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Dyspnoea and Symptom Burden in Mild-Moderate COPD: the Canadian Cohort Obstructive Lung Disease Study

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Social Media "Take Home" Message: Individuals from a population-based study with mild COPD are more symptomatic than non-COPD peers. Worse dyspnea and quality of life was reported by people with mild COPD who are female, have a physician-diagnosis of COPD or recent exacerbations.

ABSTRACT

Rationale: Studies assessing dyspnoea and health-related quality of life (HRQoL) in chronic obstructive pulmonary disease (COPD) have focused on patients in clinical settings, not the general population.

Objectives: Compare the prevalence and severity of dyspnoea and impaired HRQoL in individuals with and without COPD from the general population, focusing on mild-moderate COPD.

Methods: Analysis of the 3-year Canadian Cohort Obstructive Lung Disease (CanCOLD) study included four subgroups: mild-COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD] 1); moderate-COPD (GOLD 2); non-COPD smokers; and non-COPD never-smokers. The primary outcome was dyspnoea (Medical Research Council [MRC] scale), and the secondary outcome was HRQoL (COPD Assessment Test [CAT] score; Saint George's Respiratory Questionnaire [SGRQ] score). Subgroups were analysed by sex, physician-diagnosed COPD status, and exacerbations.

Results: 1443 participants (mild-COPD [*n*=397]; moderate-COPD [*n*=262]; smokers [*n*=449], and never-smokers [*n*=335]) were studied. People with mild-COPD were more likely to report more severe dyspnoea (MRC 2 versus 1 [MRC2vs1]) than those without COPD (OR [95%CI]: 1.42 [1.05,1.91]), and non-COPD never-smokers (OR [95%CI]: 1.64 [1.07,2.52]). Among people with mild-COPD, more severe dyspnoea was reported in women versus men (MRC2vs1; OR [95%CI]: 3.70 [2.23,6.14]); people with, versus without, physician-diagnosed COPD (MRC2vs1; OR [95%CI]: 3.27 [1.71,6.23]), and people with, versus without, recent exacerbations (MRC2vs1; ≥2 versus 0 exacerbations: OR [95%CI]: 3.62 [1.02,12.86]; MRC≥3 versus 1 [MRC≥3vs1]; 1 versus 0 exacerbation: OR [95%CI]: 9.24 [2.01,42.42]). Similar between-group differences were obtained for CAT and SGRQ scores.

Conclusions: Careful assessment of dyspnoea and HRQoL could help identify individuals for earlier diagnosis and treatment.

INTRODUCTION

Dyspnoea is a cardinal symptom of COPD, across all severities of airflow obstruction [1]. Over 70% of people with diagnosed COPD seen in primary care experience dyspnoea, with 32% of people with mild airflow limitation (GOLD1) experiencing moderate-to-severe dyspnoea (MRC Scale ≥3) [1, 2]. Dyspnoea can precede COPD diagnosis, with people often misattributing this symptom to ageing, smoking, or deconditioning, thereby contributing to COPD under/late diagnosis [3-8].

Approximately half of Canadians with spirometrically-defined COPD are estimated to have mild disease [9]; however, few studies have examined dyspnoea and HRQoL in this prevalent group [10, 11]. Therefore, our understanding of dyspnoea and impaired HRQoL on people with mild or undiagnosed COPD is limited. Addressing this knowledge gap is important because earlier diagnosis and treatment of COPD may reduce disease burden [12] and improve long-term health outcomes. In addition, dyspnoea relief is prioritized as an important patient-centred outcome and goal of COPD treatment [7, 13].

Facilitating earlier COPD diagnosis may be particularly important for women, who experience higher levels of dyspnoea, more frequent exacerbations and hospitalizations, and poorer HRQoL than men of a similar age and airflow obstruction [14, 15]. Women are further disadvantaged by male-dominated bias in physician awareness, and the comparative lack of female representation in COPD clinical trials [16, 17]. Population-based studies in people with physician-diagnosed mild-COPD have demonstrated that 23-34% experienced exacerbations versus 12-19% in undiagnosed people [18]. Yet, most exacerbation studies focus on people with diagnosed, moderate-to-very-severe COPD [19-21]. Furthermore, people with and without a physician diagnosis of COPD require similar healthcare services access for exacerbation-like respiratory events [18].

The primary objective of this analysis of the CanCOLD study population [22] was to compare the prevalence and severity of dyspnoea and impaired HRQoL among people with mild (GOLD1) and

moderate (GOLD2) COPD with both ever and never-smoking controls without COPD. Secondary objectives were to compare the prevalence and severity of dyspnoea and impaired HRQoL based on sex; physician-diagnosed COPD status; and recent history of exacerbations.

METHODS

Study design

This analysis used data from the 3-year Canadian Cohort Obstructive Lung Disease (CanCOLD) study; a longitudinal population-based cohort of randomly-sampled people from non-clinical settings in nine Canadian cities [18, 22]. The sampling strategy is elaborated in the **Supplement**.

CanCOLD comprised people with (post-bronchodilator forced-expiratory-volume-in-1-second/forced-vital-capacity [FEV_1/FVC] <0.70) and without (post-bronchodilator FEV_1/FVC ≥0.70) COPD and was subdivided into: mild-COPD (FEV_1≥80% predicted; GOLD1), moderate-COPD (50%≤FEV_1<80% predicted; GOLD2), non-COPD current/former smokers (>20 packs in a lifetime, or >1 cigarette/day for ≥1 year) and non-COPD never-smokers (**Figure 1**). Socio-demographics, clinical status, spirometry, MRC dyspnoea ratings, CAT scores, and SGRQ scores, were assessed at baseline (V1), 1.5 years (V2), and 3 years (V3). Exacerbation incidence was assessed every 3 months by telephone or online questionnaires. See the **Supplement** for key operational definitions. All participants provided written consent prior to enrolment in CanCOLD, and ethics and review board approval was obtained at all 9 sites. The STROBE checklist [23] was used in the creation of this manuscript.

Outcomes

Dyspnoea was assessed using the MRC dyspnoea scale of 1–5 [24] because of its prognostic value [25] and use by the Canadian Thoracic Society [26]. HRQoL was assessed using the CAT and the SGRQ. The CAT was used for its clinical utility [26] and responsiveness [27], while the SGRQ was selected for its multidimensionality [28]. For more on outcome selection, see the **Supplement**. MRC, CAT, and SGRQ scores from V1 were used for all analyses, except when analysing outcomes among

people with different exacerbation frequencies where outcomes collected at V3 were used so as to have prior exacerbation history available. Exacerbation history, collected every 3 months, was limited to the 12 months before V3; the analysis of these data only included people with data available from V3.

Statistical analysis

For the primary objective, differences in the prevalence and severity of dyspnoea between people with COPD (mild and moderate) and those without COPD were compared using Chi-squared or Fisher's exact tests for categorical variables. Sensitivity analyses were conducted to (1) compare the mild-COPD subgroup with the non-COPD group, and particularly with never-smokers ;(2) excluding participants with a physician-diagnosis of asthma; and (3) excluding participants on respiratory medications. Multinomial logistic regression models were used to estimate adjusted odds ratios (OR) with 95% confidence intervals (CI) for MRC 2 versus MRC 1 (MRC2vs1) and MRC≥3 versus MRC 1 (MRC≥3vs1), adjusting for relevant covariates (see the **Supplement**). Linear regression models were used to estimate adjusted β with 95% CI for CAT and SGRQ scores. For secondary objectives, differences were assessed using separate logistic regression models to compare outcomes between relevant groups, with results adjusted for the same covariates.

The study was powered for the primary analysis, comparing the odds of reporting MRC2vs1 between COPD (*n*=659) and non-COPD (*n*=784) groups. With a proportion of MRC2 among the non-COPD group of 0.27, the study had >95% power to detect a proportion of MRC2 of >0.37 in the COPD group. The probability of a Type I error was 0.05.

RESULTS

Study population

The CanCOLD cohort assessed 1561 individuals at V1; 80 were excluded because MRC could not be assessed due to non-ambulatory functional status attributed to comorbidities other than COPD

(**Supplement** for details). An additional 38 people with GOLD3+ COPD were also excluded. Among the 1443 people included, 659 had COPD (mild, *n*=397; moderate, *n*=262) and 784 did not have COPD (smokers, *n*=449; never-smokers, *n*=335). People without COPD were generally younger, women, and with a lesser smoking history compared with people with COPD. More people with, versus without, COPD self-reported having physician-diagnosed asthma (30.7% versus 15.8%) and were prescribed respiratory medications (32.6% versus 10.8%) (**Table1**). Characteristics according to sex, physician-diagnosed COPD status, and exacerbation frequency among people with COPD are shown in **TableE4.**

Dyspnoea and HRQoL by COPD severity

The prevalence of MRC≥2 at baseline was greater in people with COPD (mild and moderate) versus people without COPD (smokers and never-smokers). MRC≥3 was reported more frequently in people with moderate-COPD (12.2%) than in people with mild-COPD (3.5%), and non-COPD smokers (4.5%) and never-smokers (3.3%) (**Figure2A**). Additionally, people with mild-COPD were more likely to report MRC2vs1 than people without COPD (OR [95%CI]: 1.42 [1.05,1.91]), and particularly versus never-smokers (OR [95%CI]: 1.64 [1.07,2.52]) (**Figure3**). There were no statistically significant differences in reporting MRC≥3vs1 between people with mild-COPD and those without COPD. Similar results were obtained when participants with a physician-diagnosis of asthma or who reported use of respiratory medication(s) were excluded **(TableE5,E6).** HRQoL was worse in people with COPD (mild and moderate) compared to people without COPD (higher CAT (β [95%CI]: 1.06 [0.48,1.64]) and SGRQ scores (β [95%CI]: 4.34 [2.84,5.84]) **(Figure4)**. No differences in HRQoL were seen between people with mild-COPD compared to people without COPD or never smokers.

Dyspnoea and HRQoL by sex

Within the COPD group, more women had MRC≥2 compared to men (**Figure5A**). Women with COPD were more likely to report MRC2vs1 (OR [95%CI]: 3.12 [2.14,4.55]), and MRC≥3vs1 (OR [95%CI]: 4.50 [2.27,8.92]) (**Figure3**). Women with COPD also reported worse HRQoL, as evidenced by higher CAT (β

[95%CI]: 2.25 [1.33,3.18]) and SGRQ scores (β [95%CI]: 5.55 [3.43,7.66]) **(Figure4,6A,6B).** Similarly, among people with mild-COPD, women had a higher mean baseline MRC **(Table2)** and were more likely to report MRC2vs1 (OR [95%CI]: 3.70 [2.23,6.14]) and MRC≥3vs1 (OR [95%CI]: 5.56 [1.74,17.79]) (**Figure3)**. Women compared to men with mild-COPD reported worse HRQoL (CAT; β [95%CI]: 1.40 [0.39,2.40]; SGRQ; β [95%CI]: 3.88 [1.60,6.15] **(Figure4,Table2).**

Dyspnoea and HRQoL by physician-diagnosed COPD

Among people with COPD, those with, versus without, physician-diagnosed COPD reported greater dyspnoea severity (**Figure5B**). People with, versus without, a diagnosis were more likely to report MRC2vs1 (OR [95%CI]: 2.64 [1.71,4.08]), MRC≥3vs1 (OR [95%CI]: 5.01 [2.40,10.45]) (**Figure3**), and worse HRQoL (CAT; β [95%CI]: 4.78 [3.76,5.80]; SGRQ; β [95%CI]: 10.08 [7.74,12.42]) **(Figure4,6C,6D).** Among the mild-COPD subgroup, people with a diagnosis had a higher mean baseline MRC **(Table2)** and were more likely to report MRC2vs1 (OR [95%CI]: 3.27 [1.71,6.23]), and both a higher CAT score (β [95%CI]: 3.29 [2.01,4.57]) and higher SGRQ score (β [95%CI]: 7.23 [4.33,10.12]) (**Figure3,4**).

