EFFECT OF ASTHMA-COPD OVERLAP COMPARED TO COPD ON CARDIOPULMONARY EXERCISE TEST OUTCOMES: INSIGHTS FROM THE CANCOLD STUDY

by

JAYCIE TRIANDAFILOU

B.A., New England College, 2018

M.Sc., Merrimack College, 2019

A THESIS SUBMITTED TO McGILL UNIVERSITY IN PARTIAL FULLFILLMENT OF

THE REQUIREMENTS OF THE DEGREE OF

MASTER OF SCIENCE

in

THE FACULTY OF EDUCATION

(Department of Kinesiology and Physical Education)

McGILL UNIVERSITY
MONTREAL, QUEBEC, CANADA

December 2022

ACKNOWLEDGEMENTS

First and foremost, I'd like to thank my supervisor Dr. Dennis Jensen for his help, mentorship, and contribution to this research and thesis. I am truly grateful for all the support and guidance he has provided me with over the last 2 years; especially given the circumstances of COVID, which effected most of my time as I was faced with a lot of difficult challenges, personally and professionally. You believed in me and provided me with all the resources necessary to succeed. Thank you for giving me the opportunity to be a part of CERPL; I am honored to have been part of such an incredible group.

I'd also like to thank Dr. Alex Jenkins for his commitment and dedication to this project, for being a role model, and a friend. From further explaining concepts I did not fully understand (aka anything to do with statistical analyses), editing my writing (even if at some points it was painful), and providing me with new insights (both personally and professionally), there are no words to express how appreciative I am.

I would like to thank my committee members, Drs Michael Stickland and Jordan Guenette, for their interest and valuable feedback to this thesis. Not to mention their willingness to be available under unfavorable conditions and time constraints.

Thank you to all CERPL members, past and present, who have worked with me over the last two and a half years; you have made this an unforgettable experience. Thank you to Dr. Amir Hadid for letting me help out in his WE SENSE study. Being able to partake in this and being a part of his team was one of the biggest highlights for me during my program; I considered it a privilege to have worked with someone as knowledgeable and accomplished as him. A special thanks to Ahzum Mujaddid, Rachelle Aucoin, Emily Russell, and Nikki van Noord for being there every step of the way, despite everything (good and bad) faced; I could not have done this without you all.

Finally, thank you to Nicolas Potvin for always being by my side, to my friends and family for providing me with endless love and support throughout this journey. I would not have made it this far if it had not been for your constant encouragement.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Introduction: Asthma-COPD overlap (ACO) is a chronic lung health condition in which individuals can have clinical features of both asthma and chronic obstructive pulmonary disease (COPD). Even though universally accepted criteria for the diagnosis of ACO do not exist, studies have consistently reported that people with ACO have higher respiratory symptom burden, lower health status, and poorer pulmonary function than people with COPD alone. However, it remains unclear whether these differences in clinical and patient-reported outcomes are associated with greater pathophysiological abnormalities in exercise tolerance and the physiological and/or perceptual response to exercise among people with ACO compared to COPD. **Objective:** To compare detailed physiological and perceptual responses at the symptom-limited peak of exercise between people with ACO and COPD. **Methods:** Participants included 411 male or female, ever smokers with a post-bronchodilator forced expiratory volume in 1-sec to forced vital capacity ratio <0.70 who completed pulmonary function tests and a symptom-limited incremental cardiopulmonary cycle exercise test as part of the baseline (cross-sectional) visit of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study – a longitudinal population-based cohort of randomly-sampled Canadian adults aged ≥40 years. ACO was defined using three clinical definitions: ACO_1 (n=103), self-reported presence of respiratory allergies and/or hay fever (atopy); ACO_2 (n=125), self-reported physician diagnosed asthma; and ACO_3 (n=65), combination of self-reported atopy and physician diagnosed asthma. Participants were identified as having COPD (no-ACO) when they did not self-report atopy and/or physician diagnosed asthma (n=248). **Results:** Compared to people with COPD alone, people with ACO (largely independent of the clinical definition

used) had significantly lower respiratory-related health status (i.e., higher St. George's Respiratory Questionnaire and COPD Assessment Test total scores), higher respiratory symptom burden (i.e., more frequent reports of chronic cough, phlegm, wheeze, and bronchitis; and Medical Research Council dyspnea scale ratings), worse baseline pulmonary function (i.e., lower % predicted FEV_1), greater bronchodilator reversibility, and greater use of respiratory medication(s), especially inhaled corticosteroids alone or in combination with a long-acting bronchodilator. Nevertheless, people with ACO (regardless of how it was defined) had remarkably similar physiological responses to symptom-limited incremental cycle CPET without evidence of greater pathophysiological abnormalities in peak exercise capacity (i.e., peak rate of O_2 consumption and power output) compared to people with COPD. **Conclusion:** Despite presenting with significantly worse clinical and patient-reported health outcomes, people with ACO had similarly impaired exercise tolerance without evidence of greater abnormalities in the cardiometabolic, ventilation, breathing pattern, gas exchange and dynamic breathing mechanic responses to exercise.

RÉSUMÉ

Introduction: Le chevauchement entre l'asthme et la BPCO (ACO) est un problème de santé pulmonaire chronique dans lequel les individus peuvent présenter des caractéristiques cliniques à la fois d'asthme et de bronchopneumopathie chronique obstructive (BPCO). Bien qu'il n'existe pas de critères universellement acceptés pour le diagnostic du chevauchement de l'asthme et de la BPCO, des études ont régulièrement rapporté que les personnes souffrant de chevauchement de l'asthme et de la BPCO présentent une charge de symptômes respiratoires plus importante, un état de santé moins bon et une fonction pulmonaire moins bonne que les personnes souffrant uniquement de BPCO. Cependant, on ne sait toujours pas si ces différences dans les résultats cliniques et les résultats rapportés par les patients sont associées à des anomalies physiopathologiques plus importantes dans la tolérance à l'exercice et la réponse physiologique et/ou perceptive à l'exercice chez les personnes atteintes d'ACO par rapport aux personnes atteintes de BPCO. **Objectif:** Comparer les réponses physiologiques et perceptives détaillées au pic d'exercice limité par les symptômes chez les personnes atteintes de BCA et de BPCO. **Méthodes:** Les participants comprenaient 411 hommes ou femmes, fumeurs invétérés, avec un volume expiratoire forcé en 1 seconde post-bronchodilatateur par rapport à la capacité vitale forcée <0,70, qui ont effectué des tests de fonction pulmonaire et un test d'exercice cardio-pulmonaire incrémental limité par les symptômes dans le cadre de la visite de base (transversale) de l'étude Canadian Cohort Obstructive Lung Disease (CanCOLD) - une cohorte longitudinale basée sur la population d'adultes canadiens âgés de ≥40 ans échantillonnés au hasard. Le BCA a été défini à l'aide de trois définitions cliniques : ACO1 (n=103),

présence autodéclarée d'allergies respiratoires et/ou de rhume des foins (atopie) ; ACO2 (n=125), asthme autodéclaré diagnostiqué par un médecin ; et ACO3 (n=65), combinaison d'atopie autodéclarée et d'asthme diagnostiqué par un médecin. Les participants ont été identifiés comme ayant une BPCO (no-ACO) lorsqu'ils ne déclaraient pas d'atopie et/ou d'asthme diagnostiqué par un médecin (n=248).

Résultats: Comparativement aux personnes souffrant uniquement de BPCO, les personnes souffrant d'ACO (en grande partie indépendamment de la définition clinique utilisée) présentaient un état de santé respiratoire significativement plus faible (c.-à-d. des scores totaux plus élevés au Questionnaire respiratoire de St-Georges et au Test d'évaluation de la BPCO), une charge de symptômes respiratoires plus élevée (c.-à-d. des rapports plus fréquents de toux chronique, d'asthme et d'autres symptômes), rapports plus fréquents de toux chronique, d'expectoration, de respiration sifflante et de bronchite ; et évaluations de l'échelle de dyspnée du Medical Research Council), fonction pulmonaire de base moins bonne (c.-à-d. % inférieur de VEMS prédit), réversibilité plus grande des bronchodilatateurs et utilisation plus importante de médicaments respiratoires, en particulier de corticostéroïdes inhalés seuls ou en association avec un bronchodilatateur à action prolongée. Néanmoins, les personnes atteintes d'ACO (quelle que soit la façon dont elles ont été définies) présentaient des réponses physiologiques remarquablement similaires à l'EEPC incrémentielle limitée par les symptômes, sans preuve d'anomalies physiopathologiques plus importantes dans la capacité d'exercice maximale (c'est-à-dire le taux maximal de consommation d'oxygène et la puissance de sortie) par rapport aux personnes atteintes de BPCO. **Conclusion:** Bien qu'elles présentent des résultats cliniques et de santé rapportés par les patients significativement

plus mauvais, les personnes atteintes d'ACO ont une tolérance à l'exercice altérée de manière similaire sans preuve de plus grandes anomalies dans les réponses cardiométaboliques, de ventilation, de schéma respiratoire, d'échange gazeux et de mécanique respiratoire dynamique à l'exercice.

CHAPTER 1. Literature Review

1.1 Prevalence and Burden of COPD, Asthma, and Asthma-COPD Overlap

Chronic obstructive pulmonary disease (COPD) and asthma are both chronic lung conditions with high and increasing prevalence in the general population. In Canada, the prevalence of spirometrically-defined COPD is ~17% [4, 5]. Asthma prevalence taken from multiple countries is estimated to be between 1-18% of the population [6]. It is estimated that, worldwide, more than 325 million individuals are affected by COPD [7] and that 300 million individuals live with asthma [8]. COPD is the 3rd leading cause of death worldwide, whereas asthma accounts for ~180,000 global deaths each year [8, 9]. Consequentially, the burden of COPD and asthma, on the patient, healthcare systems, and economically, is substantial and increasing [4]. For instance, in Canada, the annual direct costs of primary and secondary care visits related to COPD was estimated at ~$2,000 CAD per patient [4]. In addition, the estimated cost of COPD exacerbations in Canada alone was estimated to be $646-736 million CAD per year [10]. Whereas, it was reported in the year 2012 that the direct costs of asthma per person-year was $1,028 in Canada [11]. Individually, COPD and asthma are prevalent and costly chronic lung health conditions.

It is well established that some individuals present with clinical features of both COPD and asthma – a chronic lung health condition commonly referred to as asthma-COPD overlap (ACO). Although the prevalence of ACO is difficult to estimate because of longstanding controversies regarding its clinical definition (or diagnostic criteria), current estimates range from 10% to 40% depending on the definition [12, 13]. Regardless of the definition used, previous studies consistently report that people with ACO present with evidence of poorer patient-reported and clinical health outcomes than those with COPD

only [12, 14]. Specifically, people with ACO are reported to have greater symptom burden, more frequent exacerbations, more impaired lung function, more rapid longitudinal decline in lung function, higher mortality rate, higher prevalence of comorbidities, and lower health-related quality of life compared to individuals with only COPD [12, 14, 15] .

To date, it remains unknown whether the differences in clinical and patient-reported outcomes commonly reported in people with ACO compared to COPD are associated with contemporaneous differences in exercise tolerance (i.e., peak rate of O_2 consumption [$V'O_{2peak}$] on cardiopulmonary exercise testing [CPET]) and the physiological and perceptual factors influencing exercise tolerance [14]. Further research is needed to address this knowledge and improve clinical and patient-centered outcomes of people living with ACO *via* more precise physiological phenotyping and perhaps also more individualized/personalized targeted therapies.

1.2 COPD and asthma disease development

1.2.1 Definition and Etiology of COPD

COPD is preventable, common, and treatable; defined as a heterogeneous lung condition characterized by chronic respiratory symptoms that include, dyspnea (breathlessness), cough, mucus production, and exacerbations [9]. These symptoms are due to abnormalities of the airways (bronchiolitis) and/or alveoli destruction (emphysema) that cause persistent airflow obstruction that is often progressive and can differ in severity depending on the individual [9, 16].

These pathological conditions, associated with lung function loss, are enhanced by chronic inflammatory processes involving increased number of inflammatory cells (mainly neutrophils) and inflammatory cell mediator release in the small airways and lung

parenchyma [17]. Persistent chronic inflammation contributes to the complex remodeling process of the airways causing reduced lung elastic recoil, compromised alveolar structure, damaged lung tissue, and increased airway resistance, that is associated with parenchymal destruction [18-20]. The repeated injury to tissue (remodeling) that occurs as a consequence of parenchymal destruction and peripheral airways wall fibrosis are the two main components that take place during the remodeling process; this makes airways susceptible to collapse and hinders the force that is able to fully drive air out of the lungs during expiration [19, 20]. In COPD remodeling changes involve the damage of gas exchange structures; respiratory bronchiole attachments, alveolar ducts, and alveoli that are associated with mucus hypersecretion, mucociliary dysfunction, and decreased mucus clearing [21]. The structural abnormalities and inflammatory processes associated with COPD play key roles in progression of disease.

Furthermore, the development of COPD is related to a variety of risk factors that lead to the clinical manifestations underpinning COPD [9]. The most important causal factor of COPD is cigarette (tobacco) smoking [22, 23]. However, never-smokers may also develop chronic airflow limitation with research showing that 25-45% of COPD patients are self-reported never smokers [24]. The literature indicates that other non-smoking risk factors can largely attribute to the burden of this disease [23, 24]. Long-term exposure to air pollution, occupational dusts/chemicals, passive smoking as well as genetic factors (i.e., alpha-1 antitrypsin deficiency) and premature birth have all been identified and considered important contributors to COPD development [9, 23].

