training Principles

The application and reporting of the exercise training principles across the included trials varied substantially, as seen in Figure 19. Across the seven training principles assessed, the median (Q1-Q3) number adequately reported per study was 1 (0–2) and no trials reported on all principles. Sixty percent of all trials reported one or two principles (Figure 19A). Specificity and initial values were the most frequently described, while periodisation and reversibility were seldom reported (Figure 19B). The number of training principles reported was consistently low over time (Figure 19C).

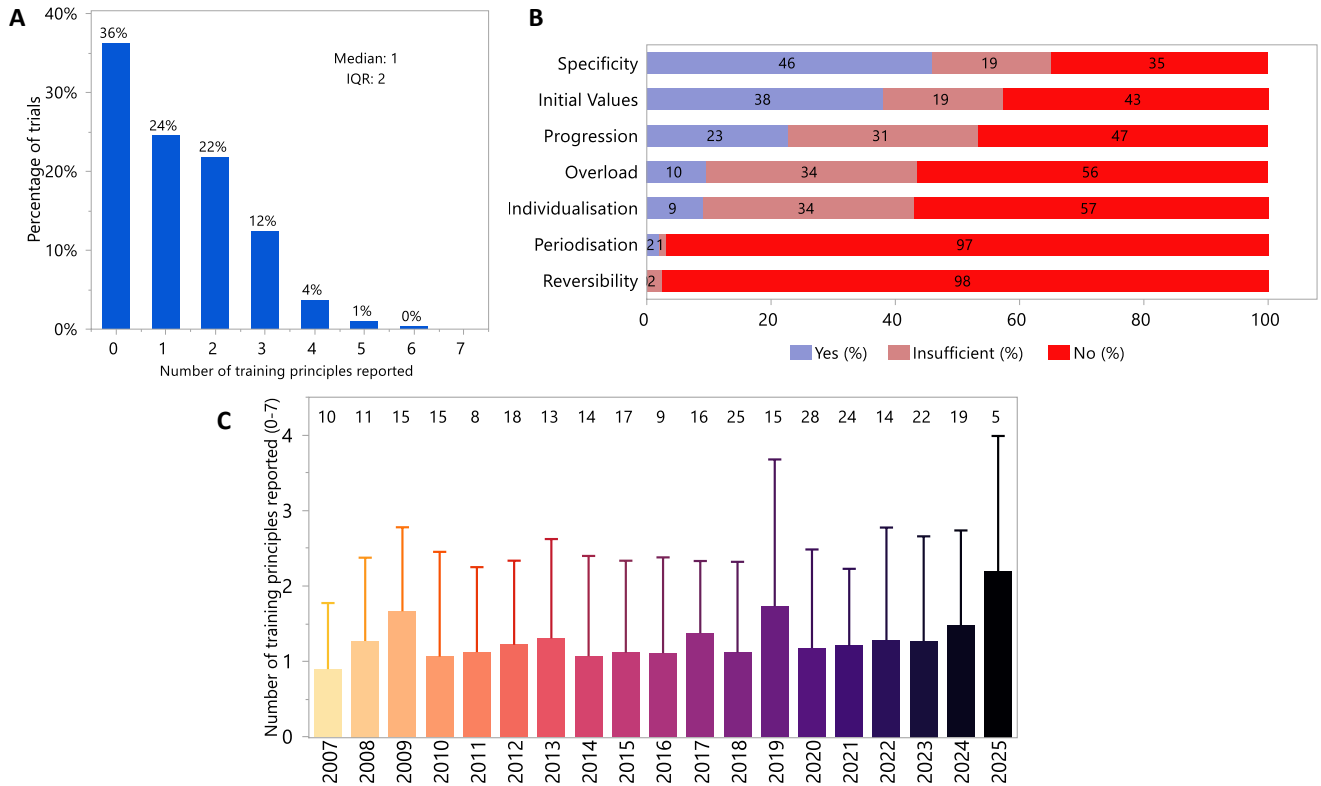

***Figure 19*. Reporting of training principles in randomised controlled trials with aerobic training in COPD (n = 298 trials). (A)** Distribution of reported training principles summary scores across all included trials. **(B)** Percentage of trials adequately reporting each training principle. "Yes": The variable is adequately reported; "Insufficient": The variable in inadequately reported; "No": The variable is not reported. **(C)** Temporal trend in number of training principles applied. Bars represent mean training principles summary scores per publication year ± SD; numbers above bars indicate the number of included trials per year

Discussion

Chronic obstructive pulmonary disease is characterized by persistent respiratory symptoms and airflow limitation but is also associated with a range of extrapulmonary manifestations. Exercise training is a key component of COPD management, as recommended by international guidelines[8,11]. This doctoral thesis aimed to contribute to the development of effective exercise strategies for the management of COPD. It sought to advance the understanding of the feasibility, physiological responses and methodological considerations of supramaximal HIIT in people with COPD and to evaluate the reporting quality in existing aerobic exercise interventions in the COPD literature.

Through experimental studies and a systematic review, this thesis explores novel approaches to exercise testing and training in COPD, while also identifying gaps in current research practice. It demonstrates that supramaximal HIIT is feasible in people with COPD and allows for significantly higher external exercise intensity with reduced ventilatory demand, while eliciting a similar acute increase in plasma BDNF compared to that of traditional MICT (Paper I). The mBCST was shown to be feasible and applicable in people with COPD as an alternative exercise test to CPET when prescribing supramaximal exercise (Paper II). The design and methodological framework of the ongoing COPD-HIIT RCT is outlined in Paper III. Preliminary baseline data shows that a broad and clinically representative sample of participants with COPD have been enrolled in the RCT, alongside a control group that is relatively well-matched for sex, age and objectively measured physical activity. Finally, a systematic review including 298 trials highlights substantial shortcomings in the reporting and application of training principles in aerobic exercise trials for COPD (Paper IV).

This discussion addresses the main findings and methodological considerations of the thesis. First, the feasibility of the studied exercise modalities and testing procedures is considered; second, their acute physiological responses are discussed, both with emphasis on COPD. Third, examination of group differences in baseline characteristics and exercise responses between COPD and controls are examined. Finally, methodological aspects and the reporting quality in COPD exercise trials are addressed.

Feasibility

In Paper I, we found that supramaximal HIIT is a feasible exercise modality in people with COPD, characterized by high exercise fidelity, high participant preference and lower ventilatory demand compared to MICT.

While interval training at external intensities at 80%-100% of MAP[290,292,424] is relatively well-studied in COPD, few studies have explored the use of supramaximal intensities. Butcher et al. (2013)[235] investigated 30-second intervals at ~140% of MAP with 90 seconds of active recovery and found it feasible. When performed until symptom limitation, it allowed for an increased total work with similar end-exercise physiological responses. In contrast, Nymand and colleagues (2023)[425] attributed intensity as a barrier to adherence when using 60-second intervals at 100% of MAP with 3-minute active recovery periods. However, our findings suggest that intensity per se is not necessarily a limiting factor, even when exercising at ~200% of MAP. Rather, feasibility appears to depend on the interaction between external intensity, interval duration, and work-to-rest ratio. Whereas both Butcher and Nymand used 1:3 work-to-rest ratios, our protocol employed a 1:9 ratio, combining short intervals with relatively long recovery periods. This design likely allowed sufficient ventilatory relief, while the short interval duration itself may prevent full buildup of ventilatory demand within each effort, leveraging the slow pulmonary kinetics typical in COPD[295,296].

Participants in Paper I primarily had mild to moderate COPD, which may limit generalizability to those with more advanced disease (GOLD stages III–IV, GOLD class E). Yet, no indication emerged that those with greater airflow obstruction found supramaximal HIIT more difficult to perform. Consistent with previous findings from the Umeå-HIT RCT, which demonstrated good tolerability of a similar protocol in older adults (mean age 70 years)[310,315], our findings suggest that supramaximal HIIT is feasible also in even older adults (mean age 74 years, range 60 – 88 years), including those with multiple comorbidities and varying degrees of COPD severity. However, the long-term feasibility of this supramaximal HIIT regimen in COPD remains to be determined.

Long-Term Feasibility and Exercise Progression

Findings from Paper I indicated that the exercise intensity in the supramaximal HIIT protocol could be increased considerably during the early phase of the training intervention, without compromising feasibility or inducing excessive levels of dyspnea or discomfort (e.g., we found that patients with COPD without any prior training could perform a supramaximal HIIT session at 80% of MPO6). Yet, for the RCT, we retained 60% of MPO6 as an attainable starting point for the

intervention, providing a reasonable intensity for most participants. However, we made sure to allow for liberal progression of intensity already after the first session (up to 10%) based on participants perceived dyspnea and RPE. In contrast, the starting intensity for MICT was set at 50% of MAP, informed by the findings from Paper I, where 60% of MAP elicited a maximal effort in some participants. Notably, this prescribed intensity is slightly lower than most current recommendations, which typically suggest initiating MICT at ≥60% of MAP for 20–30 minutes. However, as one-third of participants were unable to complete a single session at a starting intensity of 60% of MAP in Paper I, we chose to begin the MICT group at 50% of MAP in the subsequent RCT. The inability to sustain exercise at 60% of MAP may partly be explained by the way the CPET was conducted. For example, participants in Papers I–II reached a median (Q1-Q3) Borg rating of 9 (7–10) for both dyspnea and leg fatigue at the end of CPET, indicating a high level of effort. By comparison, in a pooled sample of over 4000 participants from multiple trials[426], the mean (SD) end-CPET ratings of dyspnea and leg fatigue were 6.7 (2.3) and 6.3 (2.6), respectively, indicating a somewhat submaximal exertion in that cohort. This indicates that our participants may have exercised to a greater degree of physiological strain than typically observed in COPD trials or standard clinical exercise testing settings thereby achieving a higher MAP.

Additionally, while increasing the external workload (intensity) is our primary progression target in the supramaximal HIIT protocol, we reasoned that increasing the number of intervals would be both feasible and an appropriate means of enhancing total training volume. We hypothesized that supramaximal HIIT has greater potential for exercise progression, compared to MICT, where ventilatory constraints tend to hinder progression[235,237].

The supramaximal HIIT protocol used in Paper I was adapted from a previously developed protocol for healthy, inactive older adults by Hedlund et al. (2019)[309]. In their study, participants began training at 219 ± 42 % of MAP (65% of MPO6) and reached 299 ± 67% at the end of a six-week intervention. In a subsequent 12-week RCT, the intensity increased from a median (range) 169% (125-266%) of MAP (60% of MPO6), to 323% (196-442%) of MAP, or 112% (88-136%) of MPO6[315]. Although there are differences between our studies in exercise testing methods, instrumentation, and population characteristics, it is reasonable to expect a similar progression over time in our sample of individuals with COPD and healthy controls.

Our preliminary data on exercise progression are in line with findings from the RCT by Simonsson et al. (2023)[310]. Expressed as %MPO6, participants with COPD performed their last session at a median (Q1-Q3) of 127% (101 – 143%), slightly higher than the healthy controls at 113 % (108 – 124%). Thus, our healthy

controls cohort progress to a similar extent, while those with COPD increase slightly more in %MPO6. In %MAP the values in our dataset (COPD: median 294%; healthy control: 280%) were lower compared to those reported by Simonsson et. al. This is likely explained by methodological differences in training and testing procedures to some extent.

For example, the CPET used by Simonsson et al. was terminated at RPE ≥ 17, whereas ours had no upper limit, likely yielding a MAP closer to the true maximum. For comparison, their participants achieved an average MAP of 131 W, while our healthy control group, despite being slightly older, reached a higher average MAP of 154 W which might explain why %MPO6 and not %MAP was similar between the two studies. Differences between the exercise progression between the two supramaximal HIIT protocols likely reflect variations in baseline testing, progression strategy, workload regulation, and interval execution. The current RCT applied automated workload control and an option to increase the number of intervals, while the protocol by Simonsson et al. used manual adjustments to the workload and a fixed number of intervals. Such methodological distinctions should be acknowledged when comparing results across studies.

Regarding physiological adaptations, it remains speculative how supramaximal HIIT compares to MICT in chronic training responses in COPD. In non-exercising older adults, the Umeå-HIT study found, in supramaximal HIIT and moderate-intensity training, similar improvements in VO_2peak, 30-second chair stand, leg power, balance and blood pressure, while supramaximal HIIT had a superior effect on anaerobic cycling performance (mBCST)[310,315]. Previous evidence indicates that short-duration, low-volume high-intensity protocols can effectively induce peripheral and central adaptations, provided the intensity is sufficiently high as in all-out sprint interval training[318,319,427].

However, the protocol applied here is controlled and watt-regulated, ensuring that efforts are performed at a predetermined, controlled workload rather than an all-out effort. While this approach may somewhat reduce cardiometabolic stress, it might be in favor of feasibility and tolerability, particularly in non-exercising older adults and individuals with COPD. As rigorously examined in the Umeå-HIT study, a similar protocol did not negatively affect the affective state or exercise-related self efficacy[315]. Further supported by a meta-analysis, exercise programs that do not include all-out sprints, likely have a less negative impact on affective state[317], a concern raised regarding supramaximal exercise intensities[428,429].

In the preliminary dataset, session attendance was relatively high across all groups during phase 1, with median attendance ranging from 25 to 27 (83-90%)

out of 30 planned sessions. Although attendance rates are not consistently reported in the literature, these figures are comparable to those reported in other studies, examining HIIT in older adults including clinical populations[430,431]. In COPD, attendance rates are poorly reported[432]. As demonstrated in Paper IV, attendance rates were adequately reported in only 28% of trials. This limits the ability to evaluate and compare the feasibility of previously performed protocols. Nevertheless, those studies that have reported these data generally show similar attendance rates between interval and continuous training[237,290].

In summary, these preliminary findings suggest that supramaximal HIIT can be well-progressed and performed with a relatively high attendance over a 3-month period, comparable to that typically seen with MICT. This indicates that the approach is both feasible and tolerable for individuals with COPD when appropriately prescribed and supervised. Nonetheless, larger studies with longer follow-up are needed to confirm these results, evaluate long-term adherence and feasibility, also during free-living conditions, and determine the potential for clinical implementation. Such work is currently being pursued in the ongoing COPD-HIIT trial.

Assessment and Prescription of Exercise Intensity

To ensure that exercise training is both feasible and appropriately targeted, accurate assessment and prescription of exercise intensity are essential. In this context, the mBCST appears to be a feasible exercise test for both individuals with COPD and healthy controls, enabling supramaximal external workloads while remaining submaximal in terms of cardiorespiratory demand. This was evident from its lower ventilatory, and cardiovascular responses compared with CPET.

The primary objective of using the mBCST was to identify appropriate external workloads to prescribe supramaximal HIIT. Evidently, the achieved workloads were supramaximal and enabled adequate exercise prescription of a feasible session of supramaximal HIIT at 150-200% of MAP, as implemented in Paper I. In line with the principle of specificity, exercise prescription is more accurate when based on physiological anchors closely aligned with the targeted exercise domain. Therefore, mBCST-derived intensities are likely more appropriate than MAP-derived intensities for prescribing supramaximal HIIT. This seems to be especially relevant in COPD, where the mBCST workload/MAP ratio shows greater heterogeneity compared to healthy controls. If MAP alone were used as the reference point, there is a higher risk of under- or over-prescribing exercise intensity, which could either reduce the training stimulus or compromise feasibility.

Feasibility of the test was high, with 94% of participants with COPD completing the mBCST, a rate almost identical to that of healthy older adults. Nevertheless, the requirement to maintain a high target cadence (80–90 RPM) may pose challenges for some individuals. Indeed, one participant was unable to complete the familiarization bout, raising the possibility that cycling naïveté or reduced lower-limb muscle power, both common in older adults and people with COPD[166 433] could limit execution of the test. While a cadence of 80-90 RPM was used in Paper II, it is not per se a necessity in the mBCST or during supramaximal HIIT, if an RPM-independent ergometer is used. However, higher cadences facilitate short-duration intervals against high external resistance[309] and high-cadence familiarization is likely beneficial in this context.

Beyond its feasibility, it is important to consider the physiological underpinnings of performance during an exercise test. Individuals with COPD typically exhibit reductions in both maximal neuromuscular power, anaerobic work capacity (W'), and peak aerobic power, i.e. MAP, each contributing to performance in the mBCST. Yet, the proportion of peak neuromuscular power supported by aerobic metabolism, by some referred to as the aerobic power index, is disproportionately lower in COPD compared to healthy controls[303]. This highlights the dual impact of muscle weakness and impaired oxygen transport, with some evidence suggesting that the latter may be more severely affected in COPD. Consequently, the latent neuromuscular power reserve at the end of a CPET is increased in COPD compared to matched peers and reflects a cardiovascular or pulmonary limitation. This is supported by our findings in Paper II and the RCT, showing no between-group difference in peak mBCST workload when expressed as a percentage of MAP.

By reducing the cardiopulmonary demand and shortening test duration, the mBCST likely depletes the neuromuscular and anaerobic power reserve (W'), to a higher degree than a CPET, thereby providing a more accurate reflection of short-duration power output capacity. This makes the test potentially useful for exercise prescription, as mBCST-derived workloads may better reflect an individual's tolerable high-intensity capacity, allowing for more targeted and individualised supramaximal HIIT in COPD.

While the mBCST may provide a practical means of estimating short-duration power capacity and informing exercise prescription, other methods can offer more detailed physiological profiling. One such approach is the neuromuscular CPET, which quantifies peak neuromuscular power, the aerobic power index, and the power reserve by assessing neuromuscular power before and immediately after a traditional CPET[303]. Although this approach provides comprehensive insight into the interplay between aerobic and neuromuscular function, its complexity and equipment demand (cycle ergometer able to immediately switch

to isokinetic mode) limit clinical feasibility. In this context, the mBCST offers a simpler alternative with greater potential for implementation in clinical practice, while also providing relevant information for exercise prescription, particularly in the setting of supramaximal HIIT.

Another important distinction is that the mBCST is externally paced, performed at a controlled cadence and less strenuous than a CPET, neuromuscular-CPET or a 30-second Wingate test often used to estimate anaerobic capacity. All-out tests, with higher physiological demands, high and uncontrolled pedalling cadence likely requires substantial motivation and is considered challenging for older adults, and externally paced tests might be preferable for exercise naïve individuals[309,434,435].

Physiological Responses

In addition to evaluating feasibility and exercise prescription, the physiological demands of supramaximal HIIT, MICT, and the mBCST were also assessed in the studies and are discussed below.

Cardiorespiratory Demand

The ventilatory demand was lower during supramaximal HIIT compared with MICT despite the higher exercise intensity used. This was in line with the hypothesis and is an encouraging finding considering that ventilatory limitations are a concern not just in high-intensity exercise, but in most forms of exercise in individuals with COPD[137,234,271].

The intermittent structure of supramaximal HIIT, together with its reduced ventilatory load and lower perceived breathlessness, likely explains its higher feasibility and participant preference. Among individuals with COPD, peak dyspnea ratings during supramaximal HIIT were 2.0 (HIIT60) and 0.8 (HIIT80) points lower compared with MICT when assessed using the Borg CR10 scale, exceeding the minimally clinically relevant change of 1 point during the HIIT60 session. Notably, breathlessness in supramaximal HIIT occurs intermittently and was assessed immediately after each six-second effort, whereas in MICT, dyspnea increases continuously and progressively throughout the session. Consistent with this, in individuals with COPD, breathing frequency and minute ventilation were higher during MICT, where participants exercised at approximately 70% of maximum voluntary ventilation, compared with ≈60% during supramaximal HIIT.

The reduced ventilatory strain during supramaximal HIIT may be partly explained by the short duration of work intervals and the relatively long recovery

periods, allowing partial relief of dynamic hyperinflation. Unfortunately, although measurements of dynamic hyperinflation were conducted during exercise, the data quality was sufficient in only a few participants, limiting the ability to draw firm conclusions regarding this mechanism. In addition, the overall mechanical work and oxygen requirement per unit of time are lower during supramaximal HIIT compared with MICT, further reducing the need for sustained ventilatory effort.