Dyspnoea and HRQoL by exacerbation history

Of the 659 people with COPD, V3 follow up data was available for 467 people at the time of analysis **(**see the **Supplement).** People with COPD who had exacerbations in the 12 months preceding V3 reported higher mean MRC at V3 than people who had not experienced an exacerbation (**Figure5C)**. People who experienced ≥2 exacerbations were more likely to report MRC2vs1 (OR [95%CI]: 2.49 [1.12,5.56]), MRC≥3vs1 (OR [95%CI]: 5.30 [1.41,19.92]) and worse HRQoL (CAT; β [95%CI]: 2.79 [0.82, 4.76]; SGRQ; β [95%CI:] 12.21 [7.98,16.44]) than people who had not experienced an exacerbation **(Figure3,4)**. People who experienced 1 exacerbation in the preceding 12 months were more likely to report MRC≥3vs1 (OR [95%CI]: 4.76 [1.85,12.26]) and worse HRQoL (CAT; β [95%CI]: 2.85 [1.39,4.32]; SGRQ; β [95%CI]: 8.55 [5.38,11.72]) than those with no exacerbations (**Figure3,4**).

Of the people with mild-COPD, 19.5% experienced ≥1 exacerbation in the previous 12 months. People with mild-COPD who experienced ≥2 exacerbations in the previous 12 months were more likely to report MRC2vs1 (OR [95%CI]: 3.62 [1.02,12.86]), MRC≥3vs1 (OR [95%CI]: 12.11 [1.30,112.93]), and higher SGRQ score (β [95%CI]: 10.61 [4.54,16.68]) than people who had not experienced an exacerbation. No statistically significant difference was seen in the CAT score between people with mild-COPD who reported ≥2 exacerbations versus 0 exacerbations. People with mild-COPD who experienced 1 exacerbation in the previous 12 months were more likely to report MRC≥3vs1 (OR [95%CI]: 9.24 [2.01,42.42]) and worse HRQoL (CAT; β [95%CI]: 2.15 [0.23,4.06]; SGRQ; β [95%CI]: 6.67 [2.61,10.73]) than those with no exacerbations (**Figure3,Figure4,Table 2**).

DISCUSSION

CanCOLD is the first observational cohort study to compare dyspnoea and HRQoL in people with mild-COPD versus people without COPD from a large non-clinical population. Interestingly, it reveals that individuals with mild-COPD were more likely to report clinically-significant dyspnoea (MRC2vs1) and worse HRQoL than those without COPD, particularly never-smokers, confirming that symptoms can be significant even in mild-COPD. Among people with mild-COPD, more severe dyspnoea and worse HRQoL were reported by women, people with physician-diagnosed COPD, and people with recent exacerbation(s). These findings were independent of age, body mass index, smoking-history, respiratory medication use, and comorbidities including asthma. These results are unique and extend our knowledge on the prevalence and severity of dyspnoea and impaired HRQoL beyond patients with moderate-to-very severe COPD recruited from clinical settings to people with mild-COPD recruited from the general-population.

Few studies have focused solely on mild-COPD [1, 10]. A large observational study using general-practitioner data reported that of 7359 people with GOLD1 COPD, 28.0% had MRC1, 40.5% had MRC2, and 31.5% had MRC≥3 [1]. Furthermore, in a study across 56 primary-care and specialty centres, >50% of people with GOLD1 COPD reported dyspnoea of modified MRC (mMRC)≥2

(equivalent to MRC≥3) [10]. In contrast, people with GOLD1 COPD in our study reported predominantly MRC1 (65.0%), with 31.5% and 3.5% reporting MRC2 and MRC≥3, respectively. Also, a study of people with GOLD2 COPD recruited from outpatient-clinics reported a mean mMRC of 1.3 (equivalent to mean MRC of 2.3) [29]. By comparison, people with GOLD2 in our study reported a slightly lower mean MRC of 1.7. These variations in dyspnoea severity may be because earlier studies recruited from clinical settings and included participants with physician-diagnosed COPD. Neither did they include direct comparisons to controls without COPD. Conversely, our cohort was a random sample from the general-population and included people with COPD confirmed by post-bronchodilator spirometry, and many who never received a physician-diagnosis [1, 10]. Accordingly, we observed that people reporting a physician-diagnosis of COPD prior to their participation in CanCOLD had more dyspnoea and worse HRQoL than people with COPD without a prior physician-diagnosis. Our study is unique in that it demonstrates that dyspnoea can be clinically-relevant even in people with mild-COPD, and that HRQoL is worse among people with mild-moderate COPD, recruited from the general-population. However, when comparing individuals with mild-COPD to those without COPD, no statistically significant difference in HRQoL measures were found. It is possible that people with mild-COPD may not recognize their dyspnoea but modify their levels of physical activity to avoid this distressing symptom, and consequently do not notice a change in their HRQoL [30, 31]. Indeed, people with mild-moderate COPD have reported abnormally low daily step-rates and physical-activity compared with healthy controls [32]. The results of our study suggest that dyspnoea is a feature of people with mild-COPD even in a population-based cohort, and that they can be identified provided they are carefully questioned about their level of dyspnoea using the MRC scale. Failure to identify dyspnoea in people with undiagnosed mild-COPD may contribute to delayed diagnosis and treatment initiation. To overcome this, there is a need to implement standardized methods to measure exertional dyspnoea in people at risk of COPD [30, 31].

We also demonstrated that women with mild-COPD reported greater dyspnoea and worse HRQoL. This is consistent with previous population-based studies which found that women had more severe

dyspnoea and exacerbations than men, despite similar airflow limitation [16, 33]. These discrepancies may be attributed to societal and/or biological factors [34]. For example, women with COPD are more likely to utilize healthcare resources [14]. Women tend to have smaller lungs, narrower airways [17, 34, 35], greater airway hyperresponsiveness [16], and exhibit different smoking patterns and metabolism of cigarette-smoke [16, 17, 34]. One study demonstrated that dyspnoea was higher for a given ventilation and power output during exercise testing in women than men with mild-COPD [36]. However, the differences were no longer seen when power output was adjusted for body mass, and ventilation was adjusted for maximum voluntary ventilation, indicating that differences in body size and lung volume contribute importantly to the sex disparity in dyspnoea [36]. Indeed, Ekstrom *et al.* demonstrated that higher prevalence and severity of dyspnoea among women in the general-population is related to smaller absolute lung volumes [37, 38]. Therefore, mild-COPD may have greater symptomatic consequences in women because of biologically lower maximal ventilatory capacity.

People with COPD who had experienced exacerbations during the previous year reported more dyspnoea and worse HRQoL than those who did not. Our study found that 19.5% of people with mild-COPD experienced exacerbations, in keeping with the “exacerbation-susceptible” phenotype identified within the ECLIPSE study [39]. Additionally, given that MRC dyspnoea score correlates with exacerbation frequency [39], these findings may indicate that identifying dyspneic individuals with mild-COPD could allow for the recognition of the “exacerbation-susceptibility” phenotype earlier in the course of COPD and for earlier interventions to reduce exacerbations, healthcare utilization, and, potentially, alter disease progression. Our findings need not imply a causal relationship. Exacerbations are patient-defined events, and it is plausible that individuals with heightened perception of somatic sensations, particularly respiratory sensations, experience more exacerbations

The major strength of our study is that participants were randomly sampled from a non-clinical population. This provides a unique insight early in the COPD disease course, even prior to diagnosis.

This is the only study to directly compare dyspnoea and HRQoL among people with mild-COPD with those without COPD, identifying significant symptom burden in mild-COPD. In addition, as this study included people with mild-COPD, these results may be more relevant to primary care practices than previous studies [1, 10, 29]. Tan *et al.* estimated that 16.7% of Canadian adults aged ≥40 years had COPD (defined as FEV_1/FVC <0.7) according to post-bronchodilator spirometry, with approximately 53% of these people being classified to have mild (GOLD1) COPD [9]. Another advantage of CanCOLD is that it used the same sampling methodology for prevalence assessment as the multinational Burden of Obstructive Lung Disease study, which was conducted across 12 sites worldwide [40], thereby allowing cautious extrapolation of our findings to other countries.

This study has its limitations. Dyspnoea is a complex symptom that manifests in three domains: symptom impact; sensory perception; and affective distress [41]. In our study, only symptom impact was measured. Nonetheless, these domains are intrinsically linked, with dyspnoea symptoms able to induce secondary responses in sensory and affective dimensions [42]. In people with chronic dyspnoea, higher perceived severity of breathlessness and its unpleasantness is associated with worse perceived HRQoL [43]. Although our findings demonstrated that people with mild-COPD are more dyspneic than those without COPD, particularly never-smokers, this was based on MRC2vs1 only and was not maintained for MRC≥3vs1. This reflects the fact that only a few people with mild-COPD or without COPD reported MRC≥3. Therefore, meaningful conclusions cannot be drawn when comparing MRC≥3vs1 for these subgroups. Also, by using a fixed post-bronchodilator FEV_1/FVC ratio of <0.7 to diagnose COPD, instead of the lower limit of normal FEV_1/FVC [44], there could have been some overdiagnosis of COPD in older people; however, a recent study by Bhatt *et al.* supports use of the fixed threshold to identify individuals at risk of clinically significant COPD [45]. The pathophysiological mechanisms underlying the observed differences in the prevalence and severity of dyspnoea in people with compared to without mild-COPD were not explored in this study. However, based on physiological studies in symptomatic adults with diagnosed mild-COPD recruited from clinical settings [46, 47], it is reasonable to hypothesize that these observed between-group

differences reflect abnormalities in pulmonary microvasculature, small airways, pulmonary gas exchange, and/or lung volume dynamics in people with mild-COPD. We also cannot exclude the possibility that reports of greater dyspnoea are the consequence of diagnostic labelling. Additionally, given the large Caucasian representation in CanCOLD, our results may not be generalizable to non-Caucasian populations.

In conclusion, our findings provide new, important information that aid healthcare professionals who see people at-risk of developing COPD and people with mild-COPD. Specifically, our findings highlight the importance of carefully questioning people at-risk of COPD about dyspnoea or any impairment of HRQoL for earlier identification of individuals with mild-COPD. Nonetheless, questions remain regarding exertional dyspnoea in mild-COPD, and more sensitive, comprehensive means to assess people with mild-COPD with clinically significant symptoms are required. Furthermore, our study highlights the need to develop a more detailed understanding of the mechanisms of dyspnoea in women and among people who exacerbate frequently in order to facilitate more targeted identification, diagnosis, and treatment initiation.

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FIGURE CAPTIONS

Figure 1: Study design and subgroups analysed

*Current or former smokers were defined as smoking >20 packs in a lifetime, or >1 cigarette/day for ≥1 year. †Exacerbation history was limited to the 12 months before Visit 3. The analysis of these data only included people for whom there was Visit 3-specific data.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Figure 2: Prevalence and severity of dyspnoea (A), and health related quality of life [CAT total score (B); SGRQ total score (C) at baseline

Figure 2A: *†‡Means with the same symbol are significantly different from each other after Tukey adjustment for multiple comparisons (P<0.05). *Figures 2B and 2C:* *†‡Medians with the same symbol are significantly different from each other after Tukey adjustment for multiple comparisons (P<0.05). Error bars represent quartiles 1 and 3.

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

Figure 3: Comparative odds ratios of dyspnoea severity* for: (A) MRC 2 versus MRC 1 and (B) MRC ≥3 versus MRC 1

*MRC was measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history. †For analysis by exacerbation status, N numbers were as follows: COPD: N=467; Mild-COPD (GOLD1): N=282; Moderate-COPD (GOLD2): N=185.