1.2.2 Diagnosis of COPD

According to guidelines established by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a diagnosis of COPD is considered when an individual presents with a history of exposure to risk factors and symptoms of COPD (breathlessness, chronic cough, or sputum production) [9]. In such patients, spirometry is required to make a clinical diagnosis of COPD; the reading of a post-bronchodilator forced expiratory volume in 1-sec to forced vital capacity (FEV_1/FVC) ratio of <0.70 confirms the presence of persistent airflow limitation [9]. Once diagnosed, the severity of COPD is staged according to the post-bronchodilator FEV_1 expressed as a percentage of predicted: GOLD 1 (mild) ≥80% predicted; GOLD 2 (moderate) 50-79% predicted; GOLD 3 (severe) 30-49% predicted; and GOLD 4 (very severe) <30% predicted [9].

1.2.3 Definition and Etiology of Asthma

Asthma is a multifactorial, complex disease that results from different gene-environment interactions [25]. In asthma, the presence of airflow obstruction is mainly reversible, unlike in COPD [25]. Asthma is characterized by chronic airway inflammation that, with increased severity, leads to airway remodeling. Airway remodeling is associated with increased airway hyperresponsiveness (bronchoconstriction) to direct or indirect stimuli; this leads to recurrent symptoms of wheeze, breathlessness, chest tightness and cough, as well as permanent changes in the airways associated with lung function loss [6, 25, 26]. These respiratory symptoms can vary over time and in intensity, in combination with variable expiratory airflow limitation, which are usually triggered by factors such as exercise, dust or allergen exposure, weather change, or viral respiratory infections [6, 25, 26]. Some structural changes in the airways include features such as

mucus hypersecretion, smooth muscle hyperplasia and hypertrophy, subepithelial fibrosis, blood vessel proliferation, and infiltration of inflammatory cells, primarily eosinophils [25].

1.2.4 Diagnosis of Asthma

In clinical practice, the diagnostic criteria of asthma include the presence and history of respiratory symptom patterns and evidence of variable expiratory airflow limitation (which can be confirmed when FEV_1/FVC is reduced, usually to <0.80 in adults) that later in the course of the disease may become persistent and not fully reversible [6].

Compared to well-controlled asthma, poorly controlled asthma is associated with larger variability in lung function [6]. Variability, identified over the time period of one day, in lung function can be confirmed by lung function tests, such as spirometry and/or peak expiratory flow tests [6]. Obtaining evidence of abnormally high variability in expiratory lung function in individuals with respiratory symptoms is an essential component to the diagnosis of asthma [6]. Some specific examples of excessive variability confirmation in expiratory lung function are after the administration of a bronchodilator or controller treatment lung function is increased, after exercise or during a bronchoprovocation test lung function is decreased, and when excessive variation of lung function (beyond the normal range) is repeatedly seen overtime [6]. The greater the variations in lung function and the more excessive variation is seen the more likely the diagnosis is asthma [6].

In adults that present with typical respiratory symptoms of asthma, an accepted measure of variation shown to be consistent with asthma is a change in FEV_1 of >12% and >200 mL from baseline following inhalation of a short-acting bronchodilator, i.e.,

bronchodilator reversibility [6]. However, between healthy adults and people with chronic lung disease (e.g., COPD) there can be overlap of variation measures (i.e., bronchodilator reversibility) that does not necessarily indicate the presence of asthma in an individual [6]. Furthermore, depending on the individual, additional assessments may be necessary to confirm the diagnosis of asthma and therefore provide proper treatment to control symptoms and mitigate future risk for exacerbations [6].

1.3 COPD vs Asthma: Distinguishing Features

Even though COPD and asthma are both chronic inflammatory lung disorders, they are unique in several important ways. The most important feature to distinguish asthma and COPD is the nature of the inflammation because it affects the response to pharmacological agents [25]. In COPD, pulmonary inflammation is driven mostly by neutrophils, whereas in asthma pulmonary inflammation is drive primarily by eosinophils [27]. However, as outlined in **Table 1.1**, there are other commonly used features beyond the nature of airway inflammation that distinguish COPD from asthma, including, for example, age of onset and pattern (chronicity) of respiratory symptoms [6].

Table 1.1. Asthma vs. COPD: Distinguishing features.

Feature	Asthma	COPD
Age of onset	Usually childhood onset (<20 years) but can develop at any age	Usually >40 years
Pattern of respiratory symptoms	May vary overtime (day-to-day), usually limiting activity. Exercise, dust, and exposure to allergens often trigger symptoms	Chronic usually continuous symptoms, specifically during exercise
Lung function	Current and/or historical variable expiratory airflow limitation	FEV_1 may be improved by therapy, but persistent expiratory airflow limitation
Lung function between symptoms	May be normal	Persistent airflow obstruction
Past history or family history	Personal history of asthma or family history of asthma, and other allergic conditions	Past diagnosis, history of exposure to noxious particles and gases
Time course	No worsening of symptoms, but variation with seasons or yearly. Often improves spontaneously or with treatment	Slowly worsening over the years (progressive), despite treatment
Exacerbations	Risk reduced by treatment	Risk reduced by treatment comorbidities may contribute
Chest X-ray	Usually normal	Severe hyperinflation & other emphysematous changes
Airway inflammation	Primarily eosinophils ± neutrophils	Primarily neutrophils ± eosinophils in sputum; may have systemic inflammation

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1-sec. Adapted from References [28, 29].

1.4 Disease burden comparisons

From a patient (clinical) perspective, the burden of asthma or COPD is often assessed by evaluating respiratory symptom burden (breathlessness, wheeze, cough, chest tightness), health-related quality of life (HRQoL), and daytime physical activity levels, all of which are negatively affected by COPD or asthma, especially in the presence of co-morbidities (which are common among people with COPD or asthma) such as anxiety/depression, obesity, cardiometabolic disease, and malnutrition/sarcopenia [1, 30-35]. Although both patient groups experience abnormally high respiratory symptom burden and abnormally low HRQoL and daytime physical activity levels, the impact of COPD on these patient-oriented outcomes is typically more severe and burdensome, likely reflecting differences in clinical and physiological features between these two chronic lung health conditions, as summarized in **Table 1.1**. The experience of living with COPD or asthma is multifaceted, and, although distinguishing features separate them, there are many overlapping clinical and pathophysiological features that make it challenging to know whether they co-exist (overlap), which complicates disease/symptom management.

1.5 Exercise pathophysiology of COPD and asthma

Laboratory-based exercise tests, specifically the symptom-limited incremental cardiopulmonary exercise test (CPET), are the gold-standard for identifying pathophysiological abnormalities in people with chronic lung diseases like COPD or asthma because they permit simultaneous evaluation of gas exchange, cardiac,

ventilatory, breathing pattern, dynamic operating lung volume, and symptom responses to exercise [34, 36, 37].

1.5.1 COPD. As reviewed in detail elsewhere [34, 38-40], pathophysiological abnormalities in breathing mechanics (both static and dynamic) and pulmonary gas exchange efficiency among people with COPD combine to increase the perception (intensity) of activity-related breathlessness, which in turn limits exercise capacity as evidenced by people with COPD often having, for example, abnormally low peak rates of O_2 consumption ($V'O_{2peak}$) on symptom-limited incremental CPET (**Fig. 1.1**). In people with COPD, static and dynamic lung hyperinflation (consequent to expiratory flow limitation) serve to decrease both inspiratory capacity (IC) and inspiratory reserve volume (IRV), where IC represents the true operating limits for tidal volume (V_T) expansion in people with COPD; that is, as static (resting) and dynamic (exercise) IC and IRV decline, the capacity to expand V_T in the transition from rest to peak exercise decreases [3, 41, 42] (**Fig. 1.1**). Dynamic lung hyperinflation forces people with COPD to expand their V_T on the upper alinear (non-compliant) part of the respiratory system's sigmoid pressure volume curve where the inspiratory muscles (e.g., diaphragm) shorten and become functionally weak whilst simultaneously needing to generate abnormally high intrapulmonary pressures (effort) to overcome the greater elastic recoil forces [34, 38-40]. Under these circumstances, abnormally high levels of central inspiratory neural drive and respiratory muscle work are required to overcome critical inspiratory constraints and achieve any given level of ventilation (V'_E) during exercise in people with compared to without COPD [3, 41] (**Fig. 1.1**). As a result, people with COPD typically report abnormally

high intensity ratings of exertional breathlessness, which become intolerable at abnormally low exercise intensities ($V'O_{2peak}$) and levels of V'_E [3, 41] (**Fig. 1.1**).

Despite pathophysiological abnormalities in static and dynamic breathing mechanics (manifesting as an abnormally low ventilatory capacity), people with COPD have an abnormally high ventilatory demand, as evidenced by their abnormally high V'_E for any given rate of CO_2 output ($V'_E/V'CO_2$) during exercise [43, 44]. The abnormally high $V'_E/V'CO_2$ response to exercise in COPD (reflecting exercise ventilatory inefficiency) is the consequence of "wasted" ventilation within their abnormally high physiological dead space [43-45]. The underlying cause of "wasted" ventilation in COPD is the ventilation-perfusion mismatching that manifests due to variable combinations of emphysema, bronchitis, pulmonary microvascular destruction with loss of pulmonary blood flow, and adoption of an abnormally rapid and shallow breathing pattern [43, 44]. The abnormally high $V'_E/V'CO_2$ response to exercise in COPD is mechanistically linked to the abnormally low exercise tolerance *via* its contribution to the abnormally high exertional breathlessness burden [43, 45, 46].

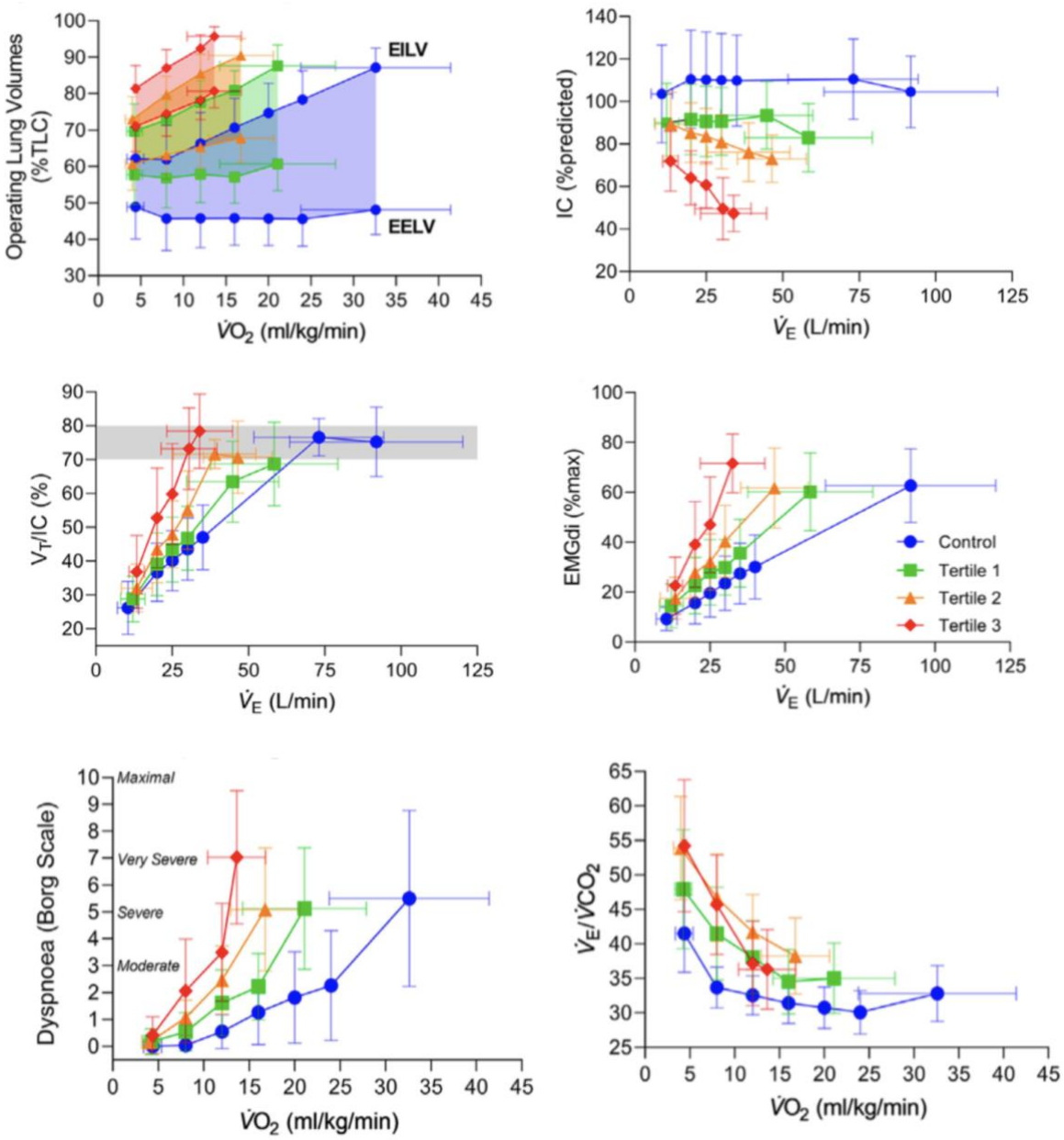

Figure 1.1. Dynamic operating lung volumes (upper left & right panels), critical inspiratory constraints (middle left panel), inspiratory neural drive (middle right panel), dyspnea intensity ratings (lower left panel) and the ventilatory equivalent for CO_2 (lower right panel) are shown plotted against minute ventilation (V'_E) or the rate of O_2 consumption ($V'O_2$) during cycle exercise testing in people with mild (Tertile 1), moderate (Tertile 2) and severe chronic obstructive pulmonary disease (Tertile 3) relatively to healthy control subjects. TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; IC, inspiratory capacity; V_T, tidal volume; EMGdi, crural diaphragm electromyogram; $V'_E/V'CO_2$, ventilatory equipment for CO_2. Adapted from reference [3].

