Components of the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test associated with cardiopulmonary exercise test outcomes among people with Global Initiative for Obstructive Lung Disease grade 1 or 2, group A COPD: Results from the Canadian Cohort Obstructive Lung Disease study

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Abstract

It remains unknown whether chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) sub-items, particularly the breathlessness and pulmonary symptoms sub-items, carry useful information regarding the existence of impaired exercise tolerance among people with COPD. This retrospective study used data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study to test the hypothesis that people with Global Initiative for Obstructive Lung Disease (GOLD) grade 1 (mild) or 2 (moderate), group A COPD with (i) higher compared to lower CAT breathlessness sub-item scores or (ii) higher compared to lower CAT pulmonary symptom sub-items cluster scores have lower exercise tolerance (peak rate of O_2 consumption [$V'O_{2peak}$]) in association with greater abnormalities in exercise physiological and perceptual responses. To this end, we compared physiological and perceptual responses at the symptom-limited peak of incremental cardiopulmonary cycle exercise testing amongst 310 people with GOLD grade 1 (n=209) or 2 (n=101), group A COPD with (i) CAT breathlessness sub-item score of 0 (n=154) versus ≥1 out of 5 (n=156) or (ii) CAT pulmonary symptoms sub-item cluster score of <5 (n=247) versus ≥5 out of 20 (n=63). The optimal cut-point for each of the CAT breathlessness sub-item score and the CAT pulmonary symptoms sub-item cluster score was one that best predicted (according to the Youden Index) an individual with GOLD grade 1 or 2, group A COPD of having an abnormally low $V'O_{2peak}$, defined as <85% of the predicted reference value. We found that people with a higher compared to lower CAT breathlessness sub-item score or a higher compared to lower CAT pulmonary symptoms cluster score had broadly similar baseline characteristics (including pulmonary function) but nevertheless presented with significantly lower exercise tolerance ($V'O_{2peak}$) in association with greater critical inspiratory constraints and exertional breathlessness. From a clinical management perspective, the results our study suggest that a CAT breathlessness sub-item score ≥1 or a CAT pulmonary symptoms sub-item cluster score ≥5 might help healthcare providers identify people with GOLD grade 1 or 2, group A COPD with

clinically relevant exercise intolerance as manifested by greater critical inspiratory constraints and exertional breathlessness that might otherwise be overlooked and that might have a preferential response to available inhaled respiratory medication(s).

Resumé

On ne sait toujours pas si les sous-éléments du test d'évaluation (CAT) de la maladie pulmonaire obstructive chronique (MPOC), en particulier les sous-éléments de l'essoufflement et des symptômes pulmonaires, contiennent des informations utiles concernant l'existence d'une tolérance altérée à l'exercice chez les personnes atteintes de MPOC. Cette étude rétrospective a utilisé les données de l'étude Canadian Cohort Obstructive Lung Disease (CanCOLD) pour tester l'hypothèse selon laquelle les personnes atteintes de la Global Initiative for Obstructive Lung Disease (GOLD) de grade 1 (léger) ou 2 (modéré), groupe A MPOC avec (i) supérieur par rapport aux scores inférieurs des sous-éléments d'essoufflement du CAT ou (ii) supérieur par rapport aux scores inférieurs des sous-éléments des symptômes pulmonaires du CAT ont une tolérance à l'exercice inférieure (taux maximal de consommation d'O2 [V'O2peak]) en association avec de plus grandes anomalies physiologiques de l'exercice et les réponses perceptives. À cette fin, nous avons comparé les réponses physiologiques et perceptuelles au pic limité par les symptômes des tests d'effort incrémentiels du cycle cardio-pulmonaire chez 310 personnes atteintes de GOLD grade 1 (n = 209) ou 2 (n = 101), groupe A MPOC avec (i) CAT score du sous-item d'essoufflement de 0 (n = 154) versus ≥1 sur 5 (n = 156) ou (ii) score du groupe de sous-items des symptômes pulmonaires CAT < 5 (n = 247) versus ≥5 sur 20 (n=63). Le point de coupure optimal pour chacun des scores de sous-item d'essoufflement CAT et du score de groupe de sous-items de symptômes pulmonaires CAT était celui qui prédisait le mieux (selon l'indice de Youden) un individu atteint de BPCO GOLD de grade 1 ou 2, groupe A de ayant un pic de V'O2 anormalement bas, défini comme < 85 % de la valeur de référence prédite. Nous avons constaté que les personnes ayant un score de sous-élément d'essoufflement CAT supérieur à inférieur ou un score de groupe de symptômes pulmonaires CAT supérieur à inférieur avaient des caractéristiques de base globalement similaires (y compris la fonction pulmonaire), mais présentaient néanmoins une tolérance à l'exercice

significativement inférieure (V'O2peak) en association avec des contraintes inspiratoires critiques plus importantes et un essoufflement à l'effort. Du point de vue de la prise en charge clinique, les résultats de notre étude suggèrent qu'un score de sous-élément d'essoufflement CAT $\geq$1 ou un score de groupe de sous-éléments de symptômes pulmonaires CAT $\geq$5 pourrait aider les prestataires de soins de santé à identifier les personnes atteintes de BPCO GOLD de grade 1 ou 2, groupe A avec intolérance à l'exercice cliniquement pertinente, qui se manifeste par des contraintes inspiratoires critiques plus importantes et un essoufflement à l'effort qui pourraient autrement être négligés et qui pourraient avoir une réponse préférentielle aux médicaments respiratoires inhalés disponibles.

Chapter 1: Literature Review

1.1 *COPD as a disease*

1.1.1. Prevalence and burden

Leung et al. (1) recently estimated that the population-based prevalence of spirometrically-defined (post-bronchodilator forced expiratory volume in 1-sec to forced vital capacity ratio (FEV_1/FVC) <0.70) chronic obstructive pulmonary disease (COPD) among Canadian adults aged ≥40 years is 16.2%. An earlier study by Tan et al. (2) similarly reported a population-based prevalence of spirometrically-defined COPD in Canada of 16.7%, an estimate ~2.5 times higher than the 6.9% of Canadians that self-reported having a prior physician diagnosis of COPD (**Figure 1.1**). What is clear (and troubling) from the discrepancy in these prevalence estimates is the large population of older Canadian adults unaware that they have measurable lung function impairment consistent with a diagnosis of COPD and that might be amenable to available inhaled respiratory medication(s). The reasons for this discrepancy are multifactorial, but likely include spirometry rarely being performed in primary care clinics as most individuals in the general population have a mild form of the disease and are often largely asymptomatic (2). Indeed, **Figure 1.1**, from Tan et al. (3), illustrates that ~53% of Canadian adults with spirometrically-defined COPD (~56% from Leung et al. (1)) meet Global Initiative for Obstructive Lung Disease (GOLD) criteria for mild (grade 1) COPD and ~92% meet the criteria for mild or moderate (grade 1 or 2) COPD (~93% from Leung et al (1)).

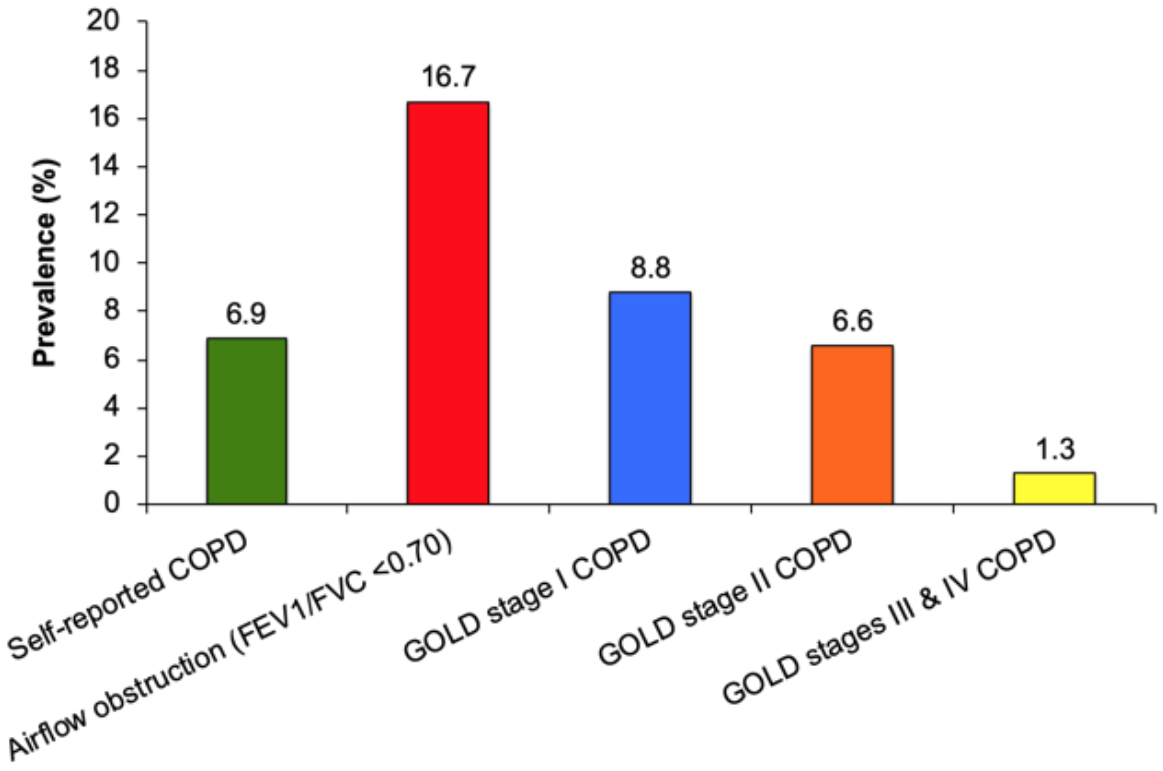

Figure 1.1: Prevalence of COPD among non-institutionalized Canadian adults aged ≥40 years (data obtained from Tan et al. (2)). FEV_1/FVC = ratio of forced expiratory volume in 1-sec to forced vital capacity, GOLD = Global Initiative for Obstructive Lung Disease, GOLD stage I = mild COPD, stage II = moderate COPD, stage III = severe COPD, stage IV = very severe COPD (3).

According to the World Health Organization, COPD accounted for over three million global deaths in 2019 (4). This number is soon expected to be greater than 5.4 million as the prevalence of cigarette smoking continues to increase and the global population continues to age (5,6). According to disability adjusted life years[1], COPD was previously expected to be the 4th leading cause of death and the 7th most burdensome disease worldwide by 2020 (7). Despite being a very prevalent and burdensome chronic health condition, COPD is still under-recognized and under-diagnosed (8).

[1] Compilation of the years of life lived with disability and composite years lost due to premature mortality, independent of the severity of disability (7)

1.1.2 Causes and risk factors

The most notable modifiable risk factor for the development of COPD is cigarette smoking (3). Although there is evidence that never smokers develop chronic airflow limitation (12.2% among 4,291 never smokers in one study by Lamprecht et al. (9)) people with COPD and a history of cigarette smoke exposure tend to have greater symptom burden, more extra-pulmonary comorbidities (e.g., systemic inflammation), and are at greater risk of premature death compared to people without a history of cigarette smoke exposure (10,11). Exposure to second-hand cigarette smoke and other noxious particles such as occupational dusts, chemical agents/fumes, wood smoke, and air pollution are other potentially modifiable risk factors for the development of COPD (12). Non-modifiable risk factors for COPD include genetic factors such as alpha-1 antitrypsin deficiency (AATD), ageing, abnormal lung development, low birth weight, and premature birth (3,12). History of asthma (13), poverty (14), and low socioeconomic status (15,16) are other risk factors for the development of COPD, which can either be modifiable or non-modifiable depending on their etiology, severity and progression (12,17,18).

1.2 *COPD Pathogenesis and Pathophysiology*

1.2.1. Pathogenesis

The pathogenesis of COPD is complex, but it is generally understood that exposure to noxious irritants induce an irregular (exaggerated) inflammatory response of the lungs and airways that leads to a progressive decline in pulmonary structure and function (3). A detailed description of the exaggerated inflammatory response is beyond the scope of this thesis, but studies support a complex interplay between increased oxidative stress (19,20), increased release of pro-inflammatory cytokines (3,21–23), and protease-antiprotease imbalance (24). Regardless of the underlying cellular and molecular mechanisms, the exaggerated inflammatory response manifests as increased bronchomotor tone, mucus hypersecretion, and destruction of the lung parenchyma that make the airways narrow and collapsible, and that decreases the

surface area for pulmonary gas exchange (23). These factors combine to simultaneously increase ventilatory demand and decrease ventilatory capacity by decreasing pulmonary gas exchange efficiency and causing expiratory flow limitation, pulmonary gas trapping, and lung hyperinflation. The combination of these factors, in turn, contribute to abnormally high pulmonary symptom burden (breathlessness, cough, phlegm, chest tightness) with abnormally low exercise tolerance and health status (3). Additionally, individuals with COPD may often modify (decrease) their levels of physical activity (e.g., walk less and slower, avoid hills and stairs) as a way to avoid provocation of breathlessness (dyspnea), as highlighted in **Figure 1.2**. Breathlessness is *"a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity"* (25).

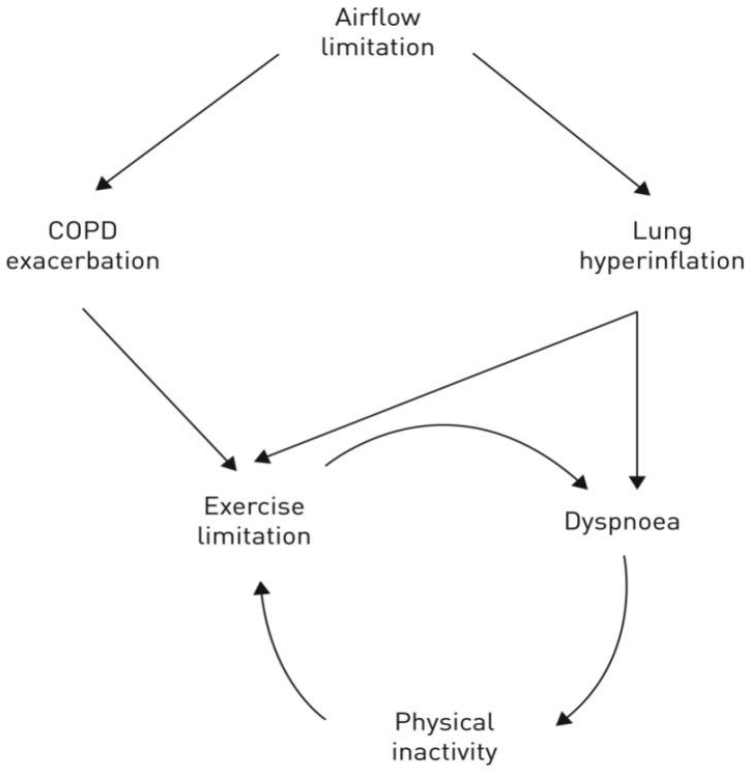

Figure 1.2: Cycle of disability in COPD (retrieved from Ramon et al. (26))

1.2.2. Pathophysiology

A pathophysiological hallmark of COPD is persistent airflow limitation. Clinically, this is indexed by GOLD (3) and the Canadian Thoracic Society (27) as a post-bronchodilator FEV_1/FVC

<0.70 and/or <LLN, where LLN represents the lower limit of normal and defines the bottom 5% of a healthy “normal” population (3). Expiratory flow limitation occurs due to airway obstruction, particularly of the smaller peripheral airways (28). Additionally, fibrosis of the alveoli due to destruction of extracellular matrix proteins and alveolar walls result in loss of lung elastic recoil, which decreases expiratory driving pressure and increases collapsibility of the airways. The combination of these two factors make the airways more susceptible to dynamic compression when intrapulmonary pressures increase during expiration (3,28). Hogg et al. (23) showed that reduced FEV_1 and FEV_1/FVC correlated with the severity of inflammation, fibrosis and accumulation of inflammatory exudates in the small airways of ever smokers without COPD as well as in people with mild to advanced COPD (134).

The progression of airflow limitation and abnormal anatomical changes in the lung during the course of COPD leads to ventilation/perfusion (V’/Q’) mismatching with attendant gas exchange abnormalities between the alveoli and pulmonary arteries responsible for pulmonary perfusion (29,30). As the severity of COPD progresses, exchange of O_2 and CO_2 across the lung-blood interface often worsens (3,29). People with a predominant emphysematous phenotype of COPD often have a high V’/Q’ ratio due to poor perfusion of alveolar units that have been compromised with subsequent increased physiological dead space (29,31). Those with a predominant bronchitis phenotype of COPD often have a low V’/Q’ ratio and subsequent hypoxemia (29). Impaired respiratory muscle mechanics and function, severe airflow limitation and associated pulmonary gas trapping and lung hyperinflation, can lead to breathlessness, especially during physical activity (exercise) when metabolic, ventilatory and pulmonary gas exchange requirements increase above resting levels (3,29). The impacts of emphysema and bronchitis on V’/Q’ mismatch is detectable in people with mild COPD (GOLD grade 1) which represent 50-55% of the population of adults in Canada with COPD (1,2,32–34). Therefore, an understanding of the pathophysiological mechanisms of health deterioration in people with mild COPD is important to prevent or delay health status deterioration by targeted therapeutics.