Adjusted OR were obtained by performing multivariate multinomial logistic regression models, adjusted for sex, age, BMI, smoking history, cardiovascular comorbidities, and other respiratory comorbidities. For women versus men comparisons, sex was not included as a covariate. For smokers versus never-smokers, smoking history was not included as a covariate. To estimate the

association between exacerbations and MRC, exacerbations were observed in preceding 12 months at Visit 3.

BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; MRC, Medical Research Council; OR, odds ratio.

Figure 4: Comparative adjusted β of health-related quality of life * for: (A) CAT and (B) SGRQ

*CAT and SGRQ were measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history. [†]For analysis by exacerbation status, N numbers were as follows: COPD: N=467; Mild-COPD (GOLD1): N=282; Moderate-COPD (GOLD2): N=185.

Adjusted β were obtained by performing multivariate linear regression models, adjusted for sex, age, BMI, smoking history, cardiovascular co-morbidities, and other respiratory comorbidities. For women versus men comparisons, sex was not included as a covariate. For smokers versus never-smokers, smoking history was not included as a covariate. To estimate the association between exacerbations and CAT or SGRQ, exacerbations were observed in preceding 12 months at Visit 3.

BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SGRQ, St George's Respiratory Questionnaire.

Figure 5: Dyspnoea severity* for people with COPD by: (A) sex, (B) the presence of a physician diagnosis of COPD, and (C) exacerbation frequency

*MRC was measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history. [†]Means with the same symbol are significantly different from each other (P<0.001).

P-values were obtained by performing Chi-square or Fisher exact test for category variables. For continuous variables, *P*-values were obtained by *t*-test (normal distribution) or Mann–Whitney U test (not normal distribution) for sex and physician diagnosis subgroups. Analysis of variance analyses (normal distribution) or Kruskal–Wallis test (not normal distribution) were performed for exacerbation subgroups. Analysis of variance subgroup comparisons of mean (SD) differences by sex, presence of a physician diagnosis of COPD, and exacerbation frequency were all significant (*P*<0.001).

COPD, chronic obstructive pulmonary disease; MRC, Medical Research Council; SD, standard deviation.

Figure 6: Health-related quality of life severity* for people with COPD by: (A, B) sex, (C, D) the presence of a physician diagnosis of COPD, and (E, F) exacerbation frequency

*CAT and SGRQ were measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history. Error bars represent quartiles 1 and 3. *P*-values were obtained by *t*-test (normal distribution) or Mann–Whitney U test (not normal distribution) for sex and physician diagnosis subgroups. Analysis of variance analyses (normal distribution) or Kruskal–Wallis test (not normal distribution) were performed for exacerbation subgroups. Analysis of variance subgroup comparisons of median (Q1, Q3) differences by sex, presence of a physician diagnosis of COPD, and exacerbation frequency were all significant (*P*<0.05).

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life; Q, quartile; SGRQ, St George's Respiratory Questionnaire.

TABLES

Table 1: Demographics and baseline characteristics

	COPD (*N*=659)	**Non-COPD (*N*=784)**	***P*-value***	**COPD**		**Non-COPD**		***P*-value†**
				Mild-COPD (GOLD1) (*N*=397)	**Moderate-COPD (GOLD2) (*N*=262)**	**Smokers (*N*=449)**	**Never-smokers (*N*=335)**	
Age, years, mean (SD)	67.2 (10.1)	65.9 (9.6)	**0.019**	68.0 (9.8)[§‖]	65.9 (10.3)[‖]	65.6 (9.4)[§]	66.3 (9.8)	**0.008**
Men, *n* (%)	404 (61.3)	412 (52.6)	**<0.001**	259 (65.2)	145 (55.3)	262 (58.4)	150 (44.8)	**<0.001**
BMI, mean (SD)	27.2 (4.8)	27.8 (5.2)	0.122	26.9 (4.4)[§]	27.6 (5.2)	28.1 (5.2)[§]	27.4 (5.2)	**0.017**
Never-smokers, *n* (%)	190 (28.8)	335 (42.7)	**<0.001**	132 (33.2)[§]	58 (22.1)[§]	0	335 (100.0)	**<0.001**
Former smokers, *n* (%)	352 (53.4)	346 (44.1)	**<0.001**	212 (53.4)[§]	140 (53.4)[‖]	346 (77.1)[§‖]	0	**<0.001**
Current smokers, *n* (%)	117 (17.8)	103 (13.1)	**0.015**	53 (13.4)[§‖]	64 (24.4)[‖]	103 (22.9)[§]	0	**<0.001**
GOLD1, *n* (%)	397 (60.2)	0	-	397 (100.0)	0	0	0	-
GOLD2, *n* (%)	262 (39.8)	0	-	0	262 (100.0)	0	0	-
Self-reported physician-diagnosed asthma, *n* (%)	202 (30.7)	124 (15.8)	**<0.001**	93 (23.4)[§]	109 (41.6)[§‖]	76 (16.9)[‖]	48 (14.3)[§]	**<0.001**
Any respiratory medication prescription[‡], *n* (%)	215 (32.6)	85 (10.8)	**<0.001**	81 (20.4)[§‖]	134 (51.1)[§‖]	54 (12.0)[‖]	31 (9.3)[§]	**<0.001**
Emphysema score, mean (SD)	1.8 (3.1)	0.5 (1.3)	**<0.001**	1.4 (2.5)[§]	2.3 (3.7)[§]	0.7 (1.5)[§]	0.2 (0.7)[§]	**<0.001**
RV/TLC %, mean (SD)	42 (9.6)	37.5 (8.2)	**<0.001**	39.2 (8.7)[‖]	46.3 (9.4)[§‖]	37.4 (8.0)[‖]	37.6 (8.5)[§]	**<0.001**
Chronic Bronchitis, *n* (%)	112 (17.0)	99 (12.6)	**0.0019**	44 (11.1)[∝]	68 (26.0)[‖∂∝]	69 (15.4)[∂]	30 (9.0)[‖]	**<0.001**

**P*-values were obtained by performing Chi-square or Fisher exact test for category variables, and *t*-test (normal distribution) or Mann–Whitney U tests (non-normal distribution) for continuous variables.

[†]*P*-values were obtained by performing Chi-square or Fisher exact tests for category variables, and analysis of variance (normal distribution) or Kruskal–Wallis test (not normal distribution) for continuous variables.

[‡]Respiratory medicines included were: SAMA/SABA; LABA ± SAMA/SABA; LAMA ± SAMA/SABA; LAMA+LABA ± SAMA/SABA; ICS ± SAMA/SABA; LABA+ICS ± SAMA/SABA; LAMA+ICS ± SAMA/SABA; LAMA+LABA+ICS ± SAMA/SABA.

[§||∂]Values with the same symbol are significantly different from each other after Tukey adjustment for multiple comparisons (P<0.05).

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; RV/TLC, residual volume/total lung capacity; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

Table 2: Dyspnoea severity* and health related quality of life by sex, COPD physician-diagnosis status, and exacerbation frequency for people with mild (GOLD1) or moderate (GOLD2) COPD

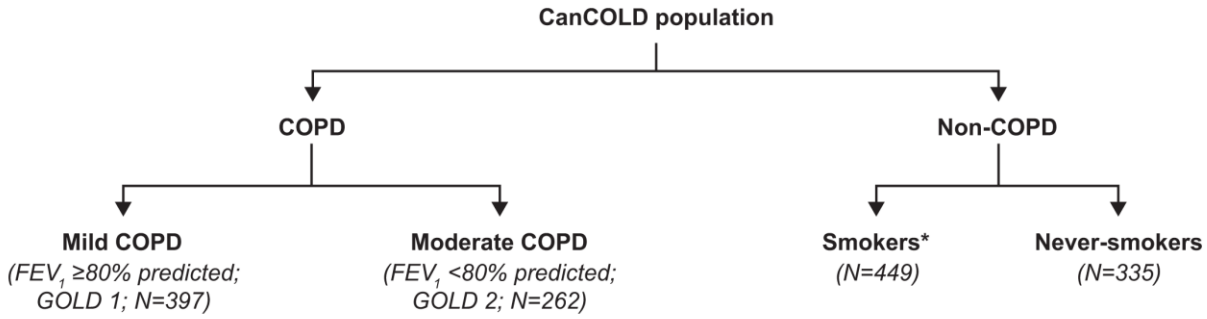
		Mean (SD) MRC	MRC 1, *n* (%)	MRC 2, *n* (%)	MRC ≥3, *n* (%)	Median CAT total score, (Q1, Q3)	Median SGRQ total score, (Q1, Q3)
Dyspnoea and HRQoL by sex							
Mild-COPD (GOLD1) (*N*=397)	Men (*N*=259)	1.3 (0.5)	190 (73.4)	63 (24.3)	6 (2.3)	4.0 (2.0, 7.0)	6.8 (2.3, 12.4)
	Women (*N*=138)	1.6 (0.6)	68 (49.3)	62 (44.9)	8 (5.8)	5.0 (3.0, 9.0)	8.0 (2.7, 17.1)
	P-value	***<0.001***	***<0.001***	***<0.001***	*0.073*	***0.049***	***0.039***
Moderate-COPD (GOLD 2) (*N*=262)	Men (*N*=145)	1.6 (0.7)	69 (47.6)	61 (42.1)	15 (10.3)	7.0 (4.0, 12.5)	14.6 (5.2, 28.5)
	Women (*N*=117)	1.9 (0.8)	40 (34.2)	60 (51.3)	17 (14.5)	9.0 (5.0, 15.0)	21.0 (9.3, 31.4)
	P-value	***0.026***	***0.029***	*0.137*	*0.304*	***0.028***	***0.023***
Dyspnoea and HRQoL by COPD diagnosis							
Mild-COPD (GOLD1) (*N*=397)	Diagnosed COPD (*N*=66)	1.6 (0.6)	28 (42.4)	35 (53.0)	3 (4.5)	7.0 (5.0, 12.0)	13.9 (7.1, 20.0)
	Undiagnosed COPD (*N*=331)	1.3 (0.6)	230 (69.5)	90 (27.2)	11 (3.3)	4.0 (2.0, 7.0)	6.2 (2.0, 12.4)
	P-value	***<0.001***	***<0.001***	***<0.001***	*0.712*	***<0.001***	***<0.001***
Moderate-COPD (GOLD2) (*N*=262)	Diagnosed COPD (*N*=97)	2.0 (0.8)	27 (27.8)	51 (52.6)	19 (19.6)	12.0 (7.0, 17.0)	24.9 (14.9, 34.9)
	Undiagnosed COPD *(N*=165)	1.6 (0.7)	82 (49.7)	70 (42.4)	13 (7.9)	6.0 (3.0, 10.0)	11.7 (4.5, 25.2)
	P-value	***<0.001***	***<0.001***	*0.111*	***0.005***	***<0.001***	***<0.001***
Dyspnoea and HRQoL by exacerbation frequency†							
Mild-COPD (GOLD1) (*N*=282)	0 (*N*=227)	1.3 (0.5)	163 (71.8)	59 (26.0)	5 (2.2)	4.0 (2.0, 7.0)	5.1 (1.6, 12.3)
	1 (*N*=39)	1.6 (0.8)	23 (59.0)	9 (23.1)	7 (17.9)	7.0 (3.0, 11.0)	12.6 (6.8, 21.5)
	≥2 (*N*=16)	1.8 (0.7)	6 (37.5)	8 (50.0)	2 (12.5)	8.5 (3.5, 15.0)	20.7 (8.4, 35.6)
	Overall P-value	***0.002***	***0.007***	*0.094*	***<0.001***	***<0.001***	***<0.001***
Moderate-COPD (GOLD2) (*N*=185)	0 (*N*=128)	1.5 (0.6)	75 (58.6)	44 (34.4)	9 (7.0)	6.5 (3.0, 11.0)	11.5 (3.6, 24.3)
	1 (*N*=35)	1.9 (0.8)	13 (37.1)	15 (42.9)	7 (20.0)	11.0 (6.0, 17.0)	24.0 (15.3, 35.4)
	≥2 (*N*=22)	1.8 (0.7)	8 (36.4)	11 (50.0)	3 (13.6)	9.5 (5.0, 18.0)	32.5 (12.5, 42.8)

	Overall P-value	***<0.011***	***0.024***	*0.300*	*0.066*	***0.002***	***<0.001***

*MRC was measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history. †Number of exacerbations in the 12 months preceding Visit 3.