Our findings in Paper I indicate that, while the external workload during supramaximal HIIT is supramaximal, the cardiorespiratory strain beyond the ventilatory requirements, in terms of $\dot{V}O_2$ and heart rate, aligns more closely with moderate-to-vigorous intensity levels[247]. In contrast, MICT elicited a sustained vigorous intensity over a longer duration. In relation to concerns about safety and tolerability of supramaximal HIIT[428,429,436], our data do not support the view that it is inherently excessive or accompanied by uniformly high discomfort; the non–all-out, watt-controlled format is likely important in this respect. Consistent with this, the blood pressure response was lower in supramaximal HIIT than MICT, there was no evidence of exercise-induced desaturation and RPE/session RPE tended to be lower during supramaximal HIIT, though not always statistically significant. Still, a comprehensive analysis of adherence and adverse events rates in the COPD-HIIT RCT is needed to establish long-term feasibility, applicability and safety of supramaximal HIIT in COPD.

In line with its intended purpose, the mBCST elicited a submaximal cardiorespiratory response. Compared with the CPET, all cardiopulmonary parameters except $\dot{V}O_2$ and thus $\dot{V}O_2$/heart rate and gas equivalents, were lower during mBCST. Likewise, symptom ratings were reduced. These features position the mBCST as a practical adjunct to CPET, assessing short-duration power outputs without an excessive cardiopulmonary demand.

Exercise-Induced Exerkine Response

The acute effects of exercise on circulating BDNF levels have rarely been studied in COPD. De Araujo[437] reported a decreased level of plasma BDNF, following a session of pulmonary rehabilitation. However, they utilised a relatively low exercise intensity, which likely was too low to elicit an increase in plasma BDNF. As our study is, to the best of my knowledge, the first to study changes in BDNF to intensive exercise in COPD, our findings need to be replicated. Yet, our novel observation indicating that both supramaximal HIIT and MICT elicited an increase in plasma BDNF in individuals with COPD is important, provided the evidence pointing to exercise-induced increase in BDNF being an important mediator for improve cognitive performance[330,331]. Considering the high prevalence of cognitive impairments in COPD, this finding is promising and

warrants further investigation. Notably, individuals with COPD demonstrated an exercise-induced increase in BDNF comparable to that of healthy controls, suggesting that the neurotrophic response to exercise is preserved in COPD and may support the potential for neuroprotective benefits from regular training.

The higher concentration of BDNF in serum compared to plasma is in line with the literature[408,438]. While serum BDNF increased during HIIT80 and MICT for healthy controls, no significant increase was seen in people with COPD. This might reflect a combination of methodological and biological factors. As serum BDNF is influence by platelet degranulation during clotting[439], it might be less sensitive to detecting acute, exercise-induced changes. This might be particularly relevant in the presence of disease, including COPD, in which platelet function might be altered[440]. Notably, the COPD group consumed more medications including corticosteroids and anticoagulants, that might alter platelet function[441]. Provided these considerations and the likely greater physiological importance of plasma, rather than serum BDNF, the lack of a serum BDNF increase in COPD is not considered central to our conclusions.

We also found an increase in clusterin, following both supramaximal HIIT and MICT. While research in clusterin in this context is in its infancy, it is suggested to be involved in reducing neuroinflammation and to, as BDNF, mediate effects of exercise in improving cognitive function[442,443]. It is therefore an interesting finding, warranting further investigation.

The cytokine response was generally similar between supramaximal HIIT and MICT: both elicited an increase in IL-6 at 30 minutes post-exercise, with no notable changes in other pro- or anti-inflammatory markers. This aligns with prior studies in COPD reporting modest acute elevations in inflammatory mediators following exercise[444,445]. The rise in IL-6 is often considered beneficial given its pleiotropic, exercise-linked actions—including anti-inflammatory signalling[2,446]. Collectively, these findings suggest that the exercise-induced cytokine response, even with supramaximal external workloads in COPD, differs from infection-related inflammatory cascades and may contribute to a net anti-inflammatory effect over time[2,446,447]. These responses could be relevant for extrapulmonary outcomes in COPD, including cognition, cardiovascular function and muscle function, where systemic inflammation is implicated[10].

Taken together, both MICT and supramaximal HIIT appear capable of eliciting a potentially beneficial exercise-induced exerkine response. However, the higher feasibility of the supramaximal HIIT protocol, combined with the greater BDNF response when accounting for exercise duration and the more pronounced progression in exercise intensity observed in our preliminary data suggests that supramaximal HIIT may offer certain advantages over MICT in individuals with

COPD. Nevertheless, these findings remain preliminary and will require confirmation upon completion of the full trial.

COPD versus Controls: Exercise Response and Characteristics

Acute Responses

Cardiopulmonary responses in COPD compared to healthy controls have mainly been studied in low- and moderate-intensity constant-load exercise, but not HIIT. Our findings in Paper I demonstrate that, although minute ventilation was similar, participants with COPD exercised closer to their maximal voluntary ventilation and exhibited higher ventilatory equivalents for both O_2 and CO_2, also during supramaximal HIIT. Although both groups exercised at a similar relative intensity when expressed as %peak VO_2, the continuous nature of MICT required COPD participants to sustain this intensity at a higher ventilatory cost, which is an expected finding. One can argue that such prolonged strain is more likely to provoke intolerable dyspnea and fatigue, limiting training duration and adherence. The symptom ratings were consistent with this pattern. At the same %MAP, dyspnea and leg fatigue were higher in COPD across sessions. During MICT, those with COPD reported higher dyspnea and RPE than healthy controls already after one minute. In Supramaximal HIIT, these differences took longer to manifest: dyspnea after the fifth interval/minute, and RPE only at end-of sessions, suggesting delayed onset of symptoms compared to MICT.

A novel finding from Paper I is that individuals with COPD can increase plasma BDNF levels in response to exercise to a similar extent as matched healthy controls. Given the established role of BDNF in supporting neuroplasticity and brain health, this is an encouraging finding that merits further study in larger and longer-term studies.

Not surprisingly, as seen in Paper II, those with COPD achieved significantly lower workloads in the mBCST and CPET, compared to age- sex- and physical activity matched healthy controls. Yet, their performance relative to MAP was, in average, similar at ≈150% of MAP but showed a greater heterogeneity (Figure 13). The average mBCST workload/MAP ratio is confirmed in the preliminary findings from the RCT (145% in both groups), as well as the greater heterogeneity in this ratio, although not as marked.

The COPD-HIIT RCT: Participant Characteristics

The COPD cohort enrolled to date, in line with our aim and the broad eligibility criteria, represents a heterogeneous sample with respect to disease severity,

clinical characteristics and physical capacity. On average, participants present with moderate airflow limitation (FEV_1 %predicted: 63%), a moderate impact of disease (CAT score: 14.9), and a markedly reduced exercise capacity compared with matched healthy controls.

Approximately 20%, 50%, and 30% of enrolled participants exhibit mild (GOLD I), moderate (GOLD II), and severe to very severe (GOLD III–IV) airflow limitation, respectively. This distribution aligns with international data showing GOLD II as the most common stage among people with COPD (~50%), followed by GOLD I, with fewer cases in GOLD III–IV[448]. Compared with Swedish population studies, which report very low population prevalence of severe stages, our proportion of GOLD III–IV is slightly higher[18,449]. This is to some extent influenced by the higher proportion of GOLD III–IV among participants recruited in Belgium. Thus far, the COPD cohort provides a clinically representative sample, including all spectrums of the disease, also regarding symptom burden.

The COPD and healthy control groups are well matched for age and sex. Physical activity (steps per day) is not statistically different, but clinically meaningful. Future enrolment will strive to include healthy controls with a lower step count, to better mirror the COPD group. Yet, this is not always easy. As expected, participants with COPD report a greater smoking history, and they also report higher occupational exposures and adult-life passive smoking, suggesting that factors beyond cigarette smoking contribute to the disease. Notably, the groups differ in education level. While not a pre-specified matching criterion, this may influence cognitive outcomes. Consequently, years of education should be considered as a covariate in analyses involving cognition in the statistical analysis plan that will be finished before the enrolment of the last participant in the RCT[381].

The finding that individuals with COPD performed worse across multiple cognitive domains, including a twofold higher frequency of scores below suggested MoCA cut-offs for mild cognitive impairment, is not unexpected. However, the CANTAB tests represent raw performance scores, and their clinical relevance remains to be determined in the final dataset, for example by comparing results with normative values and performance of the healthy controls. Yet, it reinforces that cognitive impairment is an extrapulmonary consequence of COPD, also among those with relatively preserved cardiorespiratory fitness and lung function. Notably, the groups showed comparable levels of systemic inflammation, as indicated by fibrinogen. Within the RCT, further analyses will examine additional inflammatory markers and underlying mechanisms of cognitive impairment.

Lastly, given that quadriceps weakness is often reported in COPD[165-167], the similar quadriceps 1-repetition maximum observed between COPD and healthy controls is somewhat unexpected. This might be explained by the testing mode. We used isotonic testing, i.e. constant external torque across the full range of motion. Subsequently, performance is limited by the weakest joint-angle, which typically is at end-extension, and not by mid-range capacity where humans are generally strongest. Notably, this limitation did not preclude between-group differences in functional capacity, muscle endurance or power output on the mBCST, indicating that strength assessed in this manner may be less sensitive to COPD-related impairments than power, endurance- or function-oriented measures. Yet, the findings of a greater impairment in quadriceps power and endurance compared to strength properties of the muscle are in line with a previous international multicentre study executed by our research group[166].

Methodology and Reporting Quality

The systematic review (Paper IV) is the first study to comprehensively evaluate the quality of reporting and application of training principles in RCTs with aerobic training in COPD. The findings confirmed that, despite the important role of aerobic training in pulmonary rehabilitation, there are considerable shortcomings in the quality of reporting in aerobic training trials within the COPD literature.

Overall, reporting of participant and intervention characteristics showed considerable variability. Fundamental information such as age, sex, and pulmonary function was generally well reported, although not consistently, despite the fact that such information should be included in all clinical trials[351]. Among the FITT components, exercise frequency and type were generally well-documented, whereas duration and intensity were frequently omitted or inadequately defined, limiting the interpretation of training dose. Similarly, delivery format, supervision, and group size were poorly reported, which is troublesome given their likely influence on feasibility and adherence[346]. Reporting of attendance and adherence was also sparse, which further hinders evaluation of intervention fidelity and the actual training undertaken. These gaps hinder comparison between studies and make replication and clinical translation challenging.

The mean CERT score of 5.4 (3.0) was lower than that observed in other clinical populations such as chronic heart failure[450] and hip osteoarthritis[451]. This discrepancy might be partly explained by the fact that aerobic training is usually one of several components and may receive less detailed documentation. Yet also

stand-alone aerobic interventions showed low CERT scores, suggesting that insufficient reporting standards persist across the field.

Most trials applied few exercise training principles, with specificity being the most frequently addressed. In general, the number of principles applied was comparable, but lower, compared to exercise trials in e.g. cancer[348,359]. This suggests that aerobic training interventions in COPD might not always be grounded in established exercise science frameworks.

While this is the first study addressing the quality of reporting in aerobic training trials involving individuals with COPD, Moecke et al. (2023)[362] systematically reviewed 27 trials in which COPD patient were given rehabilitation after an exacerbation, and similar reviews have been performed in other clinical population, including cancer[353,360], cardiac rehabilitation[452] and peripheral artery disease[356]. While Moecke et al. also found suboptimal reporting of the FITT components and exercise adherence, the trials in their reviews generally reported a slightly higher number of training principles (median: 3)[362]. Differences in definitions and in the inclusion of the principle of diminishing returns (used by Moecke et al. instead of individualization) may explain this discrepancy to some extent. Notably, several of the trials included in Moecke et al. were also part of our systematic review, and the results from both studies point toward the same overall conclusion: reporting quality in COPD exercise trials remains poor. That is, it could use some training itself.

While this study focused on the reporting of exercise-specific details using the CERT framework and established training principles, it did not assess adherence to broader reporting checklists such as CONSORT. The primary aim was to evaluate how aerobic interventions and participant characteristics were described. Some overlap exists with CONSORT and particularly TIDieR, but the emphasis here was on the quality and completeness of exercise-related reporting.

The systematic review (Paper IV) has been highly labour-intensive and resource-demanding undertaking, requiring extensive work among multiple reviewers. Each study was screened and all data extracted in duplicate, with a third reviewer resolving discrepancies and verifying agreement across a large set of variables. It is plausible that this represents one of the last generations of manually conducted systematic reviews, as ongoing advances in artificial intelligence and large language models are likely to substantially automate and transform future evidence synthesis. Recently, leveraged by the recent advances in large language models, a large-scale study evaluated the reporting quality of 21 041 RCTs in the field of medicine, in terms of CONSORT compliance. While reporting has improved over time, critical methodological components remain underreported[339].

Implications of Poor Reporting

The inadequate reporting of interventions has important implications for the translation and implementation of research findings. Poorly reported interventions limits reproducibility, hinder evidence synthesis, and contribute to research waste by making studies difficult to interpret, replicate, or implement clinically.

To advance the field, future studies should prioritize transparent and standardized reporting. This includes adherence to established reporting guidelines such as CONSORT for trial design and outcomes, CERT for exercise-specific details, along with TIDieR for describing the intervention in sufficient detail to allow replication. Consistent use of these frameworks will improve the reproducibility of findings, enable meta-analyses, and ultimately facilitate the integration of aerobic training into routine COPD care in a more evidence-informed and effective manner.

In light of this, the present thesis placed emphasis on detailed reporting of exercise protocols and participant characteristics across the included papers. Although reporting space is often limited in journals, Paper III provides comprehensive documentation of the methods, supported by tables following the TIDieR and CERT frameworks, alongside the SPIRIT checklist.

Although Paper III could not incorporate the findings of Paper IV, as the latter was completed after its publication, the use of the TIDieR and CERT frameworks in Paper III resulted in comprehensive documentation of key intervention details. Specifically, all four FITT principles, all seven training principles, and 16 out of 16 applicable CERT items were reported (as a protocol, e.g. number of adverse events and exercise adherence cannot be reported but only how it will be reported). Notably, certain items can only be fully reported once the study is finished, such as the actual qualifications of the supervisors, the final attendance rate and number of dropouts etc, but preliminary information was included and deemed adequate in our self-evaluation These results show that systematic use of the CERT guideline, as done in Paper III, can improve reporting quality and make studies easier to replicate, something less often seen in the trials reviewed in Paper IV.

Methodological Considerations

The studies included in this thesis demonstrate several methodological strengths alongside certain limitations.

Guidelines, Pre-registrations, Bias and Sample Size

Overall, reporting across the studies adhered to relevant guidelines. Paper I followed applicable items from the CONSORT statement for cross-over designs; Paper II adhered to The Strengthening the Reporting of Observational Studies in Epidemiology statement; and Paper III was reported in accordance with SPIRIT, TIDieR, and CERT. Paper IV followed PRISMA, with its protocol developed following PRISMA-P and prospectively registered in PROSPERO. For the RCT, pre-registration and protocol publication, including prespecified primary and secondary outcomes, enhance transparency and reproducibility[337,453].

Regarding the RCT, the use of randomisation, concealed allocation, blinded outcome assessors and intention-to-treat analyses is used to minimise bias, according to guidelines[351]. High-quality RCTs remain important in the context of HIIT, supramaximal HIIT, and exercise interventions in COPD[454,455]. Also, regarding sample size, the COPD-HIIT RCT is comparatively large within this field. While there are some large trials on pulmonary rehabilitation, these often comprise of a generic and less-controlled exercise training regimens, combined with multi-modal rehabilitation[456-458].

While it is best to blind as many as possible in a trial[459], neither training supervisors nor participants can be blinded given the nature of the interventions. Nevertheless, potential bias from unblinded supervisors should be limited based on the pre-specified criteria for exercise progression, and tablet-guided intervals. To reduce performance bias, participants were informed about the general purpose of the trial but not the rationale and hypothesis of supramaximal HIIT.

Data validity and reliability depend on robust collection methods[460]. Accordingly, standardization was emphasized across Papers I-III. This includes uniform instructions, warm-up and assessment protocols and rest intervals, for example. The same assessor was used for pre- and post-intervention assessments, to the extent possible, as a step to reduce bias between assessors. To control for circadian effects in performance and physiological responses, repeated visits in Paper I, as well as the pre- and post-intervention assessment in the RCT, were scheduled at the same time of day. Cross-centre standardization was supported by identical equipment, protocols and site visits to align training supervisors and assessors.

Blood Analyses

While an extensive discussion could be devoted to blood sampling methodology, including pre- and post-analytical considerations, I will highlight two key points regarding blood sample analyses and BDNF, a primary outcome in Paper I.

In Paper I, biomarker concentrations were adjusted for exercise-induced changes in plasma volume, ensuring that observed changes reflected physiological response rather than shifts due to haemoconcentration[390]. This correction attenuated the increase in analyte levels by approximately 5-10%. Notably, without this adjustment, several analytes would have appeared to increase significantly, potentially leading to an overestimation of the exercise effect. This highlights a possible source of bias that may be present in other studies when this correction is not performed, perhaps influenced by the tendency to emphasize positive or novel findings.

Further, similar to much of the existing literature on BDNF, the analysis did not differentiate between its two primary isoforms: mature BDNF and proBDNF. In brief, these isoforms have opposing biological actions with mature BDNF responsible for the neuroprotective and neuroplastic benefits via its binding to Trk receptors, while proBDNF is associated with apoptotic and neurodegenerative processes[461]. The lack of isoform-specific analysis, along with methodological differences such as the use of plasma versus serum, may contribute to inconsistencies in the literature. Nevertheless, some recent evidence suggests that proBDNF is unresponsive to exercise stimuli[462] suggesting that acute exercise-induced changes in circulating BDNF are primarily driven by increases in mature BDNF. Thus, BDNF analyses in the RCT should analyse mature BDNF.

Monitoring

One methodological strength shared by Paper I and II is the use of thorough measurement protocols. This included continuous monitoring of indirect calorimetry and physiological parameters, symptom ratings, perceived exertion and external workload. As such, we were able to characterize the exercise response across the physiological, subjective and objective domains, providing a nuanced understanding of the exercise load. These insights also offered valuable information to guide our further research in the RCT and tailoring the exercise protocols. In Paper I and II, different systems for indirect calorimetry were used during the CPET compared to that during supramaximal HIIT, MICT and, mBCST, which introduces a source of bias. While this does not affect comparisons between the COPD and healthy controls, or comparisons between supramaximal

HIIT and MICT, data expressed as a percentage of CPET values should be interpreted with this limitation in mind.

Ceiling Effects?

A potential limitation in the RCT is ceiling effects in some outcomes. That is, when the highest possible performance or score is not high enough, or there is little or no improvement in performance of the task despite true gains in capacity. Given the heterogeneity of participants' physical function, certain assessments are easy for some and difficult for others (e.g., stair-climb power and five-times-sit-to-stand). For isotonic quadriceps power on the Biodex, the low breaking force (1 Nm), while being found to be reliably in a healthy population, likely produces ceiling effects in participants with well-preserved neuromuscular function. A higher breaking force, such as a percentage of 1-repetition maximum, would maybe better detect change. These constraints reduce responsiveness, particularly in healthy controls of younger age. As a mitigation, we will consider sensitivity analyses excluding high baseline performers (e.g., those above 400 °/s in the Biodex quadriceps power test or those climbing a 10-step flight of stairs in ~3 seconds). Notably, some outcomes are indeed responsive based on previous literature and our perception as assessors within the RCT, highlight that not least the CWRT (time to exhaustion)[426], the isotonic quadriceps strength and endurance test, as well as the TMTs are highly responsive. Still, no formal analysis has yet been performed in the RCT and will only be performed once all participants have been included in each phase of the study.

Usual Care Arm

The primary aim of including the usual care arm is to enable us to evaluate if exercise training, regardless of exercise intensity, impacts neurodegeneration trajectories over time. Including this arm in randomisation was avoided for pragmatic reasons, mainly recruitment feasibility. Participants in this arm are not required to attend supervised sessions, allowing inclusion of those living farther from trial centres, as they only attend baseline and 24-month assessments. In Umeå, this has facilitated inclusion of participants from locations such as Örnsköldsvik (110 km away), Lycksele (128 km away) and even Luleå (265 km away). However, as randomisation minimizes bias associated with allocation[351,463], this introduces selection bias and potentially a group that differs systematically from those in the other intervention arms. To mitigate this limitation, participants in the usual care arm will be matched to those in the intervention arms based on key variables: age, sex, disease severity, education level, and objectively measured physical activity. While this matching approach helps reduce confounding, it does not fully replace the benefits of randomisation.

Practical Implications and Future Research

The findings of this thesis have several practical implications for the design, implementation, and reporting of exercise training for people with COPD. Collectively, the findings support supramaximal HIIT as a feasible and physiologically adequate training modality in COPD, while also identifying major gaps in how exercise interventions are reported in the scientific literature.