Mucus hypersecretion, as occurs in people with COPD with chronic productive cough, is another major consequence of the disease (3,28,35). Due to the heterogeneity of the disease, not all people with COPD experience this symptom and it is not necessarily affiliated with airflow limitation but is often observed in people with chronic bronchitis (3,28,35). People with the chronic bronchitis phenotype experience sputum production with their cough and have difficulty in expectorating and maintaining adequate airflow due to the underlying ciliary dysfunction and mucus hypersecretion (3,28,35). Hogg et al. (36) demonstrated that people with COPD and mucus hypersecretion have a 3.5-fold greater risk of premature death than those without mucus hypersecretion. Therefore, this phenotypic manifestation should not be ignored within clinical care and research settings.

In response to hypoxemic conditions experienced by individuals with pathological abnormalities in COPD, the body triggers a vasoconstriction reflex (3,28). As a consequence, pulmonary hypertension can develop, but typically not until later in the course of the disease. Pulmonary hypertension can lead to right ventricular hypertrophy and dysfunction, which can progress to right sided heart failure, a potentially deadly chronic health condition (3,28). In addition to these cardiopulmonary characteristics, COPD imposes systemic effects (e.g., sarcopenia, osteoporosis, diabetes) that contribute to abnormally high rates of morbidity and mortality (37–39). Many of these comorbidities manifest naturally with ageing but are more prevalent at an earlier age in people with compared to without COPD (8). Impacted by systemic comorbidities, people with COPD often have significantly compromised exercise capacity, feel socially isolated, anxious and/or depressed, and experience a generally poor health status (37).

1.2.3. Pathophysiological and perceptual responses to exercise

Exercise capacity is typically assessed by measuring: (1) the rate of O_2 consumption at the symptom limited peak of incremental exercise testing ($V'O_{2peak}$, an established measure of cardiorespiratory [aerobic] fitness) and sometimes also peak power output (PPO) during an

incremental cardiopulmonary cycle ergometer or treadmill/shuttle walking exercise test (CPET); (2) the duration of exercise during a constant-load cycle ergometer or treadmill/shuttle walking exercise test, i.e., exercise endurance time (EET); or (3) the distance walked during a 6-min walk test (6MWD). In people with COPD, pathophysiological abnormalities in breathing mechanics (both static and dynamic) and pulmonary gas exchange efficiency combine to increase the perception of activity-related breathlessness, which in turn limits exercise capacity as evidenced by people with COPD often having abnormally low $V'O_{2peak}$, PPO, EET and/or 6MWD (40,41). The close relationship between exercise intolerance and risk of premature death among people with COPD was also highlighted by Oga et al. (42), where $V'O_{2peak}$ was a strong independent predictor of 5-year all-cause mortality in COPD. In fact, in that study, $V'O_{2peak}$ was a better independent predictor of premature death than FEV_1. Similar associations between $V'O_{2peak}$ and premature death have been reported by Myers et al. (43), Neder et al. (44) and Ewert et al. (45). In another study by Oga et al. (46), $V'O_{2peak}$ emerged as a stronger predictor of premature death in COPD than each of the modified BODE (body mass index, airflow obstruction, dyspnea, exercise capacity), ADO (age, dyspnea, and airflow obstruction), and DOSE (dyspnea, airflow obstruction, smoking status, and exacerbation frequency), which are three well known discriminative and prognostic multidimensional indices for COPD survival. The collective results of these studies suggest that assessment of COPD burden at rest, including resting spirometry, does not necessarily highlight disease severity (or heterogeneity) with regards to important clinical health outcomes, most notably survival.

The importance of evaluating $V'O_{2peak}$ to assess disease severity in COPD has been highlighted by studies showing the association of $V'O_{2peak}$ with FEV_1. For instance, a systematic review of 45 studies reported a moderate to strong positive association (r=0.42-0.83) between $V'O_{2peak}$ and FEV_1 across various severities of COPD (47). In other words, as FEV_1 decreases (and the degree of airflow limitation increases), exercise capacity as assessed by $V'O_{2peak}$ decreases. As illustrated in **Figure 1.3,** a similar association between FEV_1 and constant-load

cycling EET was shown by O'Donnell et al. (48). As discussed in more detail below, there is a clear mechanistic link between the pulmonary pathophysiology of COPD and both exertional breathlessness and exercise intolerance (3).

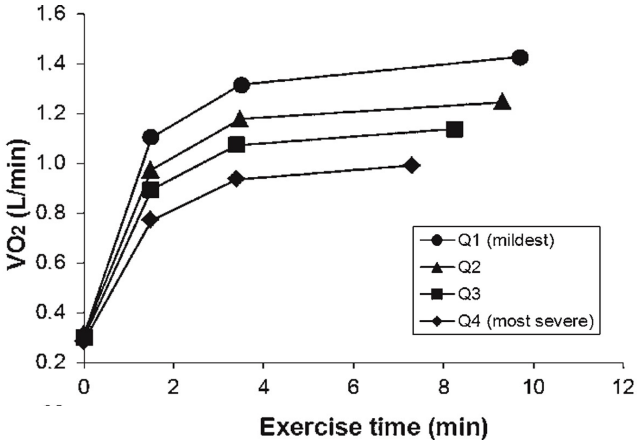

Figure 1.3: Constant-load cycle exercise endurance time (EET) and $V'O_{2peak}$ decrease with worsening FEV_1 quartile as shown in the upper right panel (retrieved from O'Donnell et al. (48)). Q1 = mild COPD, Q2 = moderate COPD, Q3 = severe COPD, Q4 = very severe COPD.

The pathophysiological and perceptual determinants of exercise intolerance (e.g., abnormally low $V'O_{2peak}$) in COPD highlight the burden of the disease, particularly exertional breathlessness. The combination of abnormal dynamic respiratory mechanics and pulmonary gas exchange inefficiency lead to abnormally high levels of exertional breathlessness with attendant physical activity limitation/avoidance and exercise intolerance (**Figure 1.2**) (3). People with COPD have an abnormally high resting end-expiratory lung volume (EELV) due to expiratory flow limitation (49). The consequence of a COPD patient's inability to fully empty their lungs of gas during expiration prior to the start of inspiration is lung hyperinflation (i.e., EELV exceeds the relaxation volume of the respiratory system under static conditions). Acute episodes of worsening expiratory flow limitation that often occur in people with COPD when ventilatory demand increases during the transition from rest to exercise results in dynamic lung hyperinflation, which is characterized by a temporary increase in EELV above its abnormally high resting level (50–55). Static and dynamic lung hyperinflation 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 expiratory flow limitation (e.g., COPD); that is, as static (resting) and dynamic (exercise) IC and IRV decline, the capacity to expand V_T in the rest to exercise transition decreases (48,56,57). As illustrated in **Figure 1.4,** 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 (56,58). A consequence of breathing at high lung volumes (i.e., where end-inspiratory volume (EILV) approaches total lung capacity and IRV declines toward 0 liters) is that the inspiratory muscles (e.g., diaphragm) shorten and become functionally weak whilst simultaneously needing to generate abnormally high intrapulmonary pressures (effort) in order to overcome the greater elastic recoil forces of the lung and achieve a given level of V_T expansion (48,56,59,60). In other words, abnormally high levels of central respiratory motor output command (or drive) and respiratory muscle work (or effort) are required to overcome critical inspiratory constraints and achieve any given level of ventilation during exercise in people with compared to without COPD. In the face of critical inspiratory constraints, people with COPD adopt a tachypneic breathing pattern characterized by an abnormally high frequency of breathing (F_b) (48,56,59,61); and report abnormally high levels of breathlessness, which become intolerable at abnormally low exercise intensities (i.e., $V'O_{2peak}$) and levels of ventilation **(Figure 1.5)**. Under these circumstances, intolerable breathlessness is identified as the primary cause of exercise intolerance in many people with COPD (see Figure 1 of O'Donnell et al. (62)).

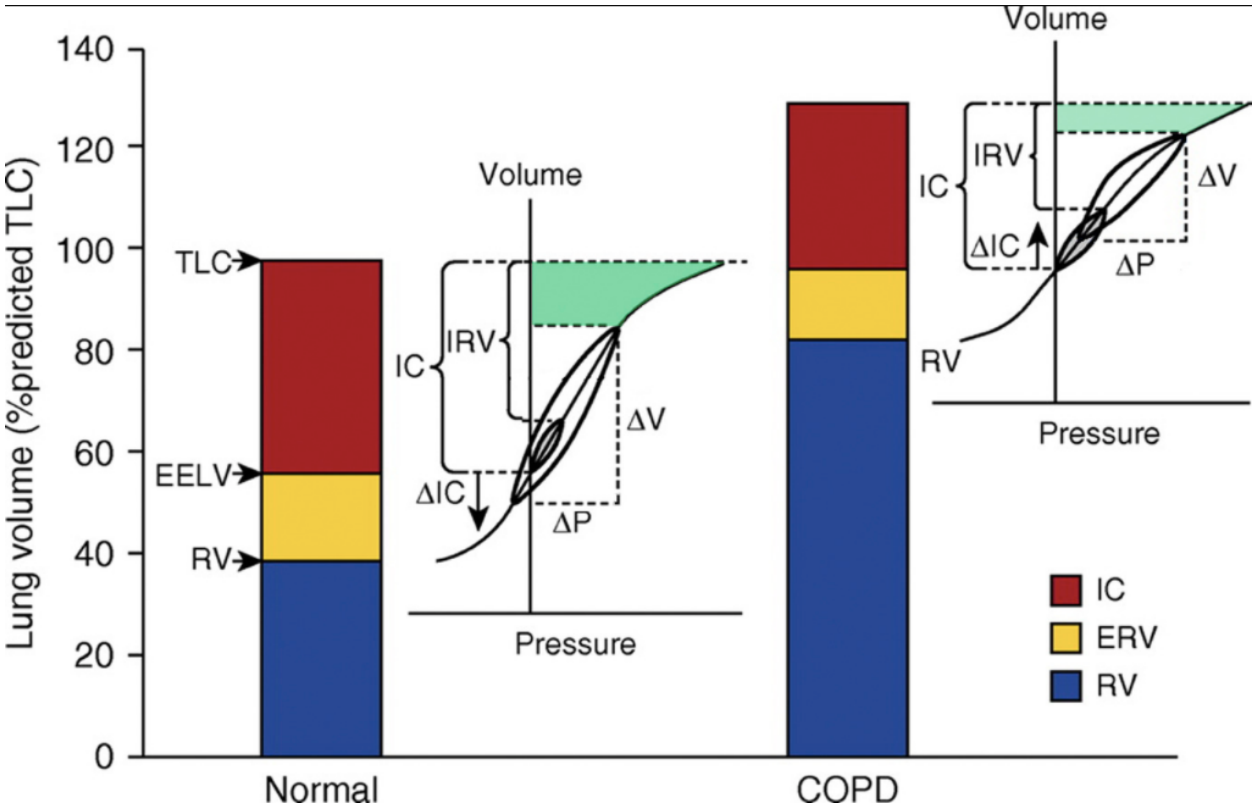

Figure 1.4: Pressure-volume relationships in healthy individuals (left) and in COPD (right) (retrieved from O'Donnell et al. (58)). EELV = End-expiratory lung volume, IRV = Inspiratory reserve volume, RV = Residual volume, P = Pressure, V = Volume, TLC = Total Lung Capacity.

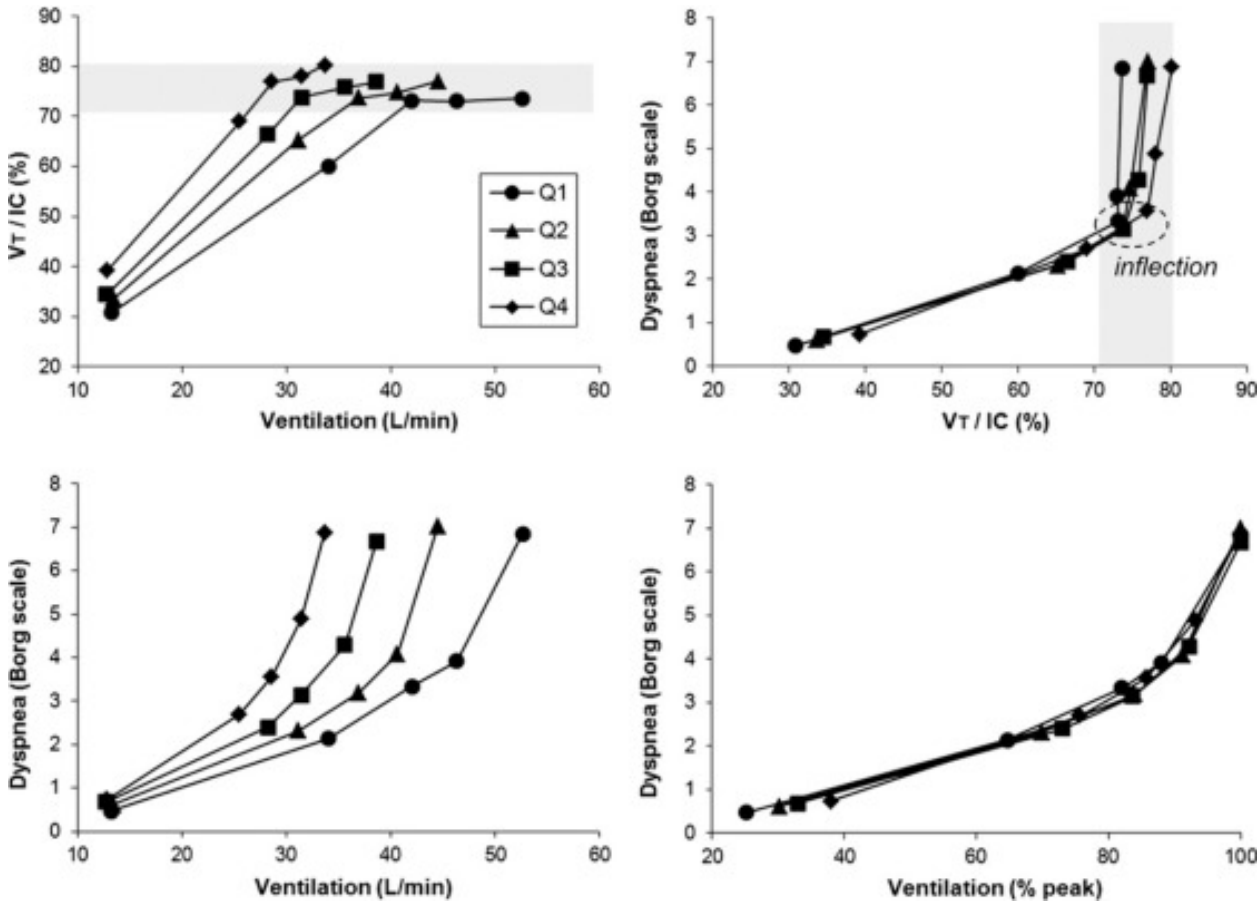

Figure 1.5: Interrelationships between tidal volume (V_T) expansion, minute ventilation, frequency of breathing (F_b), and dyspnea (retrieved from O'Donnell et al. (48)). The panels at the top illustrate that as V_T plateaus, there is a compensatory increase F_b to support V_E during exercise from mild to very severe COPD. The bottom two panels illustrate differences in the breathlessness-V_E relationship across mild to very severe COPD, which can be corroborated by the mechanism (i.e., critical inspiratory constraints) shown in the top two panels. Q1 – Q4 represents categorization of COPD severity in increasing severity.

Despite their abnormally low ventilatory capacity, people with COPD have an abnormally high ventilatory demand, as evidenced by their abnormally high minute ventilation for any given rate of CO_2 output ($V'_E/V'CO_2$) (56,63). The excessive exercise ventilation (or ventilatory inefficiency) is the consequence of "wasted" ventilation within their abnormally high physiological dead space (64). The underlying cause of "wasted" ventilation in COPD is the V'/Q' 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 (64–67). An abnormally high $V'_E/V'CO_2$ during exercise has even been reported in people with GOLD grade 1 (mild) COPD where respiratory mechanical abnormalities are not as severe as in people with more advanced disease (68,69). Symptomatically, the exaggerated $V'_E/V'CO_2$ response to exercise in COPD contributes importantly to the abnormally high exertional breathlessness burden (70). Ofir et al. (71) were among the first to show a relationship between an abnormally high exercise $V'_E/V'CO_2$ response and exertional breathlessness in symptomatic adults with GOLD grade 1 (mild) COPD, where ventilation was elevated by 30% or more for any given power output during incremental cycle CPET relative to healthy controls. Neder et al. (72) similarly showed that, during exercise, $V'_E/V'CO_2$ was abnormally high in people with GOLD grade 1 (mild) COPD and worsened with increasing disease severity (or GOLD grade).