P-values were obtained by performing Chi-square or Fisher exact test for category variables, and t- test (normal distribution) or Mann Whitney U test (not normal distribution) for continuous variables.

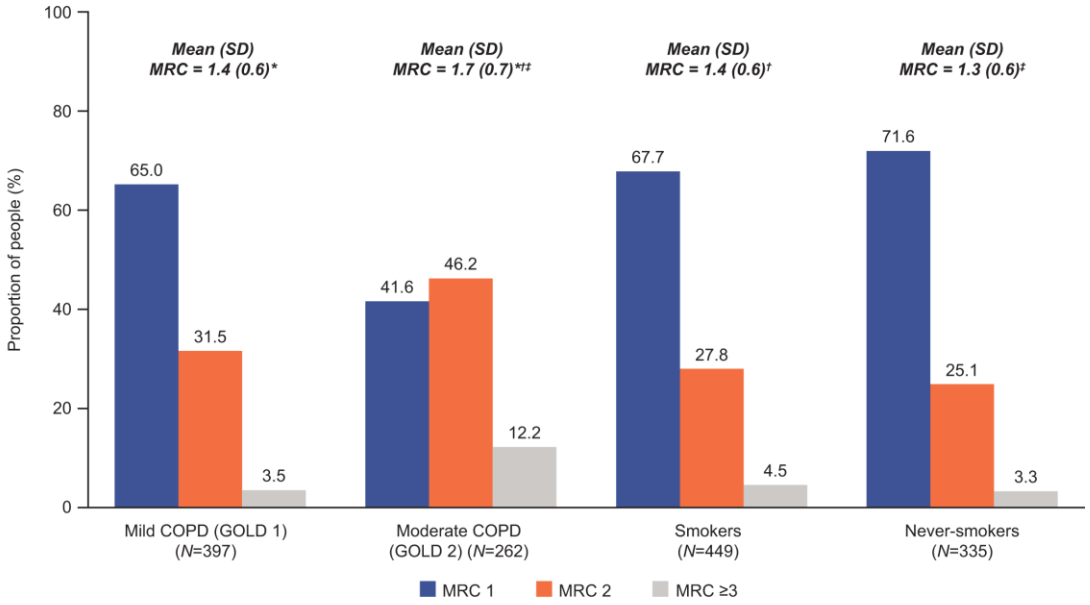
CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; MRC, Medical Research Council; Q, quartile; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.



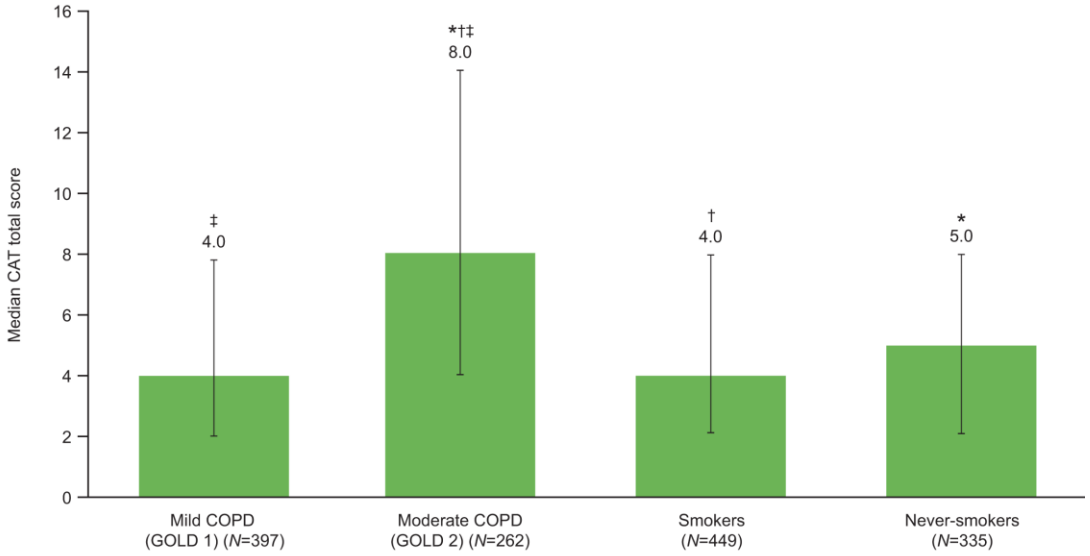
Subgroup analyses conducted for participants with COPD:

1. Women versus men
2. Physician-diagnosed COPD versus physician-undiagnosed COPD
3. People with and without a recent history of exacerbations†

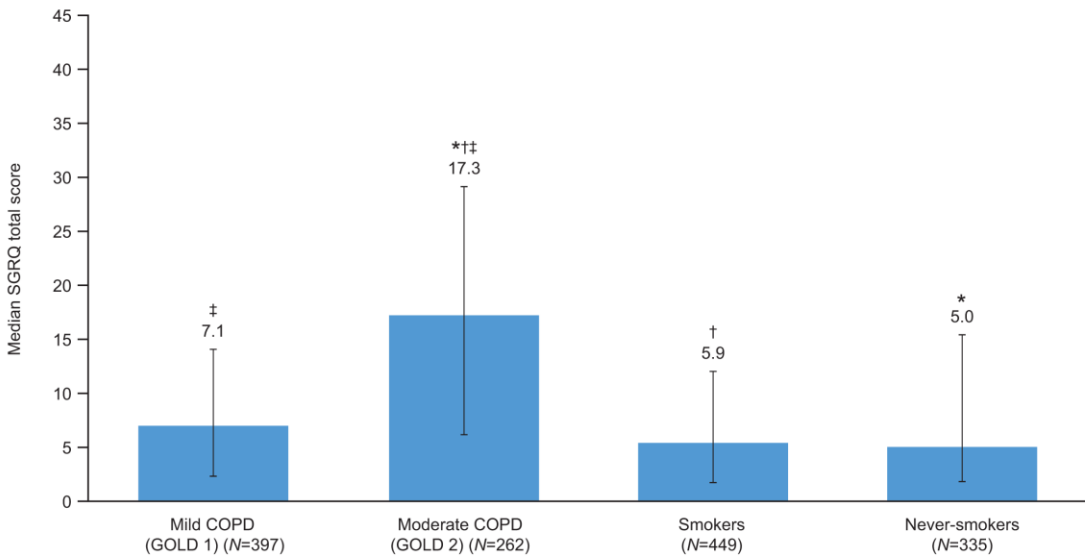
A


Mean (SD)
MRC = 1.4 (0.6)*
Mean (SD)
MRC = 1.7 (0.7)*†‡
Mean (SD)
MRC = 1.4 (0.6)†
Mean (SD)
MRC = 1.3 (0.6)‡
Proportion of people (%)
100
80
60
40
20
0
65.0
31.5
3.5
41.6
46.2
12.2
67.7
27.8
4.5
71.6
25.1
3.3
Mild COPD (GOLD 1) (N=397)
Moderate COPD (GOLD 2) (N=262)
Smokers (N=449)
Never-smokers (N=335)
MRC 1
MRC 2
MRC ≥3

B

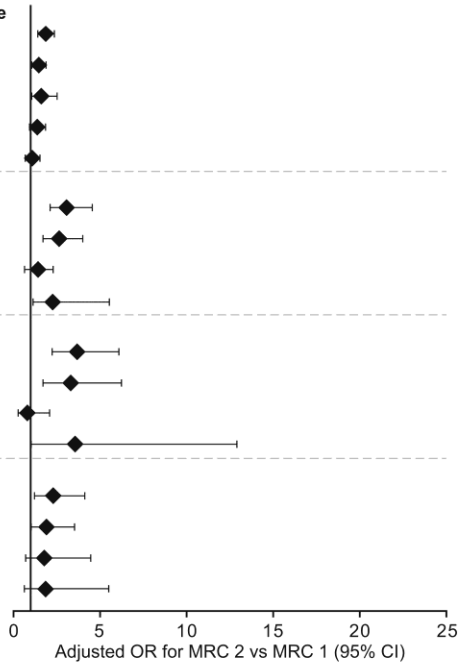

Median CAT total score
16
14
12
10
8
6
4
2
0
‡
4.0
*†‡
8.0
†
4.0
*
5.0
Mild COPD (GOLD 1) (N=397)
Moderate COPD (GOLD 2) (N=262)
Smokers (N=449)
Never-smokers (N=335)

C


Median SGRQ total score
45
40
35
30
25
20
15
10
5
0
‡
7.1
*†‡
17.3
†
5.9
*
5.0
Mild COPD (GOLD 1) (N=397)
Moderate COPD (GOLD 2) (N=262)
Smokers (N=449)
Never-smokers (N=335)

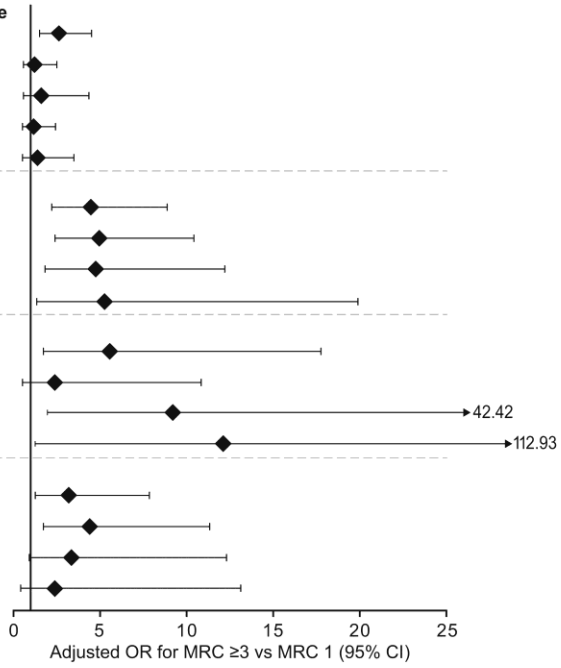
A

	Adjusted OR (95% CI)	*P*-value
Overall (*N*=1443)		
COPD (*n*=659) vs non-COPD (*n*=784)	1.83 (1.42, 2.37)	**<0.001**
Mild COPD (*n*=397) vs non-COPD (*n*=784)	1.42 (1.05, 1.91)	**0.022**
Mild COPD (*n*=397) vs never-smokers (*n*=335)	1.64 (1.07, 2.52)	**0.023**
Mild COPD (*n*=397) vs smokers (*n*=449)	1.35 (0.98, 1.88)	0.070
Smokers (*n*=449) vs never-smokers (*n*=335)	1.04 (0.69, 1.57)	0.862
COPD (*N*=659)†		
Women (*n*=255) vs men (*n*=404)	3.12 (2.14, 4.55)	**<0.001**
Diagnosed (*n*=163) vs undiagnosed (*n*=496)	2.64 (1.71, 4.08)	**<0.001**
1 exacerbation (*n*=74) vs 0 exacerbation (*n*=355)	1.23 (0.65, 2.30)	0.528
≥2 exacerbations (*n*=38) vs 0 exacerbation (*n*=355)	2.49 (1.12, 5.56)	**0.026**
Mild COPD (GOLD 1) (*N*=397)†		
Women (*n*=138) vs men (*n*=259)	3.70 (2.23, 6.14)	**<0.001**
Diagnosed (*n*=66) vs undiagnosed (*n*=331)	3.27 (1.71, 6.23)	**<0.001**
1 exacerbation (*n*=39) vs 0 exacerbation (*n*=227)	0.81 (0.31, 2.11)	0.664
≥2 exacerbations (*n*=16) vs 0 exacerbation (*n*=227)	3.62 (1.02, 12.86)	**0.047**
Moderate COPD (GOLD 2) (*N*=262)†		
Women (*n*=117) vs men (*n*=145)	2.28 (1.26, 4.12)	**0.006**
Diagnosed (*n*=97) vs undiagnosed (*n*=165)	1.93 (1.04, 3.55)	**0.036**
1 exacerbation (*n*=35) vs 0 exacerbation (*n*=128)	1.82 (0.74, 4.47)	0.191
≥2 exacerbations (*n*=22) vs 0 exacerbation (*n*=128)	1.91 (0.67, 5.49)	0.229