From a clinical perspective, supramaximal HIIT provides a time-efficient and attractive alternative to MICT. The protocol allowed participants with COPD to exercise at higher external workloads without increasing dyspnea or overall ventilatory strain. When appropriately prescribed, supervised, and individually progressed, supramaximal HIIT can therefore represent a viable, potentially superior, exercise strategy within pulmonary rehabilitation, perhaps particularly for patients limited by dyspnea during sustained continuous exercise.

The use of RPM-independent cycle ergometers in this thesis ensured precise control of workload during supramaximal HIIT, without requiring manual resistance adjustments. In the RCT, shis setup also enabled measurement of the work performed and objective tracking of adherence during phase 2, as all exercise data were automatically recorded. A similar protocol has also been successfully applied in healthy older adults using conventional cadence-dependent ergometers[310,315]. For broader clinical and community use, guidance on how to reach the intended intensity through cadence, resistance, or perceived dyspnea or exertion could support implementation. Workload-controlled systems offer advantages for standardisation and supervision, but conventional ergometers remain a practical alternative when properly standardized. Future work should evaluate and refine these methodological adaptations to ensure safety, fidelity and effectiveness across diverse training settings. Recently, it was shown that supramaximal HIIT can be implemented for older adults in a community setting, provided adequate support is available[464], although its long-term effectiveness in healthy and clinical populations remains to be established.

The mBCST showed promise as a clinically applicable method to determine individualised workloads for supramaximal HIIT. It enabled prescription of high external intensities while reducing ventilatory strain. This approach could help clinicians better match exercise prescription to an individual's tolerance, to improve training outcomes. However, further evaluation of other measurement properties, including reliability and responsiveness, still needs to be performed. While the mBCST workloads in this thesis were based on MAP achieved during CPET, a CPET is not strictly required to perform the test. Workload increments could instead be estimated from predicted MAP values using normative

equations, such as those in the ERS CPET guidelines[298]. This may broaden mBCST applicability where CPET is unavailable, though further validation is needed before such approaches can be recommended, especially for older individuals with COPD or other chronic respiratory diseases.

From a methodological standpoint, the systematic review revealed that many aerobic exercise trials in COPD fail to adequately describe important aspects of their interventions. This lack of transparency limits reproducibility and the ability to interpret and apply findings in clinical settings. The low reporting of training principles indicates that aerobic interventions in COPD are not optimally designed, possibly reducing intervention efficacy. As such, individuals with COPD may not receive full benefits that better designed exercise program could provide.

Looking ahead, long-term RCTs are needed to determine the effectiveness of supramaximal HIIT on improving extrapulmonary manifestations in COPD, which will be addressed in the ongoing COPD-HIIT RCT. Phase 2 of this trial, where participants train relatively independently, including at home, provides an initial step toward real-world implementation, but more rigorous implementation research is needed to evaluate feasibility, safety, and adherence in clinical and non-clinical settings. Future studies could also investigate the optimal duration and type of recovery in between the supramaximal bouts to optimise prescription, as these parameters influence the tolerance to repeated bouts[465]. It would also be of interest to explore the applicability of supramaximal HIIT in other populations where dyspnea and limited exercise capacity are key features, such as chronic heart failure[466] and other chronic respiratory diseases including interstitial lung disease[467]. Finally, future trials within pulmonary rehabilitation should consistently apply standardized reporting frameworks (CONSORT, TIDieR, CERT) to improve transparency, replication, clinical translation and reduce research waste.

Conclusions

Based on the findings of this thesis, the following conclusions can be drawn:

- Short-duration, watt-controlled supramaximal HIIT appears feasible for individuals with COPD. It allows higher external exercise intensities while reducing ventilatory demand and perceived dyspnea compared with MICT.

- Both supramaximal HIIT and MICT acutely increased plasma BDNF levels in individuals with COPD and in healthy controls, indicating preserved neurotrophic responsiveness to exercise in COPD, that could contribute to the cognitive and neuroprotective benefits of exercise training.

- The mBCST is a feasible test in people with COPD and matched healthy controls. It enables supramaximal external workloads and may be better suited than CPET for prescribing supramaximal exercise intensities.

- The ongoing COPD-HIIT RCT has currently enrolled more than half of its target sample size. A representative COPD cohort and a relatively well-matched control group have been included, and the first participants have completed their 24-month follow-up.

- At baseline, participants with COPD demonstrate reductions in cognitive, cardiorespiratory and quadriceps function. The COPD-HIIT RCT will provide insights into the effectiveness of supramaximal HIIT to improve these extrapulmonary outcomes.

- The reporting quality and application of exercise training principles in aerobic training RCTs involving COPD is suboptimal. Improved adherence to established reporting frameworks is essential to enhance reproducibility, clinical translation, and evidence-based practice.

Acknowledgements – Tack

The completion of this thesis was made possible through the support, guidance, and participant of many people, to whom I am deeply grateful.

To ***all participants*****,** for your contribution to this research through your time, energy, and dedication. Your participation has been central to advancing knowledge and improving the management for people with COPD. Thank you for completing demanding assessments that challenged both body and mind, and showing up for training sessions even in harsh and cold weather. Your commitment made this work possible.

André Nyberg*,* my main supervisor and incurable yet remarkably successful time optimist. I am grateful that our paths crossed when I, at last, secured a PhD student position. Your mentorship over these years has been invaluable, equipping me with the tools, skills, and experience needed for academia, and for that, I am genuinely thankful. Your solution-oriented approach to every challenge and hinder along the way has inspired me throughout these years, an attitude I hope to carry forward in both work and life.

Jana De Brandt*,* co-supervisor and endless provider of office chocolate. I couldn't have asked for better co-supervisor and colleague. A true teammate during the most hectic periods of data collection, always bringing positivity and energy. Your eye for detail is so sharp that few typos or errors ever stood a chance.

Per Stål**,** co-supervisor, for your encouraging attitude and for the stimulating discussions that have supported and enriched this research.

Christer Malm, my first mentor and employer in academia. For almost a decade, you have been intellectually challenging me. Your advice (and occasional nagging) has been important in shaping my approach to science. I am grateful for your support and for pushing me to think critically.

Jonas Westman*,* for being a steady, down-to-earth presence and an easy-going office companion throughout this journey and for stepping in when needed.

Evelina Sund and ***Dries Cops****,* for being great teammates throughout this project and for your steady support and good company along the way.

Michael Svensson, my examiner, for keeping track of my progress throughout the years, and for always being a source of ideas, inspiration, and kind attention.

Emma Simonsson, for, during our time as office colleagues, regularly interrupting my work with thoughtful questions, reminding me to take breaks, and being one of few Swedes who has an interest in professional cycling.

Mattias Hedlund, for your stimulating ideas, shared enthusiasm for physiology, and valued support and input during these years.

Peter Klijn, for your positive spirit and extensive work with the aerobic training review.

Harry Rossiter, for kindly hosting me during my research stay at the Lundquist Institute in Los Angeles, and for sharing your inspiring and characteristically deep physiological thinking.

Anna-Clara Rullander, for your careful and skilled work in taking blood samples from less-than-cooperative veins during exercise, and for your assistance in Paper I. ***Thomas Sandström,*** for your prompt assessments of important matters, often despite a very limited schedule. ***Tobias Stenlund***, for patiently putting up with my constant bothering about lab equipment, calibration and maintenance and for always finding a way to help, when you perhaps did not really have the time. ***Joel Kärrman,*** for helping with testing during hectic periods, always with a smile. ***Linus Karlsson***, for your persistent assistance with sometimes monotonous tasks. ***Jonas Lorentzon,*** for taking care of the important things and for being one of the few still at work after 3 PM on a Friday.

Chris Burtin, Harry Gosker, Carl-Johan Boraxbekk, Nina Karalija, David Ruttens, Anouk Stoffels, Erik Frykholm, Eva Sunna and all other co-authors and collaborators, assisting to the projects within this thesis, one way or another.

To all colleagues who provided valuable feedback throughout the development of this thesis, not least ***Apostolos Theos*** who ended up being involved all stages from admission seminar to pre-defence.

I also want to acknowledge some teachers who, over the course of my twenty-something years in school, helped steer me gently in this direction. ***Monica Sundqvist*** and ***Stina Johansson***, for your inspiring energy and love of teaching natural science. Also, a thought to a few naprapaths and opticians whose skill at their craft deserves recognition for making the work with this thesis a bit more comfortable.

Mina vänner, för de stunder då ni fått mig att släppa tankarna på arbete och tänka på annat.

Mormor, du har länge sagt att du hoppas vara vid livet vid min disputation. We made it!

Darwin, för att du höll oss sällskap på ditt eget självständiga sätt. För att du påminde mig om vad som verkligen betyder något i livet. Inte är det en presentation på forskningskongress i Wien. Sov i ro.

Cecilia, Kenneth och ***Piteåfamiljen***. För ert stora hjärta – där det sällan är tyst men alltid fullt av liv och värme.

Min familj, för er kärlek och ert stöd. ***Mamma,*** för att du påminner mig om vad verklig styrka och uthållighet innebär. Din förmåga att hantera motgångar och se det positiva i livet inspirerar mig varje dag. ***Pappa***, för att du är min största supporter vad jag än tar mig för. Din omsorg om andra betyder mycket för många. Tack för att ni alltid finns där.

Tina, min livspartner, för ditt tålamod, stöd och din kärlek. Tack för att du finns vid min sida. Nu väntar vårt största äventyr, tillsammans.

This work was funded by the Swedish Research Council; The Swedish Heart and Lung Foundation; The European Research Council; Strategisk forskningsresurs Medicinska fakulteten, Umeå Universitet and Strategiska Forskningsområdet– Vårdvetenskap (SFO-V) with supporting grants from JC Kempes Stipendiefond; Anna Cederbergs stiftelse; Knut och Alice Wallenbergs Stiftelse; Arnerska forskningsfonden; Sven och Dagmar Salens stiftelser och Svenska Sällskapet för Medicinsk Forskning.

References

1 Celli, B. R. *et al.* An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. *Am. J. Respir. Crit. Care Med.* **204**, 1251-1258 (2021). https://doi.org:10.1164/rccm.202108-1819PP

2 Chow, L. S. *et al.* Exerkines in health, resilience and disease. *Nat. Rev. Endocrinol.* **18**, 273-289 (2022). https://doi.org:10.1038/s41574-022-00641-2

3 Buchheit, M. & Laursen, P. B. High-Intensity Interval Training, Solutions to the Programming Puzzle. *Sports Med.* **43**, 313-338 (2013). https://doi.org:10.1007/s40279-013-0029-x

4 Pedersen, B. K. Muscle as a secretory organ. *Compr Physiol* **3**, 1337-1362 (2013). https://doi.org:10.1002/cphy.c120033

5 Poole, D. C., Burnley, M., Vanhatalo, A., Rossiter, H. B. & Jones, A. M. Critical Power: An Important Fatigue Threshold in Exercise Physiology. *Med. Sci. Sports Exerc.* **48** (2016).

6 de Oca, M. M. *et al.* The global burden of COPD: epidemiology and effect of prevention strategies. *The Lancet Respiratory Medicine* **13**, 709-724 (2025). https://doi.org:10.1016/S2213-2600(24)00339-4

7 World Health Organization. *The top 10 causes of death* <https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death> (2025).

8 GOLD. The Global Strategy for Diagnosis, Management and Prevention of COPD, 2025 report. (2024).

9 Organization, W. H. *Chronic obstructive pulmonary disease (COPD)*, <https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)> (2025).

10 Barnes, P. J. & Celli, B. R. Systemic manifestations and comorbidities of COPD. *Eur. Respir. J.* **33**, 1165 (2009). https://doi.org:10.1183/09031936.00128008

11 Rochester, C. L. *et al.* Pulmonary Rehabilitation for Adults with Chronic Respiratory Disease: An Official American Thoracic Society Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* **208**, e7-e26 (2023). https://doi.org:10.1164/rccm.202306-1066ST

12 Garrod, R., Marshall, J., Barley, E. & Jones, P. W. Predictors of success and failure in pulmonary rehabilitation. *The European respiratory journal* **27**, 788-794 (2006).

13 Desachy, M. *et al.* High Prevalence of Non-Responders Based on Quadriceps Force after Pulmonary Rehabilitation in COPD. *Journal of Clinical Medicine* **12** (2023).

14 Burtin, C. *et al.* Effectiveness of exercise training in patients with COPD: The role of muscle fatigue. *Eur. Respir. J.* **40**, 338-344 (2012).

15 Adeloye, D. *et al.* Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review

and modelling analysis. *The Lancet Respiratory Medicine* (2022). https://doi.org:10.1016/S2213-2600(21)00511-7

16 Safiri, S. *et al.* Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ* **378**, e069679 (2022). https://doi.org:10.1136/bmj-2021-069679

17 Stolz, D. *et al.* Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. *The Lancet* (2022). https://doi.org:10.1016/S0140-6736(22)01273-9

18 Backman, H. *et al.* Decreased COPD prevalence in Sweden after decades of decrease in smoking. *Respir. Res.* **21**, 283 (2020). https://doi.org:10.1186/s12931-020-01536-4

19 Danielsson, P., Ólafsdóttir, I. S., Benediktsdóttir, B., Gíslason, T. & Janson, C. The prevalence of chronic obstructive pulmonary disease in Uppsala, Sweden--the Burden of Obstructive Lung Disease (BOLD) study: cross-sectional population-based study. *Clin. Respir. J.* **6**, 120-127 (2012). https://doi.org:10.1111/j.1752-699X.2011.00257.x

20 Lopez, A. D. *et al.* Chronic obstructive pulmonary disease: current burden and future projections. *Eur. Respir. J.* **27**, 397-412 (2006). https://doi.org:10.1183/09031936.06.00025805

21 Sleeman, K. E. *et al.* The escalating global burden of serious health-related suffering: projections to 2060 by world regions, age groups, and health conditions. *Lancet Glob Health* **7**, e883-e892 (2019). https://doi.org:https://doi.org/10.1016/S2214-109X(19)30172-X

22 Adeloye, D. *et al.* Global and regional estimates of COPD prevalence: Systematic review and meta-analysis. *J Glob Health* **5**, 020415 (2015). https://doi.org:10.7189/jogh.05.020415

23 Landis, S. H. *et al.* Continuing to Confront COPD International Patient Survey: methods, COPD prevalence, and disease burden in 2012-2013. *Int. J. Chron. Obstruct. Pulmon. Dis.* **9**, 597-611 (2014). https://doi.org:10.2147/copd.S61854

24 Chen, S. *et al.* The global economic burden of chronic obstructive pulmonary disease for 204 countries and territories in 2020-50: a health-augmented macroeconomic modelling study. *Lancet Glob Health* **11**, e1183-e1193 (2023). https://doi.org:10.1016/s2214-109x(23)00217-6

25 HjärtLung, R. Kolrapporten (2023).

26 NIH. *Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)*, <https://report.nih.gov/funding/categorical-spending#/> (2024).

27 Fletcher, C. & Peto, R. The natural history of chronic airflow obstruction. *Br. Med. J.* **1**, 1645-1648 (1977). https://doi.org:10.1136/bmj.1.6077.1645

28 Agustí, A., Melén, E., DeMeo, D. L., Breyer-Kohansal, R. & Faner, R. Pathogenesis of chronic obstructive pulmonary disease: understanding the contributions of gene-environment interactions across the lifespan. *Lancet Respir Med* **10**, 512-524 (2022). https://doi.org:10.1016/s2213-2600(21)00555-5

29 Alvar, A. *et al.* Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD Executive Summary. *Eur. Respir. J.* **61**, 2300239 (2023). https://doi.org:10.1183/13993003.00239-2023

30 Yang, I. A., Jenkins, C. R. & Salvi, S. S. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med* **10**, 497-511 (2022). https://doi.org:10.1016/s2213-2600(21)00506-3

31 Lu, W. *et al.* Tobacco and COPD: presenting the World Health Organization (WHO) Tobacco Knowledge Summary. *Respir. Res.* **25**, 338 (2024). https://doi.org:10.1186/s12931-024-02961-5

32 Chen, P., Li, Y., Wu, D., Liu, F. & Cao, C. Secondhand Smoke Exposure and the Risk of Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. *Int. J. Chron. Obstruct. Pulmon. Dis.* **18**, 1067-1076 (2023). https://doi.org:10.2147/copd.S403158

33 Raad, D. *et al.* Effects of water-pipe smoking on lung function: a systematic review and meta-analysis. *Chest* **139**, 764-774 (2011). https://doi.org:10.1378/chest.10-0991

34 Tan, W. C. *et al.* Marijuana and chronic obstructive lung disease: a population-based study. *CMAJ* **180**, 814-820 (2009). https://doi.org:10.1503/cmaj.081040

35 Assad, N. A., Balmes, J., Mehta, S., Cheema, U. & Sood, A. Chronic obstructive pulmonary disease secondary to household air pollution. *Semin. Respir. Crit. Care Med.* **36**, 408-421 (2015). https://doi.org:10.1055/s-0035-1554846

36 Guo, C. *et al.* Effect of long-term exposure to fine particulate matter on lung function decline and risk of chronic obstructive pulmonary disease in Taiwan: a longitudinal, cohort study. *Lancet Planet Health* **2**, e114-e125 (2018). https://doi.org:10.1016/s2542-5196(18)30028-7

37 Kohansal, R. *et al.* The Natural History of Chronic Airflow Obstruction Revisited. *Am. J. Respir. Crit. Care Med.* **180**, 3-10 (2009). https://doi.org:10.1164/rccm.200901-0047OC

38 Agusti, A. & Faner, R. Lung function trajectories in health and disease. *Lancet Respir Med* **7**, 358-364 (2019). https://doi.org:10.1016/s2213-2600(18)30529-0

39 Cho, M. H., Hobbs, B. D. & Silverman, E. K. Genetics of chronic obstructive pulmonary disease: understanding the pathobiology and heterogeneity of a complex disorder. *Lancet Respir Med* **10**, 485-496 (2022). https://doi.org:10.1016/s2213-2600(21)00510-5

40 Strange, C. Alpha-1 Antitrypsin Deficiency Associated COPD. *Clin. Chest Med.* **41**, 339-345 (2020). https://doi.org:10.1016/j.ccm.2020.05.003

41 Stoller, J. K. & Aboussouan, L. S. Alpha1-antitrypsin deficiency. *Lancet* **365**, 2225-2236 (2005). https://doi.org:10.1016/s0140-6736(05)66781-5

42 Townend, J. *et al.* The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study. *Eur. Respir. J.* **49** (2017). https://doi.org:10.1183/13993003.01880-2016

43 Beran, D., Zar, H. J., Perrin, C., Menezes, A. M. & Burney, P. Burden of asthma and chronic obstructive pulmonary disease and access to essential medicines in low-income and middle-income countries. *Lancet Respir Med* **3**, 159-170 (2015). https://doi.org:10.1016/s2213-2600(15)00004-1

44 Martínez-García, M. *et al.* Chronic Bronchial Infection Is Associated with More Rapid Lung Function Decline in Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc* **19**, 1842-1847 (2022). https://doi.org:10.1513/AnnalsATS.202108-974OC

45 Byrne, A. L., Marais, B. J., Mitnick, C. D., Lecca, L. & Marks, G. B. Tuberculosis and chronic respiratory disease: a systematic review. *Int. J. Infect. Dis.* **32**, 138-146 (2015). https://doi.org:10.1016/j.ijid.2014.12.016

46 Bigna, J. J., Kenne, A. M., Asangbeh, S. L. & Sibetcheu, A. T. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. *Lancet Glob Health* **6**, e193-e202 (2018). https://doi.org:10.1016/s2214-109x(17)30451-5

47 Gingo, M. R. *et al.* Decreased Lung Function and All-Cause Mortality in HIV-infected Individuals. *Ann Am Thorac Soc* **15**, 192-199 (2018). https://doi.org:10.1513/AnnalsATS.201606-492OC

48 Celli, B. *et al.* Definition and Nomenclature of Chronic Obstructive Pulmonary Disease: Time for Its Revision. *Am. J. Respir. Crit. Care Med.* **206**, 1317-1325 (2022). https://doi.org:10.1164/rccm.202204-0671PP

49 Hogg, J. C. & Timens, W. The pathology of chronic obstructive pulmonary disease. *Annu. Rev. Pathol.* **4**, 435-459 (2009). https://doi.org:10.1146/annurev.pathol.4.110807.092145