1.5.2 Asthma. With few exceptions, and in contrast to people with COPD, the physiological and perceptual responses to exercise are often normal among people with asthma, at least those with well-controlled mild-to-moderate asthma [2, 47, 48]. For instance, Cortes-Telles et al. (2015) reported that, compared to age and activity-matched non-asthmatic control subjects (n=14), sedentary adults with well-controlled asthma (n=14) had: similar $V'O_{2peak}$ (30.6 vs. 31.8 ml/kg/min), peak power output (144 vs. 134 watts) and $V'O_2$ at the anaerobic threshold (19.9 vs. 22.9 ml/kg/min); and virtually identical metabolic, cardiac, V'_E, breathing pattern, and perceptual (breathlessness, leg fatigue) responses to symptom-limited incremental cycle CPET (**Fig. 1.2**). Furthermore, available evidence suggests that the $V'_E/V'CO_2$ response to exercise is normal in people with asthma [49]; that is, asthma does not affect exercise ventilatory efficiency.

Dynamic lung hyperinflation is reported to occur during exercise in ~35-65% of people with asthma, although the prevalence is higher among asthmatics with more severe airflow obstruction at rest [50]. Compared to asthmatics that do not dynamically hyperinflate during exercise, those that do dynamically hyperinflate are reported to have lower peak exercise capacity (peak power output of 75 vs. 95% predicted) whilst experiencing slightly higher intensity ratings of breathlessness (by 0.5-1.0 Borg 0-10 scale units) during exercise at intensities greater than ~65% of peak power output [51]. In keeping with these findings, a study of 16 adults with stable mild-to-moderate asthma by Laveneziana et al. [52] found that exercise endurance time was lower (375 vs. 440 sec, $p>0.05$) and breathlessness intensity ratings were higher (7.4 vs. 3.9 Borg 0-10 scale units, $p<0.05$) in the setting of relatively greater critical inspiratory constraints (IRV, 0.2 vs. 0.8 liters and V_T/IC, 85 vs. 67%, both $p<0.05$) at the symptom-limited peak of constant

load cycle exercise testing in a subgroup of asthmatics with more (n=6) compared to less (n=10) severe airflow obstruction and expiratory flow limitation at rest (FEV_1/FVC, 74 vs. 81% and 28 vs. 4% of V_T overlap on the maximal expiratory flow-volume envelope, both $p<0.05$). A more detailed study by Moore et al. [1] found that, compared to age, sex and BMI-matched non-asthmatic control subjects (n=16), adults with well-controlled asthma (n=16) reported greater intensity ratings of exertional breathlessness in association with higher dynamic operating lung volumes (as evidenced by lower IC and IRV [or higher end-inspiratory and end-expiratory lung volumes]) during symptom-limited incremental cycle CPET (**Fig. 1.3**), even after single-dose inhalation of a short-acting bronchodilator. Nevertheless, Moore et al. [1] found that exercise tolerance was not significantly different between people with compared to without asthma ($V'O_{2peak}$, 47 vs. 48 ml/kg/min and peak power output, 121 vs. 116% predicted), suggesting that the relatively greater breathlessness and dynamic operating lung volumes during exercise in people with asthma did not affect their peak exercise capacity. Thus, the functional consequences of asthma-related abnormalities in exertional breathlessness and the behavior of dynamic operating lung volumes remains unclear.

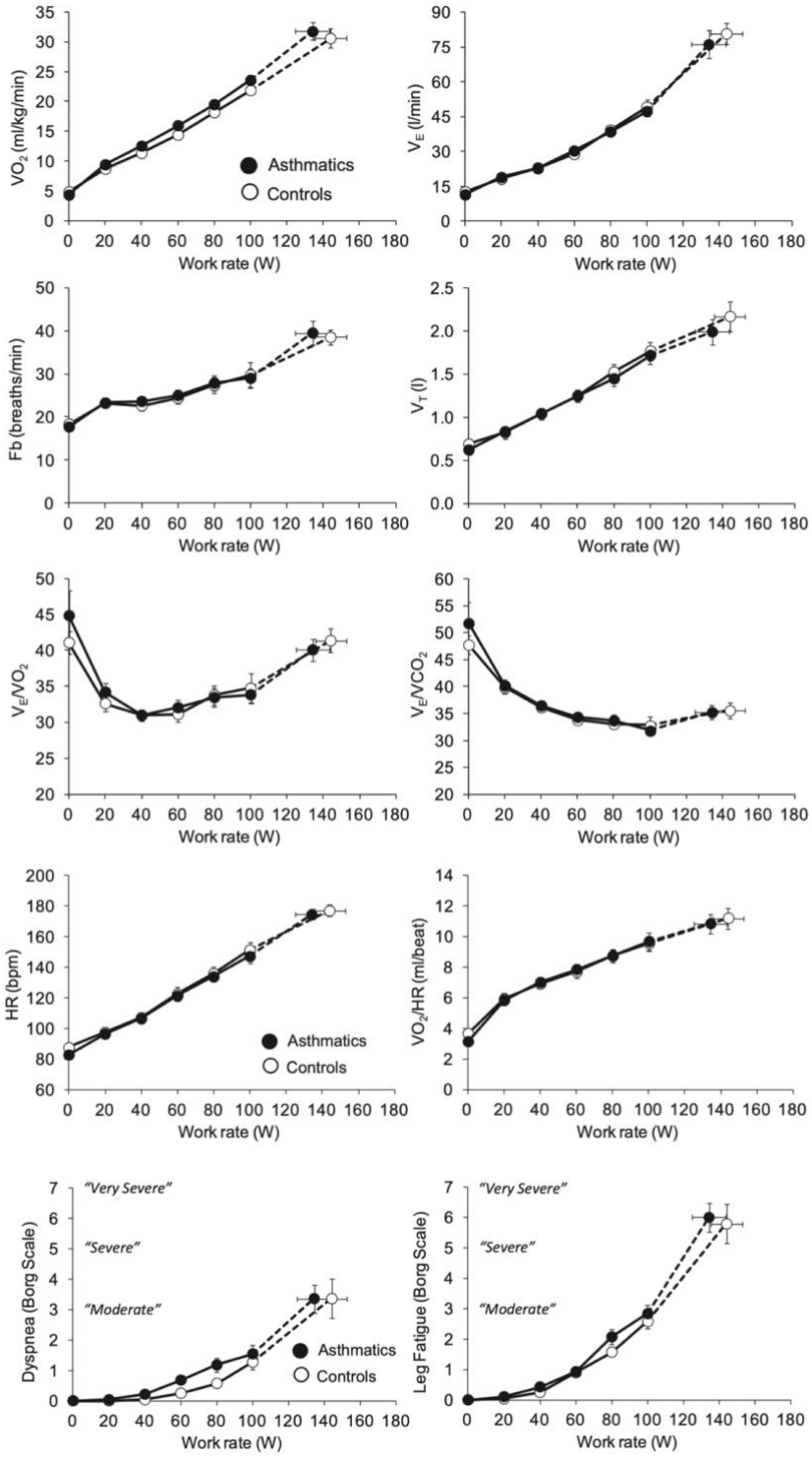

Figure 1.2. Physiological and perceptual responses to symptom-limited incremental cardiopulmonary cycle exercise testing in people with well-controlled asthma compared to age- and activity-matched healthy control subjects. $V'O_2$, rate of O_2 consumption; V'_E, minute ventilation; Fb, breathing frequency; V_T, tidal volume; $V'_E/V'O_2$, ventilatory equivalent for O_2; $V'_E/V'CO_2$, ventilatory equivalent for CO_2; HR, heart rate; $V'O_2$/HR, oxygen pulse; W, watts. Adapted from reference [2].

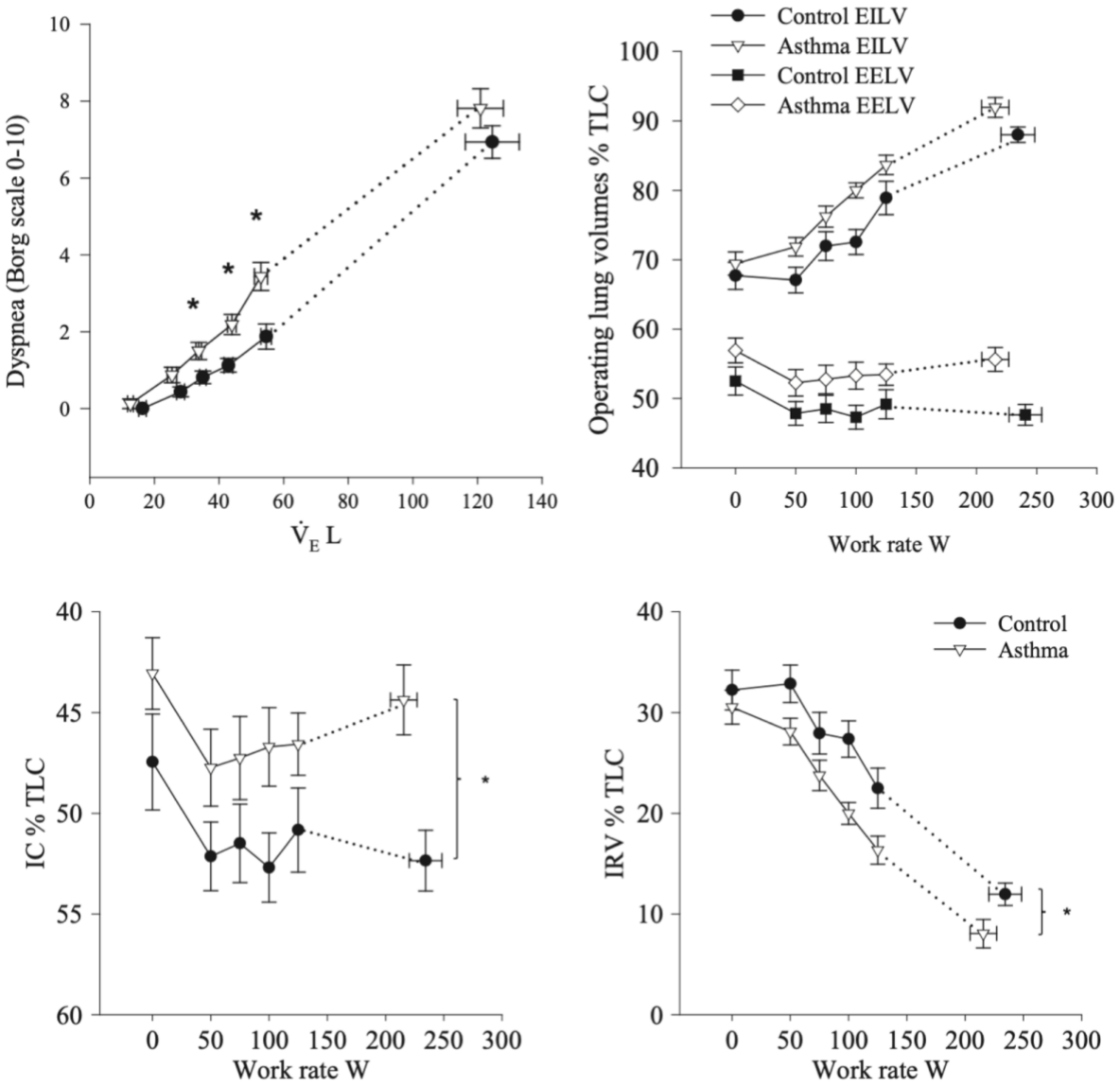

Figure 1.3. Dyspnea (upper left panel) and dynamic operating lung volumes (upper right, and lower left & right panels) are shown plotted against minute ventilation (V'_E) or work rate during symptom-limited incremental cardiopulmonary cycle exercise testing in people with well-controlled asthma relative to age, sex and body mass index-matched non-asthmatic control subjects. V'_E, minute ventilation; TLC, total lung capacity; EILV, end-inspiratory lung volume; EELV, end-expiratory lung volume; IC, inspiratory capacity; IRV, inspiratory reserve volume; W, watts. Adapted from reference [1].

1.6 Asthma-COPD overlap (ACO)

Asthma-COPD overlap (ACO) is a chronic health condition in which individuals can have persistent airflow limitation with clinical features that support a diagnosis of both asthma and COPD [53]. Although the prevalence of ACO is difficult to estimate because of longstanding controversies regarding its clinical definition / diagnostic criteria (*see below*), current estimates range from 10% to 40% [12, 13]. The overall healthcare cost per capita is affected due to higher hospital admissions and emergency department visits among individuals with ACO compared to COPD or asthma [54]. Additionally, compared with either asthma or COPD, ACO may be associated with greater risk of premature death [28].

A key issue to managing and further understanding the concept of ACO is the inconsistent definition used based on differing features and criteria; as shown in **Table 1.2,** the clinical features of each asthma, COPD, and asthma-COPD overlap [28]. The use of different definitions makes it challenging to compare outcomes among various studies of ACO [28]. Another issue is that individuals with overlapping COPD and asthma have been traditionally excluded from therapeutic clinical trials, which has limited identification of much needed evidence-based treatment options [28].

According to Leung and Sin [53], the important components of the definition for ACO, based upon all the studies published to date, include: 1) chronic airflow limitation defined as a post-bronchodilator $FEV_1/FVC < 0.70$; 2) a significant history of exposure to tobacco smoking and/or noxious inhalants; 3) a clinical diagnosis of asthma before age of 40 years; and 4) a significant bronchodilator response, i.e., increase in FEV_1 >15 % and >400 ml following bronchodilatation [53].