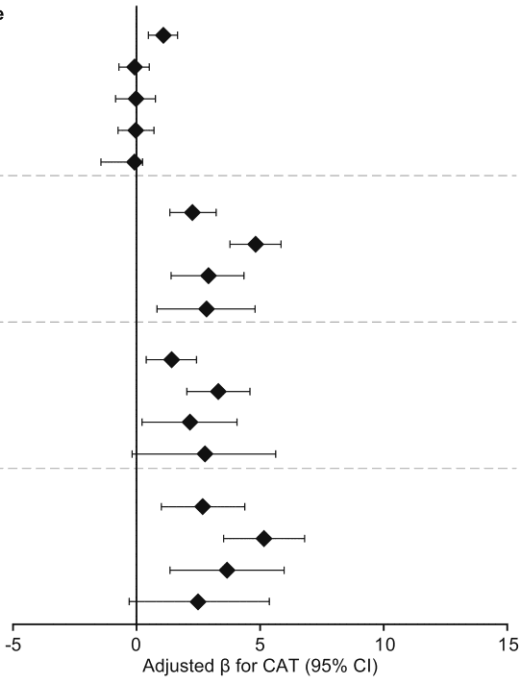
B

	Adjusted OR (95% CI)	*P*-value
Overall (*N*=1443)		
COPD (*n*=659) vs non-COPD (*n*=784)	2.65 (1.55, 4.51)	**<0.001**
Mild COPD (*n*=397) vs non-COPD (*n*=784)	1.26 (0.62, 2.54)	0.522
Mild COPD (*n*=397) vs never-smokers (*n*=335)	1.60 (0.58, 4.41)	0.361
Mild COPD (*n*=397) vs smokers (*n*=449)	1.14 (0.54, 2.44)	0.728
Smokers (*n*=449) vs never-smokers (*n*=335)	1.40 (0.55, 3.53)	0.481
COPD (*N*=659)†		
Women (*n*=255) vs men (*n*=404)	4.50 (2.27, 8.92)	**<0.001**
Diagnosed (*n*=163) vs undiagnosed (*n*=496)	5.01 (2.40, 10.45)	**<0.001**
1 exacerbation (*n*=74) vs 0 exacerbation (*n*=355)	4.76 (1.85, 12.26)	**0.001**
≥2 exacerbations (*n*=38) vs 0 exacerbation (*n*=355)	5.30 (1.41, 19.92)	**0.014**
Mild COPD (GOLD 1) (*N*=397)†		
Women (*n*=138) vs men (*n*=259)	5.56 (1.74, 17.79)	**0.004**
Diagnosed (*n*=66) vs undiagnosed (*n*=331)	2.47 (0.56, 10.86)	0.231
1 exacerbation (*n*=39) vs 0 exacerbation (*n*=227)	9.24 (2.01, 42.42)	**0.004**
≥2 exacerbations (*n*=16) vs 0 exacerbation (*n*=227)	12.11 (1.30, 112.93)	**0.029**
Moderate COPD (GOLD 2) (*N*=262)†		
Women (*n*=117) vs men (*n*=145)	3.19 (1.29, 7.86)	**0.012**
Diagnosed (*n*=97) vs undiagnosed (*n*=165)	4.45 (1.75, 11.36)	**0.002**
1 exacerbation (*n*=35) vs 0 exacerbation (*n*=128)	3.37 (0.92, 12.33)	0.066
≥2 exacerbations (*n*=22) vs 0 exacerbation (*n*=128)	2.43 (0.45, 13.14)	0.303



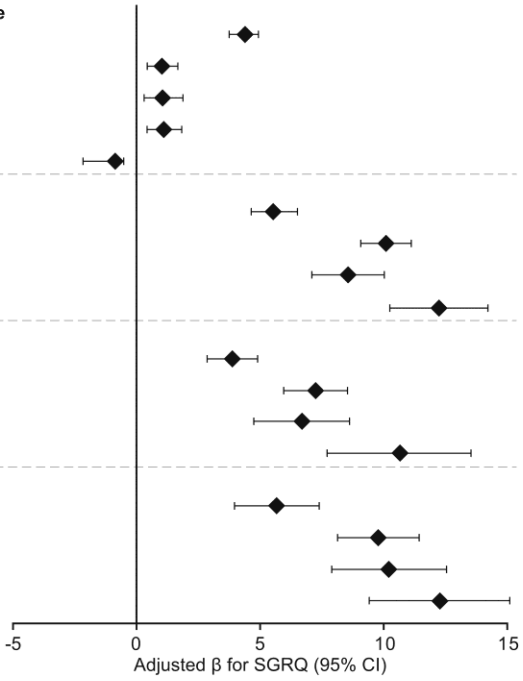
A

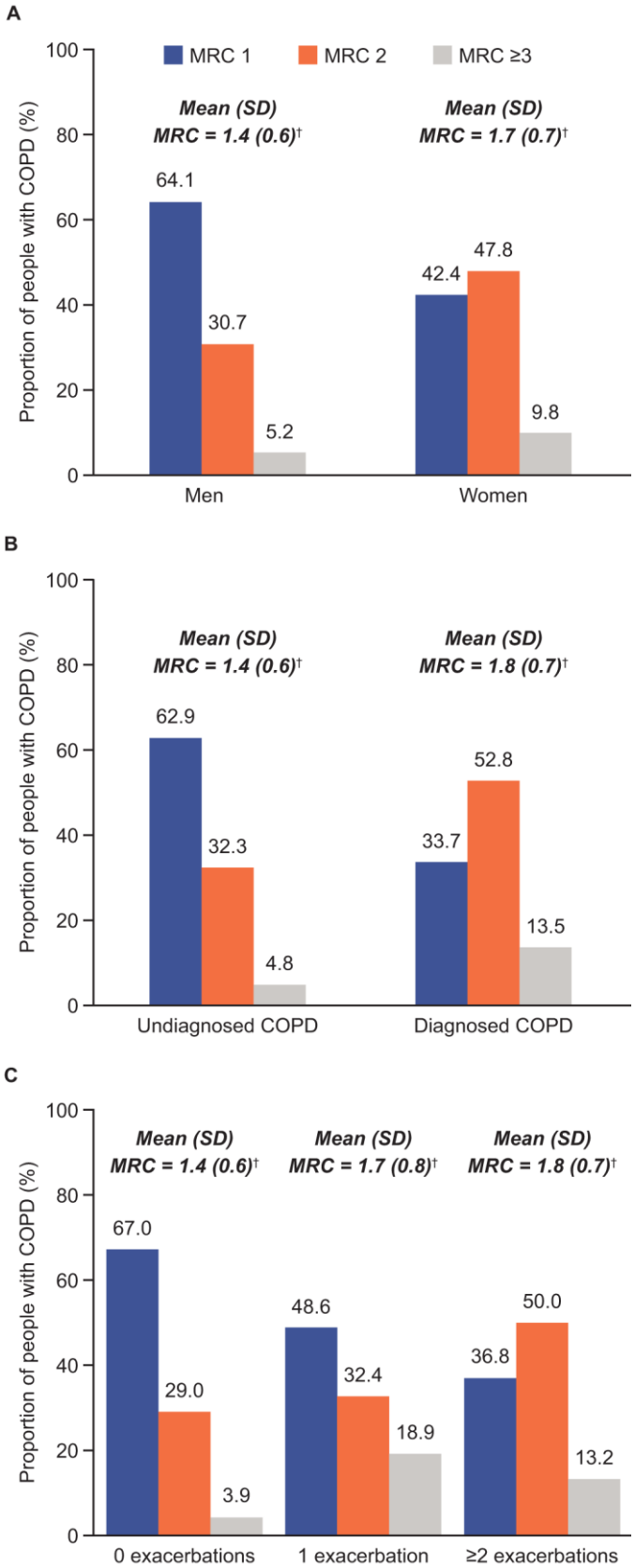
Overall (*N*=1443)	**Adjusted β (95% CI)**	***P*-value**
COPD (*n*=659) vs non-COPD (*n*=784)	1.06 (0.48, 1.64)	**<0.001**
Mild COPD (*n*=397) vs non-COPD (*n*=784)	-0.10 (-0.71, 0.50)	0.741
Mild COPD (*n*=397) vs never-smokers (*n*=335)	-0.06 (-0.83, 0.72)	0.884
Mild COPD (*n*=397) vs smokers (*n*=449)	-0.02 (-0.72, 0.69)	0.963
Smokers (*n*=449) vs never-smokers (*n*=335)	-0.60 (-1.42, 0.23)	0.155
COPD (*N*=659)†		
Women (*n*=255) vs men (*n*=404)	2.25 (1.33, 3.18)	**<0.001**
Diagnosed (*n*=163) vs undiagnosed (*n*=496)	4.78 (3.76, 5.80)	**<0.001**
1 exacerbation (*n*=74) vs 0 exacerbation (*n*=355)	2.85 (1.39, 4.32)	**<0.001**
≥2 exacerbations (*n*=38) vs 0 exacerbation (*n*=355)	2.79 (0.82, 4.76)	**0.006**
Mild COPD (GOLD 1) (*N*=397)†		
Women (*n*=138) vs men (*n*=259)	1.40 (0.39, 2.40)	**0.006**
Diagnosed (*n*=66) vs undiagnosed (*n*=331)	3.29 (2.01, 4.57)	**<0.001**
1 exacerbation (*n*=39) vs 0 exacerbation (*n*=227)	2.15 (0.23, 4.06)	**0.028**
≥2 exacerbations (*n*=16) vs 0 exacerbation (*n*=227)	2.71 (-0.20, 5.62)	0.068
Moderate COPD (GOLD 2) (*N*=262)†		
Women (*n*=117) vs men (*n*=145)	2.66 (0.98, 4.34)	**0.002**
Diagnosed (*n*=97) vs undiagnosed (*n*=165)	5.12 (3.49, 6.75)	**<0.001**
1 exacerbation (*n*=35) vs 0 exacerbation (*n*=128)	3.63 (1.32, 5.94)	**0.002**
≥2 exacerbations (*n*=22) vs 0 exacerbation (*n*=128)	2.50 (-0.33, 5.33)	0.083