1.2.4. The impact of symptoms on COPD burden

People with COPD often experience both pulmonary and extra-pulmonary symptoms (73). Eckerblad et al. (74) found that people with moderate-severe COPD experienced an average of 7.9 symptoms, with breathlessness, dry mouth, cough, sleep deprivation, and lack of energy being the most common. A population-based study of 49,438 adults with COPD seeking primary care by Mullerova et al. (75) found that 46% reported a Medical Research Council (MRC) dyspnea scale rating of ≥3 out of 5, indicating the presence of chronic and disabling breathlessness. In that same study, 32% of the individuals with GOLD grade 1 (mild) COPD reported chronic and disabling breathlessness **(Figure 1.6)**; and the prevalence of chronic and disabling breathlessness increased as a function of increasing disease severity (GOLD grade) (75). As illustrated in **Figure 1.7**, the degree of disability due to breathlessness as assessed by the MRC dyspnea scale has emerged as an independent predictor of 5-year mortality in COPD (41). In fact, MRC dyspnea scale ratings (like $V'O_{2peak}$, as discussed in *Section 1.2.3* above)) were a stronger predictor of premature death in COPD than FEV_1 (41). Research suggests that the prevalence of chronic and disabling breathlessness (modified MRC [mMRC] dyspnea rating ≥2, which is

equivalent to a MRC dyspnea rating ≥3) is as high as ~75% among people with GOLD grade 4 (very severe) COPD, despite these people being treated with inhaled triple therapy and physiotherapy (76).

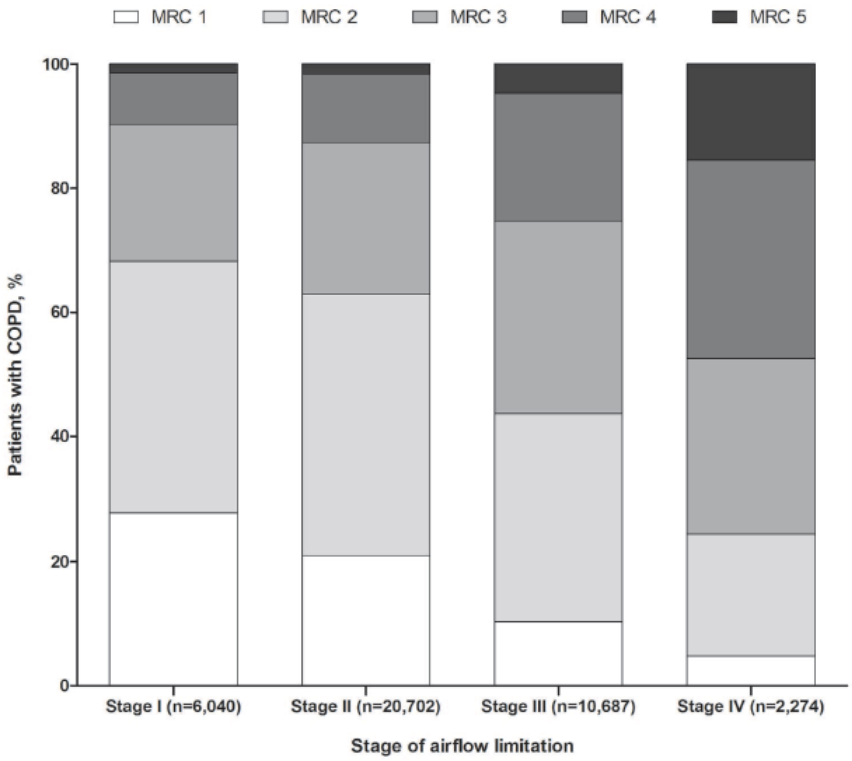

Figure 1.6. MRC breathlessness grade distribution by stage of airflow limitation (retrieved from Mullerova et al. (75)). MRC = Medical Research Council dyspnea scale, COPD = Chronic Obstructive Pulmonary Disease, Stage I = mild airflow limitation, Stage II = moderate airflow limitation, Stage III = severe airflow limitation, Stage IV = very severe airflow limitation.

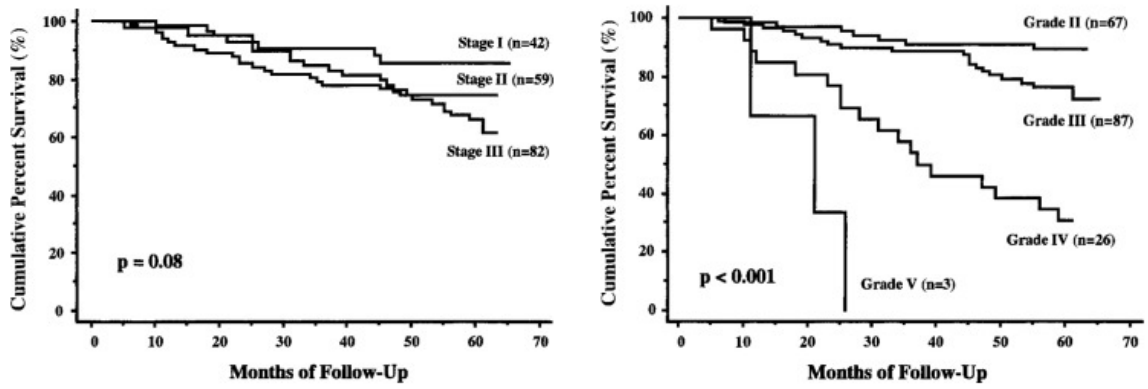

Figure 1.7: Left panel showing five-year survival according to the COPD staging of disease severity as per the American Thoracic Society (ATS) guidelines. Right panel showing five-year survival according to the level of breathlessness as measured by the MRC dyspnea scale. Stage I = Forced expiratory volume in 1-sec (FEV_1) >50% of the predicted normal value, Stage II = FEV_1 ≥35 and ≤49% of the predicted normal value, Stage III = FEV_1 < 35% of the predicted normal value. Grade II-V as described by the MRC. (Figure retrieved from Nishimura et al., 2002 (41)).

Symptoms experienced by people with COPD can have detrimental impacts on their daily life activities and health status. A longitudinal study of 791 adults with COPD demonstrated a significant association between worsening of respiratory symptom burden (as measured by the St. George's Respiratory Questionnaire [SGRQ]) and deterioration of health status over a 1-year follow up (77). Another study reported that cough, breathlessness, fatigue, and sputum production were the symptoms most commonly reported during an exacerbation and that had the greatest adverse effect on the health status of people with COPD (78). Cherian et al. (79) recently reported that Canadian adults with GOLD grade 1 (mild) or 2 (moderate) COPD were more likely to report clinically-significant breathlessness (MRC dyspnea score of 2 vs 1 out of 5) than never smokers without COPD. Earlier identification of an abnormally high symptom burden (particularly breathlessness burden) has the potential to facilitate earlier identification/diagnosis and treatment of COPD (80) with attendant improvements in clinical and patient-reported outcomes, including exercise capacity, health status, and perhaps also mortality. Overall, COPD symptoms (both pulmonary and extra-pulmonary) have a negative impact on health status, exercise tolerance and prognosis.

1.3. *COPD diagnosis and assessment*

1.3.1. COPD diagnosis

The diagnosis of COPD requires a multifactorial evaluation of: (1) an individual's symptom burden, including presence of breathlessness, chronic cough and/or sputum production; (2) an individual's medical history and exposure to risk factors such as cigarette smoking; and (3) the presence of airflow obstruction by spirometry, particularly in individuals aged ≥40 years (3). According to GOLD and Canadian Thoracic Society guidelines for the diagnosis and management of COPD, a post-bronchodilator $FEV_1/FVC < 0.70$ is required to establish a clinical diagnosis of COPD (3,27). GOLD guidelines recommend that post-bronchodilator spirometry only be performed in individuals who meet the other clinical criteria for diagnosis (presence of symptoms and history of exposure to risk factors) and are, thus, at abnormally high risk for COPD. These steps are necessary to consider the heterogeneity of COPD, as it has been shown that FEV_1 does not accurately represent the heterogenous functional impairment and symptom burden that often characterize people living with this disease (81).

1.3.2. COPD staging

Once the diagnosis of COPD has been established, the severity of airflow limitation, pathophysiological impact on an individual's health status, and risk of exacerbation and progression of disease dictate the treatment options for healthcare providers to consider (3). As illustrated in **Table 1.1**, the 2021 GOLD guidelines grade the severity of COPD as mild (grade 1), moderate (grade 2), severe (grade 3) and very severe (grade 4) based on post-bronchodilator FEV_1 values expressed as a percentage of age, height, sex, and race specific reference values (FEV_1%predicted) (82). The Canadian Thoracic Society uses the same evaluative criteria (27).

Table 1.1: Classification of airflow limitation severity in COPD (based on post-bronchdoliator FEV_1) (retreived from GOLD 2021 (3)**)**		
In people with a post-bronchodilatory $FEV_1/FVC < 0.70$:		
GOLD grade 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD grade 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD grade 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD grade 4:	Very Severe	$FEV_1 < 30\%$ predicted

GOLD = Global Initative for Obstructive Lung Disease. FEV_1/FVC = post-bronchodilator forced expiratory volume in 1-sec (FEV_1) to forced vital capacity (FVC) ratio.

1.3.3.i Modified Medical Research Council Dyspnea (mMRC) Scale

Clinical assessment of people with COPD (or suspected of having COPD) includes evaluating symptom burden and health status. The MRC dyspnea scale, which was later modified (mMRC) from a 1-5 scale to a 0-4 scale (**Table 1.2**), is used to assess the impact (burden) of breathlessness on activities of daily life (83). The mMRC was believed to sufficiently measure symptom burden as it correlated with other measures of health status (84). Precisely, this was shown in a study (84) including people with a MRC dyspnea score of ≥3 (mMRC ≥2), representing moderate to severe disability due to breathlessness, before they started a pulmonary rehabilitation program. The MRC was found to correlate with markers of (i) impaired exercise capacity, including decreased shuttle walking distance (SWD) and The Nottingham Extended Activities of Daily Living scores; and (ii) impaired health status, including increased SGRQ and Chronic Respiratory Questionnaire (CRQ) scores (84). **Figure 1.8** highlights the association between mMRC dyspnea ratings and other tools commonly used to evaluate health status in COPD. Overall, mMRC is a good predictor of health status (84) and premature death (41,85) in people with COPD.

Table 1.2: The Modified Medical Research Council (mMRC) Dyspnea Scale (retrieved from GOLD 2021 (3)).	
mMRC Grade 0	I only get breathless with strenous exercise.
mMRC Grade 1	I get short of breath when hurrying on the level or walking up a straight hill.
mMRC Grade 2	I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.
mMRC Grade 3	I stop for breath after walking about 100 meters or after a few minutes on the level.
mMRC Grade 4	I am too breathless to leave the house or I am breathless when dressing or undressing.

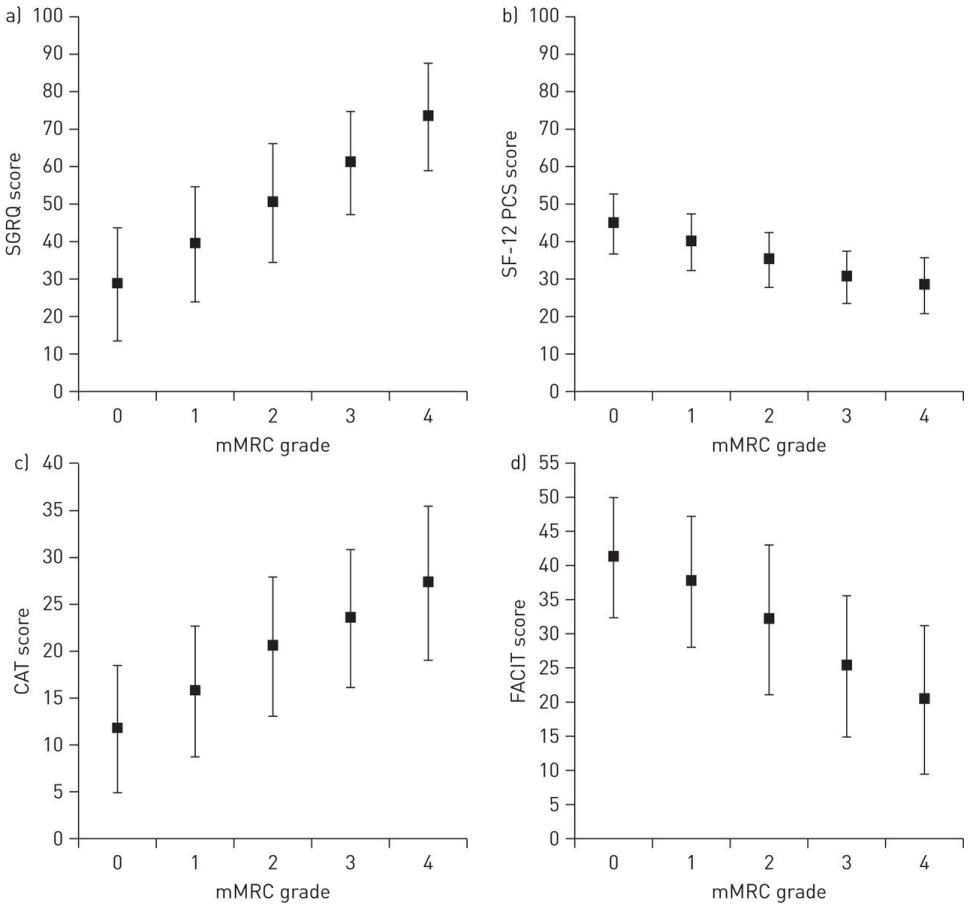

Figure 1.8: Association between the modified Medical Research Council dyspnea scale (mMRC) grade and health status measures in COPD populations (retrieved from Jones et al., (86). SGRQ = St. George's Respiratory Questionnaire, SF-12 PCS = Physical component score of the 12-item Short-form Health Survey, CAT = COPD Assessment Test, FACIT = Functional Assessment of Chronic Illness Therapy score.

Despite being an adequate tool to assess breathlessness burden in COPD, the mMRC has some notable limitations that are more prevalent in people with GOLD grade 1 (mild) and 2 (moderate) COPD where breathlessness is not yet as prevalent and/or disabling, at least not according to measurements made using the mMRC dyspnea scale (**Figure 1.6**) (3,86–88). GOLD and the Canadian Thoracic Society advocate for use of a mMRC dyspnea rating cut-off ≥2 (MRC ≥3) to classify an individual as having an abnormally high breathlessness burden. However, studies have demonstrated that even people with COPD and a mMRC dyspnea rating <2 (MRC <3) carry a significant symptomatic burden of disease (3,86,88). Indeed, Cherian et al. (79) showed that the vast majority (~93%) of Canadian adults with GOLD grade 1 or 2 COPD reported

MRC dyspnea ratings of 1 or 2. Jones et al. (86) reported that among 1,817 adults with COPD, a mMRC dyspnea score of 1 was associated with abnormally low COPD-related health status according to SGRQ and COPD Assessment Test (CAT) total scores. Such studies have led to questioning of the GOLD (and Canadian Thoracic Society) cut-off values for mMRC in differentiating between COPD patients with higher (mMRC ≥2 [MRC ≥3]) compared to lower breathlessness burden (mMRC <2 [MRC <3]). A multicenter study by Rhee et al. (89) showed that a mMRC dyspnea rating of 1 was better than a mMRC rating of 2 at differentiating between people with relatively normal (CAT total score <10) compared to poor COPD-related health status (CAT total score ≥10). Evidently, the mMRC dyspnea scale does not fully capture all the symptomatic manifestations of COPD, whether pulmonary and/or extra-pulmonary.

1.3.3.ii. COPD Assessment Test (CAT)

The CAT is a multidisciplinary subjective questionnaire consisting of eight unique questions focused on pulmonary (items 1-4) and extra-pulmonary symptoms (items 5-8), including cough (item 1), phlegm (item 2), chest tightness (item 3), breathlessness on exertion (item 4), activity limitation (item 5), confidence leaving home (item 6), sleep (item 8), and energy levels (item 8) (90) (**Table 1.3**). The eight sub-items are individually scored from 0-5 and summed to create a total (composite) score out of 40, where health status worsens as CAT total score approaches 40 (90). The CAT has emerged as an effective screening tool for COPD that is responsive to therapeutic interventions such as pulmonary rehabilitation, and that can be used to help identify the presence of co-morbidities in people with COPD (91–93).

The CAT may also help identify individuals with COPD at greater risk of exacerbations and hospitalizations. In one study, people with COPD with higher compared to lower CAT total scores were more likely to report a recent exacerbation (94). Kardos et al. (95) showed that people with COPD with frequent or severe exacerbations, relative to those who did not exacerbate, had worse long-term deterioration in health status indexed by a significantly higher CAT total score.