Table 1.2. Clinical features for asthma, COPD, and asthma-COPD overlap.

Feature	Asthma	COPD	Asthma-COPD overlap	More likely to be asthma if several of	More likely to be COPD if several of
Age of onset	Usually childhood onset (<20 years) but can develop at any age	Usually >40 years	Usually >40 years but may have earlier symptoms	Onset before age 20 years	Onset after age 40 years
Pattern of respiratory symptoms	May vary overtime (day-to-day), usually limiting activity. Exercise, dust, and exposure to allergens often trigger symptoms	Chronic usually continuous symptoms, specifically during exercise	Symptoms persistent, may show variability	Variable min, hour, day-day, worse in morning/night triggered by exercise, dust, allergens	Persistent despite treatment. Good and bad days - always present during exercise, onset of dyspnea chronic cough/sputum proceed
Lung function	Current and/or historical variable expiratory airflow limitation	FEV_1 may be improved by therapy, but persistent expiratory airflow limitation	Obstruction not fully reversible	Record of variable airflow obstruction	Record of persistent airflow obstruction
Lung function between symptoms	May be normal	Persistent airflow obstruction	Persistent airflow obstruction	Lung function normal between symptoms	Lung function abnormal between symptoms
Past history or family history	Personal history of asthma or family history of asthma, and other	Past diagnosis, history of exposure to noxious particles and gases	Personal and family history of asthma, allergies, and	Previous doctor diagnosis of asthma. Family history of asthma or	Previous doctor diagnosis of COPD, chronic bronchitis, emphysema. Heavy exposure to a risk factor (e.g., tobacco smoke)

	allergic conditions		noxious exposure	other allergic conditions	
Time course	No worsening of symptoms, but variation with seasons or yearly. Often improves spontaneously or with treatment	Slowly worsening over the years (progressive), despite treatment	Symptoms but reduced with treatment	No worsening symptoms overtime, spontaneous improvement or immediate response to BD or ICS over weeks	Symptoms slowly worsening overtime, rapid-acting BD provides immediate relief
Exacerbations	Risk reduced by treatment	Risk reduced by treatment; comorbidities may contribute	May be more common than in COPD but responsive to treatment		
Chest X-ray	Usually normal	Severe hyperinflation & other emphysematous changes	Similar to COPD	Normal	Severe hyperinflation
Airway inflammation	Primarily eosinophils ± neutrophils	Primarily neutrophils ± eosinophils in sputum; may have systemic inflammation	Eosinophils ± neutrophils in sputum		
COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1-sec; BD: bronchodilator; ICS: inhaled corticosteroid. Adapted from reference [28].					

Regardless of how ACO is defined, individuals with ACO present with greater symptom burden, poorer HRQoL, more comorbid health conditions, and more frequent and severe respiratory exacerbations compared to people with asthma or COPD [28, 53]. In fact, individuals with ACO utilize more medical services and the associated costs are substantially higher compared to individuals with COPD alone [53]. For instance, a sub-study of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study published by Barrecheguren et al. [14] compared multiple clinical and patient-reported health outcomes between ever-smokers with spirometrically-defined COPD and ACO based on seven definitions commonly used in clinical practice:

1. Bronchodilator reversibility (>12% and >200 mL increase in FEV_1 from baseline)
2. Large bronchodilator reversibility (>15% and >400 mL increase in FEV_1 from baseline)
3. Atopy: self-reported presence of respiratory allergies and/or hay fever
4. Self-reported physician diagnosis of asthma
5. Bronchodilator reversibility and atopy, i.e., Definitions 1 + 3
6. Atopy and self-report physician diagnosis of asthma, i.e., Definitions 3 + 4
7. Bronchodilator reversibility and atopy and self-reported physician diagnosis of asthma, i.e. Definitions 1 + 3 + 4

Regardless of the ACO definition used, Barrecheguren et al. [14] found that that people with ACO compared to non-ACO COPD had significantly worse clinical and patient-reported outcomes, including lower % predicted FEV_1, higher COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ) total scores (i.e., lower health status), more frequent and severe exacerbation-like respiratory events, and greater

longitudinal decline in FEV_1. Furthermore, the three clinical definitions of ACO that included atopy and/or self-reported physician diagnosed asthma (definitions 3, 4, and 6 from the enumerated list above) identified people with ACO who, on average, presented with the largest differences in pulmonary function, exacerbation-like respiratory events, and respiratory symptom burden/health status compared to people with COPD [14].

To date, it remains unknown whether the differences in clinical and patient-reported outcomes reported by Barrecheguren et al. [14] and others [28, 53] in people with ACO compared to COPD are associated with contemporaneous differences in exercise tolerance ($V'O_{2peak}$) and its physiological and perceptual determinants (i.e., exertional breathlessness, exercise ventilatory efficiency, dynamic operating lung volumes). Addressing this knowledge gap represents the overarching aim of this Master's thesis research project.

1.7 Objective: Utilizing the CanCOLD database, the objective of this research is to extend the work of Barrecheguren et al. [14] by comparing physiological and perceptual responses at the symptom-limited peak of incremental cycle CPET in people with COPD and ACO.

1.8 Hypothesis: Compared to people with COPD, people with ACO will have more severe exercise intolerance (lower $V'O_{2peak}$) in association with greater pathophysiological abnormalities in exertional breathlessness, exercise ventilatory efficiency (e.g., greater nadir $V'_E/V'CO_2$), and dynamic breathing mechanics (e.g., more prevalent and severe dynamic lung hyperinflation).

CHAPTER 2. MANUSCRIPT

2.1. ABSTRACT

Background: It is currently unknown whether differences in clinical and patient-reported outcomes that have been reported among people with asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) compared to COPD are associated with contemporaneous differences in exercise tolerance and its physiological and perceptual determinants. This study tested the hypothesis that, compared to people with COPD, people with ACO will have more severe exercise intolerance in association with greater pathophysiological abnormalities in exertional breathlessness, exercise ventilatory inefficiency, and dynamic breathing mechanics. **Methods:** 411 participants who completed a cardiopulmonary cycle exercise test (CPET) as part of Canadian Cohort Obstructive Lung Disease (CanCOLD) *Visit 1* were included. Participants were identified into five groups: ACO_1 (n=103), self-reported presence of respiratory allergies and/or hay fever (atopy); ACO_2 (n=125), self-reported physician diagnosed asthma; and ACO_3 (n=65), combination of self-reported atopy and physician diagnosed asthma, Any-ACO (n=163), participants meeting either one or combination of the definitions for ACO_{1-3}; and COPD (n=248), (no-ACO) they did not self-report atopy and/or physician diagnosed asthma. **Results:** Compared to people with COPD alone, people with ACO had similar physiological responses to symptom-limited incremental cycle CPET without evidence of greater pathophysiological abnormalities in peak exercise capacity. **Conclusion:** This study added to the physiological characterization of ACO by demonstrating, for the first time, that, above and beyond the established negative effect of COPD on exercise tolerance, the co-existence of asthma had no added detrimental effect.

2.2. INTRODUCTION

Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is a chronic health condition in which individuals present with clinical features that support a diagnosis of both asthma and COPD, including, most notably: chronic airflow limitation (post-bronchodilator forced expiratory volume in 1-sec to forced vital capacity ratio (FEV_1/FVC) <0.70); a significant history of exposure to tobacco smoke and/or other noxious inhalants; physician diagnosis of asthma before age 40 years; and a significant bronchodilator response [53]. Although the prevalence of ACO is difficult to estimate because of longstanding controversies regarding its clinical definition (or diagnostic criteria), current estimates range from 10% to 40% [12, 13, 28].

Regardless of how ACO is defined, a growing body of evidence suggests that individuals with ACO present with greater symptom burden, lower health status, more comorbid health conditions, more frequent and severe respiratory exacerbations, and higher risk of premature death compared to people with COPD [28, 53]. For instance, a recent Canadian Cohort Obstructive Lung Disease (CanCOLD) sub-study by Barrecheguren et al. [14] compared multiple clinical and patient-reported health outcomes between ever-smokers with spirometrically-defined COPD and ACO, where ACO was defined using seven common clinical definitions: (1) bronchodilator reversibility (>12% and >200 mL increase in FEV_1 from pre- to post-bronchodilatation); (2) large bronchodilator reversibility (>15% and >400 mL increase in FEV_1 from pre- to post-bronchodilatation); (3) atopy (self-reported presence of respiratory allergies or hay fever); (4) self-reported physician diagnosis of asthma; (5) bronchodilator reversibility + atopy, i.e., definitions 1 + 3; (6) atopy + self-report physician diagnosis of asthma, i.e., definitions

3 + 4; and (7) bronchodilator reversibility + atopy + self-reported physician diagnosis of asthma, i.e. definitions 1 + 3 + 4. Barrecheguren et al. [14] found that, regardless of the ACO definition used, people with ACO had significantly worse clinical and patient-reported outcomes, including lower FEV_1 (% predicted), lower health status (i.e., higher CAT and SGRQ total scores), more frequent and severe exacerbation-like respiratory events, and greater longitudinal decline in FEV_1 compared to their counterparts with COPD alone. Furthermore, the three clinical definitions of ACO that included atopy and/or self-reported physician diagnosed asthma (definitions 3, 4, and 6 from the enumerated list above) identified people with ACO who, on average, presented with the largest differences in pulmonary function, exacerbation-like respiratory events, symptom burden and health status compared to people with COPD [14].

It is currently unknown whether differences in clinical and patient-reported outcomes reported by Barrecheguren et al. [14] and others [28, 53] among people with ACO compared to COPD are associated with contemporaneous differences in exercise tolerance ($V'O_{2peak}$) and its physiological and perceptual determinants (e.g., exertional breathlessness, exercise ventilatory efficiency, dynamic breathing mechanics). Addressing this knowledge gap has the potential to improve clinical and patient-centered outcomes of people living with ACO *via* more precise physiological phenotyping and perhaps also more individualized/personalized targeted therapies.

The objective of this CanCOLD sub-study was to extend the work of Barrecheguren et al. [14] by comparing physiological and perceptual responses at the symptom-limited peak of incremental cycle CPET in people with COPD and ACO. We hypothesized that, compared to people with COPD, people with ACO would have more

severe exercise intolerance (lower $V'O_{2peak}$) in association with greater pathophysiological abnormalities in exertional breathlessness, exercise ventilatory efficiency, and dynamic breathing mechanics.

2.3. METHODS

This study was a retrospective analysis of participant data collected between November 2009 and August 2015 as part of CanCOLD, which is a prospective population-based cohort of noninstitutionalized adults aged ≥40 years recruited by random telephone digit dialing from nine sites in Canada (ClinicalTrials.gov Identifier: NCT00920348); further methodologic details have been published elsewhere [55]. All participants provided written informed consent prior to study assessments. The Research Ethics Board of each participating institution approved the study protocol.

2.3.1. Participants**.** Male or female participants with a history of tobacco smoke exposure, a post-bronchodilator FEV_1/FVC <0.70, and who completed a symptom-limited incremental CPET as part of the initial CanCOLD cross-sectional assessment phase (*Visit 1*) were eligible for inclusion in this analysis. For the purpose of this analysis, people were identified as having ACO in four ways based on the work of Barrecheguren et al. [14]: ACO_1, atopy according to self-reported presence of respiratory allergies and/or hay fever; ACO_2, self-report physician diagnosis of asthma; ACO_3, atopy + self-report physician diagnosis of asthma; and Any-ACO, participants meeting either one or combination of the definitions for ACO_{1-3}. Also, for the purpose of this analysis, people were identified as having COPD alone when they did not self-report atopy and/or a physician diagnosis of asthma. Participants were excluded if they: were missing post-bronchodilator spirometry

data; stopped exercise for non-physiological reason(s); and/or were missing $V'O_{2peak}$ data.

2.3.2. Measures. As part of CanCOLD, at *Visit 1*, participants had their body height and mass assessed, and completed: a structured interview with a trained researcher, where they self-reported sociodemographic and health information; the Medical Research Council (MRC) dyspnea scale to assess breathlessness burden [56]; the CAT and SRGQ to assess COPD-related health status [57, 58]; and spirometry (performed before and 15-min after inhalation of 200 μg of albuterol/salbutamol that was administered from a metered-dose inhaler with spacer device [100 μg/actuation]), single-breath diffusing capacity of the lungs for carbon monoxide (D_LCO), and lung volumes measured by body plethysmography in accordance with recommended techniques using automated equipment. Pulmonary function parameters were expressed as a percentage of predicted reference values [59-61].

2.3.3. Cardiopulmonary exercise testing. Cardiopulmonary exercise tests were performed in accordance with established guidelines [37, 62] on an electronically braked cycle ergometer with the use of a computerized CPET system. The CPET protocol consisted of a steady-state pre-exercise baseline period of 3-10 minutes, followed by one minute of unloaded pedaling (warm-up), and then 10-W/min increases in power output (starting at 10 W) until symptom limitation.

Gas exchange and breathing pattern parameters were collected breath-by-breath with participants breathing through a mouthpiece and low resistance flow transducer with

nasal passages occluded by a nose clip. Heart rate (HR) and peripheral oxygen saturation (SpO_2) were assessed by 12-lead ECG and finger pulse oximetry, respectively. Maximal voluntary inspiratory capacity (IC) maneuvers were performed [63], and participants rated the intensity of their perceived breathlessness and leg discomfort using Borg's modified 0-10 category ratio scale [64] during the pre-exercise baseline period, every 2 minutes during exercise, and at peak exercise. At end-exercise, participants identified their reason(s) for stopping exercise: breathlessness; leg discomfort; combination of breathlessness and leg discomfort; or other.