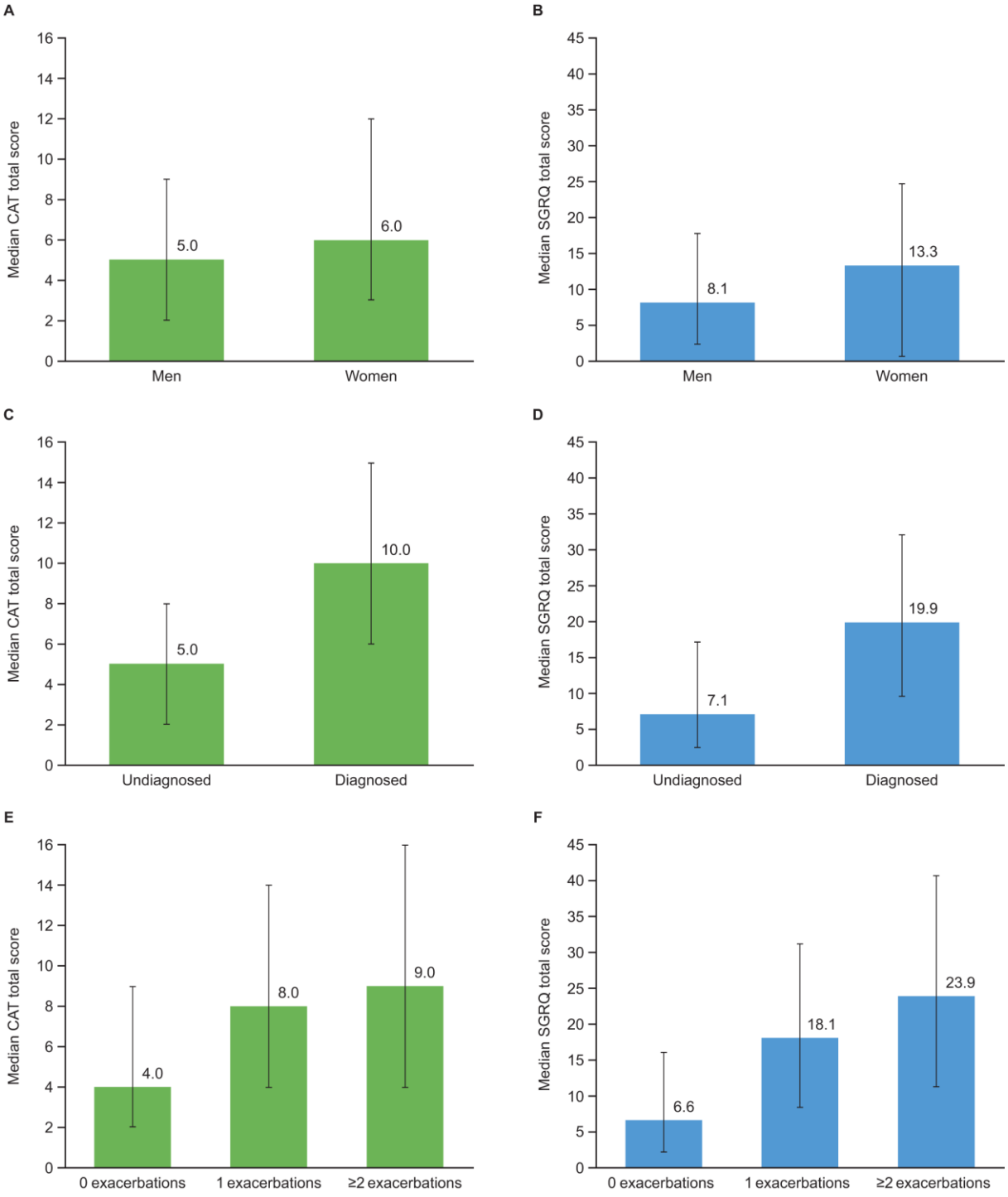


B

Overall (*N*=1443)	**Adjusted β* (95% CI)**	***P*-value**
COPD (*n*=659) vs non-COPD (*n*=784)	4.34 (2.84, 5.84)	**<0.001**
Mild COPD (*n*=397) vs non-COPD (*n*=784)	1.06 (-0.44, 2.57)	0.166
Mild COPD (*n*=397) vs never-smokers (n=335)	1.09 (-1.80, 3.99)	0.459
Mild COPD (*n*=397) vs smokers (*n*=449)	1.13 (-0.44, 2.71)	0.158
Smokers (*n*=449) vs never-smokers (*n*=335)	-0.77 (-3.76, 2.22)	0.613
COPD (*N*=659)†		
Women (*n*=255) vs men (*n*=404)	5.55 (3.43, 7.66)	**<0.001**
Diagnosed (*n*=163) vs undiagnosed (*n*=496)	10.08 (7.74, 12.42)	**<0.001**
1 exacerbation (*n*=74) vs 0 exacerbation (*n*=355)	8.55 (5.38, 11.72)	**<0.001**
≥2 exacerbations (*n*=38) vs 0 exacerbation (*n*=355)	12.21 (7.98, 16.44)	**<0.001**
Mild COPD (GOLD 1) (*N*=397)†		
Women (*n*=138) vs men (*n*=259)	3.88 (1.60, 6.15)	**<0.001**
Diagnosed (*n*=66) vs undiagnosed (*n*=331)	7.23 (4.33, 10.12)	**<0.001**
1 exacerbation (*n*=39) vs 0 exacerbation (*n*=227)	6.67 (2.61, 10.73)	**0.001**
≥2 exacerbations (*n*=16) vs 0 exacerbation (*n*=227)	10.61 (4.54, 16.68)	**<0.001**
Moderate COPD (GOLD 2) (*N*=262)†		
Women (*n*=117) vs men (*n*=145)	2.55 (0.90, 7.21)	**0.003**
Diagnosed (*n*=97) vs undiagnosed (*n*=165)	3.99 (1.28, 12.48)	**<0.001**
1 exacerbation (*n*=35) vs 0 exacerbation (*n*=128)	2.97 (0.66, 13.32)	**<0.001**
≥2 exacerbations (*n*=22) vs 0 exacerbation (*n*=128)	2.24 (0.35, 14.26)	**<0.001**




A
MRC 1
MRC 2
MRC ≥3
Proportion of people with COPD (%)
100
80
60
40
20
0
Mean (SD)
MRC = 1.4 (0.6)†
Mean (SD)
MRC = 1.7 (0.7)†
64.1
30.7
5.2
42.4
47.8
9.8
Men
Women
B
Proportion of people with COPD (%)
Mean (SD)
MRC = 1.4 (0.6)†
Mean (SD)
MRC = 1.8 (0.7)†
62.9
32.3
4.8
33.7
52.8
13.5
Undiagnosed COPD
Diagnosed COPD
C
Proportion of people with COPD (%)
Mean (SD)
MRC = 1.4 (0.6)†
Mean (SD)
MRC = 1.7 (0.8)†
Mean (SD)
MRC = 1.8 (0.7)†
67.0
29.0
3.9
48.6
32.4
18.9
36.8
50.0
13.2
0 exacerbations
1 exacerbation
≥2 exacerbations


A
Median CAT total score
16
14
12
10
8
6
4
2
0
5.0
6.0
Men
Women
B
Median SGRQ total score
45
40
35
30
25
20
15
10
5
0
8.1
13.3
Men
Women
C
Median CAT total score
16
14
12
10
8
6
4
2
0
5.0
10.0
Undiagnosed
Diagnosed
D
Median SGRQ total score
45
40
35
30
25
20
15
10
5
0
7.1
19.9
Undiagnosed
Diagnosed
E
Median CAT total score
16
14
12
10
8
6
4
2
0
4.0
8.0
9.0
0 exacerbations
1 exacerbations
≥2 exacerbations
F
Median SGRQ total score
45
40
35
30
25
20
15
10
5
0
6.6
18.1
23.9
0 exacerbations
1 exacerbations
≥2 exacerbations

Dyspnoea and Symptom Burden in Mild-Moderate COPD: the Canadian Cohort Obstructive Lung Disease Study

Authors: Mathew Cherian, Dennis Jensen, Wan C. Tan, Sara Mursleen, Emma C. Goodall, Gilbert A. Nadeau, Amnah M. Awan, Darcy D. Marciniuk, Brandie L. Walker, Shawn D. Aaron, Denis E. O'Donnell, Kenneth R. Chapman, François Maltais, Paul Hernandez, Don D. Sin, Andrea Benedetti, Jean Bourbeau

Supplementary Material

Table of Contents

1. Sampling Strategy

Participants in the Canadian Cohort Obstructive Lung Disease (CanCOLD) study were randomly sampled from 9 cities across Canada: Calgary, Halifax, Kingston, Montreal, Ottawa, Quebec City, Saskatoon, Toronto and Vancouver.

The CanCOLD study was built upon the Canadian Obstructive Lung Disease (COLD) population-based prevalence study [1]. Briefly, the COLD study randomly sampled 6,551 non-institutionalized men and women above the age of 40 years from areas with a population greater than 250,000 in the previously mentioned 9 cities. Random samples of eligible participants were identified using Statistics Canada census data and were recruited using random digit dialing.

Participants from the COLD prevalence study were invited to enrol in CanCOLD with the purpose of establishing a Canadian longitudinal population-based COPD cohort. First, the two COPD subgroups were recruited from the COLD participant group and split into either (1) mild COPD (post-bronchodilator $FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ predicted) or (2) moderate COPD (post-bronchodilator $FEV_1/FVC < 0.70$ and $50\% \leq FEV_1 < 80\%$ predicted). Second, age and sex matched non-COPD peers were recruited into either (1) non-COPD ever smokers (post-bronchodilator $FEV_1/FVC \geq 0.70$ and positive smoking history) or (2) non-COPD never smokers (post-bronchodilator $FEV_1/FVC \geq 0.70$ and negative smoking history) groups.

2. Key Definitions

2.1 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification

For the severity of airflow obstruction, GOLD has been classified using National Health and Nutrition Examination Survey (NHANES) equations [2]; classification was similar using the Global Lung Function Initiative (GLI) [3].

2.2 Physician Diagnosis

Participants with spirometrically-defined COPD (post-bronchodilator $FEV_1/FVC < 0.70$) who reported having received a previous physician-diagnosis of COPD (chronic bronchitis, emphysema, COPD, chronic obstructive pulmonary disease) upon entering the CanCOLD study were identified as having "diagnosed" COPD. Participants with spirometrically-defined COPD, who reported not having received a physician diagnosis of COPD prior to entry in the CanCOLD study, were identified as having "undiagnosed" COPD.

2.3 COPD Exacerbation

CanCOLD used two different operational definitions. One definition was 'symptom-based', requiring a change in at least one major symptom (dyspnoea, sputum purulence, sputum volume) that lasts at least 48 hours. The other definition was 'event-based', requiring a change of at least one major symptom that lasts at least 48 hours and use of antibiotics and/or systemic corticosteroids or health services. The purpose of considering both definitions was to be able to capture all exacerbation-like respiratory events, with varying levels of severity, in order to capture a truer incidence of exacerbations in our cohort.

3. Covariate Selection

Logistic regression models for our primary and secondary objectives were adjusted for: age; body mass index (BMI); smoking history in pack year units; cardiovascular comorbidities; and presence of other respiratory comorbidities, not including asthma. These covariates were selected based on prior knowledge of associations between these variables and the primary outcome (MRC dyspnoea scale). Furthermore, exploratory univariate analysis showed significant association ($p<0.05$) between each of these covariates with our primary outcome measure, MRC dyspnoea scale rating, and with COPD severity (based on %predicted FEV1). Thus, these were considered confounding variables and were appropriately adjusted for in our models.