In addition, a study of 518 people with GOLD grades 1-4 (mild-very severe) COPD reported a significant negative correlation between CAT total score and each of the 6MWD and $V'O_{2peak}$ prior to the start of a pulmonary rehabilitation program (96). Pulmonary rehabilitation-induced improvements in the CAT total score were also significantly correlated with improvements in 6MWD. Other studies by Carvalho-Jr et al. (97) and Pisi et al. (98) in people with GOLD grades 1-4 COPD both reported a negative association between CAT total score and $V'O_{2peak}$. Overall, the CAT has proved to be a simple, reliable, and responsive tool to assess health status in COPD.

Table 1.3: COPD Assesment Test (CAT) (retrieved from Jones et al. (90)).			
For each item below, place a mark (x) in the box that best describes you currently. Be sure to only select one response for each question.			
Example: I am very happy.	0 1 2 3 4 5	I am very sad.	Score 1
I never cough.	0 1 2 3 4 5	I cough all the time.	
I have no phlegm (mucus) in my chest at all.	0 1 2 3 4 5	My chest is compeltely full of phlegm (mucus).	
My chest does not feel tight at all.	0 1 2 3 4 5	My chest feels very tight.	
When I walk up a hill or one flight of stairs I am not breathless.	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless.	
I am confident leaving my home despite my lung condition.	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition.	
I sleep soundly.	0 1 2 3 4 5	I don't sleep soundly because of my lung condition.	
I have lots of energy.	0 1 2 3 4 5	I have no energy at all.	
		Total Score:	

1.3.4. GOLD ABCD Assessment

Both GOLD and the Canadian Thoracic Society recommend that pharmacological treatment of COPD be guided by an individual's health status, breathlessness burden, and risk of exacerbation (3,27). As per GOLD's ABCD assessment tool, a CAT total score ≥10 and mMRC

dyspnea rating ≥2 (MRC ≥3) reflects poor health status and high breathlessness burden, respectively (3). According to the ABCD assessment tool (**Table 1.4)**, people with COPD in:

- GOLD group A have low exacerbation risk and good health status ***or*** low breathlessness burden.
- GOLD group B have low exacerbation risk and poor health status ***or*** high breathlessness burden.
- GOLD group C have high exacerbation risk and good health status ***or*** low breathlessness burden.
- GOLD group D have high exacerbation risk and poor health status ***or*** high breathlessness burden.

It is based on symptom burden and exacerbation risk groupings that therapy is guided. A detailed description of the treatment options is beyond the scope of this thesis, but presented in **Table 1.4**. Briefly, pharmacotherapy is less intensive for people with COPD in group A or C, and more intensive for people in group B or D. Individuals in group A would be prescribed a short acting β_2-agonist bronchodilator (SABA) and those in group C a long acting muscarinic agonist (LAMA). Whereas, people in group B would be prescribed a LAMA or long acting β_2-agonist bronchodilator (LABA) and those in group D a LAMA, or LAMA and LABA, or LABA and inhaled corticosteroid (ICS).

Table 1.4: GOLD ABCD Assessment Tool to guide Pharmacological Treatment of COPD (retrieved from GOLD 2021 (3)).		
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA ** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1 **or** CAT <10	mMRC ≥2 **or** CAT ≥10

GOLD = Global Initiative for Obstructive Lung Disease, CAT = COPD Assessment Test, mMRC = modified Medical Research Council scale, LAMA = Long-acting Muscarinic Agonist, LABA = Long-acting Beta-Agonist, ICS = Inhaled Corticosteroids.

Discordance between a CAT total score ≥10 and mMRC dyspnea rating ≥2 to guide pharmacotherapy can have a significant impact on the management of people with COPD due to misclassification of their treatment plan subsequent to misclassification of them being in GOLD group A, B, C or D (99). This discordance was highlighted by Kim et al. (100) in a study of 257 people with COPD, where: using the CAT total score criteria of ≥10 resulted in 23.3%, 21%, 8.2% and 47.1% of the participants being assigned to GOLD group A, B, C and D, respectively; and using the mMRC criteria of ≥2 resulted in 37.7%, 7%, 24.1% and 31.1% of the participants being assigned into GOLD groups A, B, C and D, respectively. The apparent discrepancy in GOLD group classification when using CAT or mMRC criteria risks under-identification of asymptomatic or intermittently symptomatic individuals who may be asymptomatic between exacerbations (101). Many of these individuals, who have GOLD grade 1 (mild) or 2 (moderate) COPD, may have early signs and symptoms of COPD that are not captured by the current mMRC dyspnea rating and/or CAT total score cut-off values advocated for use by GOLD (101,102) and the Canadian Thoracic Society (27). Therefore, the lack of agreement between CAT total score and mMRC dyspnea rating to categorize people into GOLD ABCD groups can risk missing or not capturing people for potentially effective therapeutic intervention, especially those people with

relatively asymptomatic GOLD grade 1 (mild) or 2 (moderate) COPD, which make up majority of the population of adults with COPD in Canada (2,79). Indeed, according to the results of Cherian et al. (79), the majority of these people with GOLD grade 1 or 2 COPD meet the criteria for GOLD group A (**Table 1.4**) because they (i) most often report CAT total scores <10 and/or mMRC dyspnea ratings 0-1 and (ii) have a low risk of exacerbation-like respiratory events. Additionally, ~75% of these people with GOLD grade 1 or 2 COPD did not report having received a prior physician diagnosis of COPD (~75.3%) nor were they taking any doctor prescribed respiratory medication(s) (79). Cardiopulmonary exercise testing might help to identify people with GOLD grade 1 or 2 COPD with pathophysiological abnormalities in exercise tolerance, ventilatory demand and breathing mechanics that might be otherwise overlooked by routine spirometry, and assessment of health status using CAT total score cut-off value of ≥10 and/or breathlessness burden using a mMRC dyspnea rating cut-off value of ≥2 (or MRC ≥3). An effort to improve COPD patient care with earlier and/or more aggressive therapeutic intervention(s) has the potential to decrease symptom burden, improve health status, and mitigate the risk of adverse long-term health outcomes, including exacerbations, hospitalizations and/or premature death.

1.4 *Added value of CAT sub-items*

Although the GOLD ABCD assessment tool is designed to help healthcare providers manage their patients with COPD, two of its core evaluative components - the CAT total score and mMRC dyspnea rating - may be unreliable. For instance, amongst people with GOLD grade 1 or 2, group A COPD, which, as previously discussed, make up the majority of the Canadian COPD population (1,2), there might be people different symptomatic phenotypes that need to be identified (e.g., people with higher vs. lower breathlessness [or higher vs. lower pulmonary symptom burden] burden but relatively preserved health status, as indicated by a CAT total score

<10) and that may respond differently to therapy. Recent studies have explored whether there is an added clinical value of using any one or combination of the CAT's eight sub-items (see *Section 1.3.3.ii* and **Table 1.3**) in the assessment of people with COPD or at-risk of developing COPD.

Raghavan et al. (103) showed that the CAT breathlessness sub-item score (**Table 1.3**), not the CAT total score, helped to identify individuals from the general population with a high probability of having COPD and for whom post-bronchodilator spirometry is recommended to confirm (or deny) a diagnosis of COPD. Specifically, their cross-sectional analysis of the Canadian Obstructive Lung Disease study divided a sub-set of participants into groups of people with (*n*=51) or without (*n*=481) spirometrically-defined COPD. A 3-item COPD screening (or case finding) algorithm was developed that incorporated use of the CAT breathlessness sub-item score in association with age and smoking status (**Figure 1.9**). Of note, the CAT breathlessness sub-item score was more sensitive in identifying people with COPD according to post-bronchodilator spirometry than the mMRC dyspnea score. The authors suggested that this might reflect (i) a greater discriminatory value of the CAT breathlessness sub-item score than mMRC dyspnea score among people with only mild airway obstruction, and (ii) the broader standardized task categories of the mMRC dyspnea scale (**Table 1.2**) compared to the CAT breathlessness sub-item, which is focused specifically on burden of breathlessness when walking up a hill or one flight of stairs (**Table 1.3**). In addition, the 3-item tool developed in this study was statistically impressive with an Area Under the Receiver Operating Characteristic Curve (AUC) of 0.77, sensitivity of 77%, and a negative predictive value of 96.5% in predicting COPD (103).

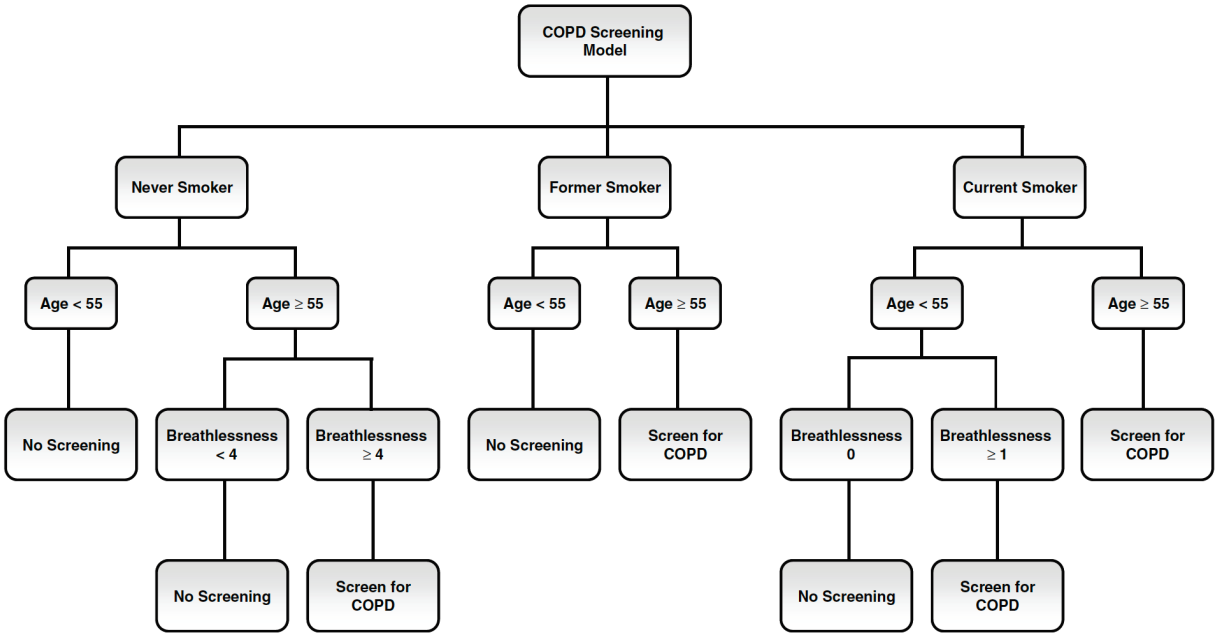

Figure 1.9: 3-item case-finding tool to screen for COPD (Retrieved from Raghavan et al. (103))

Jan et al. (104) similarly assessed the value of the CAT and each of its sub-items in screening for people with COPD among a large population of dairy farmers who are more likely to be impacted by occupation hazards of farming than cigarette smoke. In this study, COPD was diagnosed by post-bronchodilator spirometry after a health check-up in participants reporting chronic cough, bronchitis, wheezing and/or mMRC dyspnea score ≥1. The authors developed a 3-item screening model that accurately predicted the presence of COPD based on the presence of active smoking, years on-farm, and CAT breathlessness sub-item score ≥2. Similar to Raghavan et al. (103), the CAT breathlessness sub-item emerged amongst CAT total score and all other CAT sub-items as a unique identifier of undiagnosed COPD within this population of dairy farmers. Another interesting finding from Jan et al. (104) was that the other three pulmonary sub-items (cough, phlegm, chest tightness) individually performed well (AUC=0.86-0.88 for pulmonary sub-items versus AUC=0.87 for CAT total score) in identifying dairy farmers with undiagnosed COPD. This speaks to the potential importance of using CAT pulmonary symptoms sub-item scores whilst screening people for COPD.

Kart et al. (105) evaluated the utility of spirometry and the CAT in detecting COPD in a group of 648 ever-smokers aged >40 years with no known history of chest disease, including COPD. Interestingly, in that study, each of the four CAT pulmonary symptom sub-item scores were significantly higher in people with (n=110) compared to without COPD (n=538) following the screening procedure for COPD: cough, 2 (1-3) vs. 1 (0-2); phlegm, 2 (0-3) vs. 1 (0-3); chest tightness, 3 (1-4) vs. 2 (0-3); and breathlessness, 4 (3-5) vs. 3 (2-4). In contrast, none of the four CAT extra-pulmonary symptom sub-item scores were significantly different between groups: activity limitation, 1 (0-3) vs. 1 (0-3); confidence leaving home, 0 (0-0) vs. 0 (0-0); sleep, 0 (0-1) vs. 0 (0-2); and energy, 3 (1-5) vs. 3 (1-4). The collective results of studies by Raghavan et al. (103), Jan et al. (104) and Kart et al. (105) support the use of CAT pulmonary symptom sub-item scores (especially the breathlessness sub-item score) in screening people for COPD.

A cross-sectional study by Gil et al. (106) that included 815 people with COPD characterized as having high (CAT total score <10), medium (10≤ CAT total score <20) or low health status (CAT total score ≥20), evaluated the weight of each CAT sub-item score among the total score. As illustrated in **Figure 1.10**, the CAT total score <10 group presented with relatively higher scores on the four pulmonary sub-items (CAT sub-items 1-4; **Table 1.3**) than the four extra-pulmonary sub-items (CAT sub-items 5-8; **Table 1.3**). As the CAT total score increased (health status decreased), the relative contribution of pulmonary and extra-pulmonary sub-item scores progressively decreased and increased, respectively (**Figure 1.10**). Importantly, the CAT breathlessness sub-item was the most highly scored (predominant) of the eight sub-items in each of the three different CAT total score groups. Based on these observations, it is reasonable to suggest that healthcare providers should focus greater attention on CAT pulmonary sub-item scores, particularly the breathlessness sub-item score, which appear to drive the CAT total score of people with relatively normal health status (i.e., CAT total score <10) who are also people more likely to have GOLD grade 1 or 2 COPD (79), which, again, constitute the majority of the population of Canadian adults with COPD (1,2).

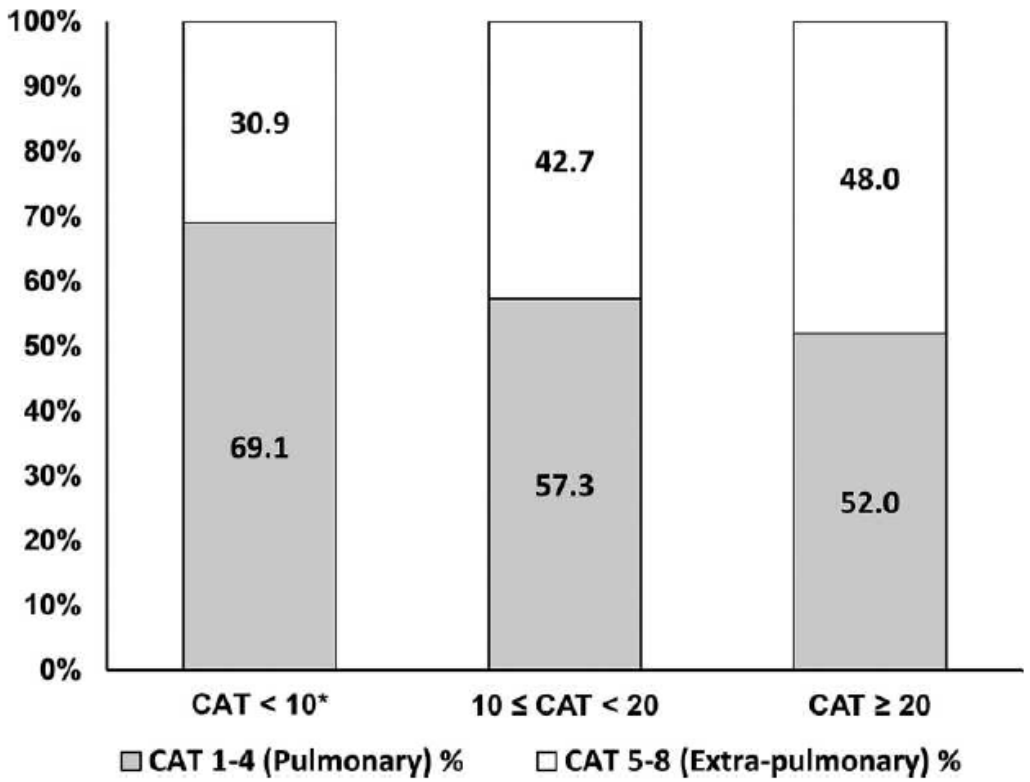

Figure 1.10. Relative (%) contribution of the CAT pulmonary sub-items (CAT 1-4) and CAT extra-pulmonary sub-items (CAT 5-8) to the CAT total score, according to low (0≤CAT<10), medium (10≤CAT<20), and high (20≤CAT≤40) symptom burden (retrieved from Gil et al. (106)). CAT = COPD Assessment Test.

A clinical trial of 2,270 people with GOLD grade 1 (mild), 2 (moderate) or 3 (severe) COPD by Von Siemens et al. (107) reported a significant positive correlation between the percentage of emphysema on chest CT scan and each of the CAT breathlessness and CAT physical activity limitation sub-item scores, but not the CAT total score. Von Siemens et al. (107) also reported a significant negative correlation between FEV_1%predicted and each of the CAT total score, CAT breathlessness sub-item score, and CAT physical activity limitation sub-item score.