50 Barnes, P. J. Inflammatory mechanisms in patients with chronic obstructive pulmonary disease. *J. Allergy Clin. Immunol.* **138**, 16-27 (2016). https://doi.org:10.1016/j.jaci.2016.05.011

51 Barnes, P. J. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. *Clin. Chest Med.* **35**, 71-86 (2014). https://doi.org:10.1016/j.ccm.2013.10.004

52 Domej, W., Oettl, K. & Renner, W. Oxidative stress and free radicals in COPD--implications and relevance for treatment. *Int. J. Chron. Obstruct. Pulmon. Dis.* **9**, 1207-1224 (2014). https://doi.org:10.2147/copd.S51226

53 Stockley, R. A. Neutrophils and protease/antiprotease imbalance. *Am. J. Respir. Crit. Care Med.* **160**, S49-52 (1999). https://doi.org:10.1164/ajrccm.160.supplement_1.13

54 Putman, R. K. *et al.* Association Between Interstitial Lung Abnormalities and All-Cause Mortality. *JAMA* **315**, 672-681 (2016). https://doi.org:10.1001/jama.2016.0518

55 Peinado, V. I. *et al.* Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *Am. J. Physiol.* **274**, L908-913 (1998). https://doi.org:10.1152/ajplung.1998.274.6.L908

56 McDonough, J. E. *et al.* Small-airway obstruction and emphysema in chronic obstructive pulmonary disease. *N. Engl. J. Med.* **365**, 1567-1575 (2011). https://doi.org:10.1056/NEJMoa1106955

57 O'Donnell, D. E. & Laveneziana, P. The clinical importance of dynamic lung hyperinflation in COPD. *Copd* **3**, 219-232 (2006). https://doi.org:10.1080/15412550600977478

58 O'Donnell, D. E. & Laveneziana, P. Dyspnea and activity limitation in COPD: mechanical factors. *Copd* **4**, 225-236 (2007). https://doi.org:10.1080/15412550701480455

59 O'Donnell, D. E., Lam, M. & Webb, K. A. Spirometric correlates of improvement in exercise performance after anticholinergic therapy in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **160**, 542-549 (1999). https://doi.org:10.1164/ajrccm.160.2.9901038

60 Casanova, C. *et al.* Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **171**, 591-597 (2005). https://doi.org:10.1164/rccm.200407-867OC

61 Tantucci, C. *et al.* Inspiratory capacity predicts mortality in patients with chronic obstructive pulmonary disease. *Respir. Med.* **102**, 613-619 (2008). https://doi.org:10.1016/j.rmed.2007.11.004

62 O'Donnell, D. E., Revill, S. M. & Webb, K. A. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **164**, 770-777 (2001). https://doi.org:10.1164/ajrccm.164.5.2012122

63 O'Donnell, D. E., Lam, M. & Webb, K. A. Measurement of symptoms, lung hyperinflation, and endurance during exercise in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **158**, 1557-1565 (1998). https://doi.org:10.1164/ajrccm.158.5.9804004

64 Sinderby, C. *et al.* Diaphragm activation during exercise in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **163**, 1637-1641 (2001). https://doi.org:10.1164/ajrccm.163.7.2007033

65 O'Donnell, D. E., D'Arsigny, C., Fitzpatrick, M. & Webb, K. A. Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation. *Am. J. Respir. Crit. Care Med.* **166**, 663-668 (2002).

66 Barberà, J. A. *et al.* Mechanisms of worsening gas exchange during acute exacerbations of chronic obstructive pulmonary disease. *Eur. Respir. J.* **10**, 1285-1291 (1997). https://doi.org:10.1183/09031936.97.10061285

67 Rodríguez-Roisin, R. *et al.* Ventilation-perfusion imbalance and chronic obstructive pulmonary disease staging severity. *J Appl Physiol (1985)* **106**, 1902-1908 (2009). https://doi.org:10.1152/japplphysiol.00085.2009

68 Sapey, E. & Stockley, R. A. COPD exacerbations . 2: aetiology. *Thorax* **61**, 250-258 (2006). https://doi.org:10.1136/thx.2005.041822

69 Parker, C. M., Voduc, N., Aaron, S. D., Webb, K. A. & O'Donnell, D. E. Physiological changes during symptom recovery from moderate exacerbations of COPD. *Eur. Respir. J.* **26**, 420-428 (2005). https://doi.org:10.1183/09031936.05.00136304

70 Bhowmik, A., Seemungal, T. A., Sapsford, R. J. & Wedzicha, J. A. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. *Thorax* **55**, 114-120 (2000). https://doi.org:10.1136/thorax.55.2.114

71 Donaldson, G. C., Seemungal, T. A., Bhowmik, A. & Wedzicha, J. A. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* **57**, 847-852 (2002). https://doi.org:10.1136/thorax.57.10.847

72 Celli, B. R. & MacNee, W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur. Respir. J.* **23**, 932-946 (2004). https://doi.org:10.1183/09031936.04.00014304

73 Miravitlles, M. *et al.* Observational study to characterise 24-hour COPD symptoms and their relationship with patient-reported outcomes: results from the ASSESS study. *Respir. Res.* **15**, 122 (2014). https://doi.org:10.1186/s12931-014-0122-1

74 Phillips, D. B. *et al.* Impaired Ventilatory Efficiency, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease: Results from the CanCOLD Study. *Am. J. Respir. Crit. Care Med.* **205**, 1391-1402 (2022). https://doi.org:10.1164/rccm.202109-2171OC

75 Stridsman, C., Skär, L., Hedman, L., Rönmark, E. & Lindberg, A. Fatigue Affects Health Status and Predicts Mortality Among Subjects with COPD: Report from the Population-Based OLIN COPD Study. *Copd* **12**, 199-206 (2015). https://doi.org:10.3109/15412555.2014.922176

76 Goërtz, Y. M. J. *et al.* Fatigue is highly prevalent in patients with COPD and correlates poorly with the degree of airflow limitation. *Ther. Adv. Respir. Dis.* **13**, 1753466619878128 (2019). https://doi.org:10.1177/1753466619878128

77 Läkemedelsverket. 6 (2023).

78 Agusti, A. *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir. Res.* **11**, 122 (2010). https://doi.org:10.1186/1465-9921-11-122

79 Woodruff, P. G. *et al.* Clinical Significance of Symptoms in Smokers with Preserved Pulmonary Function. *N. Engl. J. Med.* **374**, 1811-1821 (2016). https://doi.org:10.1056/NEJMoa1505971

80 Jones, P. W. COPD assessment test --rationale, development, validation and performance. *Copd* **10**, 269-271 (2013). https://doi.org:10.3109/15412555.2013.776920

81 Mahler, D. A. & Wells, C. K. Evaluation of clinical methods for rating dyspnea. *Chest* **93**, 580-586 (1988). https://doi.org:10.1378/chest.93.3.580

82 Ewert, R. *et al.* Value of Cardiopulmonary Exercise Testing in the Prognosis Assessment of Chronic Obstructive Pulmonary Disease Patients: A Retrospective, Multicentre Cohort Study. *Respiration* **101**, 353-366 (2022). https://doi.org:10.1159/000519750

83 Torres-Sánchez, I. *et al.* Cognitive impairment in COPD: a systematic review. *J. Bras. Pneumol.* **41**, 182-190 (2015). https://doi.org:10.1590/s1806-37132015000004424

84 Siraj, R. A. Comorbid Cognitive Impairment in Chronic Obstructive Pulmonary Disease (COPD): Current Understanding, Risk Factors, Implications for Clinical Practice, and Suggested Interventions. *Medicina (Kaunas)* **59** (2023). https://doi.org:10.3390/medicina59040732

85 André, S. *et al.* COPD and Cardiovascular Disease. *Pulmonology* **25**, 168-176 (2019). https://doi.org:10.1016/j.pulmoe.2018.09.006

86 Maltais, F. *et al.* An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **189**, e15-62 (2014). https://doi.org:10.1164/rccm.201402-0373ST

87 Bui, K.-L., Nyberg, A., Rabinovich, R., Saey, D. & Maltais, F. The Relevance of Limb Muscle Dysfunction in Chronic Obstructive Pulmonary Disease: A Review For Clinicians. *Clin. Chest Med.* **40**, 367-383 (2019). https://doi.org:https://dx.doi.org/10.1016/j.ccm.2019.02.013

88 Breyer, M.-K. *et al.* Prevalence of metabolic syndrome in COPD patients and its consequences. *PLoS One* **9**, e98013 (2014). https://doi.org:https://dx.doi.org/10.1371/journal.pone.0098013

89 Fekete, M. *et al.* Metabolic syndrome in patients with COPD: Causes and pathophysiological consequences. *Physiology International* **109**, 90-105 (2022). https://doi.org:10.1556/2060.2022.00164

90 Chen, Y. W., Ramsook, A. H., Coxson, H. O., Bon, J. & Reid, W. D. Prevalence and Risk Factors for Osteoporosis in Individuals With COPD: A Systematic Review and Meta-analysis. *Chest* **156**, 1092-1110 (2019). https://doi.org:10.1016/j.chest.2019.06.036

91 Yohannes, A. M. & Alexopoulos, G. S. Depression and anxiety in patients with COPD. *European respiratory review : an official journal of the European Respiratory Society* **23**, 345-349 (2014). https://doi.org:https://dx.doi.org/10.1183/09059180.00007813

92 Schneider, C., Jick, S. S., Bothner, U. & Meier, C. R. COPD and the risk of depression. *Chest* **137**, 341-347 (2010). https://doi.org:10.1378/chest.09-0614

93 Jones, S. E. *et al.* Sarcopenia in COPD: prevalence, clinical correlates and response to pulmonary rehabilitation. *Thorax* **70**, 213-218 (2015). https://doi.org:https://dx.doi.org/10.1136/thoraxjnl-2014-206440

94 De Brandt, J. *et al.* Update on the Etiology, Assessment, and Management of COPD Cachexia: Considerations for the Clinician. *International Journal of COPD* **17**, 2957-2976 (2022). https://doi.org:10.2147/COPD.S334228

95 Lainscak, M., Gosker, H. R. & Schols, A. M. W. J. Chronic obstructive pulmonary disease patient journey: hospitalizations as window of opportunity for extra-pulmonary intervention. *Curr. Opin. Clin. Nutr. Metab. Care* **16**, 278-283 (2013). https://doi.org:https://dx.doi.org/10.1097/MCO.0b013e328360285d

96 Watz, H. *et al.* Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *Am. J. Respir. Crit. Care Med.* **177**, 743-751 (2008).

97 Vanfleteren, L., Spruit, M. A., Wouters, E. F. M. & Franssen, F. M. E. Management of chronic obstructive pulmonary disease beyond the lungs. *Lancet Respir Med* **4**, 911-924 (2016). https://doi.org:10.1016/s2213-2600(16)00097-7

98 Crişan, A. F. *et al.* Cognitive Impairment in Chronic Obstructive Pulmonary Disease. *PLoS One* **9**, e102468 (2014). https://doi.org:10.1371/journal.pone.0102468

99 Pelgrim, C. E. *et al.* Psychological co-morbidities in COPD: Targeting systemic inflammation, a benefit for both? *Eur. J. Pharmacol.* **842**, 99-110 (2019). https://doi.org:https://doi.org/10.1016/j.ejphar.2018.10.001

100 Wang, T. *et al.* Influencing Factors and Exercise Intervention of Cognitive Impairment in Elderly Patients with Chronic Obstructive Pulmonary Disease. *Clin. Interv. Aging* **15**, 557-566 (2020). https://doi.org:10.2147/CIA.S245147

101 Pelgrim, C. E. *et al.* Psychological co-morbidities in COPD: Targeting systemic inflammation, a benefit for both? *Eur. J. Pharmacol.* **842**, 99-110 (2019). https://doi.org:10.1016/j.ejphar.2018.10.001

102 Emtner, M. & Wadell, K. Effects of exercise training in patients with chronic obstructive pulmonary disease--a narrative review for FYSS (Swedish Physical Activity Exercise Prescription Book). *Br. J. Sports Med.* **50**, 368-371 (2016). https://doi.org:10.1136/bjsports-2015-095872

103 Chang, S. S., Chen, S., McAvay, G. J. & Tinetti, M. E. Effect of coexisting chronic obstructive pulmonary disease and cognitive impairment on health outcomes in older adults. *J. Am. Geriatr. Soc.* **60**, 1839-1846 (2012). https://doi.org:10.1111/j.1532-5415.2012.04171.x

104 Marquis, K. *et al.* Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **166**, 809-813 (2002). https://doi.org:10.1164/rccm.2107031

105 van Beers, M., Janssen, D. J. A., Gosker, H. R. & Schols, A. M. W. J. Cognitive impairment in chronic obstructive pulmonary disease: disease burden, determinants and possible future interventions. *Expert Rev. Respir. Med.* **12**, 1061-1074 (2018). https://doi.org:https://dx.doi.org/10.1080/17476348.2018.1533405

106 Hung, W. W., Wisnivesky, J. P., Siu, A. L. & Ross, J. S. Cognitive Decline among Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **180**, 134-137 (2009). https://doi.org:10.1164/rccm.200902-0276OC

107 Grant, I. *et al.* Progressive neuropsychologic impairment and hypoxemia. Relationship in chronic obstructive pulmonary disease. *Arch. Gen. Psychiatry* **44**, 999-1006 (1987). https://doi.org:10.1001/archpsyc.1987.01800230079013

108 Yohannes, A. M., Chen, W., Moga, A. M., Leroi, I. & Connolly, M. J. Cognitive Impairment in Chronic Obstructive Pulmonary Disease and Chronic Heart Failure: A Systematic Review and Meta-analysis of Observational Studies. *J. Am. Med. Dir. Assoc.* **18**, 451.e451-451.e411 (2017). https://doi.org:10.1016/j.jamda.2017.01.014

109 Dodd, J. W. Lung disease as a determinant of cognitive decline and dementia. *Alzheimers Res. Ther.* **7**, 32 (2015). https://doi.org:10.1186/s13195-015-0116-3

110 Cleutjens, F. A. H. M. *et al.* Cognitive impairment and clinical characteristics in patients with chronic obstructive pulmonary disease. *Chron. Respir. Dis.* **15**, 91-102 (2018). https://doi.org:https://dx.doi.org/10.1177/1479972317709651

111 Henkle, B. E. *et al.* Cognitive function and inhaler technique following recovery from exacerbations of COPD. *ERJ Open Research* **9**, 00627-02022 (2023). https://doi.org:10.1183/23120541.00627-2022

112 O'Conor, R. *et al.* Effects of health literacy and cognitive abilities on COPD self-management behaviors: A prospective cohort study. *Respir. Med.* **160**, 105630 (2019). https://doi.org:https://doi.org/10.1016/j.rmed.2019.02.006

113 Iamthanaporn, C., Wisitsartkul, A. & Chuaychoo, B. Cognitive impairment according to Montreal Cognitive Assessment independently predicts the ability of chronic obstructive pulmonary disease patients to maintain proper inhaler

technique. *BMC Pulm. Med.* **23** (2023). https://doi.org:10.1186/s12890-023-02448-x

114 Dodd, J. W., Getov, S. V. & Jones, P. W. Cognitive function in COPD. *Eur. Respir. J.* **35**, 913-922 (2010). https://doi.org:10.1183/09031936.00125109

115 Dobric, A. *et al.* Novel pharmacological strategies to treat cognitive dysfunction in chronic obstructive pulmonary disease. *Pharmacol. Ther.* **233**, 108017 (2022). https://doi.org:https://doi.org/10.1016/j.pharmthera.2021.108017

116 Yin, M. *et al.* Patterns of brain structural alteration in COPD with different levels of pulmonary function impairment and its association with cognitive deficits. *BMC Pulm. Med.* **19**, 203 (2019). https://doi.org:10.1186/s12890-019-0955-y

117 Ortapamuk, H. & Naldoken, S. Brain perfusion abnormalities in chronic obstructive pulmonary disease: comparison with cognitive impairment. *Ann. Nucl. Med.* **20**, 99-106 (2006). https://doi.org:10.1007/bf02985621

118 Antonelli-Incalzi, R. *et al.* Correlation between cognitive impairment and dependence in hypoxemic COPD. *J. Clin. Exp. Neuropsychol.* **30**, 141-150 (2008). https://doi.org:10.1080/13803390701287390

119 Liesker, J. J. *et al.* Cognitive performance in patients with COPD. *Respir. Med.* **98**, 351-356 (2004). https://doi.org:10.1016/j.rmed.2003.11.004

120 Ozsoy, I. *et al.* Cognitive and motor performances in dual task in patients with chronic obstructive pulmonary disease: a comparative study. *Ir. J. Med. Sci.* **190**, 723-730 (2021). https://doi.org:10.1007/s11845-020-02357-6

121 Park, S. K. & Larson, J. L. Cognitive Function as Measured by Trail Making Test in Patients With COPD. *West. J. Nurs. Res.* **37**, 236-256 (2014). https://doi.org:10.1177/0193945914530520

122 Aghjayan, S. L. *et al.* Aerobic exercise improves episodic memory in late adulthood: a systematic review and meta-analysis. *Commun Med (Lond)* **2**, 15 (2022). https://doi.org:10.1038/s43856-022-00079-7

123 Tari, A. R., Walker, T. L., Huuha, A. M., Sando, S. B. & Wisloff, U. Neuroprotective mechanisms of exercise and the importance of fitness for healthy brain ageing. *The Lancet* **405**, 1093-1118 (2025). https://doi.org:10.1016/S0140-6736(25)00184-9

124 Ludyga, S., Gerber, M., Pühse, U., Looser, V. N. & Kamijo, K. Systematic review and meta-analysis investigating moderators of long-term effects of exercise on cognition in healthy individuals. *Nat Hum Behav* **4**, 603-612 (2020). https://doi.org:10.1038/s41562-020-0851-8

125 Eisenstein, T., Giladi, N., Hendler, T., Havakuk, O. & Lerner, Y. Hippocampal and non-hippocampal correlates of physically active lifestyle and their relation to episodic memory in older adults. *Neurobiol. Aging* **109**, 100-112 (2022). https://doi.org:10.1016/j.neurobiolaging.2021.08.017

126 Wilckens, K. A. *et al.* Exercise interventions preserve hippocampal volume: A meta-analysis. *Hippocampus* **31**, 335-347 (2021). https://doi.org:10.1002/hipo.23292

127 Jonasson, L. S. *et al.* Aerobic Exercise Intervention, Cognitive Performance, and Brain Structure: Results from the Physical Influences on Brain in Aging (PHIBRA) Study. *Front. Aging Neurosci.* **8** (2017). https://doi.org:10.3389/fnagi.2016.00336

128 Desveaux, L. *et al.* Effects of exercise training on cognition in chronic obstructive pulmonary disease: A systematic review. *Respir. Med.* **139**, 110-116 (2018). https://doi.org:https://dx.doi.org/10.1016/j.rmed.2018.05.006

129 Kodama, S. *et al.* Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA* **301**, 2024-2035 (2009). https://doi.org:10.1001/jama.2009.681

130 Laukkanen, J. A., Isiozor, N. M. & Kunutsor, S. K. Objectively Assessed Cardiorespiratory Fitness and All-Cause Mortality Risk: An Updated Meta-analysis of 37 Cohort Studies Involving 2,258,029 Participants. *Mayo Clin. Proc.* **97**, 1054-1073 (2022). https://doi.org:10.1016/j.mayocp.2022.02.029

131 Mølmen, K. S. *et al.* Chronic obstructive pulmonary disease does not impair responses to resistance training. *J. Transl. Med.* **19**, 1-22 (2021). https://doi.org:10.1186/s12967-021-02969-1

132 Gouzi, F. *et al.* Impaired training-induced adaptation of blood pressure in COPD patients: implication of the muscle capillary bed. *Int. J. Chron. Obstruct. Pulmon. Dis.* **11**, 2349-2357 (2016).

