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

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Supplementary Material

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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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