Martinez et al. (108) assessed the importance of the four CAT pulmonary sub-items (vs. the CAT total score) in identifying people at risk of exacerbation-like respiratory events among 880 adults with a history of cigarette smoke exposure but otherwise normal spirometry. They found that a CAT pulmonary symptoms sub-item cluster score ≥7 out of 20 best predicted

exacerbation-like respiratory events and poor health status (an indicated by a CAT total score ≥10) after 12-months follow-up. Specifically, a CAT pulmonary symptoms sub-item cluster cut-off value of ≥7 identified 88.5% of the participants with a total CAT score of ≥10 (poor health status). Within this analysis, the groups of people with a CAT total score ≥10 (n=456) and a CAT pulmonary symptoms sub-item cluster score of ≥7 (n=403) had similar demographic and clinical characteristics, including: frequency of comorbidities and proportion of people with mMRC dyspnea rating ≥2; FEV_1% predicted; 6MWD; and mean SGRQ and CAT total scores (108). These results suggested that the four CAT pulmonary symptom sub-items (**Table 1.3**) may be valuable in helping to identify people at-risk for the development of COPD with impaired exercise tolerance, chronic and disabling breathlessness, and poor health status.

In light of the above, it is reasonable to postulate that two individuals with COPD that share otherwise identical physical and clinical characteristics, including CAT total scores and mMRC dyspnea scores, may not suffer from the same degree and/or type of symptom burden nor the same underlying pathophysiological abnormalities in pulmonary function (beyond routine spirometry) and functional (exercise) capacity based on their differential responses to the eight CAT sub-items. Consider, for example, individuals A and B in **Figure 1.11** with the same sex, age, body mass index, spirometric and plethysmographic lung function test findings, mMRC dyspnea score, CAT total score, and history of exacerbation-like respiratory events. Individual A's CAT total score of 8 reflects the presence of pulmonary symptoms, whereas individual B's CAT total score of 8 reflects the presence of extra-pulmonary symptoms. In the context of GOLD's ABCD classification system, it remains unclear whether the pathophysiological manifestations of COPD differ between these two otherwise identical individuals with GOLD grade 1, group A COPD. The collective results of Raghavan et al. (103), Jan et al. (104), Kart et al. (105), Gil et al. (106), Von Siemens et al. (107) and Martinez et al. (108) support the hypothesis that, despite having the same CAT total score and mMRC dyspnea rating, the pathophysiological consequences of GOLD grade 1 (mild), group A COPD likely differ between these two individuals.

It stands to reason that these two individuals might also respond differently to therapeutics, such as inhaled bronchodilators.

Figure 1.11: Despite their similarities, are these two individuals with GOLD Grade 1 COPD the same?

	CAT 1 "cough"	CAT 2 "phlegm"	CAT 3 "chest tightness"	CAT 4 "dyspnea"	CAT 5 "home activity"	CAT 6 "confidence leaving home"	CAT 7 "sleep disturbance"	CAT 8 "lack of energy"	**Total CAT score**
Score	2	2	2	2	0	0	0	0	**8**

Individual A: 45-year-old male; FEV_1%predicted = 80; FEV_1/FVC = 0.65; mMRC dyspnea rating = 1; cigarette pack-years = 15; body mass index = 28 kg/m^2; exacerbation-like respiratory events in preceding 12 months = 0.

	CAT 1 "cough"	CAT 2 "phlegm"	CAT 3 "chest tightness"	CAT 4 "dyspnea"	CAT 5 "home activity"	CAT 6 "confidence leaving home"	CAT 7 "sleep disturbance"	CAT 8 "lack of energy"	**Total CAT score**
Score	0	0	0	0	2	2	2	2	**8**

Individual B: 45-year-old male; FEV_1%predicted = 80; FEV_1/FVC = 0.65; mMRC dyspnea rating = 1; pack-years = 15; body mass index = 28 kg/m^2; exacerbation-like respiratory events in preceding 12 months = 0.

There is a pressing need for a clinically relevant method – beyond reliance on spirometry, CAT total score, and mMRC dyspnea ratings – to facilitate earlier identification of impaired exercise tolerance (abnormally low $V'O_{2peak}$) among people with GOLD grade 1 or 2 COPD, who make up the majority of the Canadian COPD population (1,2). Such a method might lend itself to more precise phenotyping and perhaps also more individualized/personalized targeted therapies. It remains unknown whether individual and/or grouped CAT sub-item scores, particularly the breathlessness sub-item score and pulmonary symptoms sub-item cluster score, carry useful

information regarding the existence of pathophysiological abnormalities in CPET outcomes (e.g., $V'O_{2peak}$) in people with GOLD grade 1 or 2 COPD. Specifically, no study has assessed whether any one or combination of CAT sub-item scores might help identify abnormally low $V'O_{2peak}$ among people with GOLD grade 1 or 2, group A COPD.

1.5 Objective and hypothesis

In the context of the GOLD ABCD classification system/assessment tool (3), the **objective** of this study is to assess whether CAT breathlessness sub-item scores and/or CAT pulmonary symptoms sub-item cluster scores are associated with abnormal CPET outcomes (specifically $V'O_{2peak}$) among people with GOLD grade 1 or 2, group A COPD.

We **hypothesized** that people with GOLD grade 1 or 2, group A COPD with (i) a higher compared to lower CAT breathlessness sub-item score or (ii) a higher compared to lower CAT pulmonary symptoms sub-item cluster score will have greater abnormalities in exercise tolerance (lower $V'O_{2peak}$), exertional symptoms (higher breathlessness/ventilation relationships), pulmonary gas exchange efficiency (abnormally high $V'_E/V'CO_2$ nadir, greater exercise-induced oxyhemoglobin desaturation), and the behaviour of dynamic operating lung volumes (more prevalent and severe dynamic lung hyperinflation with greater critical inspiratory constraints).

Chapter 2:

2.1. ABSTRACT

It remains unknown whether chronic obstructive pulmonary disease (COPD) Assessment Test (CAT) sub-items, particularly the breathlessness and pulmonary symptoms sub-items, carry useful information regarding the existence of impaired exercise tolerance among people with COPD. This retrospective study used data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study to test the hypothesis that people with Global Initiative for Obstructive Lung Disease (GOLD) grade 1 (mild) or 2 (moderate), group A COPD with (i) higher compared to lower CAT breathlessness sub-item scores or (ii) higher compared to lower CAT pulmonary symptom sub-items cluster scores have lower exercise tolerance (peak rate of O_2 consumption [$V'O_{2peak}$]) in association with greater abnormalities in exercise physiological and perceptual responses. To this end, we compared physiological and perceptual responses at the symptom-limited peak of incremental cardiopulmonary cycle exercise testing amongst 310 people with GOLD grade 1 (n=209) or 2 (n=101), group A COPD with (i) CAT breathlessness sub-item score of 0 (n=154) versus ≥1 out of 5 (n=156) or (ii) CAT pulmonary symptoms sub-item cluster score of <5 (n=247) versus ≥5 out of 20 (n=63). The optimal cut-point for each of the CAT breathlessness sub-item score and the CAT pulmonary symptoms sub-item cluster score was one that best predicted (according to the Youden Index) an individual with GOLD grade 1 or 2, group A COPD of having an abnormally low $V'O_{2peak}$, defined as <85% of the predicted reference value. We found that people with a higher compared to lower CAT breathlessness sub-item score or a higher compared to lower CAT pulmonary symptoms cluster score had broadly similar baseline characteristics (including pulmonary function) but nevertheless presented with significantly lower exercise tolerance ($V'O_{2peak}$) in association with greater critical dynamic inspiratory constraints and exertional breathlessness. From a clinical management perspective, and although additional research is needed, the results our study suggest that a CAT breathlessness sub-item score ≥1

or a CAT pulmonary symptoms sub-item cluster score ≥5 might help healthcare providers identify people with GOLD grade 1 or 2, group A COPD with clinically relevant exercise intolerance as manifested by greater critical inspiratory constraints and exertional breathlessness that might otherwise be overlooked and that might have a preferential response to available inhaled respiratory medication(s).

2.2. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by pathophysiological abnormalities in breathing mechanics and pulmonary gas exchange efficiency that combine to increase exertional breathlessness and decrease exercise capacity, as evidenced by an abnormally low peak rate of O_2 consumption ($V'O_{2peak}$) on symptom-limited incremental cardiopulmonary exercise testing (CPET) (58,110–114). It is now well established that low $V'O_{2peak}$ is an independent predictor of premature death in COPD (42–45). It follows that identifying simple and clinically relevant methods for early identification of abnormally low $V'O_{2peak}$ among people with COPD has the potential to improve patient care and clinical outcomes, including survival.

Among Canadian adults aged ≥40 years, the population-based prevalence of spirometrically-defined COPD (post-bronchodilator ratio of forced expiratory volume in 1-sec to forced vital capacity [FEV_1/FVC] <0.70 (3,27) is estimated at ~16-17% (1,2)). Importantly, ~92-93% of this large population meet the Global Initiative for Obstructive Lung Disease (GOLD) criteria for grade 1 (mild) or grade 2 (moderate) COPD (1,2), i.e., post-bronchodilator FEV_1 ≥50% predicted (3).

Both the GOLD (3) and Canadian Thoracic Society (CTS) (27) recommend that pharmacological treatment of COPD be guided by an individual's health status, breathlessness burden, and risk of exacerbation. Both the GOLD and CTS classify people as: (1) having relatively low and high health status impairment if their COPD assessment test (CAT (90)) total score is <10 and ≥10, respectively; (2) having relatively low and high breathlessness burden if their modified Medical Research Council (mMRC (84)) dyspnea scale rating is 0-1 and ≥2, respectively; (3) being at low risk of an exacerbation if they had ≤1 moderate exacerbation-like respiratory event in the last year that did not require hospitalization or emergency department visit; and (4) being at high risk of an exacerbation if they had ≥2 moderate exacerbation-like respiratory events

or ≥1 severe exacerbation-like respiratory event requiring hospitalization or emergency department visit (3,27). According to the GOLD "ABCD" assessment tool, people with COPD meeting the criteria for: *group A* have low exacerbation risk and relatively low health status impairment or relatively low breathlessness burden; *group B* have low exacerbation risk and relatively high health status impairment or relatively high breathlessness burden; *group C* have high exacerbation risk and relatively low health status impairment or relatively low breathlessness burden; and *group D* have high exacerbation risk and relatively high health status impairment or relatively high breathlessness burden (3). The results of a recent report by Cherian et al. (79) suggest that the vast majority of Canadian adults from the general population with GOLD grade 1 or 2 COPD meet the criteria for *group A*, with: 93% reporting a MRC dyspnea score of 1-2 (equivalent to a mMRC dyspnea score 0-1); median CAT total scores <10 (4.0 and 7.0 for men with GOLD grade 1 and 2 COPD, respectively; and 5.0 and 9.0 for women with GOLD grade 1 and 2 COPD, respectively); and ~92% having low exacerbation risk. Additionally, among these people with GOLD grade 1 or 2 COPD, ~75% reported not having received a prior physician diagnosis of COPD and ~67% were not taking any doctor prescribed respiratory medication(s) (79). Notwithstanding the apparently high population-based prevalence of GOLD grade 1 or 2, group A COPD, studies rarely focus solely on this group of adults, presumably because they are not often part of the patient population seen in clinical settings. Therefore, very little is known about the health status, symptom burden, and exercise capacity of adults with GOLD grade 1 or 2, group A COPD. Addressing this knowledge gap is important to improving both patient-centered and clinical outcomes *via* more precious phenotyping and perhaps also more individualized/personalized targeted therapies.

A growing body of evidence suggests that an individuals' response to selected CAT sub-items, particularly the breathlessness sub-item and sum of the four pulmonary symptom sub-items (cough, phlegm, chest tightness, breathlessness) (90), carry additional clinical information beyond the CAT total score among people with or at high-risk for COPD (103–108,115). For

instance, Raghavan et al. (103) showed that the CAT breathlessness sub-item score, not the CAT total score (or MRC dyspnea rating), helped to identify adults aged >40 years from the general population with a high probability of having COPD and for whom post-bronchodilator spirometry is recommended. A similar study by Jan et al. (104) found that the CAT breathlessness sub-item score emerged amongst the CAT total score and each of the seven other CAT sub-item scores as a unique predictor of undiagnosed COPD in a large population of dairy farmers. A cross-sectional study by Gil et al. (106), including 815 people with COPD characterized as having low (CAT total score <10), medium (10≤ CAT total score <20) or high (CAT total score ≥20) health status impairment, evaluated the weight of each CAT sub-item score among the CAT total score. In that study, the CAT total score <10 group presented with relatively higher scores on the four pulmonary symptom sub-items than the four extra-pulmonary symptom sub-items (activity limitation, confidence, sleep, energy); and the CAT breathlessness sub-item was the most highly scored of the eight sub-items in each of the low, medium and high health status impairment groups. Kart et al. (105) evaluated the utility of spirometry and the CAT in detecting COPD in a group of 648 ever-smokers aged >40 years with no known history of chest disease, including COPD. In that study, each of the four CAT pulmonary symptom sub-item scores (but not the four extra-pulmonary symptom sub-item scores) were significantly higher in people with (n=110) compared to without COPD (n=538). A clinical trial of 2,270 people with COPD by Von Siemens et al. (107) reported a significant positive correlation between the percentage of emphysema on chest computed tomography scan and each of the CAT breathlessness and CAT activity limitation sub-item scores, but not the CAT total score. Martinez et al. (108) assessed the importance of the four CAT pulmonary sub-items (relative to the CAT total score) in identifying ever-smokers with preserved lung function at higher risk for poor respiratory outcomes. They found that a CAT pulmonary symptoms sub-item cluster score ≥7 out of 20 best predicted exacerbation-like respiratory events and high health status impairment (defined as a CAT total score ≥10) after 12-months follow-up. Specifically, a CAT pulmonary symptoms sub-item cluster score cut-off value

of ≥7 identified 88.5% of the participants with a CAT total score of ≥10. Martinez et al. (108) also found that the groups of people with a CAT total score ≥10 (n=456) and CAT pulmonary symptoms sub-item cluster score ≥7 (n=403) had similar demographic and clinical characteristics, including: frequency of comorbidities; proportion of people with mMRC dyspnea rating ≥2; FEV_1% predicted; six-minute walk distance (exercise capacity); CAT total score; and St. George's Respiratory Questionnaire score. Finally, a study of 148 treatment-naïve adults newly diagnosed COPD by Kim et al. (115) recently reported that short-term (~6 months) bronchodilator therapy had no effect on CAT total score, but was associated with significant reductions (improvement) in CAT phlegm, chest tightness, and breathlessness sub-item scores. The collective results of these studies suggest that, among people with COPD reporting relatively low or high health status impairment (CAT total score <10 or ≥10, respectively), an individual's CAT breathlessness sub-item score or their CAT pulmonary symptoms sub-item cluster score may help to identify abnormally low exercise capacity.

In the context of the GOLD "ABCD" assessment tool, the objective of this analysis of the Canadian Cohort Obstructive Lung Disease study population (116) was to assess whether CAT breathlessness sub-item scores and/or CAT pulmonary symptoms sub-item cluster scores are associated with abnormally low $V'O_{2peak}$ among adults with GOLD grade 1 or 2, group A COPD recruited from the general (non-clinical) population. We hypothesized that people with GOLD grade 1 or 2, group A COPD with (i) higher compared to lower CAT breathlessness sub-item scores or (ii) higher compared to lower CAT pulmonary symptoms sub-item cluster scores would have lower $V'O_{2peak}$ (exercise capacity) in association with greater pathophysiological abnormalities in dynamic breathing mechanics, pulmonary gas exchange efficiency, and exertional breathlessness.

2.3. METHODS

This study was a retrospective analysis of participant data collected between November 2009 and August 2015 as part of the Canadian Cohort Obstructive Lung Disease (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 (116) (ClinicalTrials.gov Identifier: NCT00920348); further methodologic details have been published elsewhere (116). 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

Participants who completed a CPET as part of the initial CanCOLD cross-sectional assessment phase (*Visit 1*) were considered for inclusion in this study (n=1,367). Participants were included if they met the following criteria for GOLD grade 1 or 2, group A COPD (117): post-bronchodilator FEV_1/FVC <0.70; post-bronchodilator FEV_1 ≥50% predicted (118); COPD Assessment Test (CAT) total score <10 or Medical Research Council (MRC) dyspnea rating 1-2; and 0 or 1 moderate exacerbation-like respiratory events (not leading to hospital admission) in the 12-months after CanCOLD *Visit 1*. Participants were excluded if they: had invalid/missing CPET data; had a post-bronchodilator FEV_1/FVC ≥0.70; were missing post-bronchodilator spirometry data; stopped exercise for non-physiological reason(s); were missing data for the rate of O_2 consumption at the symptom-limited peak of CPET ($V'O_{2peak}$); were missing CAT data; or met the criteria for GOLD grade 1 or 2, group B, C or D COPD (117), including: post-bronchodilator FEV_1/FVC <0.70; post-bronchodilator FEV_1 ≥50% predicted (118); CAT total score ≥10 or MRC dyspnea rating ≥3; and ≥2 moderate exacerbation-like respiratory events or ≥1 exacerbation-like respiratory event leading to hospitalization in the 12-months after CanCOLD *Visit 1*.