133 Hartmann, J. P. *et al.* Pulmonary adaptations to 12 wk of supervised high intensity interval training in COPD: a nonrandomized controlled pilot study. *J Appl Physiol (1985)* **138**, 1543-1559 (2025). https://doi.org:10.1152/japplphysiol.00037.2025

134 Chen, W., Thomas, J., Sadatsafavi, M. & FitzGerald, J. M. Risk of cardiovascular comorbidity in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Lancet Respir Med* **3**, 631-639 (2015). https://doi.org:10.1016/s2213-2600(15)00241-6

135 O'Donnell, D. E. Ventilatory limitations in chronic obstructive pulmonary disease. *Med. Sci. Sports Exerc.* **33**, S647-655 (2001). https://doi.org:10.1097/00005768-200107001-00002

136 Vaes, A. W. *et al.* Determinants of Mortality in Patients With COPD: Physical Capacity or Physical Activity? *Chest* **167**, 1064-1067 (2025). https://doi.org:10.1016/j.chest.2024.10.032

137 Spruit, M. A. *et al.* An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am. J. Respir. Crit. Care Med.* **188**, e13-64 (2013). https://doi.org:10.1164/rccm.201309-1634ST

138 Priego-Jiménez, S. *et al.* Effect of exercise interventions on oxygen uptake in people with chronic obstructive pulmonary disease: A network meta-analysis of randomized controlled trials. *Ann. Phys. Rehabil. Med.* **67**, 101875 (2024). https://doi.org:10.1016/j.rehab.2024.101875

139 Alqahtani, J. S. *et al.* A systematic review and meta-analysis of heart rate variability in COPD. *Front Cardiovasc Med* **10**, 1070327 (2023). https://doi.org:10.3389/fcvm.2023.1070327

140 Undem, B. J. & Kollarik, M. The role of vagal afferent nerves in chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.* **2**, 355-360; discussion 371-352 (2005). https://doi.org:10.1513/pats.200504-033SR

141 Gourine, A. V. & Ackland, G. L. Cardiac Vagus and Exercise. *Physiology (Bethesda)* **34**, 71-80 (2019). https://doi.org:10.1152/physiol.00041.2018

142 Grässler, B., Thielmann, B., Böckelmann, I. & Hökelmann, A. Effects of Different Training Interventions on Heart Rate Variability and Cardiovascular Health and Risk Factors in Young and Middle-Aged Adults: A Systematic Review. *Front. Physiol.* **12**, 657274 (2021). https://doi.org:10.3389/fphys.2021.657274

143 Mohammed, J., Derom, E., Van Oosterwijck, J., Da Silva, H. & Calders, P. Evidence for aerobic exercise training on the autonomic function in patients with chronic obstructive pulmonary disease (COPD): a systematic review. *Physiotherapy* **104**, 36-45 (2018). https://doi.org:10.1016/j.physio.2017.07.004

144 Adami, A. *et al.* Muscle Oxidative Capacity Is Reduced in Both Upper and Lower Limbs in COPD. *Med. Sci. Sports Exerc.* **52**, 2061-2068 (2020). https://doi.org:10.1249/mss.0000000000002364

145 Gosselink, R., Troosters, T. & Decramer, M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am. J. Respir. Crit. Care Med.* **153**, 976-980 (1996).

146 Hamilton, A. L., Killian, K. J., Summers, E. & Jones, N. L. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. *Am. J. Respir. Crit. Care Med.* **152**, 2021-2031 (1995). https://doi.org:10.1164/ajrccm.152.6.8520771

147 Decramer, M., Gosselink, R., Troosters, T., Verschueren, M. & Evers, G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur. Respir. J.* **10**, 417-423 (1997). https://doi.org:10.1183/09031936.97.10020417

148 Marquis, K. *et al.* Midthigh muscle cross- sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **166**, 809 (2002).

149 Swallow, E. B. *et al.* Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* **62**, 115-120 (2007). https://doi.org:10.1136/thx.2006.062026

150 Couillard, A. & Prefaut, C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur. Respir. J.* **26**, 703-719 (2005). https://doi.org:10.1183/09031936.05.00139904

151 Maltais, F. *et al.* Altered expression of myosin heavy chain in the vastus lateralis muscle in patients with COPD. *Eur. Respir. J.* **13**, 850-854 (1999). https://doi.org:10.1034/j.1399-3003.1999.13d26.x

152 Vogiatzis, I. *et al.* Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* **140**, 744-752 (2011). https://doi.org:https://dx.doi.org/10.1378/chest.10-3058

153 Gosker, H. R. *et al.* Myopathological features in skeletal muscle of patients with chronic obstructive pulmonary disease. *Eur. Respir. J.* **22**, 280-285 (2003). https://doi.org:10.1183/09031936.03.00012803

154 Allaire, J. *et al.* Peripheral muscle endurance and the oxidative profile of the quadriceps in patients with COPD. *Thorax* **59**, 673-678 (2004). https://doi.org:10.1136/thx.2003.020636

155 Whittom, F. *et al.* Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med. Sci. Sports Exerc.* **30**, 1467-1474 (1998).

156 Jobin, J. *et al.* Chronic obstructive pulmonary disease: capillarity and fiber-type characteristics of skeletal muscle. *J. Cardiopulm. Rehabil.* **18**, 432-437 (1998). https://doi.org:10.1097/00008483-199811000-00005

157 Turan, N. *et al.* A Systems Biology Approach Identifies Molecular Networks Defining Skeletal Muscle Abnormalities in Chronic Obstructive Pulmonary Disease. *PLoS Comput. Biol.* **7**, e1002129 (2011). https://doi.org:10.1371/journal.pcbi.1002129

158 Pokharel, M. D. *et al.* Mitochondrial network dynamics in pulmonary disease: Bridging the gap between inflammation, oxidative stress, and bioenergetics. *Redox Biology* **70**, 103049 (2024). https://doi.org:https://doi.org/10.1016/j.redox.2024.103049

159 Gosker, H. R., Hesselink, M. K., Duimel, H., Ward, K. A. & Schols, A. M. Reduced mitochondrial density in the vastus lateralis muscle of patients with COPD. *Eur. Respir. J.* **30**, 73-79 (2007). https://doi.org:10.1183/09031936.00146906

160 Leermakers, P. A. *et al.* Molecular signalling towards mitochondrial breakdown is enhanced in skeletal muscle of patients with chronic obstructive pulmonary disease (COPD). *Sci. Rep.* **8**, 15007 (2018). https://doi.org:10.1038/s41598-018-33471-2

161 Puente-Maestu, L. *et al.* Abnormal mitochondrial function in locomotor and respiratory muscles of COPD patients. *Eur. Respir. J.* **33**, 1045-1052 (2009). https://doi.org:10.1183/09031936.00112408

162 Rabinovich, R. A. *et al.* Mitochondrial dysfunction in COPD patients with low body mass index. *The European respiratory journal* **29**, 643-650 (2007).

163 Picard, M. *et al.* The mitochondrial phenotype of peripheral muscle in chronic obstructive pulmonary disease: disuse or dysfunction? *Am. J. Respir. Crit. Care Med.* **178**, 1040-1047 (2008). https://doi.org:10.1164/rccm.200807-1005OC

164 Remels, A. H. *et al.* Peroxisome proliferator-activated receptor expression is reduced in skeletal muscle in COPD. *Eur. Respir. J.* **30**, 245-252 (2007). https://doi.org:10.1183/09031936.00144106

165 Seymour, J. M. *et al.* The prevalence of quadriceps weakness in COPD and the relationship with disease severity. *Eur. Respir. J.* **36**, 81-88 (2010). https://doi.org:10.1183/09031936.00104909

166 Tanguay, S. *et al.* Reference equations for quadriceps strength, endurance and power: a multicentre study. *ERJ Open Res* **9** (2023). https://doi.org:10.1183/23120541.00313-2023

167 Engelen, M. P., Schols, A. M., Does, J. D. & Wouters, E. F. Skeletal muscle weakness is associated with wasting of extremity fat-free mass but not with airflow obstruction in patients with chronic obstructive pulmonary disease. *Am. J. Clin. Nutr.* **71**, 733-738 (2000). https://doi.org:10.1093/ajcn/71.3.733

168 Bernard, S. *et al.* Peripheral Muscle Weakness in Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **158**, 629-634 (1998). https://doi.org:10.1164/ajrccm.158.2.9711023

169 Decramer, M., Lacquet, L. M., Fagard, R. & Rogiers, P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am. J. Respir. Crit. Care Med.* **150**, 11-16 (1994). https://doi.org:10.1164/ajrccm.150.1.8025735

170 Medicine, A. C. o. S. *ACSM's guidelines for exercise testing and prescription*. (Lippincott williams & wilkins, 2013).

171 Shah, S., Darekar, B., Salvi, S. & Kowale, A. Quadriceps strength in patients with chronic obstructive pulmonary disease. *Lung India* **36**, 417-421 (2019). https://doi.org:10.4103/lungindia.lungindia_27_19

172 Swallow, E. B. *et al.* A novel technique for nonvolitional assessment of quadriceps muscle endurance in humans. *J Appl Physiol (1985)* **103**, 739-746 (2007). https://doi.org:10.1152/japplphysiol.00025.2007

173 Killian, K. J. *et al.* Exercise Capacity and Ventilatory, Circulatory, and Symptom Limitation in Patients with Chronic Airflow Limitation. *Am. Rev. Respir. Dis.* **146**, 935-940 (1992). https://doi.org:10.1164/ajrccm/146.4.935

174 Saey, D. *et al.* Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **168**, 425-430 (2003).

175 Ogasawara, R., Jensen, T. E., Goodman, C. A. & Hornberger, T. A. Resistance Exercise-Induced Hypertrophy: A Potential Role for Rapamycin-Insensitive mTOR. *Exerc. Sport Sci. Rev.* **Publish Ahead of Print** (9000).

176 Jinha, A. & Herzog, W. Muscle power: A simple concept causing much confusion. *Journal of Sport and Health Science* **14**, 101005 (2025). https://doi.org:https://doi.org/10.1016/j.jshs.2024.101005

177 Reid, K. F. & Fielding, R. A. Skeletal muscle power: a critical determinant of physical functioning in older adults. *Exerc. Sport Sci. Rev.* **40**, 4-12 (2012). https://doi.org:10.1097/JES.0b013e31823b5f13

178 Gephine, S. *et al.* Specific Contribution of Quadriceps Muscle Strength, Endurance, and Power to Functional Exercise Capacity in People With Chronic Obstructive Pulmonary Disease: A Multicenter Study. *Phys. Ther.* **101** (2021). https://doi.org:10.1093/ptj/pzab052

179 Young, A. Rehabilitation of patients with pulmonary disease. *Ann Acad Med Singap* **12**, 410-416 (1983).

180 Decramer, M., de Bock, V. & Dom, R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **153**, 1958-1964 (1996). https://doi.org:10.1164/ajrccm.153.6.8665061

181 Willemse, B. W., Postma, D. S., Timens, W. & ten Hacken, N. H. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. *Eur. Respir. J.* **23**, 464-476 (2004). https://doi.org:10.1183/09031936.04.00012704

182 Bauer, C. M. T., Morissette, M. C. & Stämpfli, M. R. The influence of cigarette smoking on viral infections: translating bench science to impact COPD pathogenesis and acute exacerbations of COPD clinically. *Chest* **143**, 196-206 (2013). https://doi.org:10.1378/chest.12-0930

183 Scanlon, P. D. *et al.* Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am. J. Respir. Crit. Care Med.* **161**, 381-390 (2000). https://doi.org:10.1164/ajrccm.161.2.9901044

184 van Eerd, E. A., van der Meer, R. M., van Schayck, O. C. & Kotz, D. Smoking cessation for people with chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **2016**, Cd010744 (2016). https://doi.org:10.1002/14651858.CD010744.pub2

185 Wei, X. *et al.* Effects of different interventions on smoking cessation in chronic obstructive pulmonary disease patients: A systematic review and network meta-analysis. *Int. J. Nurs. Stud.* **136**, 104362 (2022). https://doi.org:10.1016/j.ijnurstu.2022.104362

186 Frazer, K. *et al.* Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst. Rev.* **2**, Cd005992 (2016). https://doi.org:10.1002/14651858.CD005992.pub3

187 Hansel, N. N., McCormack, M. C. & Kim, V. The Effects of Air Pollution and Temperature on COPD. *Copd* **13**, 372-379 (2016). https://doi.org:10.3109/15412555.2015.1089846

188 Schwartz, J. Who is sensitive to extremes of temperature?: A case-only analysis. *Epidemiology* **16**, 67-72 (2005). https://doi.org:10.1097/01.ede.0000147114.25957.71

189 Anderson, G. B. *et al.* Heat-related emergency hospitalizations for respiratory diseases in the Medicare population. *Am. J. Respir. Crit. Care Med.* **187**, 1098-1103 (2013). https://doi.org:10.1164/rccm.201211-1969OC

190 Wongsurakiat, P. *et al.* Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest* **125**, 2011-2020 (2004). https://doi.org:10.1378/chest.125.6.2011

191 Walters, J. A., Tang, J. N., Poole, P. & Wood-Baker, R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **1**, Cd001390 (2017). https://doi.org:10.1002/14651858.CD001390.pub4

192 Poole, P. J., Chacko, E., Wood-Baker, R. W. & Cates, C. J. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.*, Cd002733 (2006). https://doi.org:10.1002/14651858.CD002733.pub2

193 Calzetta, L., Matera, M. G. & Cazzola, M. Pharmacological mechanisms leading to synergy in fixed-dose dual bronchodilator therapy. *Curr. Opin. Pharmacol.* **40**, 95-103 (2018). https://doi.org:https://doi.org/10.1016/j.coph.2018.03.011

194 Mammen, M. J. *et al.* Dual LABA/LAMA Therapy versus LABA or LAMA Monotherapy for Chronic Obstructive Pulmonary Disease. A Systematic Review and Meta-analysis in Support of the American Thoracic Society Clinical Practice Guideline. *Annals of the American Thoracic Society* **17**, 1133-1143 (2020). https://doi.org:10.1513/AnnalsATS.201912-915OC

195 Miravitlles, M., Kawayama, T. & Dreher, M. LABA/LAMA as First-Line Therapy for COPD: A Summary of the Evidence and Guideline Recommendations. *J Clin Med* **11** (2022). https://doi.org:10.3390/jcm11226623

196 Boardman, C. *et al.* Mechanisms of glucocorticoid action and insensitivity in airways disease. *Pulm. Pharmacol. Ther.* **29**, 129-143 (2014). https://doi.org:10.1016/j.pupt.2014.08.008

197 Wedzicha, J. A., Calverley, P. M. & Rabe, K. F. Roflumilast: a review of its use in the treatment of COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* **11**, 81-90 (2016). https://doi.org:10.2147/copd.S89849

198 Rabe, K. F. Update on roflumilast, a phosphodiesterase 4 inhibitor for the treatment of chronic obstructive pulmonary disease. *Br. J. Pharmacol.* **163**, 53-67 (2011). https://doi.org:10.1111/j.1476-5381.2011.01218.x

199 Niewoehner, D. E. *et al.* Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N. Engl. J. Med.* **340**, 1941-1947 (1999). https://doi.org:10.1056/nejm199906243402502

200 Vollenweider, D. J., Frei, A., Steurer-Stey, C. A., Garcia-Aymerich, J. & Puhan, M. A. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **10**, Cd010257 (2018). https://doi.org:10.1002/14651858.CD010257.pub2

201 Austin, M. A., Wills, K. E., Blizzard, L., Walters, E. H. & Wood-Baker, R. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ* **341**, c5462 (2010). https://doi.org:10.1136/bmj.c5462

202 Osadnik, C. R. *et al.* Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **7**, Cd004104 (2017). https://doi.org:10.1002/14651858.CD004104.pub4

203 Cranston, J. M., Crockett, A. J., Moss, J. R. & Alpers, J. H. Domiciliary oxygen for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **2005**, Cd001744 (2005). https://doi.org:10.1002/14651858.CD001744.pub2

204 Jacobs, S. S. *et al.* Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. *Am. J. Respir. Crit. Care Med.* **202**, e121-e141 (2020). https://doi.org:10.1164/rccm.202009-3608ST

205 Ekström, M., Ahmadi, Z., Bornefalk-Hermansson, A., Abernethy, A. & Currow, D. Oxygen for breathlessness in patients with chronic obstructive pulmonary disease who do not qualify for home oxygen therapy. *Cochrane Database Syst. Rev.* **11**, Cd006429 (2016). https://doi.org:10.1002/14651858.CD006429.pub3

206 Srivali, N., Thongprayoon, C., Tangpanithandee, S., Cheungpasitporn, W. & Won, C. The use of continuous positive airway pressure in COPD-OSA overlap syndrome: A systematic review. *Sleep Med.* **108**, 55-60 (2023). https://doi.org:10.1016/j.sleep.2023.05.025

207 Raveling, T. *et al.* Chronic non-invasive ventilation for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **8**, Cd002878 (2021). https://doi.org:10.1002/14651858.CD002878.pub3

208 Marchetti, N. & Criner, G. J. Surgical Approaches to Treating Emphysema: Lung Volume Reduction Surgery, Bullectomy, and Lung Transplantation. *Semin. Respir. Crit. Care Med.* **36**, 592-608 (2015). https://doi.org:10.1055/s-0035-1556064

209 van Agteren, J. E., Carson, K. V., Tiong, L. U. & Smith, B. J. Lung volume reduction surgery for diffuse emphysema. *Cochrane Database Syst. Rev.* **10**, Cd001001 (2016). https://doi.org:10.1002/14651858.CD001001.pub3

210 Garvey, C. *et al.* Pulmonary Rehabilitation Exercise Prescription in Chronic Obstructive Pulmonary Disease: Review of Selected Guidelines: AN OFFICIAL STATEMENT FROM THE AMERICAN ASSOCIATION OF CARDIOVASCULAR AND PULMONARY REHABILITATION. *J. Cardiopulm. Rehabil. Prev.* **36**, 75-83 (2016). https://doi.org:10.1097/hcr.0000000000000171

211 McCarthy, B. *et al.* Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.*, Cd003793 (2015). https://doi.org:10.1002/14651858.CD003793.pub3

212 Gordon, C. S. *et al.* Effect of Pulmonary Rehabilitation on Symptoms of Anxiety and Depression in COPD: A Systematic Review and Meta-Analysis. *Chest* **156**, 80-91 (2019). https://doi.org:https://dx.doi.org/10.1016/j.chest.2019.04.009

213 Beauchamp, M. K., Janaudis-Ferreira, T., Goldstein, R. S. & Brooks, D. Optimal duration of pulmonary rehabilitation for individuals with chronic obstructive pulmonary disease - a systematic review. *Chron. Respir. Dis.* **8**, 129-140 (2011). https://doi.org:https://dx.doi.org/10.1177/1479972311404256

214 Gloeckl, R. *et al.* Prescribing and adjusting exercise training in chronic respiratory diseases – Expert-based practical recommendations. *Pulmonology* **29**, 306-314 (2023). https://doi.org:10.1016/j.pulmoe.2022.09.004

215 Rochester, C. L. *et al.* An Official American Thoracic Society/European Respiratory Society Policy Statement: Enhancing Implementation, Use, and Delivery of Pulmonary Rehabilitation. *Am. J. Respir. Crit. Care Med.* **192**, 1373-1386 (2015). https://doi.org:10.1164/rccm.201510-1966ST

216 Spitzer, K. A. *et al.* Participation in Pulmonary Rehabilitation after Hospitalization for Chronic Obstructive Pulmonary Disease among Medicare Beneficiaries. *Annals of the American Thoracic Society* **16**, 99-106 (2019). https://doi.org:https://dx.doi.org/10.1513/AnnalsATS.201805-332OC

217 Arne, M., Emtner, M., Lisspers, K., Wadell, K. & Stallberg, B. Availability of pulmonary rehabilitation in primary care for patients with COPD: a cross-sectional study in Sweden. *European clinical respiratory journal* **3**, 31601 (2016). https://doi.org:https://dx.doi.org/10.3402/ecrj.v3.31601

218 Effing, T. W. *et al.* Self-management programmes for COPD: moving forward. *Chron. Respir. Dis.* **9**, 27-35 (2012). https://doi.org:10.1177/1479972311433574

219 Howcroft, M., Walters, E. H., Wood-Baker, R. & Walters, J. A. Action plans with brief patient education for exacerbations in chronic obstructive pulmonary disease. *Cochrane Database Syst. Rev.* **12**, Cd005074 (2016). https://doi.org:10.1002/14651858.CD005074.pub4

220 Blackstock, F. C., Webster, K. E., McDonald, C. F. & Hill, C. J. Comparable improvements achieved in chronic obstructive pulmonary disease through pulmonary rehabilitation with and without a structured educational intervention: a randomized controlled trial. *Respirology* **19**, 193-202 (2014). https://doi.org:10.1111/resp.12203