Self-reported physician diagnosis of asthma and respiratory medication use were also found to be confounding variables from the aforementioned univariate analysis. However, given the significant difference in self-reported asthma and medication use between non COPD and the non-COPD groups (**Table 1 in main manuscript**), we conducted sensitivity analyses by removing participants with self-reported physician diagnosis of asthma and by removing participants who reported any respiratory medication use. Furthermore, in this cohort of people with mild-moderate COPD, it is possible that participants who previously received a physician diagnosis of asthma may have spirometrically-defined COPD that was misclassified as asthma. Unfortunately, there remains no definitive way to differentiate between COPD and asthma when post-bronchodilator FEV_1/FVC is <0.70. Furthermore, even in the absence of cigarette smoking, it is difficult to distinguish between COPD and asthma, given relatively high prevalence of COPD in never smokers [4]. Considering that close to a third of people with COPD in the CanCOLD cohort had self-reported physician diagnosis of asthma (30.7%)

or used a respiratory medication(s) (32.6%) these variables could have led to significant confounding. As a result, a sensitivity analysis removing people with self-reported physician diagnosis of asthma was done. [5]. Results were similar to our main results (**Figures 3 and 4 in main manuscript)** and presented in **Supplementary Tables E5 and E6.**

4. Outcome Selection

The Medical Research Council (MRC or mMRC) dyspnoea scale was selected as our primary outcome for a number of reasons. First, the MRC scale has been shown to have an excellent prognostic and discriminative value and increasing values have been shown to correlate well with increasing mortality [6]. In fact, dyspnoea quantified in MRC terms has been shown to prognosticate better than FEV_1-defined stages of COPD [7]. Additionally, it is simple to use and outcomes reported in MRC terms are easily relatable to a clinical context. MRC corresponds with the modified MRC (mMRC) as shown in **Supplementary Table E1.** The main difference between MRC and mMRC is that in an individual who is not troubled by breathlessness except on strenuous exercise is given a score of zero in mMRC which is more intuitive than giving a score of one (as in MRC) to someone who is relatively asymptomatic.

Furthermore, the MRC Dyspnoea scale was selected as a primary outcome when the CanCOLD study was initiated in 2009 because multiple guidelines and statements, which were timely then, used the MRC Dyspnoea scale. In fact, till 2017, the Canadian Thoracic Society (CTS) used the MRC scale [8]. Even though the 2019 CTS guidelines on pharmoctherapy in COPD now use mMRC in alignment with GOLD guidelines [9], the use of MRC dyspnoea scale still remains clinically relevant in the Canadian context, in which CanCOLD was conducted.

Nonetheless, the MRC Dyspnoea scale has its limitations. It is not responsive; it is unidimensional; and does not capture health related quality of life (HRQoL). Consequently, we also included the COPD Assessment Test (CAT) score and the Saint George's Respiratory Questionnaire (SGRQ) score as secondary outcomes. The CAT is a self-administered

questionnaire of 8 items that quantifies various respiratory and non-respiratory manifestations of COPD in order to get a snapshot of COPD-specific HRQoL. Each item is given a score of 1-5, for a total possible score of 40. A higher score indicates more severely impaired HRQoL. Although a clear minimally clinically important difference (MCID) is yet to be established, the CAT score has been shown to be responsive to intervention [10]. The SGRQ is a widely used, multidimensional, COPD specific HRQoL questionnaire that uses a combination of yes/no and Likert type questions. Questions address frequency and severity of symptoms, activities limited by breathlessness, and psycho-social disturbances. Responses are tallied into a total score ranging from 0-100. A higher score indicates more severely impaired HRQoL. The SGRQ has shown to have good reproducibility, reliability ,and responsiveness [11]. It has also been shown to be multidimensional [12].

Table E1: MRC dyspnoea scale

MRC scale	Definition	mMRC scale
1	Not troubled by breathlessness except on strenuous exercise	0
2	Short of breath when hurrying on a level or when walking up a slight hill	1
3	Walks slower than most people on the level, or stops after 15 minutes walking at own pace	2
4	Stops for breath walking 100 yards, or after a few minutes on level ground	3
5	Too breathless to leave the house, or breathless when dressing/undressing	4

MRC, Medical Research Council**;** mMRC, modified Medical Research Council

5. Excluded Participants

80 participants were excluded because MRC dyspnoea assessment was unavailable due to difficulties evaluating MRC score due to non-ambulatory functional status attributed to comorbidities that were not COPD. They included:

- musculoskeletal comorbidities: *n*=54 [67.5%];
- neurological comorbidities: *n*=14 [17.5%];
- cardiac comorbidities: *n*=4 [5%];
- non-specified chronic pain syndrome: *n*=2 [3%];
- undisclosed: *n*=6 [8%]).

An additional 38 people with GOLD 3+ COPD were also excluded.

5.1 Exacerbation Analysis

In the analysis of dyspnoea and HRQoL between people with COPD who did and did not have an exacerbation(s) in the preceding 12 months, outcome measures from visit 3 were used, instead of outcomes measured at visit 1 that was used for all other analysis. This was in order to have am exacerbation history of 12 months preceding visit 3 available. At the time of analysis, 321 of the 1443 people who were included in all other analyses did not yet have follow up data available at Visit 3. The baseline characteristics of people with and without follow up data at visit 3 is presented in **Supplementary Table E2.** Of the 1122 people with visit 3 follow up data available, 467 had COPD. These 467 people with COPD included 419 people who had a spirometric diagnosis of COPD at visit 1 and 48 additional people who did not have a spirometric diagnosis of COPD at visit 1 but did at visit 3.

Table E2: Demographics and baseline characteristics of people with follow up data from visit 3 compared to people without follow up data from visit 3

	Total Cohort (N=1443)	Participants with V3 follow up (N=1122)	Participants without V3 follow up (N=321)	*P*-value*
Age, years, mean (SD)	66.5 ± 9.8	66.1 ± 9.4	67.9 ± 10.9	0.003*
Men, *n* (%)	816 (56.5)	633 (56.4)	183 (57.0)	0.898
BMI, mean (SD)	27.5 ± 5.0	27.3 ± 4.9	28.2 ± 5.3	0.005*
Never-smokers, *n* (%)	525 (36.4)	433 (38.6)	92 (28.7)	0.001*
Former smokers, *n* (%)	698 (48.4)	521 (46.4)	177 (55.1)	0.006*
Current smokers, *n* (%)	220 (15.2)	168 (15.0)	52 (16.2)	0.590
GOLD 1, *n* (%)	397 (27.5)	320 (28.5)	77 (24.0)	0.109
GOLD 2, *n* (%)	262 (18.2)	194 (17.3)	68 (21.2)	0.111
Self-reported physician-diagnosed asthma, *n* (%)	326 (22.6)	263 (23.4)	63 (19.6)	0.150
Any respiratory medication prescription‡, *n* (%)	300 (20.8)	234 (20.9)	66 (20.6)	0.909
MRC Score 1, *n* (%)	911 (63.1)	736 (65.6)	175 (54.5)	<0.001*
MR Score 2, *n* (%)	455 (31.5)	340 (30.3)	115 (35.8)	0.06
MRC3+, *n* (%)	77 (5.3)	46 (4.1)	31 (9.7)	<0.001*
SGRQ score, median (Q1, Q3)	7.6 (2.7, 18.1)	7.2 (2.6, 17.0)	8.9 (3.2, 20.6)	0.088
CAT score, median (Q1, Q3)	5.0 (2.0, 9.0)	4.9 (2.0, 8.0)	5.0 (3.0, 10.0)	0.014*
Emphysema score	1.1 ± 2.4	1.0 ± 2.2	1.5 ± 3.1	0.113
RV/TLC, %	39.6 ± 9.2	39.3 ± 8.8	40.9 ± 10.3	0.031*

**P*-values were obtained by performing Chi-square or Fisher exact test for category variables, and *t*-test (normal distribution) or Mann–Whitney U tests (non-normal distribution) for continuous variables.

‡Respiratory medicines included were: SAMA/SABA; LABA ± SAMA/SABA; LAMA ± SAMA/SABA; LAMA+LABA ± SAMA/SABA; ICS ± SAMA/SABA; LABA+ICS ± SAMA/SABA; LAMA+ICS ± SAMA/SABA; LAMA+LABA+ICS ± SAMA/SABA.

BMI, body mass index; CAT, COPD Assessment Test; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; MRC, Medical Research Council; Q, quartile; RV/TLC, residual volume-to-total lung capacity ratio; SD, standard deviation; SGRQ, Saint George's Respiratory Questionnaire; V3, visit 3

6. Variation in Follow-up Duration

CanCOLD was designed for participants to have three visits: (1) Visit 1 at baseline, (2) Visit 2 at the 18 months (or 1.5 years) mark, and (3) Visit 3 at the 36-month (or 3 year) mark.

Presented below is the actual time to follow up between visits

Table E3: Variation in Duration of Follow

Visit Interval	Duration
V1 - V2, months, median (Q1-Q3)	19.2 (18.0 – 21.1)
V1 - V3, months, median (Q1-Q3)	37.4 (35.9 – 40.2)

V1, visit 1; V2, visit 2; V3, visit 3

7. Comparison of baseline characteristics by sex, physician-diagnosed COPD status, and exacerbation frequency

Compared with men, women had lower BMI, and a greater proportion: were classified as GOLD 2; reported physician-diagnosis of asthma; and were prescribed respiratory medication(s). People reporting a physician diagnosis of COPD (24.7%) had more severe disease (GOLD 2), were less likely to be never-smokers, were more likely to report having physician-diagnosed asthma, and were prescribed more respiratory medications than people with undiagnosed COPD. People with COPD who had experienced ≥2 exacerbations in the 12 months prior to Visit 3 had more severe disease (GOLD 2 vs GOLD 1), were more likely to report physician-diagnosed asthma, and were prescribed more respiratory medications compared with those who had experienced ≤1 exacerbation.

Table E4: Demographics and baseline characteristics according to sex, the presence of a COPD diagnosis, and exacerbation frequency

	Men (*N*=404)	Women (*N*=255)	*P*-value*	COPD diagnosis (*N*=163)	No COPD diagnosis (*N*=496)	*P*-value*	No exacerbation (*N*=355)	1 exacerbation (*N*=74)	≥2 exacerbations (*N*=38)	*P*-value†
Age, years, mean (SD)	67.2 (10.3)	67.2 (9.7)	0.767	66.7 (9.4)	67.4 (10.3)	0.362	70.8 (9.7)	69.5 (7.8)	69.2 (9.0)	0.404
Men, *n* (%)	404 (100.0)	0 (0.0)	-	82 (50.3)	322 (64.9)	**0.001**	227 (63.9)	43 (58.1)	19 (50.0)	0.190
BMI, mean (SD)	27.6 (4.3)	26.6 (5.3)	**<0.001**	27.2 (4.9)	27.2 (4.7)	0.902	26.9 (4.5)	28.1 (5.6)	27.5 (5.3)	0.241
Never-smokers, *n* (%)	110 (27.2)	80 (31.4)	0.253	29 (17.8)	161 (32.5)	**<0.001**	117 (33.0)	21 (28.4)	11 (28.9)	0.685
Former smokers, *n* (%)	230 (56.9)	122 (47.8)	**0.023**	90 (55.2)	262 (52.8)	0.595	189 (53.2)	37 (50.0)	20 (52.6)	0.879
Current smokers, *n* (%)	64 (15.8)	53 (20.8)	0.106	44 (27.0)	73 (14.7)	**<0.001**	49 (13.8)	16 (21.6)	7 (18.4)	0.206
GOLD 1, *n* (%)	259 (64.1)	138 (54.1)	**0.011**	66 (40.5)	331 (66.7)	**<0.001**	227 (63.9)	39 (52.7)	16 (42.1)	**0.011**
GOLD 2, *n* (%)	145 (35.9)	117 (45.9)	**0.011**	97 (59.5)	165 (33.3)	**<0.001**	128 (36.1)	35 (47.3)	22 (57.9)	**0.011**
Self-reported physician-diagnosed asthma, *n* (%)	110 (27.2)	92 (36.1)	**0.016**	76 (46.6)	126 (25.4)	**<0.001**	104 (29.3)	26 (35.1)	23 (60.5)	**<0.001**
Any respiratory medication prescription‡, *n* (%)	111 (27.5)	104 (40.8)	**<0.001**	106 (65.0)	109 (22.0)	**<0.001**	99 (27.9)	37 (50.0)	25 (65.8)	**<0.001**
Emphysema score	1.8 ± 3.1	1.6 ± 3.1	0.05	2.9 ± 4.2	1.4 ± 2.5	**<0.001**	1.3 ± 2.4	2.8 ± 4.5	1.3 ± 2.4	**0.038**
RV/TLC, %	39.8 ± 8.6	45.4 ± 10.1	**<0.001**	44.0 ± 9.5	41.3 ± 9.6	**<0.001**	41.1 ± 9.3	43.3 ± 10.3	41.1 ± 9.3	0.350
Chronic Bronchitis, *n* (%)	68 (16.8)	44 (17.3)	0.888	59 (36.2)	53 (10.7)	**<0.001**	52 (14.6)	22 (29.7)	15 (39.5)	**<0.001**

*_P_-values were obtained by performing Chi-square or Fisher exact test for category variables, and _t_-test (normal distribution) or Mann–Whitney U tests (non-normal distribution) for continuous variables.