2.3.3.i. Analysis of exercise end points. Physiological parameters were averaged over the last 30-seconds of loaded pedaling (*'peak'*) and linked with contemporaneous symptom intensity ratings and IC-derived parameters. End-inspiratory lung volume (EILV) was calculated as total lung capacity (TLC) assessed with body plethysmography at rest *minus* inspiratory reserve volume (IRV), where IRV was calculated as IC assessed at peak exercise *minus* the tidal volume (V_T) averaged over the last 30-seconds of loaded pedaling. Assuming that TLC is unaffected by exercise in people with COPD [65], dynamic lung hyperinflation was defined as a decrease in IC from baseline to end exercise. Peak power output (PPO) was defined as the highest power output that was able to be sustained for ≥30 seconds. The nadir of the ventilatory equivalent for carbon dioxide ($V'_E/V'CO_2$) was identified as the lowest 30-sec average data point observed during CPET and used as an index of exercise ventilatory (in)efficiency. Physiological responses to CPET were expressed in relation to the predicted reference values of Lewthwaite et al. [29].

2.3.4. Statistical analysis. Participants in each group (COPD, ACO_1, ACO_2, ACO_3, Any-ACO) were described by basic demographic and health characteristics. Unadjusted p-values were obtained by performing: Chi-square or Fishers exact test for between-group comparisons of categorial variables; and unpaired T-test or Mann-Whitney U test for between-group comparisons of continuous variables with normal or abnormal distribution, respectively. Adjusted p-values were obtained by performing a General Linear Model procedure for between-group comparisons of continuous variables and Logistic regression for between-group comparisons of categorial variables, adjusted for relevant co-variates: *Model 1*, age, sex, and body mass index (BMI); *Model 2*, Model 1 + co-morbidities (any musculoskeletal and any cardiovascular), self-reported prior physician diagnosis of COPD, and any current respiratory medication use. Outcome variables reported as a percentage of their respective predicted reference value were not adjusted for age, sex, and BMI. Significance was considered at $p<0.05$. Analyses were performed using SAS (version 9.4).

2.4. RESULTS

Of the 1,367 participants who completed CPET as part of CanCOLD *Visit 1*, a total of 411 met our inclusion criteria, with 103, 125, 65, 163 and 248 being classified as ACO_1, ACO_2, ACO_3, Any-ACO, and COPD, respectively (**Fig. 2.1**).

2.4.1. Baseline participant characteristics. Baseline participant characteristics are presented in **Table 2.1**. Compared to the COPD group, each of the four ACO groups were younger, but otherwise had similar: BMI; proportion of ex- and current smokers; cigarette pack year smoking history; proportion of people with any cardiovascular comorbidity; and time spent participating in moderate-to-vigorous physical activity. There was a higher proportion of males in the COPD group compared to each of the ACO_1, ACO_2 and Any-ACO groups. Compared to the COPD group, there was a significantly higher proportion of people in each of the four ACO groups with a prior physician diagnosis of COPD as well as with any musculoskeletal comorbidity. The proportion of people using any current respiratory medication(s) was 2-to-3 fold higher in each of the four ACO groups (~19% vs. ~57-77%) compared to the COPD group, with these differences driven primarily by greater current use of inhaled corticosteroids (ICS) alone (~3.5% vs. ~18.5-28%) or in combination with long-acting β_2-agonist (~4.5% vs. ~19.5-30%) by people with ACO.

2.4.2. Respiratory-related quality of life, health status, and symptom-burden. Differences in respiratory health-related quality of life, health status, and symptom burden between people with COPD and ACO are presented in **Table 2.2**. A higher proportion of people in

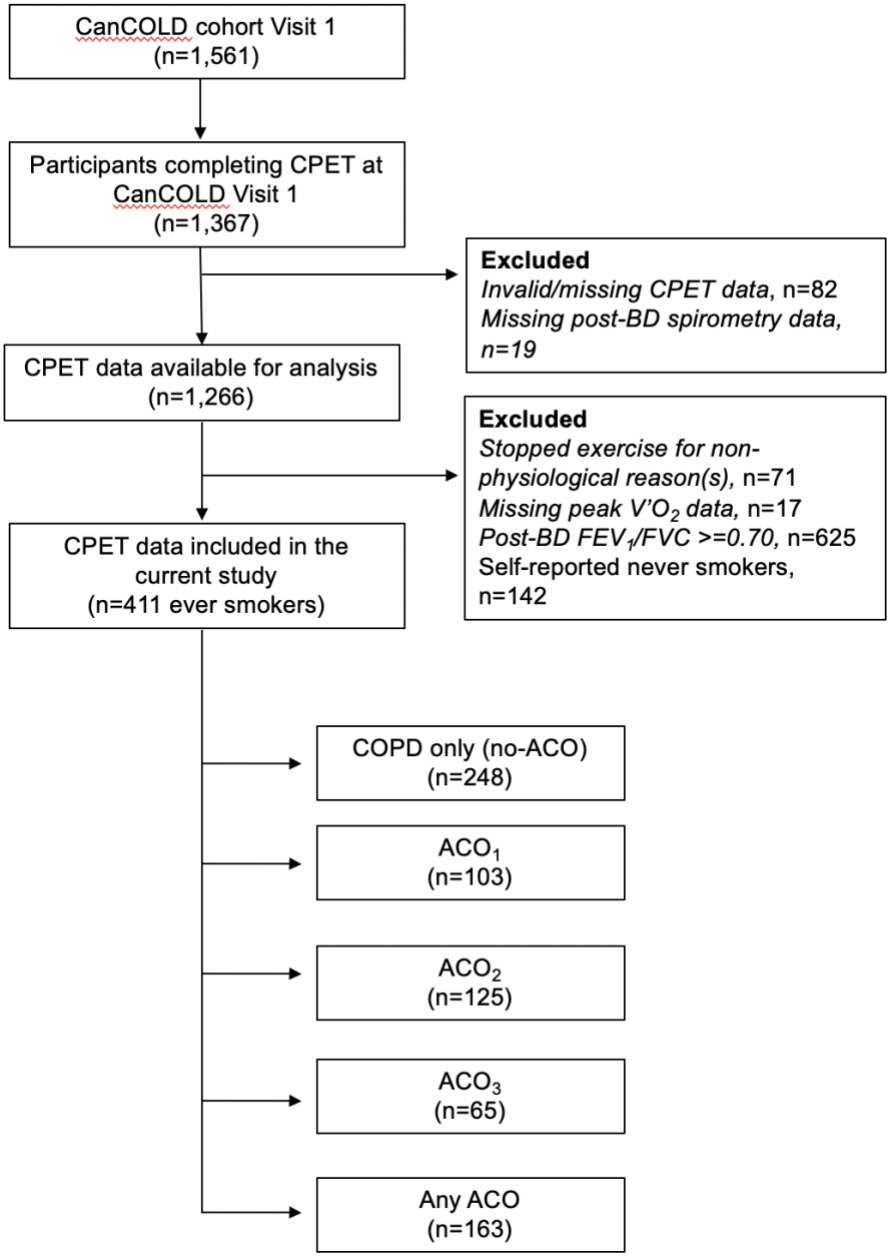

Figure 2.1. Study flowchart. CanCOLD, Canadian Cohort Obstructive Lung Disease; CPET, cardiopulmonary exercise testing; BD, bronchodilator; $V'O_2$: rate of O_2 consumption; FEV_1/FVC: ratio of forced expiratory volume in 1-sec to forced vital capacity; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap. Refer to *Section 2.3.1* for criteria used to define COPD, ACO_1, ACO_2, ACO_3, and Any-ACO.

the ACO_2 vs. COPD group self-reported chronic cough. Compared to people in the COPD group: a higher proportion of people in ACO_2, ACO_3 and Any-ACO groups self-reported chronic phlegm; a higher proportion of people in all four ACO groups self-reported wheeze, chronic bronchitis, and a history of respiratory allergies and hay fever. The SGRQ total score, CAT total score, and Medical Research Council (MRC) dyspnea score were all significantly higher (reflecting lower respiratory health-related quality of life and health status, and higher breathlessness burden) in each of the four ACO groups compared to the COPD group. Compared to the COPD group, a higher proportion of people in: each of the four ACO groups had a CAT total score ≥10 (~26% vs. ~46-52.5%); and the ACO_2 and Any-ACO groups had an MRC dyspnea score ≥3 (~5.5% vs. ~15%).

2.4.3. Pulmonary function test outcomes**.** Differences in pulmonary function test outcomes (including bronchodilator reversibility) between people with COPD and ACO are presented in **Table 2.3**. The FEV_1/FVC was significantly lower in ACO_2 and Any-ACO groups compared to the COPD group, whereas a higher proportion of people in each of the four ACO groups had a FEV_1/FVC less than the lower limit of normal (LLN) relative to the COPD group (~72-78.5% vs. ~53%). The FEV_1 (% predicted) and $FEF_{25-75\%}$ (% predicted) were significantly lower in each of the ACO_2, ACO_3 and Any-ACO groups compared to the COPD group. The proportion of people with GOLD grade 1 and 2 COPD was lower and higher, respectively, in the ACO_2 compared to COPD group. With the exception of residual volume (% predicted), which was significantly higher in each of the ACO_2 and Any-ACO groups compared to the COPD group, no differences in

plethysmographic lung volumes or D_LCO were observed between the COPD group and any of the four ACO groups.

Both absolute and relative bronchodilator-induced increases in FEV_1 were significantly greater in each of the four ACO groups compared to the COPD group (**Table 2.3**). The bronchodilator-induced increase in FEV_1 expressed as a % predicted was also significantly greater in each of the four ACO groups compared to the COPD group. With the exception of a higher proportion of people in ACO_2 vs. COPD with a bronchodilator-induced increase in FEV_1 >12% or >15% from baseline, no differences were observed in the proportion of people in either of the ACO groups compared to the COPD group with a bronchodilator-induced increase in FEV_1 >200 mL, >400 mL, >200 mL and >12%, >400 mL and >15%, and >10% predicted. Except for the % change in FVC from baseline after bronchodilatation being similar between ACO_1 and COPD, the bronchodilator-induced increase in FVC expressed in liters, as a % change from baseline, and as a % predicted was significantly greater in each of the four ACO groups compared to the COPD group. A higher proportion of people in each of the ACO_2 and ACO_3 groups compared to the COPD group had a bronchodilator-induced increase in FVC >10% predicted.

2.4.4. Symptom-limited cardiopulmonary cycle exercise test outcomes. Differences in symptom-limited incremental cycle CPET outcomes between people with COPD and ACO are presented in **Table 2.4**. Neither $V'O_{2peak}$ (% predicted) nor PPO (% predicted) were significantly different between people with COPD and ACO, regardless of how ACO was defined. Similarly, there was no difference in the proportion of people in the COPD group and each of the four ACO groups with an abnormally low $V'O_{2peak}$ of <85% predicted

(~57% vs. ~57-61.5%). After adjusting for comorbidities, prior physician diagnosis of COPD, and any current respiratory medication use in *Model 2*, the ACO_1 and ACO_3 groups had a significantly higher PPO (% predicted) than the COPD group (both $p \leq 0.002$), whereas the PPO (% predicted) was slightly lower in both the ACO_2 ($p=0.051$) and Any-ACO groups ($p=0.056$) compared to the COPD group.

Peak absolute IC (L) was significantly lower in each of the ACO_2, ACO_3 and Any-ACO groups compared to the COPD group (**Table 2.4**); however, these differences did not persist in *Model 2* after adjusting for comorbidities, prior diagnosis of COPD, and any current respiratory medication use. Compared to people in the COPD group, people in each of the four ACO groups reported higher intensity ratings of breathlessness and leg discomfort at the symptom-limited peak of exercise, with these differences persisting after adjusting for comorbidities, prior physician diagnosis of COPD, and any current respiratory medication use in *Model 2*. Otherwise, the results of adjusted *Models 1 and 2* revealed no statistically significant differences in CPET outcomes (including the reason(s) for stopping exercise) between the COPD group and either one of the four ACO groups.

Table 2.1. Comparison of baseline participant characteristics between people with chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap (ACO).