2.3.2. Measures

As part of CanCOLD, at *Visit 1*, participants had their body height and body mass assessed, and completed: a structured interview with a trained researcher, where they self-reported sociodemographic and health information; the MRC dyspnea scale to assess breathlessness burden (84); the CAT to assess COPD-related health status (90); and spirometry (performed 15 minutes 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 with automated equipment. Pulmonary function parameters were expressed as a percentage of predicted reference values (118–120). The incidence of exacerbation-like respiratory events were assessed every 3 months by telephone or online questionnaires for a period of 12 months following CanCOLD *Visit 1*. Exacerbation-like respiratory events were operationally defined as: *'symptom-based'*, requiring a change in at least one major symptom (breathlessness, sputum purulence, sputum volume) that lasts ≥48 hours; or *'event-based'*, requiring a change of at least one major symptom that lasts ≥48 hours and use of antibiotics and/or systemic corticosteroids or health services. A *'mild'* exacerbation-like respiratory event was defined as an event treated with a short-acting bronchodilator only. A *'moderate'* exacerbation-like respiratory event was defined as an event treated with a short-acting bronchodilator plus an antibiotic and/or oral corticosteroid. A *'severe'* exacerbation-like respiratory event was defined as an event (i) requiring hospitalization or visit to the emergency room and/or (ii) associated with acute respiratory failure.

2.3.3. Cardiopulmonary Cycle Exercise Testing (CPET)

CPET was performed in accordance with established guidelines (121,122) 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. Nasal passages were occluded with 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, and participants rated the intensity of their perceived breathlessness and leg discomfort using the 0-10 modified Borg scale (123) during the pre-exercise baseline period, every 2 minutes during exercise, and at peak exercise.

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 (124), 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-second 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. (109).

2.3.4. Statistical analysis

A Receiving Operating Curve (ROC) analysis was first performed to identify the optimal cut-point for each of the CAT breathlessness sub-item score (Item 4, scored from 0-5 (90)) and

the CAT pulmonary symptoms sub-item cluster score (Sum of items 1-4 [cough, phlegm, chest tightness, and breathlessness)], scored from 0-20 (90)) that best predicted (according to the Youden Index) an individual with GOLD grade 1 or 2, group A COPD of having an abnormally low $V'O_{2peak}$, defined as <85% of the predicted reference value ((109)) according to recommendations for CPET interpretation by the European Respiratory Society (122), and the American Thoracic Society and American College of Chest Physicians (121). The CAT breathlessness sub-item cut-point and CAT pulmonary symptoms sub-item cluster cut-point was then used to classify participants with GOLD grade 1 or 2, group A COPD as having: higher or lower breathlessness burden (CAT breathlessness sub-item score of 0 or ≥1 out of 5, respectively); and higher or lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score of <5 or ≥5 out of 20, respectively). In this study, the sum of the first four CAT sub-items (cough, phlegm, chest tightness, and breathlessness) was used to assess for pulmonary symptom burden based on the results of: Martinez et al. (108), who found that the sum of the first four CAT sub-items identified symptomatic ever-smokers with preserved spirometry at higher risk for poor respiratory outcomes; and Gil et al. (106), who found that the sum of the first four CAT sub-items accounted for 69.1% of the CAT total score among people with COPD reporting a CAT total score <10.

Participants 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 T-test or Wilcoxon-Mann-Whitney 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: age, sex, body mass index (BMI), comorbidities (prior physician diagnosis of asthma, any musculoskeletal comorbidity, and any cardiovascular disease comorbidity, including hypertension), cigarette pack years, and FEV_1 expressed as a

percent of the predicted reference value (FEV_1%predicted). Outcome variables reported as a percentage of the 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 310 met our eligibility criteria and were included in our analyses (**Figure 2.1**).

According to the results of the ROC analyses, a CAT breathlessness sub-item cut-point of ≥1 (Area Under the ROC Curve (AUC)=0.574, Sensitivity=0.57, Specificity=0.55) and a CAT pulmonary symptoms sub-item cluster cut-point of ≥5 out of 20 (AUC=0.551, Sensitivity=0.25, Specificity=0.83) best predicted an individual with GOLD grade 1 or 2, group A COPD of having a $V'O_{2peak}$ <85% predicted (**Figure 2.2**). Using the CAT breathlessness sub-item cut-point, 154 (49.7%) participants were classified as having lower breathlessness burden (CAT breathlessness sub-item score=0) and 156 (50.3%) participants were classified as having higher breathlessness burden (CAT breathlessness sub-item score ≥1) (**Figure 2.1**). Using the CAT pulmonary symptoms sub-item cluster cut-point, 247 (79.7%) participants were classified as having lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score <5) and 63 (30.3%) participants were classified as having higher pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score ≥5) (**Figure 2.1**).

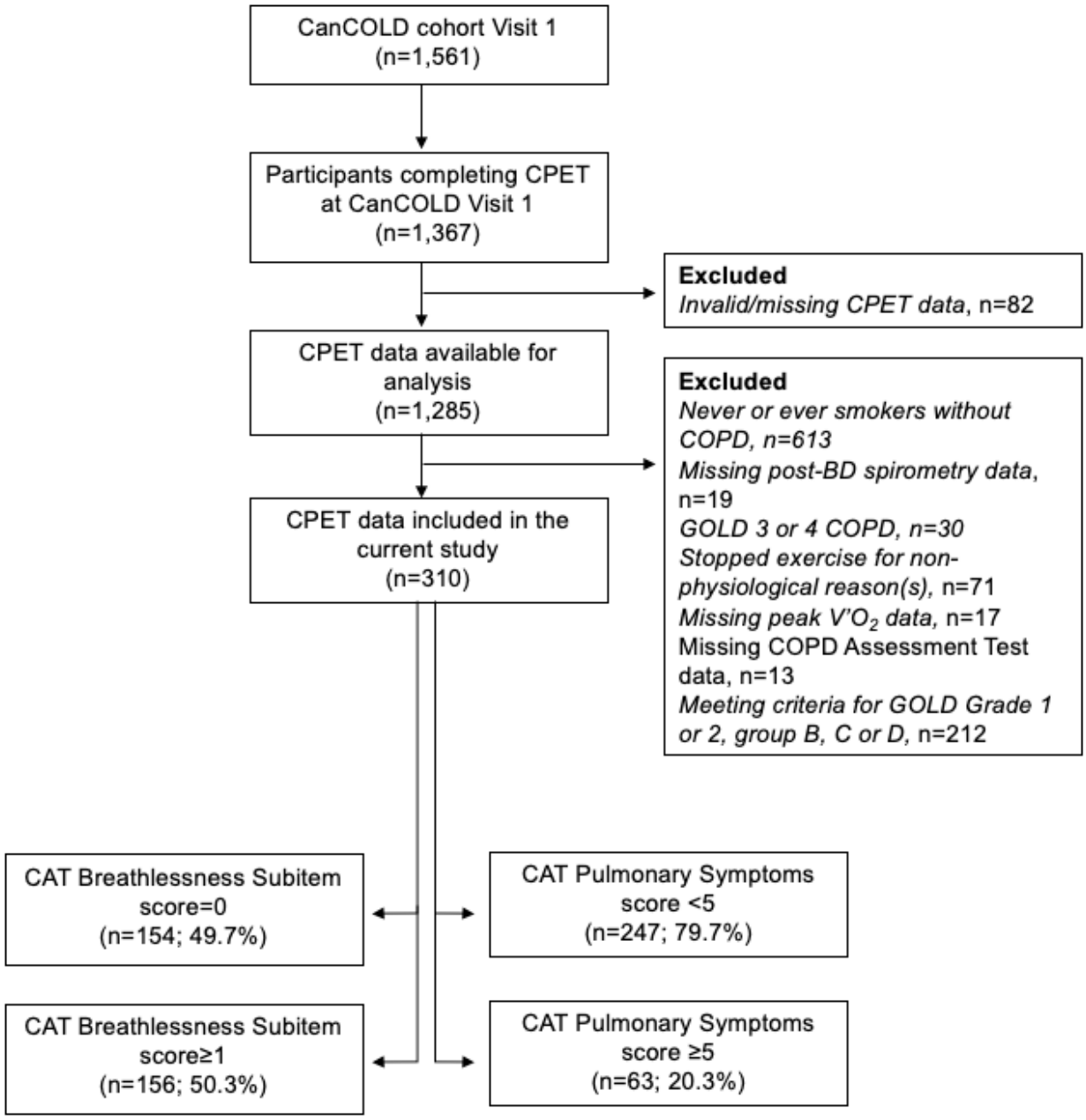

Figure 2.1. Study flowchart. CanCOLD: Canadian Cohort Obstructive Lung Disease; CPET: cardiopulmonary exercise testing; COPD: chronic obstructive pulmonary disease; BD: bronchodilator; FEV_1/FVC: ratio of forced expiratory volume in 1-sec to forced vital capacity; $V'O_2$: rate of oxygen consumption; GOLD: Global Initiative for Obstructive Lung Disease, MRC: Medical Research Council dyspnea scale; CAT: COPD Assessment Test.

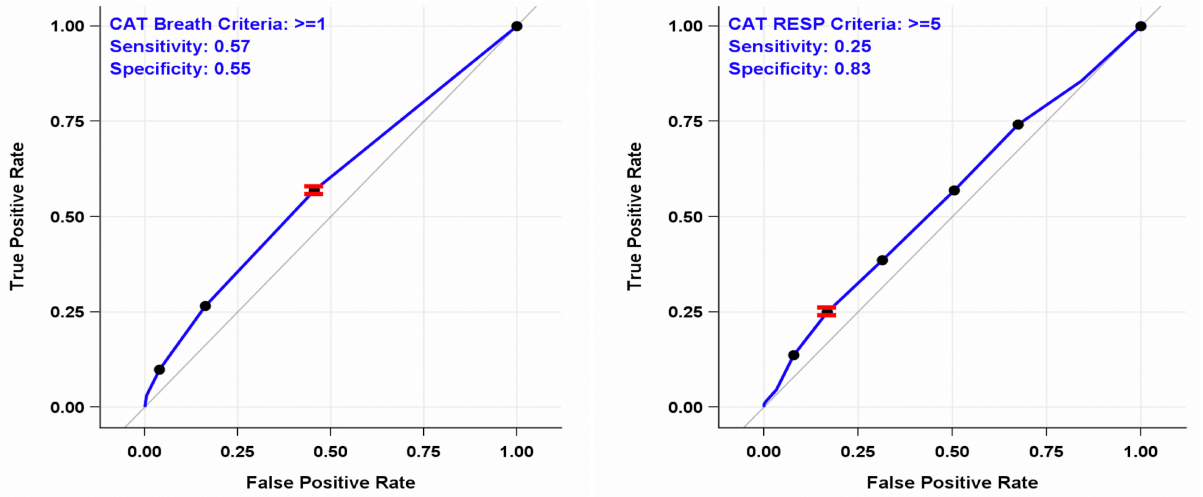

Figure 2.2. Receiver Operating Curves to identify the optimal cut-point for CAT breathlessness sub-item score (*left*) and CAT pulmonary symptoms sub-item cluster score (*right*) that best predicted an individual with GOLD grade 1 or 2, group A COPD of having a $V'O_{2peak}$ <85% of the predicted reference value. CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; $V'O_{2peak}$: rate of oxygen consumption at the symptom-limited peak of incremental cardiopulmonary cycle exercise testing; GOLD: Global Initiative for Obstructive Lung Disease.

2.4.1. Comparison of participants with higher compared to lower breathlessness burden (CAT breathlessness sub-item score of 0 versus ≥1)

2.4.1.i. Baseline participant characteristics

Compared to the lower breathlessness burden group, the higher breathlessness burden group had: a lower proportion of males; a slightly greater BMI; a lower proportion of people with GOLD grade 1 COPD and higher proportion of people with GOLD grade 2 COPD; a greater history of cigarette smoke exposure; a higher proportion of people with a prior physician diagnosis of COPD or asthma; and a higher proportion of people currently using any respiratory medication (**Table 2.1**).

Table 2.1. Comparison of baseline participant characteristics between people with GOLD grade 1 or 2, group A COPD with lower breathlessness burden (CAT Breathlessness sub-item score=0) compared to higher breathlessness burden (CAT Breathlessness sub-item score ≥1)

	Lower Breathlessness Burden (n=154)	Higher Breathlessness Burden (n=156)	P value
Age (years)	67.0 [15.0]	67.0 [11.0]	0.532
Male sex	115 (74.7)	86 (55.1)	**<0.001**
BMI (kg/m^2)	26.0 [5.3]	26.9 [6.0]	**0.022**
GOLD grade 1 COPD	116 (75.3)	93 (59.6)	**0.003**
GOLD grade 2 COPD	38 (24.7)	63 (40.4)	**0.003**
Never smoker (n=113)	62 (40.3)	51 (32.7)	0.166
Ex-smoker (n=160)	72 (46.8)	88 (56.4)	0.089
Current smoker (n=37)	20 (13.0)	17 (10.9)	0.570
Cigarette pack years*	5.2 [29.4]	14.3 [38.8]	**0.043**
Prior physician Dx of COPD	16 (10.4)	38 (24.4)	**0.001**
Prior physician Dx of asthma	30 (19.5)	44 (28.2)	0.072
Any MSK	70 (45.5)	79 (50.6)	0.361
Any CVD	74 (48.1)	71 (45.5)	0.654
Any current respiratory medication use	26 (16.9)	50 (32.1)	**0.002**

Data are presented as median [IQR] or frequency (n (%)). BMI: body mass index; GOLD: Global Initiative for Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; Dx: diagnosis; MSK: musculoskeletal; CVD: cardiovascular disease.

*Cigarette pack years = number of packs of cigarettes smoked per day (20 cigarettes/pack) x number of years the participant has smoked.

2.4.1.ii. Health status, breathlessness burden, and exacerbation-like respiratory events

Compared to the lower breathlessness burden group, the higher breathlessness burden group had: a higher CAT total score; higher scores for CAT sub-items 3 (chest tightness), 4 (breathlessness), 5 (activity limitation), 6 (confidence) and 8 (energy); higher CAT pulmonary symptoms sub-item cluster and extra-pulmonary symptoms sub-item cluster scores; and a higher MRC dyspnea rating, with a lower proportion of people reporting MRC dyspnea scores of 1 and a higher proportion of people reporting MRC dyspnea scores of 2 (**Table 2.2**).

Table 2.2. Comparison of symptom outcomes and exacerbation-like respiratory events between people with GOLD grade 1 or 2, group A COPD with lower breathlessness burden (CAT Breathlessness sub-item score=0) compared to higher breathlessness burden (CAT Breathlessness sub-item score ≥1)

	Lower Breathlessness Burden (n=154)	Higher Breathlessness Burden (n=156)	P value
CAT total score (0-40)	2.0 [4.0]	5.0 [3.0]	**<0.001**
Item 1, Cough score (0-5)	1.0 [2.0]	1.0 [0.0]	0.145
Item 2, Phlegm score (0-5)	0.0 [1.0]	0.0 [1.0]	0.382
Item 3, Chest tightness score (0-5)	0.0 [0.0]	0.0 [0.0]	**<0.001**
Item 4, Breathlessness score (0-5)	0.0 [0.0]	1.0 [1.0]	**<0.001**
Item 5, Activity limitation score (0-5)	0.0 [0.0]	0.0 [0.0]	**<0.001**
Item 6, Confidence score (0-5)	0.0 [0.0]	0.0 [0.0]	**0.004**
Item 7, Sleep (0-5)	0.0 [0.0]	0.0 [0.0]	0.637
Item 8, Energy score (0-5)	1.0 [1.0]	1.0 [2.0]	**0.003**
CAT pulmonary symptoms sub-item cluster score (0-20)*	1.0 [3.0]	3.5 [2.5]	**<0.001**
CAT extra-pulmonary symptoms sub-item cluster score (0-20)#	1.0 [2.0]	1.0 [1.5]	**0.001**
MRC dyspnea score (1-5)	1.0 [0.0]	2.0 [1.0]	**<0.001**
MRC dyspnea score=1	131 (85.6)	72 (47.7)	**<0.001**
MRC dyspnea score=2	22 (14.4)	79 (52.3)	**<0.001**
Number of symptom-based exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.095
Number of event-based exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.486
Number of mild exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.570
Number of moderate exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	1.000

Data are presented as median [IQR] or frequency (n (%)). CAT: COPD Assessment Test; GOLD: Global Initiative for Obstructive Lung Disease; MRC: Medical Research Council.

*Calculated as the sum of CAT sub-item 1-4 scores
#Calculated as the sum of CAT sub-item 5-8 scores.