†_P_-values were obtained by performing Chi-square or Fisher exact tests for category variables, and analysis of variance (normal distribution) or Kruskal–Wallis test (not normal distribution) for continuous variables.

‡Respiratory medicines included were: SAMA/SABA; LABA ± SAMA/SABA; LAMA ± SAMA/SABA; LAMA+LABA ± SAMA/SABA; ICS ± SAMA/SABA; LABA+ICS ± SAMA/SABA; LAMA+ICS ± SAMA/SABA; LAMA+LABA+ICS ± SAMA/SABA.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; RV/TLC, residual volume/total lung capacity; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

8. Sensitivity Analysis Results

Table E5: Comparative odds ratios of dyspnoea severity* and adjusted β of HRQoL: Sensitivity analysis (excluding patients with asthma)

	MRC 2 vs MRC 1		MRC ≥3 vs MRC 1		CAT total score		SGRQ total score	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted β (95% CI)	*P* value	Adjusted β (95% CI)	*P* value
Overall								
COPD vs non-COPD	1.83 (1.42, 2.37)	**<0.001**	2.65 (1.55, 4.51)	**<0.001**	1.06 (0.48, 1.64)	**<0.001**	4.34 (2.84, 5.84)	**<0.001**
Mild COPD vs non-COPD	1.42 (1.05, 1.91)	**0.022**	1.26 (0.62, 2.54)	0.522	-0.10 (-0.71, 0.50)	0.741	1.06 (-0.44, 2.57)	0.166
Mild COPD vs never-smokers	1.64 (1.07, 2.52)	**0.023**	1.60 (0.58, 4.41)	0.361	-0.06 (-0.83, 0.72)	0.884	1.09 (-1.80, 3.99)	0.459
Mild COPD vs smokers	1.35 (0.98, 1.88)	0.070	1.14 (0.54, 2.44)	0.728	-0.02 (-0.72, 0.69)	0.963	1.13 (-0.44, 2.71)	0.158
Smokers vs never-smokers	1.04 (0.69, 1.57)	0.862	1.40 (0.55, 3.53)	0.481	-0.60 (-1.42, 0.23)	0.155	-0.77 (-3.76, 2.22)	0.613
COPD								
Women vs men	3.12 (2.14, 4.55)	**<0.001**	4.50 (2.27, 8.92)	**<0.001**	2.25 (1.33, 3.18)	**<0.001**	5.55 (3.43, 7.66)	**<0.001**
Diagnosed vs undiagnosed	2.64 (1.71, 4.08)	**<0.001**	5.01 (2.40, 10.45)	**<0.001**	4.78 (3.76, 5.80)	**<0.001**	10.08 (7.74, 12.42)	**<0.001**
1 vs 0 exacerbations	1.23 (0.65, 2.30)	0.528	4.76 (1.85, 12.26)	**0.001**	2.85 (1.39, 4.32)	**<0.001**	8.55 (5.38, 11.72)	**<0.001**
≥2 vs 0 exacerbations	2.49 (1.12, 5.56)	**0.026**	5.30 (1.41, 19.92)	**0.014**	2.79 (0.82, 4.76)	**0.006**	12.21 (7.98, 16.44)	**<0.001**
Mild COPD (GOLD 1)								
Women vs men	3.70 (2.23, 6.14)	**<0.001**	5.56 (1.74, 17.79)	**0.004**	1.40 (0.39, 2.40)	**0.006**	3.88 (1.60, 6.15)	**<0.001**
Diagnosed vs undiagnosed	3.27 (1.71, 6.23)	**<0.001**	2.47 (0.56, 10.86)	0.231	3.29 (2.01, 4.57)	**<0.001**	7.23 (4.33, 10.12)	**<0.001**
1 vs 0 exacerbations	0.81 (0.31, 2.11)	0.664	9.24 (2.01, 42.42)	**0.004**	2.15 (0.23, 4.06)	**0.028**	6.67 (2.61, 10.73)	**0.001**
≥2 vs 0 exacerbations	3.62 (1.02, 12.86)	**0.047**	12.11 (1.30, 112.93)	**0.029**	2.71 (-0.20, 5.62)	0.068	10.61 (4.54, 16.68)	**<0.001**
Moderate COPD (GOLD 2)								
Women vs men	2.28 (1.26, 4.12)	**0.006**	3.19 (1.29, 7.86)	**0.012**	2.66 (0.98, 4.34)	**0.002**	5.66 (1.89, 9.42)	**0.003**
Diagnosed vs undiagnosed	1.93 (1.04, 3.55)	**0.036**	4.45 (1.75, 11.36)	**0.002**	5.12 (3.49, 6.75)	**<0.001**	9.76 (6.02, 13.51)	**<0.001**
1 vs 0 exacerbations	1.82 (0.74, 4.47)	0.191	3.37 (0.92, 12.33)	0.066	3.63 (1.32, 5.94)	**0.002**	10.20 (5.21, 15.20)	**<0.001**
≥2 vs 0 exacerbations	1.91 (0.67, 5.49)	0.229	2.43 (0.45, 13.14)	0.303	2.50 (-0.33, 5.33)	0.083	12.26 (6.15, 18.37)	**<0.001**

*MRC, CAT and SGRQ were measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history.

Adjusted OR were obtained by performing multivariate multinomial logistic regression models, adjusted for sex, age, BMI, smoking history, cardiovascular comorbidities and other respiratory comorbidities. Adjusted β were obtained by performing multivariate linear regression models, adjusted for sex, age, BMI, smoking history, cardiovascular co-morbidities, and other respiratory comorbidities. For women versus men comparisons, sex was not included as a covariate. For smokers versus never-smokers, smoking history was not included as a covariate. To estimate the association between exacerbations and MRC, exacerbations were observed in preceding 12 months at Visit 3.

BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; MRC, Medical Research Council; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire.

Table E6: Comparative odds ratios of dyspnoea severity* and adjusted β of HRQoL: Sensitivity analysis (excluding patients with a prescription for any respiratory medication in the previous year)

	MRC 2 vs MRC 1		MRC ≥3 vs MRC 1		CAT total score		SGRQ total score	
	Adjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Adjusted β (95% CI)	*P* value	Adjusted β (95% CI)	*P* value
Overall								
COPD vs non-COPD	1.43 (1.06, 1.94)	**0.019***	1.63 (0.83, 3.23)	0.158	-0.14 (-0.71, 0.43)	0.628	1.36 (-0.03, 2.74)	0.054
Mild COPD vs non-COPD	1.36 (0.98, 1.90)	0.066	1.05 (0.44, 2.51)	0.909	-0.35 (-0.97, 0.27)	0.265	0.34 (-1.10, 1.79)	0.641
Mild COPD vs never-smokers	1.60 (0.99, 2.58)	0.053	1.63 (0.49, 5.43)	0.425	-0.33 (-1.13, 0.47)	0.417	0.32 (-2.44, 3.09)	0.818
Mild COPD vs smokers	1.29 (0.90, 1.85)	0.168	0.92 (0.36, 2.34)	0.864	-0.28 (-0.99, 0.43)	0.435	0.38 (-1.12, 1.88)	0.622
Smokers vs never-smokers	1.06 (0.69, 1.65)	0.784	1.23 (0.44, 3.42)	0.698	-0.57 (-1.37, 0.23)	0.165	-0.48 (-3.31, 2.35)	0.738
COPD								
Women vs men	3.35 (2.06, 5.47)	**<0.001**	5.10 (1.83, 14.26)	**0.002**	1.38 (0.45, 2.30)	**0.004**	3.47 (1.42, 5.53)	**<0.001**
Diagnosed vs undiagnosed	2.22 (1.13, 4.37)	**0.020**	2.85 (0.74, 10.91)	0.127	2.57 (1.24, 3.90)	**<0.001**	5.42 (2.47, 8.37)	**<0.001**
1 vs 0 exacerbations	1.54 (0.65, 3.69)	0.328	7.44 (1.82, 30.36)	**0.005**	3.01 (1.25, 4.76)	**<0.001**	9.69 (5.85, 13.53)	**<0.001**
≥2 vs 0 exacerbations	2.10 (0.55, 8.08)	0.279	5.36 (0.47, 61.69)	0.178	0.91 (-2.01, 3.83)	0.541	5.06 (-1.33, 11.45)	0.120
Mild COPD (GOLD 1)								
Women vs men	3.98 (2.21, 7.19)	**<0.001**	7.40 (1.57, 34.79)	**0.011**	1.24 (0.17, 2.30)	**0.023**	3.03 (0.79, 5.28)	**0.008**
Diagnosed vs undiagnosed	3.58 (1.52, 8.45)	**0.004**	2.38 (0.23, 24.65)	0.468	2.67 (1.06, 4.27)	**0.001**	6.02 (2.63, 9.41)	**<0.001**
1 vs 0 exacerbations	0.67 (0.20, 2.24)	0.513	18.80 (1.58, 223.37)	**0.020**	2.42 (0.24, 4.59)	**0.030**	8.05 (3.27, 12.82)	**0.001**
≥2 vs 0 exacerbations	6.37 (1.26, 32.28)	**0.025**	-	-	0.83 (-3.13, 4.79)	0.681	6.64 (-2.04, 15.33)	0.133
Moderate COPD (GOLD 2)								
Women vs men	2.56 (1.01, 6.47)	**0.048**	5.06 (1.01, 25.27)	**0.048**	1.64 (-0.21, 3.50)	0.082	4.28 (-0.09, 8.64)	0.055
Diagnosed vs undiagnosed	1.09 (0.34, 3.52)	0.889	2.61 (0.41, 16.81)	0.313	2.31 (-0.09, 4.71)	0.059	4.17 (-1.43, 9.77)	0.143
1 vs 0 exacerbations	12.16 (1.92, 77.09)	**0.008**	8.77 (0.74, 103.97)	0.085	4.52 (1.39, 7.64)	**0.005**	13.74 (7.10, 20.37)	**<0.001**
≥2 vs 0 exacerbations	-	-	4.66 (0.18, 122.71)	0.356	1.08 (-3.28, 5.44)	0.623	3.28 (-5.97, 12.53)	0.483

*MRC, CAT and SGRQ were measured at baseline for comparisons by sex and physician diagnosis of COPD, and at Visit 3 for comparisons by exacerbation history.

Adjusted OR were obtained by performing multivariate multinomial logistic regression models, adjusted for sex, age, BMI, smoking history, cardiovascular comorbidities and other respiratory comorbidities. Adjusted β were obtained by performing multivariate linear regression models, adjusted for sex, age, BMI, smoking history, cardiovascular co-morbidities, and other respiratory comorbidities. For women versus men comparisons, sex was not included as a covariate. For smokers versus never-smokers, smoking history was not included as a covariate. To estimate the association between exacerbations and MRC, exacerbations were observed in preceding 12 months at Visit 3.

BMI, body mass index; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; MRC, Medical Research Council; OR, odds ratio; SGRQ, St George's Respiratory Questionnaire.

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