	COPD (n=248)	ACO_1 (n=103)	ACO_2 (n=125)	ACO_3 (n=65)	Any-ACO (n=163)
Age (years)	67.0 (12.0)	64.0 (13.0) *	64.0 (16.0) *	63.0 (13.0) *	64.0 (16.0) *
Sex (% male)	170 (68.6)	58 (56.3) *	70 (56.0) *	37 (56.9)	91 (55.8) *
BMI (kg/m^2)	26.7 (6.4)	27.4 (6.6)	27.7 (6.3)	27.2 (5.9)	27.7 (6.5)
Ex-smoker, N (% of group)	184 (74.2)	81 (78.6)	98 (78.4)	51 (78.5)	128 (78.5)
Current smoker, N (% of group)	64 (25.8)	22 (21.4)	27 (21.6)	14 (21.5)	35 (21.5)
Cigarette pack years[#]	31.5 (30.3)	27.3 (41.0)	25.1 (36.0)	21.5 (39.5)	27.0 (37.0)
Prior physician Dx of COPD, N (% of group)	64 (25.8)	41 (39.8) *	58 (46.4) *	29 (44.6) *	70 (42.9) *
Prior physician Dx of asthma, N (% of group)	0 (0.0)	65 (63.1) *	125 (100.0) *	65 (100.0) *	125 (76.7) *
Any MSK, N (% of group)	106 (42.7)	65 (63.1) *	69 (55.2) *	38 (58.5) *	96 (58.9) *
Any CVD, N (% of group)	122 (49.2)	60 (58.3)	73 (58.4)	40 (61.5)	93 (57.1)
Time spent in MVPA (hrs/week)	1.70 (2.90)	1.50 (2.20)	1.50 (2.30)	1.50 (2.20)	1.50 (2.40)
Any current respiratory medication use, N (% of group)	47 (19.0)	59 (57.3) *	92 (73.6) *	50 (76.9) *	101 (62.0) *
SABA/SAMA, N (% of group)	10 (4.0)	11 (10.7) *	10 (8.0)	7 (10.8)	14 (8.6)
LABA, N (% of group)	0 (0.0)	2 (1.9) *	2 (1.6) *	2 (3.1) *	2 (1.2) *
LAMA, N (% of group)	5 (2.0)	1 (1.0)	1 (0.8)	0 (0.0)	2 (1.2)
LABA+LAMA, N (% of group)	1 (0.4)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.6)
ICS, N (% of group)	9 (3.6)	19 (18.5) *	26 (20.8) *	18 (27.7) *	27 (16.6) *
LABA+ICS, N (% of group)	11 (4.4)	20 (19.4) *	36 (28.8) *	18 (27.7) *	38 (23.3) *
LAMA+ICS, N (% of group)	1 (0.4)	1 (1.0)	1 (0.8)	1 (1.5)	1 (0.6)
LABA+LAMA+ICS, N (% of group)	10 (4.0)	5 (4.9)	15 (12.0) *	4 (6.2)	16 (9.8) *

Data are presented as median [IQR] or frequency (n (%)). BMI: body mass index; Dx: diagnosis: MSK: musculoskeletal comorbidity; CVD: cardiovascular comorbidity; MVPA: moderate-to-vigorous physical activity; SABA: short-acting β_2-agonist bronchodilator; SAMA: short-acting anti-muscarinic bronchodilator; LABA: long-acting β_2-agonist bronchodilator; LAMA: long-acting anti-muscarinic bronchodilator; ICS: inhaled corticosteroid. [#]Cigarette pack years = number of packs of cigarettes smoked per day (20 cigarettes/pack) x number of years the participant has smoked. *p<0.05 vs. COPD.

COPD (no-ACO): ever smokers with post-bronchodilator FEV_1/FVC <0.70 who did not self-report atopy (presence of respiratory allergies and/or hay fever) and/or a physician diagnosis of asthma; ACO_1: ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy; ACO_2, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported physician diagnosis of asthma; ACO_3, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy and physician diagnosis of asthma; Any-ACO, participants meeting either one or combination the ACO_{1-3} definitions.

Table 2.2. Comparison of respiratory symptom burden and health status between people with chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap (ACO).

	COPD (n=248)	ACO_1 (n=103)	ACO_2 (n=125)	ACO_3 (n=65)	Any-ACO (n=163)
Chronic cough, N (% of group)	53 (21.4)	29 (28.2)	39 (31.2) *****	21 (32.3)	47 (28.8)
Chronic phlegm, N (% of group)	37 (14.9)	24 (23.3)	39 (31.2) *****	19 (29.2) *****	44 (27.0) *****
Wheeze, N (% of group)	72 (29.0)	59 (57.3) *****	75 (60.0) *****	44 (67.7) *****	90 (55.2) *****
Chronic bronchitis, N (% of group)	41 (16.5)	28 (27.2) *	48 (38.4) *	22 (33.9) *	54 (33.1) *
Respiratory allergies, N (% of group)	0 (0.0)	72 (69.9) *****	47 (37.6) *****	47 (72.3) *****	72 (44.2) *****
Hay fever, N (% of group)	0 (0.0)	56 (54.4) *****	36 (28.8) *****	36 (55.4) *****	56 (34.4) *****
SGRQ – total score	9.0 (17.4)	19.6 (26.0) *****	23.0 (25.4) *****	23.20 (26.0) *****	20.40 (25.1) *****
CAT total score (0-40)	6.0 (7.0)	8.00 (10.0) *	10.0 (10.0) *	10.00 (10.5) *	9.00 (10.0) *
CAT total score ≥10, N (% of group)	65 (26.2)	47 (46.1) *****	65 (52.4) *****	33 (51.6) *****	79 (48.8) *****
MRC dyspnea score (1-5)	1.0 (1.0)	2.0 (1.0) *****	2.0 (1.0) *****	2.00 (1.0) *****	2.0 (1.0) *****
MRC dyspnea score ≥3, N (% of group)	13 (5.4)	10 (10.3)	18 (15.0) *****	6 (9.5)	22 (14.3) *****

Data are presented as median [IQR] or frequency (n (%)). SGRQ: St. George's Respiratory Questionnaire; CAT: COPD Assessment Test; MRC: Medical Research Council Dyspnea scale. *p<0.05 vs. COPD.

COPD (no-ACO): ever smokers with post-bronchodilator FEV_1/FVC <0.70 who did not self-report atopy (presence of respiratory allergies and/or hay fever) and/or a physician diagnosis of asthma; ACO_1: ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy; ACO_2, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported physician diagnosis of asthma; ACO_3, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy and physician diagnosis of asthma; Any-ACO, participants meeting either one or combination the ACO_{1-3} definitions.

Table 2.3. Comparison of pulmonary function test outcomes (including bronchodilator reversibility) between people with chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap (ACO).

	COPD (n=248)	**ACO_1 (n=103)**	**ACO_2 (n=125)**	**ACO_3 (n=65)**	**Any-ACO (n=163)**
FEV_1/FVC (%)	63.8 (8.8)	62.4 (10.9)	60.7 (12.6) *****	61.2 (10.6)	61.8 (11.2) *****
FEV_1/FVC <LLN	132 (53.2)	74 (71.8) *****	97 (77.6) *****	51 (78.5) *****	120 (73.6) *****
FEV_1 (% predicted)	82.0 (25.0)	82.0 (21.0)	75.0 (23.0) *****	76.0 (19.0) *****	78.0 (25.0) *****
GOLD grade 1 COPD, N (% of group)	139 (56.1)	56 (54.4)	50 (40.0) *****	28 (43.1)	78 (47.9)
GOLD grade 2 COPD, N (% of group)	92 (37.1)	41 (39.8)	64 (51.2) *****	32 (49.2)	73 (44.8)
GOLD grade 3-4 COPD, N (% of group)	17 (6.9)	6 (5.8)	11 (8.8)	5 (7.7)	12 (7.4)
$FEF_{25-75\%}$ (% predicted)	44.3 (27.9)	41.7 (32.2)	34.0 (26.6) *****	37.6 (25.0) *****	39.2 (29.7) *****
TLC (% predicted)	109.0 (21.0)	109.0 (18.0)	109.0 (15.0)	108.0 (14.0)	110.0 (17.0)
RV (% predicted)	129.0 (55.0)	137.0 (46.0)	147.0 (42.0) *****	143.0 (31.0)	143.0 (46.0) *****
FRC (% predicted)	118.0 (37.0)	114.0 (32.5)	122.0 (33.0)	114.0 (27.0)	122.0 (33.0)
IC (% predicted)	98.5 (26.9)	100.9 (18.9)	96.1 (24.6)	97.5 (23.1)	98.1 (23.7)
D_LCO (% predicted)	86.0 ± 22.9	90.8 ± 20.7	87.1 ± 20.5	91.7 ± 18.4	87.6 ± 21.4
Bronchodilator Reversibility					
Post-dose Δ in FEV_1 (L)	0.12 (0.19)	0.15 (0.17) *****	0.16 (0.20) *****	0.18 (0.17) *****	0.15 (0.19) *****
Post-dose Δ in FEV_1 >200 mL, N (% of group)	71 (28.6)	39 (37.9)	47 (37.6)	27 (41.5)	59 (36.2)
Post-dose Δ in FEV_1 >400 mL, N (% of group)	13 (5.2)	8 (7.8)	10 (8.0)	4 (6.2)	14 (8.6)
Post-dose Δ in FEV_1 (%)	5.5 (9.1)	8.0 (8.2) *****	8.9 (9.5) *****	8.9 (7.7) *****	8.1 (9.0) *****
Post-dose Δ in FEV_1 >12%, N (% of group)	54 (21.8)	26 (25.2)	43 (34.4) *****	21 (32.3)	48 (29.5)
Post-dose Δ in FEV_1 >15%, N (% of group)	37 (14.9)	17 (16.5)	30 (24.0) *****	13 (20.0)	34 (20.9)
Post-dose Δ in FEV_1 >200 mL and >12%, N (% of group)	46 (18.6)	20 (19.4)	33 (26.4)	16 (24.6)	37 (22.7)
Post-dose Δ in FEV_1 >400 mL and >15%, N (% of group)	12 (4.8)	7 (6.8)	9 (7.2)	4 (6.2)	12 (7.4)
Post-dose Δ in FEV_1 (% predicted)	4.2 (6.7)	6.1 (5.8) *****	6.1 (6.8) *****	6.3 (5.1) *****	6.0 (6.0) *****

Post-dose Δ in FEV_1 >10% predicted, N (% of group)	37 (14.9)	16 (15.5)	29 (23.2)	13 (20.0)	32 (19.6)
Post-dose Δ in FVC (L)	0.10 (0.31)	0.15 (0.29) *	0.18 (0.30) *	0.20 (0.31) *	0.15 (0.28) *
Post-dose Δ in FVC (%)	2.8 (9.0)	4.1 (9.2)	4.7 (9.8) *	4.7 (10.6) *	4.2 (9.4) *
Post-dose Δ in FVC (% predicted)	3.0 (9.2)	3.99 (8.1) *	4.86 (8.6) *	5.27 (9.7) *	4.06 (8.4) *
Post-dose Δ in FVC >10% predicted, N (% of group)	35 (14.1)	23 (22.3)	29 (23.2) *	17 (26.2) *	35 (21.5)

Data are presented as median [IQR], mean ± SD or frequency (n (%)). FEV_1: forced expiratory volume in 1-sec; FVC: forced vital capacity: GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEF25-75%, forced expiratory flow rate between 25 and 75% of the FVC maneuver; TLC: total lung capacity; RV: residual volume; FRC: functional residual capacity; IC: inspiratory capacity: DLCO: diffusion capacity of the lung for carbon monoxide; Δ: change. *p<0.05 vs. COPD.

COPD (no-ACO): ever smokers with post-bronchodilator FEV_1/FVC <0.70 who did not self-report atopy (presence of respiratory allergies and/or hay fever) and/or a physician diagnosis of asthma; ACO_1: ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy; ACO_2, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported physician diagnosis of asthma; ACO_3, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy and physician diagnosis of asthma; Any-ACO, participants meeting either one or combination the ACO_{1-3} definitions.

Table 2.4. Comparison of symptom-limited incremental cardiopulmonary cycle exercise test outcomes between people with chronic obstructive pulmonary disease (COPD) and asthma-COPD overlap (ACO).

	COPD (n=248)	**ACO_1 (n=103)**	**ACO_2 (n=125)**	**ACO_3 (n=65)**	**Any-ACO (n=163)**
$V'O_2$ (% predicted)	80.0 (28.0)	81.0 (34.0)	78.0 (32.0)	82.0 (34.0)	78.0 (32.0)
Peak $V'O_2$ <85% predicted, N (% of group)	142 (57.26)	60 (58.3)	77 (61.6)	37 (56.9)	100 (61.4)
Power output (% predicted)	79.0 (31.0)	84.0 (33.0)	75.0 (31.0)	82.0 (35.0)	76.0 (33.0)
Respiratory exchange ratio	1.09 (0.14)	1.07 (0.11)	1.07 (0.13)	1.07 (0.11)	1.07 (0.12)
Heart rate (% predicted)	90.0 (20.0)	94.0 (23.0)	90.0 (22.0)	94.0 (22.0)	90.0 (23.0)
O_2 pulse (% predicted)	92.0 (29.0)	91.0 (33.0)	89.0 (26.0)	93.0 (36.0)	89.0 (26.0)
Ventilation (L/min)	57.4 (27.1)	52.6 (31.6)	50.8 (27.1)	52.3 (32.1)	52.1 (26.8)
Ventilation (%MVV_{EST})	69.1 (28.7)	70.8 (29.5)	76.4 (27.6)	76.0 (31.0)	73.3 (29.9)
Respiratory rate (bpm)	31.0 (10.0)	31.0 (9.0)	32.0 (8.0)	31.0 (9.0)	32.0 (8.0)
Tidal volume (% inspiratory capacity)	70.5 (14.3)	70.1 (17.4)	69.6 (17.3)	70.7 (16.6)	69.2 (16.8)
RR:V_T/IC (bpm/%IC)	0.45 (0.16)	0.46 (0.16)	0.45 (0.17)	0.45 (0.16)	0.46 (0.17)
V_T%IC:V'_E (%IC/L/min)	1.24 (0.63)	1.33 (0.71)	1.34 (0.62)	1.47 (0.75)	1.32 (0.64)
$V'_E/V'CO_2$	32.6 (5.9)	31.6 (8.9)	32.6 (8.8)	30.2 (8.7)	32.6 (9.0)
$P_{ET}CO_2$ (mmHg)	36.0 (5.3)	36.3 (6.6)	36.7 (6.9)	37.8 (6.9)	36.0 (6.8)
Nadir $V'_E/V'CO_2$	31.5 (6.7)	31.0 (7.2)	31.2 (6.8)	29.4 (6.1)	31.7 (7.2)
Nadir $V'_E/V'CO_2$ >34, N (% of group)	79 (31.9)	29 (28.2)	39 (31.2)	15 (23.1)	53 (32.5)
Nadir $V'_E/V'CO_2$ >ULN, N (% of group)	55 (22.2)	22 (21.4)	30 (24.0)	11 (16.9)	41 (25.2)
SpO_2 (%)	97.0 (3.0)	96.0 (3.0)	96.0 (2.0)	96.0 (2.0)	96.0 (3.0)
Δ in SpO_2 from rest (%)	-1.0 (2.0)	-1.0 (2.0)	-1.0 (2.0)	-1.0 (2.0)	-1.0 (2.0)
Inspiratory capacity (L)	2.64 (1.15)	2.48 (0.96)	2.36 (1.02) *****	2.34 (1.02) *****	2.43 (1.01) *****
Δ in inspiratory capacity from rest (L)	-0.13 (0.55)	-0.28 (0.51)	-0.24 (0.49)	-0.28 (0.47)	-0.24 (0.50)
Dynamic hyperinflation >150 mL, N (% of group)	112 (47.5)	57 (60.0)	69 (58.5)	36 (61.0)	90 (58.4)