221 Aliverti, A. & Macklem, P. T. The major limitation to exercise performance in COPD is inadequate energy supply to the respiratory and locomotor muscles. *J*

Appl Physiol (1985) **105**, 749-751; discussion 755-747 (2008). https://doi.org:10.1152/japplphysiol.90336.2008

222 Debigaré, R. & Maltais, F. The major limitation to exercise performance in COPD is lower limb muscle dysfunction. *J Appl Physiol (1985)* **105**, 751-753; discussion 755-757 (2008). https://doi.org:10.1152/japplphysiol.90336.2008a

223 O'Donnell, D. E. & Webb, K. A. The major limitation to exercise performance in COPD is dynamic hyperinflation. *J Appl Physiol (1985)* **105**, 753-755; discussion 755-757 (2008). https://doi.org:10.1152/japplphysiol.90336.2008b

224 Nici, L. Mechanisms and Measures of Exercise Intolerance in Chronic Obstructive Pulmonary Disease. *Clin. Chest Med.* **21**, 693-704 (2000). https://doi.org:https://doi.org/10.1016/S0272-5231(05)70178-7

225 Kasper, K. Sports Training Principles. *Curr. Sports Med. Rep.* **18** (2019).

226 Hoffman, J. *Physiological Aspects of Sport Training and Performance.*, (IL: Human Kinetics, 2002).

227 Jenkins, A. R. *et al.* Do pulmonary rehabilitation programmes improve outcomes in patients with COPD posthospital discharge for exacerbation: a systematic review and meta-analysis. *Thorax* **79**, 438 (2024). https://doi.org:10.1136/thorax-2023-220333

228 Wagner, P. D. Determinants of maximal oxygen consumption. *J. Muscle Res. Cell Motil.* **44**, 73-88 (2023). https://doi.org:10.1007/s10974-022-09636-y

229 Astrand, P. O., Cuddy, T. E., Saltin, B. & Stenberg, J. CARDIAC OUTPUT DURING SUBMAXIMAL AND MAXIMAL WORK. *J. Appl. Physiol.* **19**, 268-274 (1964). https://doi.org:10.1152/jappl.1964.19.2.268

230 Heinonen, I. Cardiac output limits maximal oxygen consumption, but what limits maximal cardiac output? *Exp. Physiol.* **n/a** (2025). https://doi.org:https://doi.org/10.1113/EP091594

231 Foulkes, S. J., Wagner, P. D., Wang, J., La Gerche, A. & Haykowsky, M. J. Physiological determinants of decreased peak leg oxygen uptake in chronic disease: a systematic review and meta-analysis. *J. Appl. Physiol.* **136**, 1293-1302 (2024). https://doi.org:10.1152/japplphysiol.00918.2023

232 Broxterman, R. M., Hoff, J., Wagner, P. D. & Richardson, R. S. Determinants of the diminished exercise capacity in patients with chronic obstructive pulmonary disease: looking beyond the lungs. *The Journal of physiology* **598**, 599-610 (2020). https://doi.org:https://dx.doi.org/10.1113/JP279135

233 Maltais, F. *et al.* Oxidative enzyme activities of the vastus lateralis muscle and the functional status in patients with COPD. *Thorax* **55**, 848-853 (2000).

234 O'Donnell, D. E. & Gebke, K. B. Activity restriction in mild COPD: a challenging clinical problem. *Int. J. Chron. Obstruct. Pulmon. Dis.* **9**, 577-588 (2014). https://doi.org:10.2147/copd.S62766

235 Butcher, S. J. *et al.* The Physiologic Effects of an Acute Bout of Supramaximal High-Intensity Interval Training Compared with a Continuous Exercise Bout in Patients with COPD. *Journal of Respiratory Medicine* **2013**, 879695 (2013). https://doi.org:10.1155/2013/879695

236 Vogiatzis, I. *et al.* Dynamic hyperinflation and tolerance to interval exercise in patients with advanced COPD. *The European respiratory journal* **24**, 385-390 (2004).

237 Puhan, M. A. *et al.* Interval versus continuous high-intensity exercise in chronic obstructive pulmonary disease: a randomized trial. *Ann. Intern. Med.* **145**, 816-825 (2006).

238 Nymand, S. B. *et al.* Exercise adaptations in COPD: the pulmonary perspective. *American Journal of Physiology-Lung Cellular and Molecular Physiology* **323**, L659-L666 (2022). https://doi.org:10.1152/ajplung.00549.2020

239 Smith, J. R., Johnson, B. D. & Olson, T. P. Impaired central hemodynamics in chronic obstructive pulmonary disease during submaximal exercise. *Journal of applied physiology (Bethesda, Md. : 1985)* **127**, 691-697 (2019). https://doi.org:https://dx.doi.org/10.1152/japplphysiol.00877.2018

240 Iepsen, U. W. *et al.* Leg blood flow is impaired during small muscle mass exercise in patients with COPD. *Journal of applied physiology (Bethesda, Md. : 1985)* **123**, 624-631 (2017). https://doi.org:https://dx.doi.org/10.1152/japplphysiol.00178.2017

241 Hartmann, J. P. *et al.* Regulation of the microvasculature during small muscle mass exercise in chronic obstructive pulmonary disease vs. chronic heart failure. *Front. Physiol.* **13**, 979359 (2022). https://doi.org:10.3389/fphys.2022.979359

242 Casaburi, R. *et al.* Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **155**, 1541-1551 (1997).

243 Mador, M. J. *et al.* Interval training versus continuous training in patients with chronic obstructive pulmonary disease. *J. Cardiopulm. Rehabil. Prev.* **29**, 126-132 (2009). https://doi.org:https://dx.doi.org/10.1097/HCR.0b013e31819a024f

244 Vaes, A. W. *et al.* Impact of pulmonary rehabilitation on activities of daily living in patients with chronic obstructive pulmonary disease. *Journal of applied physiology (Bethesda, Md. : 1985)* **126**, 607-615 (2019). https://doi.org:https://dx.doi.org/10.1152/japplphysiol.00790.2018

245 De Brandt, J. *et al.* Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: A review of the English-language literature. *Chron. Respir. Dis.* **15**, 182-219 (2018). https://doi.org:https://dx.doi.org/10.1177/1479972317709642

246 Higashimoto, Y. *et al.* Effect of pulmonary rehabilitation programs including lower limb endurance training on dyspnea in stable COPD: A systematic review and meta-analysis. *Respir Investig* **58**, 355-366 (2020). https://doi.org:10.1016/j.resinv.2020.05.010

247 Garber, C. E. *et al.* American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med. Sci. Sports Exerc.* **43**, 1334-1359 (2011). https://doi.org:10.1249/MSS.0b013e318213fefb

248 Casaburi, R. & ZuWallack, R. Pulmonary rehabilitation for management of chronic obstructive pulmonary disease. *The New England journal of medicine* **360**, 1329-1335 (2009). https://doi.org:https://dx.doi.org/10.1056/NEJMct0804632

249 Hsieh, M.-J. *et al.* Effects of high-intensity exercise training in a pulmonary rehabilitation programme for patients with chronic obstructive pulmonary disease. *Respirology (Carlton, Vic.)* **12**, 381-388 (2007).

250 Ward, T. J. *et al.* Understanding the effectiveness of different exercise training programme designs on VO(2peak) in COPD: a component network meta-analysis. *Thorax* **78**, 1035-1038 (2023). https://doi.org:10.1136/thorax-2023-220071

251 Dolmage, T. E. & Goldstein, R. S. Effects of one-legged exercise training of patients with COPD. *Chest* **133**, 370-376 (2008).

252 Moritani, T., Nagata, A., deVries, H. A. & Muro, M. Critical power as a measure of physical work capacity and anaerobic threshold. *Ergonomics* **24**, 339-350 (1981). https://doi.org:10.1080/00140138108924856

253 Bishop, D. J. *et al.* Physical Activity and Exercise Intensity Terminology: A Joint American College of Sports Medicine (ACSM) Expert Statement and Exercise and Sport Science Australia (ESSA) Consensus Statement. *J. Sci. Med. Sport* https://doi.org:10.1016/j.jsams.2024.11.004

254 Tiller, N. B., Porszasz, J., Casaburi, R., Rossiter, H. B. & Ferguson, C. Critical Power and Respiratory Compensation Point Are Not Equivalent in Patients with COPD. *Med. Sci. Sports Exerc.* (2023). https://doi.org:10.1249/mss.0000000000003124

255 Neder, J. A., Jones, P. W., Nery, L. E. & Whipp, B. J. Determinants of the Exercise Endurance Capacity in Patients with Chronic Obstructive Pulmonary Disease. *Am. J. Respir. Crit. Care Med.* **162**, 497-504 (2000). https://doi.org:10.1164/ajrccm.162.2.9907122

256 Jamnick, N. A., Pettitt, R. W., Granata, C., Pyne, D. B. & Bishop, D. J. An Examination and Critique of Current Methods to Determine Exercise Intensity. *Sports Med.* **50**, 1729-1756 (2020). https://doi.org:10.1007/s40279-020-01322-8

257 Borg, G. Perceived exertion as an indicator of somatic stress. *Scand. J. Rehabil. Med.* **2**, 92-98 (1970).

258 Borg, G. A. Psychophysical bases of perceived exertion. *Med. Sci. Sports Exerc.* **14**, 377-381 (1982).

259 Faude, O., Kindermann, W. & Meyer, T. Lactate threshold concepts: how valid are they? *Sports Med.* **39**, 469-490 (2009). https://doi.org:10.2165/00007256-200939060-00003

260 Heck, H. *et al.* Justification of the 4-mmol/l lactate threshold. *Int. J. Sports Med.* **6**, 117-130 (1985). https://doi.org:10.1055/s-2008-1025824

261 Jones, A. M. & Vanhatalo, A. The 'Critical Power' Concept: Applications to Sports Performance with a Focus on Intermittent High-Intensity Exercise. *Sports medicine (Auckland, N.Z.)* **47**, 65-78 (2017). https://doi.org:10.1007/s40279-017-0688-0

262 Coates, A. M., Joyner, M. J., Little, J. P., Jones, A. M. & Gibala, M. J. A Perspective on High-Intensity Interval Training for Performance and Health. *Sports Med.* (2023). https://doi.org:10.1007/s40279-023-01938-6

263 MacInnis, M. J. & Gibala, M. J. Physiological adaptations to interval training and the role of exercise intensity. *J. Physiol.* **595**, 2915-2930 (2017). https://doi.org:10.1113/jp273196

264 Gloeckl, R., Marinov, B. & Pitta, F. Practical recommendations for exercise training in patients with COPD. *Eur. Respir. Rev.* **22**, 178-186 (2013). https://doi.org:10.1183/09059180.00000513

265 O'Shea, S. D., Taylor, N. F. & Paratz, J. D. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest* **136**, 1269-1283 (2009). https://doi.org:https://dx.doi.org/10.1378/chest.09-0029

266 O'Shea, S. D., Taylor, N. F. & Paratz, J. Peripheral muscle strength training in COPD: a systematic review. *Chest* **126**, 903-914 (2004).

267 Vonbank, K. *et al.* Strength training increases maximum working capacity in patients with COPD – Randomized clinical trial comparing three training modalities. *Respir. Med.* **106**, 557-563 (2012). https://doi.org:https://doi.org/10.1016/j.rmed.2011.11.005

268 Pancera, S. *et al.* Muscle Power in Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-analysis. *Int. J. Sports Med.* **44**, 463-472 (2023). https://doi.org:10.1055/a-1982-9902

269 Kongsgaard, M., Backer, V., Jorgensen, K., Kjaer, M. & Beyer, N. Heavy resistance training increases muscle size, strength and physical function in elderly male COPD-patients--a pilot study. *Respir. Med.* **98**, 1000-1007 (2004).

270 Panton, L. B. *et al.* The effects of resistance training on functional outcomes in patients with chronic obstructive pulmonary disease. *Eur. J. Appl. Physiol.* **91**, 443-449 (2004).

271 Nyberg, A. *et al.* Effects of Low-Load/High-Repetition Resistance Training on Exercise Capacity, Health Status, and Limb Muscle Adaptation in Patients With Severe COPD: A Randomized Controlled Trial. *Chest* **159**, 1821-1832 (2021). https://doi.org:10.1016/j.chest.2020.12.005

272 Mador, M. J., Bozkanat, E., Aggarwal, A., Shaffer, M. & Kufel, T. J. Endurance and strength training in patients with COPD. *Chest* **125**, 2036-2045 (2004).

273 Ortega, F. *et al.* Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **166**, 669-674 (2002).

274 Bernard, S. *et al.* Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **159**, 896-901 (1999).

275 Fox, E. L. *et al.* Intensity and distance of interval training programs and changes in aerobic power. *Med. Sci. Sports* **5**, 18-22 (1973).

276 Wikipedia, c. *Fartlek*, <https://en.wikipedia.org/wiki/Fartlek#cite_note-Schatzle200211-1> (

277 Marriott, C. F. S., Petrella, A. F. M., Marriott, E. C. S., Boa Sorte Silva, N. C. & Petrella, R. J. High-Intensity Interval Training in Older Adults: a Scoping Review. *Sports Medicine - Open* **7**, 49 (2021). https://doi.org:10.1186/s40798-021-00344-4

278 Letnes, J. M. *et al.* Effect of 5 years of exercise training on the cardiovascular risk profile of older adults: The Generation 100 randomized trial. *Eur. Heart J.* **43**, 2065-2075 (2022). https://doi.org:10.1093/eurheartj/ehab721

279 Poon, E. T., Wongpipit, W., Ho, R. S. & Wong, S. H. Interval training versus moderate-intensity continuous training for cardiorespiratory fitness improvements in middle-aged and older adults: a systematic review and meta-analysis. *J. Sports Sci.* **39**, 1996-2005 (2021). https://doi.org:10.1080/02640414.2021.1912453

280 Yang, C. *et al.* High intensity interval training vs. moderate intensity continuous training on aerobic capacity and functional capacity in patients with heart failure: a systematic review and meta-analysis. *Front Cardiovasc Med* **11**, 1302109 (2024). https://doi.org:10.3389/fcvm.2024.1302109

281 Sultana, R. N., Sabag, A., Keating, S. E. & Johnson, N. A. The Effect of Low-Volume High-Intensity Interval Training on Body Composition and Cardiorespiratory Fitness: A Systematic Review and Meta-Analysis. *Sports Med.* **49**, 1687-1721 (2019). https://doi.org:10.1007/s40279-019-01167-w

282 Gripp, F. *et al.* HIIT is superior than MICT on cardiometabolic health during training and detraining. *Eur. J. Appl. Physiol.* **121**, 159-172 (2021). https://doi.org:10.1007/s00421-020-04502-6

283 Thum, J. S., Parsons, G., Whittle, T. & Astorino, T. A. High-Intensity Interval Training Elicits Higher Enjoyment than Moderate Intensity Continuous Exercise. *PLoS One* **12**, e0166299 (2017). https://doi.org:10.1371/journal.pone.0166299

284 Stork, M. J., Gibala, M. J. & Martin Ginis, K. A. Psychological and Behavioral Responses to Interval and Continuous Exercise. *Med. Sci. Sports Exerc.* **50**, 2110-2121 (2018). https://doi.org:10.1249/mss.0000000000001671

285 Troosters, T., Casaburi, R., Gosselink, R. & Decramer, M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **172**, 19-38 (2005).

286 Alexiou, C. *et al.* Effect of interval compared to continuous exercise training on physiological responses in patients with chronic respiratory diseases: A systematic review and meta-analysis. *Chron. Respir. Dis.* **18**, 14799731211041506 (2021). https://doi.org:10.1177/14799731211041506

287 Emtner, M., Porszasz, J., Burns, M., Somfay, A. & Casaburi, R. Benefits of supplemental oxygen in exercise training in nonhypoxemic chronic obstructive pulmonary disease patients. *Am. J. Respir. Crit. Care Med.* **168**, 1034-1042 (2003).

288 Casaburi, R. *et al.* Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am. Rev. Respir. Dis.* **143**, 9-18 (1991). https://doi.org:10.1164/ajrccm/143.1.9

289 Gao, M., Huang, Y., Wang, Q., Liu, K. & Sun, G. Effects of High-Intensity Interval Training on Pulmonary Function and Exercise Capacity in Individuals with Chronic Obstructive Pulmonary Disease: A Meta-Analysis and Systematic Review. *Adv. Ther.* **39**, 94-116 (2022). https://doi.org:https://dx.doi.org/10.1007/s12325-021-01920-6

290 Arnardottir, R. H., Boman, G., Larsson, K., Hedenstrom, H. & Emtner, M. Interval training compared with continuous training in patients with COPD. *Respir. Med.* **101**, 1196-1204 (2007).
291 Sabapathy, S., Kingsley, R. A., Schneider, D. A., Adams, L. & Morris, N. R. Continuous and intermittent exercise responses in individuals with chronic obstructive pulmonary disease. *Thorax* **59**, 1026-1031 (2004).
292 Vogiatzis, I., Nanas, S. & Roussos, C. Interval training as an alternative modality to continuous exercise in patients with COPD. *The European respiratory journal* **20**, 12-19 (2002).
293 Beauchamp, M. K. *et al.* Interval versus continuous training in individuals with chronic obstructive pulmonary disease--a systematic review. *Thorax* **65**, 157-164 (2010). https://doi.org:https://dx.doi.org/10.1136/thx.2009.123000
294 Casaburi, R., Whipp, B. J., Wasserman, K., Beaver, W. L. & Koyal, S. N. Ventilatory and gas exchange dynamics in response to sinusoidal work. *J Appl Physiol Respir Environ Exerc Physiol* **42**, 300-301 (1977). https://doi.org:10.1152/jappl.1977.42.2.300
295 Somfay, A., Pórszász, J., Lee, S. M. & Casaburi, R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in nonhypoxemic COPD patients. *Chest* **121**, 393-400 (2002). https://doi.org:10.1378/chest.121.2.393
296 Nery, L. E. *et al.* Ventilatory and gas exchange kinetics during exercise in chronic airways obstruction. *J Appl Physiol Respir Environ Exerc Physiol* **53**, 1594-1602 (1982). https://doi.org:10.1152/jappl.1982.53.6.1594
297 Porszasz, J. *et al.* Sinusoidal high-intensity exercise does not elicit ventilatory limitation in chronic obstructive pulmonary disease. *Exp. Physiol.* **98**, 1102-1114 (2013). https://doi.org:https://dx.doi.org/10.1113/expphysiol.2012.070375
298 Radtke, T. *et al.* ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *European Respiratory Review* **28**, 180101 (2019). https://doi.org:10.1183/16000617.0101-2018
299 Society, A. T. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am. J. Respir. Crit. Care Med.* **167**, 211-277 (2003). https://doi.org:10.1164/rccm.167.2.211
300 Butcher, S. J. & Jones, R. L. The impact of exercise training intensity on change in physiological function in patients with chronic obstructive pulmonary disease. *Sports medicine (Auckland, N.Z.)* **36**, 307-325 (2006).
301 Rud, B. *et al.* Higher skeletal muscular metabolic reserve capacity in COPD patients than healthy subjects. *Scand. J. Med. Sci. Sports* **19**, 857-864 (2009). https://doi.org:10.1111/j.1600-0838.2008.00846.x
302 Richardson, R. S. *et al.* Evidence of skeletal muscle metabolic reserve during whole body exercise in patients with chronic obstructive pulmonary disease. *Am. J. Respir. Crit. Care Med.* **159**, 881-885 (1999). https://doi.org:10.1164/ajrccm.159.3.9803049
303 Ferguson, C., Furrer, R., Murach, K. A., Hepple, R. T. & Rossiter, H. B. Power and Endurance: Polar Opposites or Willing Partners? *Med. Sci. Sports Exerc.* (2025). https://doi.org:10.1249/mss.0000000000003793
304 Cannon, D. T. *et al.* Skeletal muscle power and fatigue at the tolerable limit of ramp-incremental exercise in COPD. *Journal of applied physiology (Bethesda,*

Md. : 1985) **121**, 1365-1373 (2016). https://doi.org:https://dx.doi.org/10.1152/japplphysiol.00660.2016

305 Sandford, G. N., Kilding, A. E., Ross, A. & Laursen, P. B. Maximal Sprint Speed and the Anaerobic Speed Reserve Domain: The Untapped Tools that Differentiate the World's Best Male 800 m Runners. *Sports Med.* **49**, 843-852 (2019). https://doi.org:10.1007/s40279-018-1010-5