2.4.1.iii. Pulmonary function test outcomes

With the exception of % predicted FEV_1 being lower in the higher compared to lower breathlessness burden group, no between-group differences in baseline pulmonary function were observed (**Table 2.3**).

Table 2.3. Comparison of pulmonary function test outcomes between people with GOLD grade 1 or 2, group A COPD with lower breathlessness burden (CAT Breathlessness sub-item score=0) compared to higher breathlessness burden (CAT Breathlessness sub-item score ≥1)

	Lower Breathlessness Burden (n=154)	Higher Breathlessness Burden (n=156)	P value
FEV_1 (% predicted)	91.7 ± 15.3	84.3 ± 15.4	**<0.001**
FEV_1/FVC (%)	64.9 [6.1]	64.0 [8.5]	0.293
TLC (% predicted)	108.5 [19.5]	108.0 [18.0]	0.334
RV (% predicted)	122.0 [43.0]	130.0 [45.0]	0.299
FRC (% predicted)	114.50 [35.5]	117.00 [34.0]	0.609
IC (% predicted)	104.0 ± 17.8	101.0 ± 17.8	0.158
D_LCO (% predicted)	95.3 ± 20.5	91.2 ± 21.2	0.088

Data are presented as mean ± SD or median [IQR]. FEV_1/FVC: ratio of forced expiratory volume in 1-sec to forced vital capacity; TLC: total lung capacity; RV: residual volume, FRC: functional residual capacity; IC: inspiratory capacity; D_LCO: diffusing capacity of the lungs for carbon monoxide

2.4.1.iv. Symptom-limited cardiopulmonary cycle exercise test outcomes

As shown in **Table 2.4,** exercise tolerance was lower in the higher compared to lower breathlessness burden group, as evidenced by significantly lower values for % predicted peak power output and % predicted $V'O_{2peak}$. These differences persisted after adjustment for comorbidities, cigarette pack years, and % predicted FEV_1.

Peak heart rate and O_2 pulse (both expressed as a % predicted) were lower in the higher compared to lower breathlessness burden group (**Table 2.4**); however, only the difference in peak O_2 pulse persisted after adjusting for comorbidities, cigarette pack years, and % predicted FEV_1.

In the adjusted analyses, peak SpO_2 was slightly lower (95.7 ± 3.6% vs. 96.4 ± 2.3% [mean ± SD]) whereas the decrease in SpO_2 from baseline to peak exercise was slightly greater (-1.7 ± 3.7% vs. -1.1 ± 2.1%) in the higher compared to lower breathlessness burden group (**Table 2.4**). Otherwise, indices of exercise ventilatory / gas exchange efficiency (peak and nadir $V'_E/V'CO_2$; and peak $P_{ET}CO_2$) were similar between groups.

Compared to the lower breathlessness burden group, the higher breathlessness burden group had: a lower absolute V'_E, V_T and IC at peak exercise; greater dynamic lung hyperinflation,

as evidenced by a greater decrease in IC from baseline to peak exercise, expressed as both the absolute change in liters and relative to peak V'_E; greater critical inspiratory constraints, as evidenced by greater V_T%IC:V'_E and EILV%TLC:V'_E ratios at peak exercise; and greater exertional symptom burden, as evidenced by greater breathlessness:V'_E and leg discomfort:$V'O_2$ ratios at peak exercise (**Table 2.4**). However, only the difference in peak absolute V'_E persisted after adjusting for age, sex, BMI, comorbidities, cigarette pack years, and % predicted FEV_1.

Table 2.4. Comparison of peak cardiopulmonary exercise test outcomes between GOLD grade 1 or 2, group A COPD with lower breathlessness burden (CAT Breathlessness sub-item score=0) compared to higher breathlessness burden (CAT Breathlessness sub-item score ≥1)

	Lower Breathlessness Burden (n=154)	Higher Breathlessness Burden (n=156)	Unadjusted P value	Adjusted P value*
Power output (% predicted)	95.3 ± 24.9	86.0 ± 21.1	**<0.001**	**0.020**
$V'O_2$ (% predicted)	94.1 ± 22.9	86.3 ± 21.7	**0.002**	**0.021**
Heart rate (% predicted)	98.0 [17.5]	92.0 [22.0]	**0.018**	0.120
O_2 pulse (% predicted)	100.0 [24.5]	92.0 [27.0]	**0.007**	**0.030**
RER	1.11 ± 0.09	1.09 ± 0.09	0.098	0.397
$V'_E/V'CO_2$	31.7 [5.4]	31.7 [6.8]	0.761	0.145
$P_{ET}CO_2$ (mmHg)	36.0 ± 4.4	36.4 ± 4.6	0.496	0.379
Nadir $V'_E/V'CO_2$	29.5 [5.1]	30.3 [6.8]	0.116	0.252
SpO_2 (%)	97.0 [3.0]	97.0 [3.0]	0.388	0.050
ΔSpO_2 (%)	-1.0 [2.0]	-1.0 [2.0]	0.723	**0.044**
V'_E (L/min)	65.1 [33.9]	55.4 [24.1]	**<0.001**	**0.014**
Fb (breaths/min)	31.0 [10.0]	31.0 [8.0]	0.290	0.071
V_T (L)	2.12 [0.89]	1.82 [0.66]	**<0.001**	0.377
IC (L)	2.90 [0.85]	2.52 [1.07]	**<0.001**	0.731
ΔIC (L)	-0.07 ± 0.42	-0.19 ± 0.38	**0.011**	0.393
$\Delta IC:V'_E$ (L/L/min)	-0.00 [0.01]	-0.00 [0.01]	**<0.001**	0.077
V_T%IC	74.1 [15.9]	71.4 [14.5]	0.171	0.640
V_T%IC:V'_E (%IC/L/min)	1.09 [0.48]	1.28 [0.60]	**<0.001**	0.065
EILV%TLC	89.1 [7.6]	88.6 [7.5]	0.636	0.981
EILV%TLC:V'_E (%TLC/L/min)	1.34 [0.69]	1.56 [0.73]	**<0.001**	0.100
Breathlessness (Borg)	5.0 [5.0]	5.0 [4.0]	0.634	0.867
Breathlessness:V'_E (Borg/L/min)	0.07 [0.05]	0.09 [0.05]	**<0.001**	0.050
Leg discomfort (Borg)	7.0 [5.0]	6.0 [3.0]	0.104	0.234
Leg discomfort:$V'O_2$ (Borg/L/min)	3.41 [2.28]	3.77 [2.36]	**0.027**	0.788

Data are presented as mean ± SD, median (IQR) or frequency (n [%]).$V'O_2$: rate of oxygen uptake at peak exercise; O_2: oxygen; RER: respiratory exchange ration; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $V'_E/V'CO_2$: ventilatory equivalent for carbon dioxide; SpO_2: pulse oxygen saturation; Δ: change from baseline to peak exercise; V'_E: minute ventilation; MVV_{est}: maximum voluntary ventilation estimated as forced expiratory volume in 1-sec x 35; Fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EILV: end-inspiratory lung volume; TLC: total lung capacity.

*Analyses were adjusted for: age, sex, body mass index (BMI), comorbidities (prior physician diagnosis of asthma, any musculoskeletal comorbidity, and any cardiovascular disease comorbidity, including hypertension), cigarette pack years, and FEV_1 expressed as a percent of the predicted reference value (FEV_1%predicted).

2.4.2. Comparison of participants with higher compared to lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score of <5 *versus* ≥5)

2.4.2.i. Baseline participant characteristics

Compared to the lower pulmonary symptom burden group, the higher pulmonary symptom burden group: had a lower proportion of people with GOLD grade 1 COPD and a higher proportion of people with GOLD grade 2 COPD; a lower proportion of never smokers and higher proportion of current smokers; a greater history of cigarette smoke exposure; and higher proportion of people with a prior physician diagnosis of COPD; a higher proportion of people with any musculoskeletal comorbidity; and a higher proportion of people currently taking any respiratory medication (**Table 2.5**).

2.4.2.ii. Health status, breathlessness burden, and exacerbation-like respiratory events

Compared to the lower pulmonary symptom burden group, the higher pulmonary symptom burden group had: a higher CAT total score; higher scores for CAT sub-items 1 (cough), 2 (phlegm), 3 (chest tightness) and 4 (breathlessness); a higher CAT pulmonary symptoms sub-item cluster score; and a higher MRC dyspnea rating, with a lower proportion of people reporting MRC dyspnea scores of 1 and a higher proportion of people reporting MRC dyspnea scores of 2 (**Table 2.6**).

2.4.2.iii. Pulmonary function test outcomes

As shown in **Table 2.7**, people in the higher compared to lower pulmonary symptom burden group had: greater airflow obstruction (lower % predicted FEV_1); greater pulmonary gas trapping and static lung hyperinflation (greater % predicted RV and FRC, and lower % predicted IC); and a lower D_LCO.

Table 2.5. Comparison of participant characteristics between GOLD grade 1 or 2, group A COPD with lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score<5) compared to higher pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score≥5)

	Lower Pulmonary Symptom Burden (n=247)	Higher Pulmonary Symptom Burden (n=63)	P value
Age (years)	67.3 ± 9.6	66.8 ± 10.2	0.902
Male sex	163 (66.0)	38 (60.3)	0.400
BMI (kg/m^2)	26.6 [5.5]	26.3 [6.4]	0.632
GOLD grade 1 COPD	176 (71.3)	33 (52.4)	**0.004**
GOLD grade 2 COPD	71 (28.7)	30 (47.6)	**0.004**
Never smoker (n=113)	99 (40.1)	14 (22.2)	**0.009**
Ex-smoker (n=160)	125 (50.6)	35 (55.6)	0.483
Current smoker (n=37)	23 (9.3)	14 (22.2)	**0.005**
Cigarette pack years*	6.4 [32.3]	23.8 [28.8]	**<0.001**
Prior physician Dx of COPD	34 (13.8)	20 (31.8)	**<0.001**
Prior physician Dx of asthma	54 (21.9)	20 (31.8)	0.100
Any MSK	108 (43.7)	41 (65.1)	**0.002**
Any CVD	111 (44.9)	34 (54.0)	0.200
Any current respiratory medication use	49 (19.8)	27 (42.9)	**<0.001**

Data are presented as mean ± SD, median [IQR] or frequency (n (%)). BMI: body mass index; GOLD: Global Initiative for Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; Dx: diagnosis; MSK: musculoskeletal; CVD: cardiovascular disease.

*Cigarette pack years = number of packs of cigarettes smoked per day (20 cigarettes/pack) x number of years the participant has smoked.

Table 2.6. Comparison of symptom outcomes and exacerbation-like respiratory events between GOLD grade 1 or 2, group A COPD with lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score<5) compared to higher pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score≥5)

	Lower Pulmonary Symptom Burden (n=247)	Higher Pulmonary Symptom Burden (n=63)	P value
CAT total score (0-40)	3.0 [4.0]	7.0 [2.0]	**<0.001**
Item 1, Cough score (0-5)	1.0 [1.0]	2.0 [2.0]	**<0.001**
Item 2, Phlegm score (0-5)	0.0 [1.0]	1.0 [2.0]	**<0.001**
Item 3, Chest tightness score (0-5)	0.0 [0.0]	0.0 [1.0]	**0.002**
Item 4, Breathlessness score (0-5)	0.0 [1.0]	1.0 [2.0]	**<0.001**
Item 5, Activity limitation score (0-5)	0.0 [0.0]	0.0 [0.0]	0.154
Item 6, Confidence score (0-5)	0.0 [0.0]	0.0 [0.0]	0.222
Item 7, Sleep (0-5)	0.0 [0.0]	0.0 [0.0]	0.566
Item 8, Energy score (0-5)	1.0 [1.0]	1.0 [1.0]	0.916
CAT pulmonary symptoms sub-item cluster score (0-20)*	2.0 [2.0]	6.0 [1.0]	**<0.001**
CAT extra-pulmonary symptoms sub-item cluster score (0-20)#	1.0 [2.0]	1.0 [2.0]	0.339
MRC dyspnea score (1-5)	1.0 [1.0]	2.0 [1.0]	**<0.001**
MRC dyspnea score=1	175 (71.7)	28 (46.7)	**<0.001**
MRC dyspnea score=2	69 (28.3)	32 (53.3)	**<0.001**
Number of symptom-based exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.234
Number of event-based exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.578
Number of mild exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	0.380
Number of moderate exacerbation-like respiratory events	0.0 [0.0]	0.0 [0.0]	1.000

Data are presented as median [IQR] or frequency (n (%)). CAT: COPD Assessment Test; GOLD: Global Initiative for Obstructive Lung Disease; MRC: Medical Research Council.

*Calculated as the sum of CAT sub-item 1-4 scores
#Calculated as the sum of CAT sub-item 5-8 scores

Table 2.7. Comparison of pulmonary function test outcomes between GOLD grade 1 or 2, group A COPD with lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score<5) compared to higher pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score≥5)

	Lower Pulmonary Symptom Burden (n=247)	Higher Pulmonary Symptom Burden (n=63)	P value
FEV_1 (% predicted)	91.0 [21.0]	81.0 [22.0]	**<0.001**
FEV_1/FVC (%)	64.4 [6.5]	63.0 [8.9]	0.069
TLC (% predicted)	108.6 ± 14.0	110.7 ± 15.6	0.339
RV (% predicted)	122.5 [42.0]	138.0 [51.5]	**0.017**
FRC (% predicted)	114.0 [35.0]	122.5 [33.0]	**0.036**
IC (% predicted)	104.0 ± 18.0	96.6 ± 15.7	**0.005**
D_LCO (% predicted)	94.7 ± 21.3	87.5 ± 18.4	**0.016**

Data are presented as mean ± SD or median [IQR]. FEV_1/FVC: ratio of forced expiratory volume in 1-sec to forced vital capacity; TLC: total lung capacity; RV: residual volume, FRC: functional residual capacity; IC: inspiratory capacity; D_LCO: diffusing capacity of the lungs for carbon monoxide

2.4.2.iv. Symptom-limited cardiopulmonary cycle exercise test outcomes

Exercise tolerance was lower in the higher compared to lower pulmonary symptom burden group, as evidenced by significantly lower values for % predicted peak power output and % predicted $V'O_{2peak}$ (**Table 2.8**); however, these differences did not persist after adjustment for comorbidities, cigarette pack years, and % predicted FEV_1.

In both unadjusted and adjusted analyses, peak heart rate (expressed as a % predicted) was lower in the higher compared to lower pulmonary symptom burden group (**Table 2.8**).

In the adjusted analyses, peak SpO_2 was slightly lower (95.4 ± 4.2% vs. 96.2 ± 2.6% [mean ± SD]) whereas the decrease in SpO_2 from baseline to peak exercise was slightly greater (-2.3 ± 4.6% vs. -1.2 ± 2.5%) in the higher compared to lower pulmonary symptom burden group (**Table 2.8**). Otherwise, indices of exercise ventilatory / gas exchange efficiency (peak and nadir $V'_E/V'CO_2$; and peak $P_{ET}CO_2$) were similar between groups.

Compared to the lower pulmonary symptom burden group, the higher pulmonary symptom burden group had: a lower absolute V'_E, V_T and IC at peak exercise; greater critical inspiratory constraints, as evidence by greater V_T%IC:V'_E and EILV%TLC:V'_E ratios at peak exercise; and greater exertional symptom burden, as evidenced by greater breathlessness:V'_E and leg

discomfort:V'O_2 ratios at peak exercise (**Table 2.8**). However, only the difference in the leg discomfort:V'O_2 ratio at peak exercise persisted after adjusting for age, sex, BMI, comorbidities, cigarette pack years, and % predicted FEV_1.