Inspiratory reserve volume (L)	0.75 (0.57)	0.75 (0.42)	0.68 (0.44)	0.66 (0.41)	0.74 (0.43)
IRV:V'_E (L/L/min)	0.014 (0.011)	0.014 (0.013)	0.014 (0.012)	0.013 (0.013)	0.014 (0.012)
EILV (%TLC)	88.3 (7.5)	88.6 (7.2)	89.0 (7.2)	88.9 (6.9)	88.6 (7.2)
EILV%TLC:V'_E (%TLC/L/min)	1.52 (0.75)	1.69 (1.01)	1.69 (0.96)	1.69 (1.04)	1.69 (0.92)
Breathlessness (Borg CR10)	5.0 (4.0)	5.50 (4.0) *****	5.0 (4.0) *****	6.5 (4.0) *****	5.0 (4.0) *****
Leg discomfort (Borg CR10)	6.0 (4.0)	7.00 (4.0) *****	7.0 (4.0) *****	7.0 (4.0) *****	7.0 (4.0) *****
Reason(s) for stopping exercise					
Leg discomfort, N (% of group)	117 (48.6)	42 (41.2)	51 (41.8)	29 (45.3)	64 (40.0)
Breathlessness, N (% of group)	39 (16.2)	21 (20.6)	20 (16.4)	10 (15.6)	31 (19.4)
Leg discomfort and breathlessness, N (% of group)	41 (17.0)	18 (17.7)	27 (22.1)	11 (17.2)	34 (21.3)
Other, N (% of group)	44 (18.3)	21 (20.6)	24 (19.7)	14 (21.9)	31 (19.4)

Data are presented as median [IQR] or frequency (n (%)). $V'O_2$: rate of oxygen uptake; MVV_{EST}: maximal voluntary ventilation estimated as forced expiratory volume in 1-sec multiplied by 35; RR: respiratory rate; V_T: tidal volume; IC: inspiratory capacity; V'_E: minute ventilation; $V'_E/V'CO_2$: ventilatory equivalent for carbon monoxide; $P_{ET}CO_2$: end-tidal partial pressure of carbon dioxide; SpO_2: pulse oxygen saturation; Δ: change; IRV: inspiratory reserve volume; EILV: end-inspiratory lung volume; TLC: total lung capacity. *p<0.05 vs. COPD after adjustment for age, sex, and body mass index.

COPD (no-ACO): ever smokers with post-bronchodilator FEV_1/FVC <0.70 who did not self-report atopy (presence of respiratory allergies and/or hay fever) and/or a physician diagnosis of asthma; ACO_1: ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy; ACO_2, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported physician diagnosis of asthma; ACO_3, ever smokers with post-bronchodilator FEV_1/FVC <0.70 and self-reported atopy and physician diagnosis of asthma; Any-ACO, participants meeting either one or combination the ACO_{1-3} definitions. *

2.5. DISCUSSION

The objective of this CanCOLD sub-study was to extend the work of Barrecheguren et al. [14] by comparing physiological and perceptual responses at the symptom-limited peak of incremental cycle CPET in people with COPD and ACO uniquely identified from a random population-based sample of Canadian adults aged ≥40 years. The main finding of this study is that, compared to people with COPD alone, people with ACO had remarkably similar physiological responses to symptom-limited incremental cycle CPET without evidence of greater pathophysiological abnormalities in peak exercise capacity, even though they presented with (i) significantly higher intensity ratings of breathlessness and leg discomfort at peak exercise, and (ii) significantly lower respiratory-related health status and quality of life, higher respiratory symptom burden, worse baseline pulmonary function, greater bronchodilator reversibility, and greater use of respiratory medication(s).

As discussed already in the Introduction, an earlier CanCOLD sub-study by Barrecheguren et al. [14] reported on the prevalence, clinical characteristics and course of individuals with ACO based on seven definitions often used in clinical practice. Each of the seven clinical definitions used in that study included a post-bronchodilator FEV_1/FVC <0.70 and self-reported history of cigarette smoke exposure with three that additionally included the presence of self-reported physician-diagnosed asthma and/or atopy emerging as the most consistent over time and those that identified subgroups of individuals whose clinical and physiological traits (specifically the number of co-morbidities, and CAT and SGRQ total scores) differed the most from people with COPD alone, even after adjusting for differences in age, sex, race, current smoking, and use of

ICS. For this reason, the current study, which used data from the same cross-sectional (observational) cohort of CanCOLD study participants as Barrecheguren et al. [14], adopted the same three clinical definitions of ACO as well as the same definition of COPD (i.e., ever smokers with post-bronchodilator FEV_1/FVC <0.70 who did not self-report atopy and/or physician-diagnosed asthma). Using these definitions, Barrecheguren and colleagues' [14] analysis included 258 people with COPD, 124 with ACO_1, 162 people with ACO_2, 80 people with ACO_3, and 264 people with any-ACO, whereas our analysis included fewer people in each group because CPET data were either unavailable or excluded for some CanCOLD study participants (see **Fig. 2.1**): COPD, n=248; ACO_1, n=103; ACO_2, n=125; ACO_3, n=65; and any-ACO, n=163. Despite differences in sample size, the results of both analyses indicated that people with ACO compared to COPD: were younger and more frequently female; had similar cigarette pack year smoking history; used 2-to-3 times more respiratory medication(s), specifically ICS alone or in combination with a long-acting bronchodilator; had more prevalent and severe respiratory symptom burden and impaired health status (i.e., higher SGRQ and CAT total scores, higher MRC dyspnea score, higher proportion of people reporting a CAT total score ≥10 and MRC dyspnea score ≥3); and had more severe airflow obstruction (lower % predicted FEV_1 and $FEF_{25-75\%}$) and pulmonary gas trapping (higher % predicted RV) with similar D_LCO. The results of our analysis additionally revealed that (1) a higher proportion of people with ACO compared to COPD (i) self-reported chronic cough, phlegm, wheeze, bronchitis, and a prior physician-diagnosis of COPD (~26 vs. ~40-46%); and (ii) had a post-bronchodilator FEV_1/FVC <LLN (~53% vs. ~72-78.5%); and (2) people with ACO had greater bronchodilator reversibility than people with COPD (as indicated by

significantly greater absolute and relative increases in FEV_1 and FVC from pre- to post-bronchodilatation), although a similar proportion of people with ACO vs. COPD presented with bronchodilator-induced increases in FEV_1 and FVC that exceeded commonly used clinical thresholds (e.g., increase in FEV_1 >200 mL and/or >12% from pre- to post-bronchodilatation). The differences observed in clinical and patient-reported outcomes between people with ACO and COPD in Barrecheguren et al. [14] and the current study are consistent with those reported in multiple earlier ACO-related studies [13, 28, 66-71], and certainly support the co-existence of asthma and COPD among our participants with ACO.

Our study adds incrementally to the clinical characterization of people with ACO by assessing detailed physiological and perceptual responses at the symptom-limited peak of incremental cycle CPET. Specifically, we are the first to show that, compared to people with COPD, people with ACO (regardless of the clinical criteria used to define ACO) did not have greater pathophysiological abnormalities in peak exercise capacity (% predicted $V'O_{2peak}$ and PPO) or cardiometabolic (respiratory exchange ratio, heart rate, O_2 pulse), V'_E (expressed in L/min and $\%MVV_{EST}$), breathing pattern (respiratory rate, tidal volume [V_T]), gas exchange ($V'_E/V'CO_2$, end-tidal partial pressure of CO_2, pulse O_2 saturation), and dynamic breathing mechanic responses to CPET (severity and prevalence of dynamic hyperinflation, V_T%IC, IRV, EILV). The lack of difference in exercise capacity and its physiological determinants between people with ACO and COPD is somewhat surprising considering (i) the aforementioned and notable between-group differences in respiratory symptom burden, health status and baseline pulmonary function; and (ii) that intensity ratings of breathlessness and leg discomfort were modestly

but significantly higher by an average of 0.5-0.9 and 0.6-0.8 Borg CR10 units at peak exercise in people with ACO compared to COPD, respectively.

We interpreted the results of our study to indicate that, above and beyond the established negative effect of COPD on exercise tolerance, dynamic breathing mechanics and exercise ventilatory efficiency [34, 38-40, 43, 72], the co-existence of asthma (as clinically and variably defined in this study) had no added detrimental clinical and/or pathophysiological effect. This interpretation is bolstered by the results of studies reporting that, with few exceptions, exercise physiological responses are often normal among people with asthma, especially those with well controlled mild-to-moderate asthma [1, 2, 47-49]. For instance, Cortés-Télles et al. [2] reported that, compared to age and activity-matched non-asthmatic control subjects, sedentary adults with well-controlled asthma had: similar $V'O_{2peak}$, PPO, and $V'O_2$ at the anaerobic threshold; and virtually identical cardiometabolic, ventilation, breathing pattern, and perceptual (breathlessness, leg fatigue) responses to symptom-limited incremental cycle CPET. Furthermore, Moore et al. [1] found that exercise capacity ($V'O_{2peak}$ and PPO) was not significantly different between adults with well-controlled asthma compared to age, sex and BMI-matched non-asthmatic control subjects, even though people with asthma reported relatively greater intensity ratings of breathlessness in association with higher dynamic operating lung volumes during symptom-limited incremental cycle CPET.

In our study, the proportion of people using any current respiratory medication(s) was 2-to-3 fold higher among people with ACO compared to COPD (~57-77% vs. ~19%), with these differences reflecting, by and large, relatively greater use of ICS alone or in combination with a long-acting bronchodilator by people with ACO. Thus, it could be

argued that relative preservation of peak exercise capacity among our participants with ACO compared to COPD reflected better clinical management (treatment or control) of their underlying pulmonary pathophysiology. However, this seems unlikely considering that the results of statistical *Model 2*, which included adjustment for between-group differences in any current respiratory medication use, did not uncover a significantly lower $V'O_{2peak}$ (% predicted) and/or PPO (% predicted) among people with ACO compared to COPD. In fact, the results from statistical *Model 2* showed that ACO_1 and ACO_3 groups had a significantly higher PPO (% predicted) than the COPD group.

This study has some notable limitations. First, in the absence of a consensus definition of ACO, we used the three clinical definitions of ACO that Barrecheguren et al. [14] found were most consistent over time and that best identified subgroups of individuals from the CanCOLD cohort with clinical and physiological traits most different from people with COPD. Although self-reported physician diagnosis of asthma and/or atopy is often used in clinical research studies (especially cohort studies like CanCOLD) and people identified as having ACO in our study (regardless of the definition used) presented with clinical characteristics consistent with a diagnosis of asthma (e.g., chronic cough, phlegm, wheeze, bronchitis; more frequent use of ICS; and greater bronchodilator reversibility), we cannot rule out the possibility that our definitions of ACO were inappropriate and misclassified some participants. Second, consistent with International [9] and Canadian clinical practice guidelines [73], diagnosis of COPD was based on CanCOLD participants having a post-bronchodilator $FEV_1/FVC < 0.70$. In our study, a relatively high percentage of people within both COPD (~47%) and ACO groups (~22-28%) had a post-bronchodilator $FEV_1/FVC < 0.70$ but >LLN, which raises the possibility for misclassification

(over-diagnosis) of COPD in both groups, especially the COPD group who had a significantly lower proportion of people (~53%) with a post-bronchodilator FEV_1/FVC <LLN compared to either one of the four ACO groups (~72-78.5%). Whereas potentially greater misclassification of COPD among people in the COPD compared to ACO group(s) might account for some of the observed between-group differences in clinical and patient-reported outcomes, it should have also translated into the ACO group(s) having more severe exercise intolerance in association with greater pathophysiological abnormalities in exercise ventilatory efficiency and dynamic breathing mechanics than the COPD group. However, this is not what we observed. Third, although available through the CanCOLD database, we did not use thoracic CT scan outcomes (e.g., % emphysema) to help differentiate between people with COPD and ACO since Barrecheguren et al. [14] reported no significant between-group differences in (i) emphysema and bronchiolitis scores on the CT scan or (ii) D_LCO. In our study, neither D_LCO nor the $V'_E/V'CO_2$ response to CPET were different between people with COPD and ACO, suggesting that the severity of emphysema was likely also similar between groups. Finally, the lack of inflammatory biomarkers, especially blood eosinophil counts, is an important limitation of our study. Even though blood eosinophil counts are available from the majority of CanCOLD participants [74], our study aimed to extend the results of Barrecheguren and colleagues' [14] earlier CanCOLD sub-study by using the same three clinical definitions of ACO with the greatest consistency and clinical utility.