306 Ayalon, A., Inbar, O. & Bar-Or, O. in *Biomechanics IV* 572-577 (Springer, 1974).

307 Chura, R. L., Marciniuk, D. D., Clemens, R. & Butcher, S. J. Test-Retest Reliability and Physiological Responses Associated with the Steep Ramp Anaerobic Test in Patients with COPD. *Pulm. Med.* **2012**, 653831 (2012). https://doi.org:10.1155/2012/653831

308 Meyer, K. *et al.* Interval training in patients with severe chronic heart failure: analysis and recommendations for exercise procedures. *Med. Sci. Sports Exerc.* **29**, 306-312 (1997). https://doi.org:10.1097/00005768-199703000-00004

309 Hedlund, M., Lindelöf, N., Johansson, B., Boraxbekk, C. J. & Rosendahl, E. Development and Feasibility of a Regulated, Supramaximal High-Intensity Training Program Adapted for Older Individuals. *Front. Physiol.* **10**, 590 (2019). https://doi.org:10.3389/fphys.2019.00590

310 Simonsson, E. *et al.* Effects of Controlled Supramaximal High-Intensity Interval Training on Cardiorespiratory Fitness and Global Cognitive Function in Older Adults: The Umeå HIT Study-A Randomized Controlled Trial. *J. Gerontol. A Biol. Sci. Med. Sci.* (2023). https://doi.org:10.1093/gerona/glad070

311 Borg, G. Ratings of perceived exertion and heart rates during short-term cycle exercise and their use in a new cycling strength test. *Int. J. Sports Med.* **3**, 153-158 (1982). https://doi.org:10.1055/s-2008-1026080

312 Gist, N. H., Fedewa, M. V., Dishman, R. K. & Cureton, K. J. Sprint interval training effects on aerobic capacity: a systematic review and meta-analysis. *Sports Med.* **44**, 269-279 (2014). https://doi.org:10.1007/s40279-013-0115-0

313 Adamson, S., Kavaliauskas, M., Lorimer, R. & Babraj, J. The Impact of Sprint Interval Training Frequency on Blood Glucose Control and Physical Function of Older Adults. *Int. J. Environ. Res. Public Health* **17** (2020). https://doi.org:10.3390/ijerph17020454

314 Boullosa, D. *et al.* Effects of short sprint interval training on aerobic and anaerobic indices: A systematic review and meta-analysis. *Scand. J. Med. Sci. Sports* **32**, 810-820 (2022). https://doi.org:10.1111/sms.14133

315 Frykholm, E. *et al.* Applicability of a supramaximal high-intensity interval training program for older adults previously not engaged in regular exercise; analyses of secondary outcomes from the Umeå HIT Study. *Psychol. Sport Exerc.* **73**, 102647 (2024). https://doi.org:https://doi.org/10.1016/j.psychsport.2024.102647

316 Metcalfe, R. S., Babraj, J. A., Fawkner, S. G. & Vollaard, N. B. Towards the minimal amount of exercise for improving metabolic health: beneficial effects of reduced-exertion high-intensity interval training. *Eur. J. Appl. Physiol.* **112**, 2767-2775 (2012). https://doi.org:10.1007/s00421-011-2254-z

317 Metcalfe, R. S. *et al.* Affecting Effects on Affect: The Impact of Protocol Permutations on Affective Responses to Sprint Interval Exercise; A Systematic

Review and Meta-Analysis of Pooled Individual Participant Data. *Front Sports Act Living* **4**, 815555 (2022). https://doi.org:10.3389/fspor.2022.815555

318 Burgomaster, K. A. *et al.* Similar metabolic adaptations during exercise after low volume sprint interval and traditional endurance training in humans. *J. Physiol.* **586**, 151-160 (2008). https://doi.org:10.1113/jphysiol.2007.142109

319 Gibala, M. J. *et al.* Short-term sprint interval versus traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J. Physiol.* **575**, 901-911 (2006). https://doi.org:10.1113/jphysiol.2006.112094

320 Callahan, M. J., Parr, E. B., Hawley, J. A. & Camera, D. M. Can High-Intensity Interval Training Promote Skeletal Muscle Anabolism? *Sports Med.* **51**, 405-421 (2021). https://doi.org:10.1007/s40279-020-01397-3

321 Satiroglu, R., Lalande, S., Hong, S., Nagel, M. J. & Coyle, E. F. Four-Second Power Cycling Training Increases Maximal Anaerobic Power, Peak Oxygen Consumption, and Total Blood Volume. *Med. Sci. Sports Exerc.* **53**, 2536-2542 (2021). https://doi.org:10.1249/mss.0000000000002748

322 Gibala, M. J., Little, J. P., Macdonald, M. J. & Hawley, J. A. Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J. Physiol.* **590**, 1077-1084 (2012). https://doi.org:10.1113/jphysiol.2011.224725

323 Wu, Z. *et al.* Mechanisms controlling mitochondrial biogenesis and respiration through the thermogenic coactivator PGC-1. *Cell* **98**, 115-124 (1999). https://doi.org:10.1016/s0092-8674(00)80611-x

324 Granata, C., Jamnick, N. A. & Bishop, D. J. Training-Induced Changes in Mitochondrial Content and Respiratory Function in Human Skeletal Muscle. *Sports Med.* **48**, 1809-1828 (2018). https://doi.org:10.1007/s40279-018-0936-y

325 Egan, B. *et al.* Exercise intensity-dependent regulation of peroxisome proliferator-activated receptor coactivator-1 mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. *J. Physiol.* **588**, 1779-1790 (2010). https://doi.org:10.1113/jphysiol.2010.188011

326 Granata, C., Oliveira, R. S., Little, J. P., Renner, K. & Bishop, D. J. Sprint-interval but not continuous exercise increases PGC-1α protein content and p53 phosphorylation in nuclear fractions of human skeletal muscle. *Sci. Rep.* **7**, 44227 (2017). https://doi.org:10.1038/srep44227

327 Bishop, D. J. *et al.* High-Intensity Exercise and Mitochondrial Biogenesis: Current Controversies and Future Research Directions. *Physiology* **34**, 56-70 (2018). https://doi.org:10.1152/physiol.00038.2018

328 Stillman, C. M., Esteban-Cornejo, I., Brown, B., Bender, C. M. & Erickson, K. I. Effects of Exercise on Brain and Cognition Across Age Groups and Health States. *Trends Neurosci.* **43**, 533-543 (2020). https://doi.org:10.1016/j.tins.2020.04.010

329 Singh, B. *et al.* Effectiveness of exercise for improving cognition, memory and executive function: a systematic umbrella review and meta-meta-analysis. *Br. J. Sports Med.* **59**, 866 (2025). https://doi.org:10.1136/bjsports-2024-108589

330 Nicastri, C. M. *et al.* BDNF mediates improvement in cognitive performance after computerized cognitive training in healthy older adults. *Alzheimers Dement (N Y)* **8**, e12337 (2022). https://doi.org:10.1002/trc2.12337

331 Erickson, K. I. *et al.* Exercise training increases size of hippocampus and improves memory. *Proc. Natl. Acad. Sci. U. S. A.* **108**, 3017-3022 (2011). https://doi.org:10.1073/pnas.1015950108

332 Binder, D. K. & Scharfman, H. E. Brain-derived neurotrophic factor. *Growth Factors* **22**, 123-131 (2004). https://doi.org:10.1080/08977190410001723308

333 Wrann, Christiane D. *et al.* Exercise Induces Hippocampal BDNF through a PGC-1α/FNDC5 Pathway. *Cell Metab.* **18**, 649-659 (2013). https://doi.org:https://doi.org/10.1016/j.cmet.2013.09.008

334 Cefis, M. *et al.* Molecular mechanisms underlying physical exercise-induced brain BDNF overproduction. *Front. Mol. Neurosci.* **16** (2023). https://doi.org:10.3389/fnmol.2023.1275924

335 Rodríguez-Gutiérrez, E. *et al.* Effectiveness of high-intensity interval training on peripheral brain-derived neurotrophic factor in adults: A systematic review and network meta-analysis. *Scand. J. Med. Sci. Sports* **34**, e14496 (2024). https://doi.org:10.1111/sms.14496

336 Zare, N., Bishop, D. J., Levinger, I., Febbraio, M. A. & Broatch, J. R. Exercise intensity matters: A review on evaluating the effects of aerobic exercise intensity on muscle-derived neuroprotective myokines. *Alzheimers Dement (N Y)* **11**, e70056 (2025). https://doi.org:10.1002/trc2.70056

337 Hopewell, S. *et al.* CONSORT 2025 statement: updated guideline for reporting randomized trials. *Nat. Med.* (2025). https://doi.org:10.1038/s41591-025-03635-5

338 Turner, L., Shamseer, L., Altman, D. G., Schulz, K. F. & Moher, D. Does use of the CONSORT Statement impact the completeness of reporting of randomised controlled trials published in medical journals? A Cochrane review. *Syst Rev* **1**, 60 (2012). https://doi.org:10.1186/2046-4053-1-60

339 Srinivasan, A., Berkowitz, J., Kivelson, S., Friedrich, N. & Tatonetti, N. Evaluating the Reporting Quality of 21,041 Randomized Controlled Trial Articles. *medRxiv*, 2025.2003.2006.25323528 (2025). https://doi.org:10.1101/2025.03.06.25323528

340 Hoffmann, T. C., Erueti, C. & Glasziou, P. P. Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials. *BMJ : British Medical Journal* **347**, f3755 (2013). https://doi.org:10.1136/bmj.f3755

341 Glasziou, P. *et al.* Reducing waste from incomplete or unusable reports of biomedical research. *Lancet* **383**, 267-276 (2014). https://doi.org:10.1016/s0140-6736(13)62228-x

342 Begg, C. *et al.* Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *JAMA* **276**, 637-639 (1996). https://doi.org:10.1001/jama.276.8.637

343 Hoffmann, T. C. *et al.* Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ : British Medical Journal* **348**, g1687 (2014). https://doi.org:10.1136/bmj.g1687

344 Mesquida, C., Murphy, J., Lakens, D. & Warne, J. Replication concerns in sports and exercise science: a narrative review of selected methodological issues in the field. *Royal Society Open Science* **9**, 220946 (2022). https://doi.org:10.1098/rsos.220946

345 Arienti, C. *et al.* Methodological Issues in Rehabilitation Research: A Scoping Review. *Arch. Phys. Med. Rehabil.* **102**, 1614-1622.e1614 (2021). https://doi.org:10.1016/j.apmr.2021.04.006

346 Slade, S. C., Dionne, C. E., Underwood, M. & Buchbinder, R. Consensus on Exercise Reporting Template (CERT): Explanation and Elaboration Statement. *Br. J. Sports Med.* **50**, 1428-1437 (2016). https://doi.org:10.1136/bjsports-2016-096651

347 Jo, D. *et al.* A study of the description of exercise programs evaluated in randomized controlled trials involving people with fibromyalgia using different reporting tools, and validity of the tools related to pain relief. *Clin. Rehabil.* **33**, 557-563 (2018). https://doi.org:10.1177/0269215518815931

348 Medysky, M. E. *et al.* Attention to the Principles of Exercise Training in Exercise Studies of Persons With Lung Cancer: A Systematic Review. *J. Aging Phys. Act.*, 1-11 (2021). https://doi.org:10.1123/japa.2020-0269

349 Holden, S., Rathleff, M. S., Jensen, M. B. & Barton, C. J. How can we implement exercise therapy for patellofemoral pain if we don't know what was prescribed? A systematic review. *Br. J. Sports Med.* **52**, 385 (2018). https://doi.org:10.1136/bjsports-2017-097547

350 McArdle, W. D., Katch, F. I. & Katch, V. L. *Exercise physiology: nutrition, energy, and human performance*. (Lippincott Williams & Wilkins, 2010).

351 Hopewell, S. *et al.* CONSORT 2025 explanation and elaboration: updated guideline for reporting randomised trials. *BMJ* **389** (2025).

352 Campbell, K. L., Neil, S. E. & Winters-Stone, K. M. Review of exercise studies in breast cancer survivors: attention to principles of exercise training. *Br. J. Sports Med.* **46**, 909-916 (2012). https://doi.org:10.1136/bjsm.2010.082719

353 Neil-Sztramko, S. E., Medysky, M. E., Campbell, K. L., Bland, K. A. & Winters-Stone, K. M. Attention to the principles of exercise training in exercise studies on prostate cancer survivors: a systematic review. *BMC Cancer* **19**, 321 (2019). https://doi.org:10.1186/s12885-019-5520-9

354 Neil-Sztramko, S. E., Winters-Stone, K. M., Bland, K. A. & Campbell, K. L. Updated systematic review of exercise studies in breast cancer survivors: attention to the principles of exercise training. *Br. J. Sports Med.* **53**, 504-512 (2019). https://doi.org:10.1136/bjsports-2017-098389

355 Winters-Stone, K. M., Neil, S. E. & Campbell, K. L. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. *Br. J. Sports Med.* **48**, 987-995 (2014). https://doi.org:10.1136/bjsports-2012-091732

356 Tew, G. A., Brabyn, S., Cook, L. & Peckham, E. The Completeness of Intervention Descriptions in Randomised Trials of Supervised Exercise Training in Peripheral Arterial Disease. *PLoS One* **11**, e0150869 (2016). https://doi.org:10.1371/journal.pone.0150869

357 Jo, D. *et al.* A study of the description of exercise programs evaluated in randomized controlled trials involving people with fibromyalgia using different reporting tools, and validity of the tools related to pain relief. *Clin. Rehabil.* **33**, 557-563 (2019). https://doi.org:10.1177/0269215518815931

358 Slade, S. C., Finnegan, S., Dionne, C. E., Underwood, M. & Buchbinder, R. The Consensus on Exercise Reporting Template (CERT) applied to exercise interventions in musculoskeletal trials demonstrated good rater agreement and incomplete reporting. *J. Clin. Epidemiol.* **103**, 120-130 (2018). https://doi.org:10.1016/j.jclinepi.2018.07.009

359 Bland, K. A. *et al.* Attention to principles of exercise training: an updated systematic review of randomized controlled trials in cancers other than breast and prostate. *BMC Cancer* **21**, 1179 (2021). https://doi.org:10.1186/s12885-021-08701-y

360 Meneses-Echavez, J. F. *et al.* Analysis of reporting completeness in exercise cancer trials: a systematic review. *BMC Med. Res. Methodol.* **19**, 220 (2019). https://doi.org:10.1186/s12874-019-0871-0

361 Rohwer, J., Weisser, B., Wegner, M. & Bünzen, C. Aerobic Versus Resistance Exercise for Overweight: Is there a Difference in Reporting Quality? *Sports Med Int Open* **9**, a25962049 (2025). https://doi.org:10.1055/a-2596-2049

362 Moecke, D. P. *et al.* A systematic review of exercise studies for individuals hospitalized with an acute exacerbation of chronic obstructive pulmonary disease: Focus on the principles of exercise training. *Chron. Respir. Dis.* **20**, 14799731231215363 (2023). https://doi.org:10.1177/14799731231215363

363 Jakobsson, J. *et al.* Quality of aerobic training description and its relation to intervention efficacy in chronic obstructive pulmonary disease trials: study protocol for a systematic review, meta-analysis and meta-regression. *BMJ Open* **14**, e084296 (2024). https://doi.org:10.1136/bmjopen-2024-084296

364 Westra, B. *et al.* Quality of resistance training description in COPD trials: study protocol for a systematic review. *BMJ open* **9**, e025030 (2019). https://doi.org:https://dx.doi.org/10.1136/bmjopen-2018-025030

365 Dwan, K., Li, T., Altman, D. G. & Elbourne, D. CONSORT 2010 statement: extension to randomised crossover trials. *BMJ* **366**, l4378 (2019). https://doi.org:10.1136/bmj.l4378

366 von Elm, E. *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* **370**, 1453-1457 (2007). https://doi.org:10.1016/s0140-6736(07)61602-x

367 Jakobsson, J. *et al.* Feasibility and acute physiological responses to supramaximal high-intensity interval-training in COPD: A randomised crossover trial. *ERJ Open Research*, 01321-02024 (2025). https://doi.org:10.1183/23120541.01321-2024

368 Chan, A. W. *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* **346**, e7586 (2013). https://doi.org:10.1136/bmj.e7586

369 Butcher, N. J. *et al.* Guidelines for Reporting Outcomes in Trial Protocols: The SPIRIT-Outcomes 2022 Extension. *JAMA* **328**, 2345-2356 (2022). https://doi.org:10.1001/jama.2022.21243

370 Sundh, J. *et al.* Pulmonary rehabilitation in COPD - available resources and utilization in Swedish primary and secondary care. *Int. J. Chron. Obstruct. Pulmon. Dis.* **12**, 1695-1704 (2017). https://doi.org:10.2147/copd.S135111

371 Wadell, K. *et al.* Hospital-based pulmonary rehabilitation in patients with COPD in Sweden--a national survey. *Respir. Med.* **107**, 1195-1200 (2013). https://doi.org:https://dx.doi.org/10.1016/j.rmed.2013.04.019

372 Vasilopoulou, M. *et al.* Home-based maintenance tele-rehabilitation reduces the risk for acute exacerbations of COPD, hospitalisations and emergency department visits. *The European respiratory journal* **49** (2017). https://doi.org:https://dx.doi.org/10.1183/13993003.02129-2016

373 du Moulin, M., Taube, K., Wegscheider, K., Behnke, M. & van den Bussche, H. Home-based exercise training as maintenance after outpatient pulmonary rehabilitation. *Respiration; international review of thoracic diseases* **77**, 139-145 (2009). https://doi.org:https://dx.doi.org/10.1159/000150315

374 Wilson, A. M. *et al.* The effects of maintenance schedules following pulmonary rehabilitation in patients with chronic obstructive pulmonary disease: a randomised controlled trial. *BMJ Open* **5**, e005921 (2015). https://doi.org:10.1136/bmjopen-2014-005921

375 Barberan-Garcia, A. *et al.* Effects and barriers to deployment of telehealth wellness programs for chronic patients across 3 European countries. *Respir. Med.* **108**, 628-637 (2014). https://doi.org:https://dx.doi.org/10.1016/j.rmed.2013.12.006

376 Graham, B. L. *et al.* Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. *Am. J. Respir. Crit. Care Med.* **200**, e70-e88 (2019). https://doi.org:10.1164/rccm.201908-1590ST

377 Bhakta, N. R. *et al.* European Respiratory Society/American Thoracic Society technical statement: standardisation of the measurement of lung volumes, 2023 update. *Eur. Respir. J.* **62** (2023). https://doi.org:10.1183/13993003.01519-2022

378 Graham, B. L. *et al.* 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur. Respir. J.* **49** (2017). https://doi.org:10.1183/13993003.00016-2016

379 Vogler, A. J., Rice, A. J. & Gore, C. J. Validity and reliability of the Cortex MetaMax3B portable metabolic system. *J. Sports Sci.* **28**, 733-742 (2010). https://doi.org:10.1080/02640410903582776

380 Van Hooren, B., Souren, T. & Bongers, B. C. Accuracy of respiratory gas variables, substrate, and energy use from 15 CPET systems during simulated and human exercise. *Scand. J. Med. Sci. Sports* **34**, e14490 (2024). https://doi.org:10.1111/sms.14490

381 Jakobsson, J. *et al.* Effects and mechanisms of supramaximal high-intensity interval training on extrapulmonary manifestations in people with and without chronic obstructive pulmonary disease (COPD-HIIT): study protocol for a multi-

centre, randomized controlled trial. *Trials* **25**, 664 (2024). https://doi.org:10.1186/s13063-024-08481-3

382 Bonnevie, T. *et al.* Mid-Term Effects of Pulmonary Rehabilitation on Cognitive Function in People with Severe Chronic Obstructive Pulmonary Disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **15**, 1111-1121 (2020). https://doi.org:10.2147/copd.S249409

383 Villeneuve, S. *et al.* Mild Cognitive Impairment in Moderate to Severe COPD: A Preliminary Study. *Chest* **142**, 1516-1523 (2012). https://doi.org:https://doi.org/10.1378/chest.11-3035

384 Nasreddine, Z. S. *et al.* The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* **53**, 695-699 (2005). https://doi.org:10.1111/j.1532-5415.2005.53221.x

385 Borland, E. *et al.* The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort. *J. Alzheimers Dis.* **59**, 893-901 (2017). https://doi.org:10.3233/jad-170203