Table 2.8. Comparison of peak cardiopulmonary exercise test outcomes between GOLD grade 1 or 2, group A COPD with lower pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score<5) compared to higher pulmonary symptom burden (CAT pulmonary symptoms sub-item cluster score≥5)

	Lower Pulmonary Symptom Burden (n=247)	Higher Pulmonary Symptom Burden (n=63)	Unadjusted p value	Adjusted p value*
Power output (% predicted)	92.8 ± 23.8	82.3 ± 20.4	**0.002**	0.104
$V'O_2$ (% predicted)	91.5 ± 22.2	84.9 ± 23.7	**0.038**	0.296
Heart rate (% predicted)	97.0 [18.0]	88.0 [18.0]	**0.002**	**0.029**
O_2 pulse (% predicted)	95.0 [27.0]	95.0 [35.0]	0.980	0.645
RER	1.10 ± 0.09	1.09 ± 0.09	0.395	0.581
$V'_E/V'CO_2$	31.7 [6.3]	31.6 [5.6]	0.815	0.864
$P_{ET}CO_2$ (mmHg)	36.1 ± 4.5	36.7 ± 4.6	0.405	0.778
Nadir $V'_E/V'CO_2$	29.6 [5.8]	31.5 [6.5]	0.050	0.512
SpO_2 (%)	97.0 [3.0]	97.0 [4.0]	0.534	**0.028**
ΔSpO_2 (%)	-1.0 [2.0]	-1.0 [2.0]	0.374	**0.007**
V'_E (L/min)	62.3 [33.3]	55.6 [17.3]	**0.003**	0.062
Fb (breaths/min)	31.0 [9.0]	31.0 [8.0]	0.701	0.436
V_T (L)	1.98 [0.90]	1.73 [0.61]	**0.003**	0.056
IC (L)	2.84 [1.02]	2.54 [0.94]	**0.003**	0.132
ΔIC (L)	-0.11 ± 0.40	-0.20 ± 0.44	0.161	0.407
$\Delta IC:V'_E$ (L/L/min)	-0.00 [0.01]	-0.00 [0.01]	0.168	0.407
V_T%IC	72.3 ± 12.5	71.7 ± 12.4	0.751	0.809
V_T%IC:V'_E (%IC/L/min)	1.17 [0.55]	1.34 [0.57]	**0.012**	0.238
EILV%TLC	88.7 [7.6]	89.6 [7.4]	0.520	0.739
EILV%TLC:V'_E (%TLC/L/min)	1.41 [0.78]	1.60 [0.57]	**0.020**	0.313
Breathlessness (Borg)	5.0 [4.0]	5.0 [4.0]	0.792	0.637
Breathlessness:V'_E (Borg/L/min)	0.08 [0.05]	0.09 [0.05]	**0.020**	0.137
Leg discomfort (Borg)	6.0 [4.0]	7.0 [5.0]	0.297	0.163
Leg discomfort:$V'O_2$ (Borg/L/min)	3.43 [2.18]	4.38 [1.97]	**0.001**	**0.040**

Data are presented as mean ± SD, median (IQR) or frequency (n [%]).$V'O_2$: rate of oxygen uptake at peak exercise; O_2: oxygen; RER: respiratory exchange ration; $P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide; $V'_E/V'CO_2$: ventilatory equivalent for carbon dioxide; SpO_2: pulse oxygen saturation; Δ: change from baseline to peak exercise; V'_E: minute ventilation; MVV_{est}: maximum voluntary ventilation estimated as forced expiratory volume in 1-sec x 35; Fb: breathing frequency; V_T: tidal volume; IC: inspiratory capacity; EILV: end-inspiratory lung volume; TLC: total lung capacity.

*Analyses were adjusted for: age, sex, body mass index (BMI), comorbidities (prior physician diagnosis of asthma, any musculoskeletal comorbidity, and any cardiovascular disease comorbidity, including hypertension), cigarette pack years, and FEV_1 expressed as a percent of the predicted reference value (FEV_1%predicted).

2.5 DISCUSSION

The novel results of this study indicated that, among people with GOLD grade 1 or 2, group A COPD recruited from the general (non-clinical) population, those with a higher compared to lower CAT breathlessness sub-item score or a higher compared to lower CAT pulmonary symptoms sub-item cluster score had significantly lower exercise tolerance in association with greater critical inspiratory constraints and exertional breathlessness.

This study extends beyond the results of earlier studies on the added value of CAT breathlessness and pulmonary symptoms sub-item cluster scores in the clinical evaluation of people with COPD (103–108,115). Our study analyzed data from a unique and woefully understudied group of adults with GOLD grade 1 or 2, group A COPD (116), which, as highlighted in the Introduction (*Section 2.2*), represents the vast majority of Canadian adults from the general population with spirometrically-defined COPD (1,2). In keeping with the results of Cherian et al. (79) a minority of participants included in this analysis (i) reported having a prior physician diagnosis of COPD (10.4-31.8%); and (ii) were currently taking any doctor prescribed respiratory medication (16.9-42.9%).

The close relationship between exercise intolerance, as indexed by $V'O_{2peak}$, and risk of premature death from COPD is well understood in that those with lower compared to higher $V'O_{2peak}$ are at greater independent risk of adverse outcomes, most notably premature death (42–45). People with COPD generally have an irregular (exaggerated) inflammatory response of the lungs and airways that leads to a progressive decline in pulmonary structure and function, resulting in pathophysiological abnormalities in breathing mechanics (both static and dynamic) and pulmonary gas exchange efficiency, which combine to increase exertional breathlessness and decrease $V'O_{2peak}$ (47,125). The combination of these factors, in turn, contribute to abnormally high pulmonary symptom burden (breathlessness, cough, phlegm, chest tightness) with abnormally low exercise tolerance and health status (3). Based on this, we hypothesized that among people with GOLD Grade 1 or 2, group A COPD, those with higher compared to lower

CAT breathlessness or pulmonary symptoms sub-item cluster score would have lower $V'O_{2peak}$ in association with greater pathophysiological abnormalities in breathing mechanics, pulmonary gas exchange efficiency and exertional breathlessness.

The most likely mechanisms of differences in exercise capacity (% predicted $V'O_{2peak}$ and PPO) between groups were the greater critical inspiratory constraints (greater ΔIC, ΔIC:V'_E, V_T%IC:V'_E and/or EILV%TLC:V_E) and greater attendant exertional breathlessness (greater breathlessness:V'_E) response in the higher compared to lower CAT breathlessness groups. While there were greater inspiratory constraints, albeit with similar ΔIC and ΔIC:V'_E, and greater attendant exertional breathlessness (breathlessness:V'_E) response in the higher compared to lower CAT pulmonary symptoms sub-item cluster group, the mechanisms of differences in exercise capacity could also have been explained by greater pulmonary gas trapping (RV %predicted), static lung hyperinflation (FRC %predicted and IC %predicted), and lower D_LCO %predicted. Furthermore, differences in critical inspiratory constraints and exertional breathlessness did not persist after adjusting for comorbidities (prior physician diagnosis of asthma, any musculoskeletal comorbidity, and any cardiovascular disease comorbidity, including hypertension), cigarette pack years, and FEV_1%predicted. This suggests a contributory role for these factors included in the adjusted analysis in accounting for differences in exercise capacity between the higher compared to lower CAT breathlessness sub-item or CAT pulmonary symptoms sub-item cluster groups. The lower peak cardiac and V'_E responses likely reflected the lower $V'O_{2peak}$ and PPO in the higher compared to lower CAT breathlessness or pulmonary symptoms sub-item cluster score groups.

Regarding the pathophysiological mechanism of differences in exercise capacity between groups, participants in the higher compared to lower CAT breathlessness or pulmonary symptoms sub-item cluster score expanded their V_T resulting at a greater V_{Tpeak} (%IC)-V'_{Epeak} as a consequence of dynamic lung hyperinflation, as evidenced by lower IC and ΔIC_{peak}-V'_{Epeak} (56,58). Another consequence of the presence of dynamic lung hyperinflation among participants in the

higher compared to lower CAT breathlessness or pulmonary symptoms sub-item cluster score was greater Peak EILV (%TLC)-V'_{Epeak} ratios suggestive of these participants breathing at high lung volumes (48,56,60). The presence of critical inspiratory constraints (high V_{Tpeak} (%IC) and/or Peak EILV (%TLC)) was similar at peak exercise between those with lower compared to higher CAT breathlessness or pulmonary symptoms subitem scores but with an accelerated onset (at lower $V'O_{2peak,}$ PPO, and/or V'_{Epeak}).

Despite a growing body of evidence supporting a mechanistic link between exercise ventilatory inefficiency (as evidenced by an abnormally high $V'_E/V'CO_2$ nadir) and both exertional breathlessness and exercise intolerance in people with COPD, including people with GOLD grade 1 or 2 COPD (64,126), no between-group differences in indices of exercise ventilatory efficiency (peak and nadir $V'_E/V'CO_2$) were observed between (i) the higher compared to lower breathlessness group or (ii) the higher compared to lower pulmonary symptom burden group. While there were statistically significant differences in peak SpO_2 and/or the exercise-induced decrease in SpO_2 from baseline to peak exercise, the differences were very small and of no meaningful clinical or physiological significance. Thus, between-group differences in exercise capacity (% predicted $V'O_{2peak}$ and PPO) observed in this study could not be accounted for by contemporaneous differences in pulmonary gas exchange / ventilatory efficiency.

It is worth mentioning that even though (i) MRC dyspnea scores were significantly higher in the higher compared to lower CAT breathlessness and pulmonary symptoms sub-item cluster groups and (ii) there was a greater proportion of people in the higher compared to lower breathlessness or pulmonary symptom burden groups with MRC dyspnea values of 2, the MRC dyspnea ratings of all participants included in our analysis were <3; thus, all participants included in our analyses were considered as having low breathlessness burden according the evaluative criteria of the GOLD and CTS (3,27).

This study supports the collective results of studies by Raghavan et al. (103), Jan et al. (104) and Kart et al. (105), regarding the presence of pathophysiological heterogeneity amongst

those with CAT total score <10 with spirometrically-defined COPD. Previous work highlighted the clinical utility in the use of the CAT pulmonary symptoms sub-items (especially the breathlessness sub-item score) in screening people for COPD. Our work suggests that the sum of CAT pulmonary sub-items or breathlessness sub-item can identify people with abnormally low $V'O_{2peak}$, which is an established independent predictor of premature death in COPD (42–44,64). Furthermore, our results align with findings by Von Siemens et al. (107) who reported a significant positive correlation between the percentage of emphysema on chest CT scan and the CAT breathlessness sub-item amongst those with GOLD grade 1-3 (mild-severe) COPD, where higher % emphysema has previously been found to be independently associated with lower $V'O_{2peak}$ and PPO (127).

Regarding the pulmonary symptoms sub-item cluster, our results support the findings from Martinez et al. (108), in identifying people with COPD that have an abnormally high risk of poor health outcomes. While Martinez et al., found that a CAT pulmonary symptoms sub-item cluster score ≥7 out of 20 best predicted exacerbations and high health status impairment (CAT total score ≥10) after 12-months follow-up amongst symptomatic ever smokers at high risk for adverse respiratory outcomes, we found that a CAT pulmonary symptoms sub-item cluster score ≥5 out of 20 best predicted an individual with mild-moderate COPD of having a $V'O_{2peak}$ <85% of the predicted value.

The present study is the first to show that elevated CAT breathlessness or pulmonary symptoms cluster scores are associated with abnormal CPET outcomes (specifically $V'O_{2peak}$) among people with GOLD Grade 1 or 2, group A COPD, which make up the majority of the general public in Canada (1,2). Our study supports the existence of a “breathlessness” phenotype and a “pulmonary symptom burden” phenotype within this prevalent group of people with COPD that might otherwise be considered largely “asymptomatic” and overlooked. Indeed, among our participants meeting criteria for GOLD grade 1 or 2, group A COPD, only 10.4% and 13.8% with lower breathlessness burden and lower pulmonary symptom burden had received a prior

physician diagnosis of COPD, respectively; and only 24.4% and 31.8% with higher breathlessness burden and higher pulmonary symptom burden, respectively. In the clinical care setting of COPD, paying attention to the CAT breathlessness subitem score as well as the cumulative score of the CAT pulmonary symptoms sub-items might facilitate identification of people with GOLD grade 1 or 2 COPD and a CAT total score <10 (and/or MRC dyspnea rating 1-2 [mMRC dyspnea rating 0-1]), who make up majority of the Canadian COPD population, have impaired exercise tolerance due to greater pathophysiological abnormalities in dynamic breathing mechanics (not necessarily detected by spirometry or plethysmography) and that might have a differential (more favorable) response to therapeutic intervention. Such a method might lend itself to more precise phenotyping and perhaps also more individualized/personalized targeted therapies.

The primary strengths of this study are that it addressed a de novo objective and hypothesis, was a cross-sectional multicenter study with a large cohort of a highly prevalent group of people with GOLD grade 1 or 2, group A COPD, recruited via random sampling. The limitations of the study are (1) that it is retrospective, thus requiring prospective validation to re-enforce the main findings from our study, (2) that is not generalizable to people with GOLD 3 or 4 COPD that meet the criteria for group B, C or D, for whom similar analyses would need to be done for these groups of people because the threshold values for CAT breathlessness and CAT pulmonary symptoms sub-item cluster would be different (presumably higher threshold values) than those derived in our study from people with GOLD grade 1 or 2, group A COPD, (3) that it did not have a longitudinal follow up period preventing us from evaluating the long-term outcomes of this cohort including response to therapy, and (4) the AUC values, that identified the optimal cut-point for each of the CAT breathlessness sub-item score and the CAT pulmonary symptoms sub-item cluster scores that best predicted (according to the Youden Index) an individual with GOLD grade 1 or 2, group A COPD of having an abnormally low $V'O_{2peak}$, were slightly above 0.50. Although these AUC values may not be especially robust, our derived CAT breathlessness and CAT

pulmonary symptoms sub-item cluster threshold values were nevertheless able to identify people with GOLD grade 1 or 2, group A COPD with lower exercise tolerance in association with greater critical inspiratory constraints, which might place them at greater risk of adverse longitudinal health outcomes. Furthermore, the selection of $V'O_{2peak}$ <85% predicted being abnormally low is supported by statements on the interpretation of CPET results published by experts of the American Thoracic Society, American College of Chest Physicians, and European Respiratory Society (121,122).

There is potential to expand this study to evaluate the changes in outcomes over time (e.g., participant characteristics, health status, breathlessness burden, frequency of exacerbation-like respiratory events, PFT, CPET, etc.) in the higher compared to lower breathlessness burden groups or pulmonary symptom burden groups. Indeed, those in the higher compared to lower breathlessness burden group or pulmonary symptom burden group are expected to have more rapid longitudinal decline in $V'O_{2peak}$ secondary to varying mechanisms of pathophysiology (e.g., worse PFT parameters over time in the higher compared to lower pulmonary symptom burden group), more likely to progress from GOLD grade 1 to 2 (or beyond), from GOLD grade 2 to 3 (or beyond), and more likely to move from GOLD group A to B or C to D.

Future research opportunities should explore long-term outcomes of people with higher compared to lower breathlessness or pulmonary symptom burden amongst a population with GOLD grade 1 or 2, group A COPD receiving standard or different interventions as per GOLD or CTS guidelines (27). Perhaps people with GOLD grade 1 or 2, group A COPD with higher compared to lower CAT breathlessness or pulmonary symptom burden scores respond differently to inhaled bronchodilators and may benefit from a different combination(s) of respiratory medicines.

2.6 CONCLUSION

The findings of the current study support the hypothesis that people with GOLD grade 1 or 2, group A COPD with (i) a higher compared to lower CAT breathlessness sub-item score or (ii) a higher compared to lower CAT pulmonary sub-items cluster score have greater abnormalities in exercise capacity in association with greater critical inspiratory constraints and exertional breathlessness. Once prospectively validated, the CAT breathlessness sub-item score and pulmonary symptoms sub-item cluster score might serve as clinically relevant tools for early identification (and perhaps also therapeutic intervention) of exercise intolerance and disproportionately high breathlessness/respiratory symptom burden among people with GOLD grade 1 or 2, group A COPD, which represent the majority of people with COPD in the community at-large.

ABBREVIATIONS

COPD = Chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in 1-sec
FEV_1/FVC = forced expiratory volume in 1-sec to forced vital capacity ratio
GOLD = Global Initiative for Obstructive Lung Disease
AATD = alpha-1 antitrypsin deficiency
LLN = lower limit of normal
V'/Q' = ventilation/perfusion
$V'O_{2peak}$ = the rate of O_2 consumption at the symptom limited peak of incremental exercise testing
PPO= peak power output
CPET = cardiopulmonary cycle ergometer exercise test
EET = exercise endurance time
6MWD = 6-min walk test
BODE = body mass index, airflow obstruction, dyspnea, exercise capacity
DOSE = dyspnea, airflow obstruction, smoking status, and exacerbation frequency
EELV = end-expiratory lung volume
IC = Inspiratory capacity
IRV = inspiratory reserve volume
V_T = tidal volume
EILV = end-inspiratory volume
F_b = frequency of breathing
RV = residual volume
P = pressure
V = volume
TLC = total lung capacity
$V'_E/V'CO_2$ = minute ventilation per rate of CO_2 output
MRC = Medical Research Council
SGRQ = St. George's Respiratory Questionnaire
mMRC = modified Medical Research Council
SWD = shuttle walking distance
CRQ = Chronic Respiratory Questionnaire
SF-12 PCS = Physical component score of the 12-item Short-form Health Survey
FACIT = Functional Assessment of Chronic Illness Therapy
SABA = short acting β_2-agonist bronchodilator
LAMA = long acting muscarinic agonist
LABA = long acting β_2-agonist bronchodilator
ICS = inhaled corticosteroid
CAT = COPD Assessment Test
CanCOLD = Canadian Cohort Obstructive Lung Disease
D_LCO = diffusing capacity of the lungs for carbon monoxide
HR = heart rate
SpO_2 = peripheral oxygen saturation
BMI = body mass index
CVD = cardiovascular disease
Dx = diagnosis
MSK = musculoskeletal
V'_E = minute ventilation
MVV_{est}: maximum voluntary ventilation estimated as forced expiratory volume in 1-sec x 35
$P_{ET}CO_2$: partial pressure of end-tidal carbon dioxide
RER: respiratory exchange ration

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