In conclusion, our study showed that, despite having significantly worse clinical and patient-reported health outcomes, people with ACO (regardless of clinical definition) compared to COPD had similarly impaired exercise tolerance without evidence of greater

pathophysiological abnormalities in exercise ventilatory efficiency and/or dynamic breathing mechanics.

REFERENCES

1. Moore, L.E., et al., *Exertional dyspnea and operating lung volumes in asthma.* J Appl Physiol (1985), 2018. **125**(3): p. 870-877.
2. Cortés-Télles, A., et al., *Cardiorespiratory and sensory responses to exercise in well-controlled asthmatics.* Journal of Asthma, 2015. **52**(6): p. 576-582.
3. James, M.D., et al., *Exertional dyspnoea in patients with mild-to-severe chronic obstructive pulmonary disease: neuromechanical mechanisms.* The Journal of Physiology, 2022. **600**(18): p. 4227-4245.
4. Leung C, B.J., Sin DD, Aaron SD, FitzGerald JM, Maltais F, Marciniuk DD, O'Donnell D, Hernandez P, Chapman KR, Walker B, Road JD, Zheng L, Zou C, Hogg JC, Tan WC, *The Prevalence of Chronic Obstructive Pulmonary Disease (COPD) and the Heterogeneity of Risk Factors in the Canadian Population: Results from the Canadian Obstructive Lung Disease (COLD) Study.* International Journal of Chronic Obstructive Pulmonary Disease, 2021. **16**: p. 305-320.
5. Tan, W.C., et al., *Can age and sex explain the variation in COPD rates across large urban cities? A population study in Canada.* Int J Tuberc Lung Dis, 2011. **15**(12): p. 1691-8.
6. *Global Initiative for Asthma.* Global Strategy for Asthma Management and Prevention, 2022.
7. Quaderi, S.A. and J.R. Hurst, *The unmet global burden of COPD.* Glob Health Epidemiol Genom, 2018. **3**: p. e4.
8. Braman, S.S., *The global burden of asthma.* Chest, 2006. **130**(1 Suppl): p. 4S-12S.
9. *Global Initiative for Chronic Obstructive Lung Disease.* Global Strategy for the Diagnosis, Managment, and Prevention of Chronic Obstructive Pulmonary Disease, 2023.
10. Pakhale, S., et al., *Prevalence and burden of obstructive lung disease in the urban poor population of Ottawa, Canada: a community-based mixed-method, observational study.* BMC Public Health, 2021. **21**(1): p. 183.
11. Zafari, Z., et al., *The projected economic and health burden of sub-optimal asthma control in Canada.* Respir Med, 2018. **138**: p. 7-12.
12. Hosseini, M., et al., *Global prevalence of asthma-COPD overlap (ACO) in the general population: a systematic review and meta-analysis.* Respiratory Research, 2019. **20**(1).
13. Mekov, E., et al., *Update on Asthma-COPD Overlap (ACO): A Narrative Review.* Int J Chron Obstruct Pulmon Dis, 2021. **16**: p. 1783-1799.
14. Barrecheguren, M., et al., *Identification and definition of asthma–COPD overlap: The CanCOLD study.* Respirology, 2020. **25**(8): p. 836-849.
15. Nielsen, M., C.B. Barnes, and C.S. Ulrik, *Clinical characteristics of the asthma-COPD overlap syndrome--a systematic review.* Int J Chron Obstruct Pulmon Dis, 2015. **10**: p. 1443-54.
16. Vogelmeier, C.F., et al., *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary.* American Journal of Respiratory and Critical Care Medicine, 2017. **195**(5): p. 557-582.
17. Sethi, S., et al., *Inflammation in COPD: implications for management.* Am J Med, 2012. **125**(12): p. 1162-70.

18. Macnee, W., *Pathogenesis of chronic obstructive pulmonary disease.* Clin Chest Med, 2007. **28**(3): p. 479-513, v.
19. Jones, R.L., et al., *Airway remodelling in COPD: It's not asthma!* Respirology, 2016. **21**(8): p. 1347-1356.
20. Salazar, L.M. and A.M. Herrera, *Fibrotic response of tissue remodeling in COPD.* Lung, 2011. **189**(2): p. 101-9.
21. Quint, J.K. and J.A. Wedzicha, *The neutrophil in chronic obstructive pulmonary disease.* J Allergy Clin Immunol, 2007. **119**(5): p. 1065-71.
22. Lokke, A., et al., *Developing COPD: a 25 year follow up study of the general population.* Thorax, 2006. **61**(11): p. 935-9.
23. Eisner, M.D., et al., *An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2010. **182**(5): p. 693-718.
24. Salvi, S.S. and P.J. Barnes, *Chronic obstructive pulmonary disease in non-smokers.* The Lancet, 2009. **374**(9691): p. 733-743.
25. Buist, A.S., *Similarities and differences between asthma and chronic obstructive pulmonary disease: treatment and early outcomes.* Eur Respir J Suppl, 2003. **39**: p. 30s-35s.
26. Enilari, O. and S. Sinha, *The Global Impact of Asthma in Adult Populations.* Ann Glob Health, 2019. **85**(1).
27. Tashkin, D.P. and M.E. Wechsler, *Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 335-349.
28. Milne, S., D. Mannino, and D.D. Sin, *Asthma-COPD Overlap and Chronic Airflow Obstruction: Definitions, Management, and Unanswered Questions.* J Allergy Clin Immunol Pract, 2020. **8**(2): p. 483-495.
29. Lewthwaite, H., et al., *Normative Peak Cardiopulmonary Exercise Test Responses in Canadian Adults Aged ≥40 Years.* CHEST, 2020. **158**(6): p. 2532-2545.
30. Wijnhoven, H.A., et al., *Determinants of different dimensions of disease severity in asthma and COPD : pulmonary function and health-related quality of life.* Chest, 2001. **119**(4): p. 1034-42.
31. Stanescu, S., et al., *A systematic review of psychological, physical health factors, and quality of life in adult asthma.* NPJ Prim Care Respir Med, 2019. **29**(1): p. 37.
32. Decramer, M., et al., *Systemic effects of COPD.* Respiratory Medicine, 2005. **99**: p. S3-S10.
33. Chatila, W.M., et al., *Comorbidities in chronic obstructive pulmonary disease.* Proc Am Thorac Soc, 2008. **5**(4): p. 549-55.
34. O'Donnell, D.E., et al., *Advances in the Evaluation of Respiratory Pathophysiology during Exercise in Chronic Lung Diseases.* Frontiers in physiology, 2017. **8**: p. 82-82.
35. Troosters, T., et al., *Improving physical activity in COPD: towards a new paradigm.* Respir Res, 2013. **14**(1): p. 115.
36. Stickland, M.K., et al., *Using Cardiopulmonary Exercise Testing to Understand Dyspnea and Exercise Intolerance in Respiratory Disease.* Chest, 2022. **161**(6): p. 1505-1516.
37. Radtke, T., et al., *ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases.* Eur Respir Rev, 2019. **28**(154).
38. O'Donnell, D.E., et al., *The Pathophysiology of Dyspnea and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* Clin Chest Med, 2019. **40**(2): p. 343-366.

39. O'Donnell, D.E., et al., *The Link between Reduced Inspiratory Capacity and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* Ann Am Thorac Soc, 2017. **14**(Supplement_1): p. S30-S39.
40. O'Donnell, D.E., et al., *Chronic obstructive pulmonary disease: clinical integrative physiology.* Clin Chest Med, 2014. **35**(1): p. 51-69.
41. O'Donnell, D.E., et al., *Decline of resting inspiratory capacity in COPD: the impact on breathing pattern, dyspnea, and ventilatory capacity during exercise.* Chest, 2012. **141**(3): p. 753-762.
42. Phillips, D.B., et al., *Physiological predictors of morbidity and mortality in COPD: the relative importance of reduced inspiratory capacity and inspiratory muscle strength.* Journal of Applied Physiology, 2022. **133**(3): p. 679-688.
43. Neder, J.A., et al., *Physiological and clinical relevance of exercise ventilatory efficiency in COPD.* Eur Respir J, 2017. **49**(3).
44. Dempsey, J.A., et al., *The physiology and pathophysiology of exercise hyperpnea.* Handb Clin Neurol, 2022. **188**: p. 201-232.
45. Jones, J.H., et al., *Emphysema on Thoracic CT and Exercise Ventilatory Inefficiency in Mild-to-Moderate COPD.* COPD: Journal of Chronic Obstructive Pulmonary Disease, 2017. **14**(2): p. 210-218.
46. Phillips, D.B., et al., *Impaired Ventilatory Efficiency, Dyspnea, and Exercise Intolerance in Chronic Obstructive Pulmonary Disease: Results from the CanCOLD Study.* American Journal of Respiratory and Critical Care Medicine, 2022. **205**(12): p. 1391-1402.
47. Rossman, M.J., et al., *Effects of altered airway function on exercise ventilation in asthmatic adults.* Med Sci Sports Exerc, 2014. **46**(6): p. 1104-13.
48. Vermeulen, F., et al., *Activity limitation and exertional dyspnea in adult asthmatic patients: What do we know?* Respir Med, 2016. **117**: p. 122-30.
49. Collins, S.E., et al., *Ventilatory efficiency in athletes, asthma and obesity.* Eur Respir Rev, 2021. **30**(161).
50. Weatherald, J., et al., *Mechanisms, measurement and management of exertional dyspnoea in asthma: Number 5 in the Series "Exertional dyspnoea" Edited by Pierantonio Laveneziana and Piergiuseppe Agostoni.* Eur Respir Rev, 2017. **26**(144).
51. Kosmas, E.N., et al., *Exercise-induced flow limitation, dynamic hyperinflation and exercise capacity in patients with bronchial asthma.* Eur Respir J, 2004. **24**(3): p. 378-84.
52. Laveneziana, P., et al., *Tidal volume inflection and its sensory consequences during exercise in patients with stable asthma.* Respiratory Physiology & Neurobiology, 2013. **185**(2): p. 374-379.
53. Leung, C. and D.D. Sin, *Asthma-COPD Overlap: What Are the Important Questions?* CHEST, 2022. **161**(2): p. 330-344.
54. Dey, S., et al., *Pathogenesis, clinical features of asthma COPD overlap, and therapeutic modalities.* American Journal of Physiology-Lung Cellular and Molecular Physiology, 2022. **322**(1): p. L64-L83.
55. Bourbeau, J., et al., *Canadian Cohort Obstructive Lung Disease (CanCOLD): Fulfilling the need for longitudinal observational studies in COPD.* COPD, 2014. **11**(2): p. 125-32.
56. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-586.

57. Jones, P.W., et al., *Development and first validation of the COPD Assessment Test.* Eur Respir J, 2009. **34**(3): p. 648-54.
58. Jones, P.W., et al., *A Self-complete Measure of Health Status for Chronic Airflow Limitation: The St. George's Respiratory Questionnaire.* American Review of Respiratory Disease, 1992. **145**(6): p. 1321-1327.
59. Quanjer, P.H., et al., *Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations.* Eur Respir J, 2012. **40**(6): p. 1324-43.
60. Hall, G.L., et al., *Official ERS technical standard: Global Lung Function Initiative reference values for static lung volumes in individuals of European ancestry.* Eur Respir J, 2021. **57**(3).
61. Stanojevic, S., et al., *Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians.* Eur Respir J, 2017. **50**(3).
62. American Thoracic, S. and P. American College of Chest, *ATS/ACCP Statement on cardiopulmonary exercise testing.* Am J Respir Crit Care Med, 2003. **167**(2): p. 211-77.
63. Guenette, J.A., et al., *Inspiratory Capacity during Exercise: Measurement, Analysis, and Interpretation.* Pulm Med, 2013. **2013**: p. 956081.
64. BORG, G.A.V., *Psychophysical bases of perceived exertion.* Medicine & Science in Sports & Exercise, 1982. **14**(5): p. 377-381.
65. Stubbing, D.G., et al., *Pulmonary mechanics during exercise in subjects with chronic airflow obstruction.* Journal of Applied Physiology, 1980. **49**(3): p. 511-515.
66. Calverley, P.M.A. and P.P. Walker, *ACO (Asthma-COPD Overlap) Is Independent from COPD: The Case in Favour.* Diagnostics (Basel), 2021. **11**(7).
67. Fujino, N. and H. Sugiura, *ACO (Asthma-COPD Overlap) Is Independent from COPD, a Case in Favor: A Systematic Review.* Diagnostics (Basel), 2021. **11**(5).
68. Odimba, U., et al., *Current Knowledge of Asthma-COPD Overlap (ACO) Genetic Risk Factors, Characteristics, and Prognosis.* COPD, 2021. **18**(5): p. 585-595.
69. Ekerljung, L., et al., *Prevalence, clinical characteristics and morbidity of the Asthma-COPD overlap in a general population sample.* J Asthma, 2018. **55**(5): p. 461-469.
70. Miravitlles, M., et al., *Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status.* Respir Med, 2013. **107**(7): p. 1053-60.
71. Hardin, M., et al., *The clinical features of the overlap between COPD and asthma.* Respir Res, 2011. **12**(1): p. 127.
72. Neder, J.A., et al., *Exertional ventilation/carbon dioxide output relationship in COPD: from physiological mechanisms to clinical applications.* Eur Respir Rev, 2021. **30**(161).
73. Bourbeau, J., et al., *Canadian Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence.* Canadian Journal of Respiratory, Critical Care, and Sleep Medicine, 2019. **3**(4): p. 210-232.
74. Tan, W.C., et al., *High eosinophil counts predict decline in FEV(1): results from the CanCOLD study.* Eur Respir J, 2021. **57**(5).