386 Hernández, M. *et al.* The Relationships Between Muscle Power and Physical Activity in Older Men With Chronic Obstructive Pulmonary Disease. *J. Aging Phys. Act.* **25**, 360-366 (2017). https://doi.org:10.1123/japa.2016-0144

387 Frykholm, E. *et al.* Inter-day test-retest reliability and feasibility of isokinetic, isometric, and isotonic measurements to assess quadriceps endurance in people with chronic obstructive pulmonary disease: A multicenter study. *Chron. Respir. Dis.* **16**, 1479973118816497 (2019). https://doi.org:10.1177/1479973118816497

388 De Brandt, J., Jakobsson, J., Hedlund, M., Sandström, T. & Nyberg, A. The modified Borg cycle strength test (mBCST): Feasibility and physiological response in people with COPD and healthy older adults. *Exp. Physiol.* **n/a** (2025). https://doi.org:https://doi.org/10.1113/EP092151

389 Robertson, S., Kremer, P., Aisbett, B., Tran, J. & Cerin, E. Consensus on measurement properties and feasibility of performance tests for the exercise and sport sciences: a Delphi study. *Sports Med Open* **3**, 2 (2017). https://doi.org:10.1186/s40798-016-0071-y

390 Dill, D. B. & Costill, D. L. Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *J. Appl. Physiol.* **37**, 247-248 (1974). https://doi.org:10.1152/jappl.1974.37.2.247

391 Park, H. & Poo, M.-m. Neurotrophin regulation of neural circuit development and function. *Nature Reviews Neuroscience* **14**, 7-23 (2013). https://doi.org:10.1038/nrn3379

392 Poduslo, J. F. & Curran, G. L. Permeability at the blood-brain and blood-nerve barriers of the neurotrophic factors: NGF, CNTF, NT-3, BDNF. *Brain Res. Mol. Brain Res.* **36**, 280-286 (1996). https://doi.org:10.1016/0169-328x(95)00250-v

393 Radka, S. F., Holst, P. A., Fritsche, M. & Altar, C. A. Presence of brain-derived neurotrophic factor in brain and human and rat but not mouse serum detected by a sensitive and specific immunoassay. *Brain Res.* **709**, 122-301 (1996). https://doi.org:10.1016/0006-8993(95)01321-0

394 Herdman, M. *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual. Life Res.* **20**, 1727-1736 (2011).

395 Nolan, C. M. *et al.* The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax* **71**, 493-500 (2016). https://doi.org:10.1136/thoraxjnl-2015-207782

396 Zigmond, A. S. & Snaith, R. P. The Hospital Anxiety and Depression Scale. *Acta Psychiatr. Scand.* **67**, 361-370 (1983). https://doi.org:https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

397 Evans, R. A. *et al.* One-Legged Cycle Training for Chronic Obstructive Pulmonary Disease. A Pragmatic Study of Implementation to Pulmonary Rehabilitation. *Annals of the American Thoracic Society* **12**, 1490-1497 (2015). https://doi.org:https://dx.doi.org/10.1513/AnnalsATS.201504-231OC

398 Page, M. J. *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* **372**, n71 (2021). https://doi.org:10.1136/bmj.n71

399 Nici, L. *et al.* American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am. J. Respir. Crit. Care Med.* **173**, 1390-1413 (2006).

400 Ouzzani, M., Hammady, H., Fedorowicz, Z. & Elmagarmid, A. Rayyan—a web and mobile app for systematic reviews. *Systematic Reviews* **5**, 210 (2016). https://doi.org:10.1186/s13643-016-0384-4

401 Fisher, R. A. Statistical methods for research workers. (1934).

402 Neyman, J. & Pearson, E. S. On the use and interpretation of certain test criteria for purposes of statistical inference part I. *Biometrika* **20**, 175-240 (1928).

403 Hopkins, W. G., Marshall, S. W., Batterham, A. M. & Hanin, J. Progressive statistics for studies in sports medicine and exercise science. *Med. Sci. Sports Exerc.* **41**, 3-13 (2009). https://doi.org:10.1249/MSS.0b013e31818cb278

404 Hemming, K. *et al.* Prospective reporting of statistical analysis plans for randomised controlled trials. *Trials* **21**, 898 (2020). https://doi.org:10.1186/s13063-020-04828-8

405 Gamble, C. *et al.* Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA* **318**, 2337-2343 (2017). https://doi.org:10.1001/jama.2017.18556

406 Kahan, B. C., Jairath, V., Doré, C. J. & Morris, T. P. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* **15**, 139 (2014). https://doi.org:10.1186/1745-6215-15-139

407 Holmberg, M. J. & Andersen, L. W. Adjustment for baseline characteristics in randomized clinical trials. *JAMA* **328**, 2155-2156 (2022).

408 Dinoff, A., Herrmann, N., Swardfager, W. & Lanctôt, K. L. The effect of acute exercise on blood concentrations of brain-derived neurotrophic factor in healthy adults: a meta-analysis. *Eur. J. Neurosci.* **46**, 1635-1646 (2017). https://doi.org:https://doi.org/10.1111/ejn.13603

409 García-Suárez, P. C., Rentería, I., Plaisance, E. P., Moncada-Jiménez, J. & Jiménez-Maldonado, A. The effects of interval training on peripheral brain derived neurotrophic factor (BDNF) in young adults: a systematic review and meta-analysis. *Sci. Rep.* **11**, 8937 (2021). https://doi.org:10.1038/s41598-021-88496-x

410 Julious, S. A. Sample size of 12 per group rule of thumb for a pilot study. *Pharm. Stat.* **4**, 287-291 (2005). https://doi.org:https://doi.org/10.1002/pst.185

411 Connors, M. H. *et al.* Cognition and mortality in older people: the Sydney Memory and Ageing Study. *Age Ageing* **44**, 1049-1054 (2015). https://doi.org:10.1093/ageing/afv139

412 Van Driessche, S., Van Roie, E., Vanwanseele, B. & Delecluse, C. Test-retest reliability of knee extensor rate of velocity and power development in older adults using the isotonic mode on a Biodex System 3 dynamometer. *PLoS One* **13**, e0196838 (2018). https://doi.org:10.1371/journal.pone.0196838

413 Harden, M. & Friede, T. Sample size recalculation in multicenter randomized controlled clinical trials based on noncomparative data. *Biom. J.* **62**, 1284-1299 (2020). https://doi.org:https://doi.org/10.1002/bimj.201900138

414 Vierron, E. & Giraudeau, B. Design effect in multicenter studies: gain or loss of power? *BMC Med. Res. Methodol.* **9**, 39 (2009). https://doi.org:10.1186/1471-2288-9-39

415 Vierron, E. & Giraudeau, B. Sample size calculation for multicenter randomized trial: Taking the center effect into account. *Contemp. Clin. Trials* **28**, 451-458 (2007). https://doi.org:https://doi.org/10.1016/j.cct.2006.11.003

416 Lingsma, H., Roozenbeek, B. & Steyerberg, E. Covariate adjustment increases statistical power in randomized controlled trials. *J. Clin. Epidemiol.* **63**, 1391; author reply 1392-1393 (2010). https://doi.org:10.1016/j.jclinepi.2010.05.003

417 Roozenbeek, B. *et al.* Baseline characteristics and statistical power in randomized controlled trials: Selection, prognostic targeting, or covariate adjustment?*. *Crit. Care Med.* **37** (2009).

418 World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* **310**, 2191-2194 (2013). https://doi.org:10.1001/jama.2013.281053

419 Demeyer, H. *et al.* The Minimal Important Difference in Physical Activity in Patients with COPD. *PLoS One* **11**, e0154587 (2016). https://doi.org:https://dx.doi.org/10.1371/journal.pone.0154587

420 Na, C. & Fei, L. Influences of aerobic exercise associated with the pharmacological treatment of copd. *Revista Brasileira de Medicina do Esporte* **29**, e2023_0067 (2023).

421 Toledo, A. *et al.* The impact of noninvasive ventilation during the physical training in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). *Clinics (Sao Paulo, Brazil)* **62**, 113-120 (2007).

422 Xiaosheng, D. *et al.* A comparison between Qigong exercise and cycle ergometer exercise for the rehabilitation of chronic obstructive pulmonary disease: A pilot randomized controlled trial (CONSORT). *Medicine* **100**, 1-7 (2021). https://doi.org:10.1097/MD.0000000000026010

423 Reddy A, S. B., Srinivasan, N. M., Anil Kumar, T., Alaparthi, G. K. & Bairapareddy, K. C. Effect of Balance Training on Health Related Quality of Life in Patients with Chronic Obstructive Pulmonary Disease (COPD). *Indian Journal of Public Health Research & Development* **11** (2020).

424 Paneroni, M., Vogiatzis, I., Salvi, B., Bertacchini, L. & Vitacca, M. Interval training in COPD patients with chronic respiratory failure: a feasibility and

comparative study. *Eur. Respir. J.* **64**, PA4967 (2024). https://doi.org:10.1183/13993003.congress-2024.PA4967

425 Nymand, S. B. *et al.* Fidelity and tolerability of two high-intensity interval training protocols in patients with COPD: a randomised cross-over pilot study. *BMJ Open Sport & Exercise Medicine* **9**, e001486 (2023). https://doi.org:10.1136/bmjsem-2022-001486

426 Casaburi, R. *et al.* Validation of Constant Work Rate Cycling Endurance Time for Use in Chronic Obstructive Pulmonary Disease Clinical Trials. *Ann Am Thorac Soc* **21**, 727-739 (2024). https://doi.org:10.1513/AnnalsATS.202305-480OC

427 Reljic, D., Frenk, F., Herrmann, H. J., Neurath, M. F. & Zopf, Y. Effects of very low volume high intensity versus moderate intensity interval training in obese metabolic syndrome patients: a randomized controlled study. *Sci. Rep.* **11**, 2836 (2021). https://doi.org:10.1038/s41598-021-82372-4

428 Hardcastle, S. J., Ray, H., Beale, L. & Hagger, M. S. Why sprint interval training is inappropriate for a largely sedentary population. *Front. Psychol.* **5**, 1505 (2014). https://doi.org:10.3389/fpsyg.2014.01505

429 Ekkekakis, P. & Biddle, S. J. H. Extraordinary claims in the literature on high-intensity interval training (HIIT): IV. Is HIIT associated with higher long-term exercise adherence? *Psychol. Sport Exerc.* **64**, 102295 (2023). https://doi.org:https://doi.org/10.1016/j.psychsport.2022.102295

430 Marriott, C. F. S., Petrella, A. F. M., Marriott, E. C. S., Boa Sorte Silva, N. C. & Petrella, R. J. High-Intensity Interval Training in Older Adults: a Scoping Review. *Sports Med Open* **7**, 49 (2021). https://doi.org:10.1186/s40798-021-00344-4

431 Liang, W. *et al.* Effects of High-Intensity Interval Training on the Parameters Related to Physical Fitness and Health of Older Adults: A Systematic Review and Meta-Analysis. *Sports Medicine - Open* **10**, 98 (2024). https://doi.org:10.1186/s40798-024-00767-9

432 Williams, M. T. *et al.* Reporting of exercise attendance rates for people with chronic obstructive pulmonary disease: A systematic review. *Respirology* **19**, 30-37 (2014). https://doi.org:https://doi.org/10.1111/resp.12201

433 Roig, M., Eng, J. J., MacIntyre, D. L., Road, J. D. & Reid, W. D. Associations of the Stair Climb Power Test with muscle strength and functional performance in people with chronic obstructive pulmonary disease: a cross-sectional study. *Phys. Ther.* **90**, 1774-1782 (2010). https://doi.org:https://dx.doi.org/10.2522/ptj.20100091

434 Leone, M., Duvergé, S., Kalinova, É., Bui, H. T. & Comtois, A. S. Comparison of bioenergetics of walking during a multistage incremental shuttle walk test and a 6-min walk test in active older adults. *Aging Clin. Exp. Res.* **29**, 239-246 (2017). https://doi.org:10.1007/s40520-016-0555-0

435 Hirsch, A., Bieleke, M., Bertschinger, R., Schüler, J. & Wolff, W. Struggles and strategies in anaerobic and aerobic cycling tests: A mixed-method approach with a focus on tailored self-regulation strategies. *PLoS One* **16**, e0259088 (2021). https://doi.org:10.1371/journal.pone.0259088

436 Biddle, S. J. & Batterham, A. M. High-intensity interval exercise training for public health: a big HIT or shall we HIT it on the head? *Int. J. Behav. Nutr. Phys. Act.* **12**, 95 (2015). https://doi.org:10.1186/s12966-015-0254-9

437 de Araujo, C. L. P. *et al.* Pulmonary rehabilitation and BDNF levels in patients with chronic obstructive pulmonary disease: A pilot study. *Respir. Physiol. Neurobiol.* **259**, 63-69 (2019). https://doi.org:https://doi.org/10.1016/j.resp.2018.07.011

438 Pareja-Galeano, H. *et al.* Methodological considerations to determine the effect of exercise on brain-derived neurotrophic factor levels. *Clin. Biochem.* **48**, 162-166 (2015). https://doi.org:10.1016/j.clinbiochem.2014.11.013

439 Gejl, A. K. *et al.* Associations between serum and plasma brain-derived neurotrophic factor and influence of storage time and centrifugation strategy. *Sci. Rep.* **9**, 9655 (2019). <https://doi.org/10.1038/s41598-019-45976-5>.

440 Maclay, J. D. *et al.* Increased platelet activation in patients with stable and acute exacerbation of COPD. *Thorax* **66**, 769-774 (2011). https://doi.org:10.1136/thx.2010.157529

441 Mallah, H., Ball, S., Sekhon, J., Parmar, K. & Nugent, K. Platelets in chronic obstructive pulmonary disease: An update on pathophysiology and implications for antiplatelet therapy. *Respir. Med.* **171**, 106098 (2020). https://doi.org:https://doi.org/10.1016/j.rmed.2020.106098

442 De Miguel, Z. *et al.* Exercise plasma boosts memory and dampens brain inflammation via clusterin. *Nature* **600**, 494-499 (2021). https://doi.org:10.1038/s41586-021-04183-x

443 Lu, Y. *et al.* Recent advances on the molecular mechanisms of exercise-induced improvements of cognitive dysfunction. *Translational Neurodegeneration* **12**, 9 (2023). https://doi.org:10.1186/s40035-023-00341-5

444 Jenkins, A. R., Holden, N. S. & Jones, A. W. Inflammatory responses to acute exercise during pulmonary rehabilitation in patients with COPD. *Eur. J. Appl. Physiol.* **120**, 2301-2309 (2020). https://doi.org:10.1007/s00421-020-04452-z

445 Canavan, J. *et al.* Measurement of the acute inflammatory response to walking exercise in COPD: effects of pulmonary rehabilitation. *Int. J. Chron. Obstruct. Pulmon. Dis.* **2**, 347-353 (2007). https://doi.org:10.2147/copd.s12159968

446 Kistner, T. M., Pedersen, B. K. & Lieberman, D. E. Interleukin 6 as an energy allocator in muscle tissue. *Nature Metabolism* **4**, 170-179 (2022). https://doi.org:10.1038/s42255-022-00538-4

447 Petersen, A. M. & Pedersen, B. K. The anti-inflammatory effect of exercise. *J Appl Physiol (1985)* **98**, 1154-1162 (2005). https://doi.org:10.1152/japplphysiol.00164.2004

448 Al Wachami, N. *et al.* Estimating the global prevalence of chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMC Public Health* **24**, 297 (2024). https://doi.org:10.1186/s12889-024-17686-9

449 Lindberg, A., Bjerg, A., Rönmark, E., Larsson, L. G. & Lundbäck, B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir. Med.* **100**, 264-272 (2006). https://doi.org:10.1016/j.rmed.2005.04.029

450 Harwood, A. E. *et al.* A systematic review of rehabilitation in chronic heart failure: evaluating the reporting of exercise interventions. *ESC Heart Fail* **8**, 3458-3471 (2021). https://doi.org:10.1002/ehf2.13498

451 Burgess, L. C., Wainwright, T. W., James, K. A., von Heideken, J. & Iversen, M. D. The quality of intervention reporting in trials of therapeutic exercise for hip osteoarthritis: a secondary analysis of a systematic review. *Trials* **22**, 388 (2021). https://doi.org:10.1186/s13063-021-05342-1

452 Abell, B., Glasziou, P. & Hoffmann, T. Reporting and replicating trials of exercise-based cardiac rehabilitation: do we know what the researchers actually did? *Circ. Cardiovasc. Qual. Outcomes* **8**, 187-194 (2015). https://doi.org:10.1161/circoutcomes.114.001381

453 Warmenhoven, J. *et al.* Sports Metaresearch: An Emerging Discipline of Sport Science and Medicine. *Sports Med.* **55**, 845-856 (2025). https://doi.org:10.1007/s40279-025-02181-x

454 Bonafiglia, J. T., Islam, H., Preobrazenski, N. & Gurd, B. J. Risk of bias and reporting practices in studies comparing VO(2max) responses to sprint interval vs. continuous training: A systematic review and meta-analysis. *J Sport Health Sci* **11**, 552-566 (2022). https://doi.org:10.1016/j.jshs.2021.03.005

455 Poon, E. T., Li, H. Y., Gibala, M. J., Wong, S. H. & Ho, R. S. High-intensity interval training and cardiorespiratory fitness in adults: An umbrella review of systematic reviews and meta-analyses. *Scand. J. Med. Sci. Sports* **34**, e14652 (2024). https://doi.org:10.1111/sms.14652

456 Lou, P. *et al.* A COPD health management program in a community-based primary care setting: a randomized controlled trial. *Respir. Care* **60**, 102-112 (2015). https://doi.org:https://dx.doi.org/10.4187/respcare.03420

457 Waterhouse, J. C., Walters, S. J., Oluboyede, Y. & Lawson, R. A. A randomised 2 x 2 trial of community versus hospital pulmonary rehabilitation, followed by telephone or conventional follow-up. *Health technology assessment (Winchester, England)* **14**, i-140 (2010). https://doi.org:https://dx.doi.org/10.3310/hta14060

458 Horton, E. J. *et al.* Comparison of a structured home-based rehabilitation programme with conventional supervised pulmonary rehabilitation: a randomised non-inferiority trial. *Thorax* **73**, 29-36 (2018). https://doi.org:https://dx.doi.org/10.1136/thoraxjnl-2016-208506

459 Simon, J. D. & Douglas, G. A. Blinding in clinical trials and other studies. *BMJ* **321**, 504 (2000). https://doi.org:10.1136/bmj.321.7259.504

460 Chan, A. W. *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann. Intern. Med.* **158**, 200-207 (2013). https://doi.org:10.7326/0003-4819-158-3-201302050-00583

461 Hempstead, B. L. Brain-Derived Neurotrophic Factor: Three Ligands, Many Actions. *Trans. Am. Clin. Climatol. Assoc.* **126**, 9-19 (2015).

462 Edman, S. *et al.* Exercise-induced plasma mature brain-derived neurotrophic factor elevation in children, adolescents and adults: influence of age, maturity and physical activity. *The Journal of Physiology* **603**, 2333-2347 (2025). https://doi.org:https://doi.org/10.1113/JP288170

463 Kang, M., Ragan, B. G. & Park, J. H. Issues in outcomes research: an overview of randomization techniques for clinical trials. *J Athl Train* **43**, 215-221 (2008). https://doi.org:10.4085/1062-6050-43.2.215

464 Frykholm, E. *et al.* Supramaximal high-intensity interval training for older adults in a community setting: a pragmatic feasibility study. *Eur. Rev. Aging Phys. Act.* **22**, 13 (2025). https://doi.org:10.1186/s11556-025-00379-6

465 Bravo, D. M. *et al.* Excess ventilation in COPD: Implications for dyspnoea and tolerance to interval exercise. *Respir. Physiol. Neurobiol.* **250**, 7-13 (2018). https://doi.org:https://dx.doi.org/10.1016/j.resp.2018.01.013

466 Kupper, N., Bonhof, C., Westerhuis, B., Widdershoven, J. & Denollet, J. Determinants of Dyspnea in Chronic Heart Failure. *J. Card. Fail.* **22**, 201-209 (2016). https://doi.org:https://doi.org/10.1016/j.cardfail.2015.09.016

467 Nakazawa, A., Cox, N. S. & Holland, A. E. Current best practice in rehabilitation in interstitial lung disease. *Ther. Adv. Respir. Dis.* **11**, 115-128 (2017). https://doi.org:https://dx.doi.org/10.1177/1753465816676048