

Mild Chronic Obstructive Pulmonary Disease (COPD) and the Presence of Dyspnea: Inferences From the Canadian Cohort Obstructive Lung Disease (CanCOLD) Study

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Background

- Chronic and progressive dyspnea is the most characteristic symptom of chronic obstructive pulmonary disease (COPD),¹ and even mild dyspnea can negatively impact health-related quality of life (HRQoL).² Furthermore, dyspnea is associated with increased exacerbation rates compared with patients who do not have dyspnea.³
- Dyspnea often precedes a COPD diagnosis.⁴
- A thorough understanding of dyspnea in the early stages of COPD is currently lacking⁴ and dyspnea is yet to be characterized in a non-clinical population-based sample of adults with mild COPD.
- This secondary analysis of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study aimed to address the lack of knowledge on dyspnea in patients with mild COPD and those at risk of developing COPD.⁵

Objectives

- To compare dyspnea and HRQoL in adults with and without COPD from the CanCOLD study, and to better characterize these patients according to physician diagnosis of COPD, sex, and exacerbation frequency.

Methods

Study design

- CanCOLD (NCT00920348) was a 3-year, multicenter, prospective cohort study conducted in nine Canadian cities.⁵ Here we report a retrospective analysis of data from CanCOLD data (GSK study HO-15-15913).
- Three study visits were conducted: baseline (study entry), and 1.5 and 3 years after baseline.
- Participants were interviewed every 3 months to monitor symptom- and event-based exacerbations.
- Participants and subgroups**
- Participants were non-institutionalized adults aged ≥40 years. Participants were divided into four subgroups according to baseline COPD status:
 - Never smokers without COPD, defined as a lifetime exposure of <1/20 pack-year.
 - Smokers at risk of COPD.
 - Mild COPD (Global initiative for chronic Obstructive Lung Disease [GOLD] 1, based on GOLD 2007 staging).⁶
 - Moderate COPD (GOLD 2+, based on GOLD 2007 staging).⁶
- The COPD status groups were further subdivided for analyses based on diagnosis at baseline (patient-reported physician diagnosed/undiagnosed COPD), sex (male/female), and the number of symptom- and event-based exacerbations experienced (0, 1, ≥2) in the preceding 12 months.

Endpoints and assessments

- The primary endpoint for this analysis was the Medical Research Council (MRC) dyspnea scale, measured at baseline.
- Secondary endpoints included St George's Respiratory Questionnaire (SGRQ) total score and COPD Assessment Test (CAT) score, measured at baseline.
- Exertional dyspnea was investigated by analyzing changes in Borg scale intensity ratings of dyspnea for a given change in the rate of O₂ consumption (Δ Dyspnea/ Δ V_{O₂) and for a given change in minute ventilation (Δ Dyspnea/ Δ V^E) during symptom-limited incremental cardiopulmonary cycle exercise testing.}
- Exacerbations were assessed in the 12 months preceding the 3-year study visit.

Statistical analysis

- P-values were calculated using Chi-square or Fisher exact test for categorical variables, and analysis of variance (normal distribution) or Kruskal-Wallis test (not normal distribution) for continuous variables.
- Adjusted odds ratios (OR) were calculated using multivariate multinomial logistic regression models and adjusted β were calculated using multivariate linear regression models. All models were adjusted for age, sex (not included for female vs male comparisons), body mass index (BMI), smoking history, cardiovascular comorbidities, respiratory medications, physician-diagnosed asthma and other respiratory comorbidities, residual volume/total lung capacity ratio and emphysema score.
- Between-group comparisons for SGRQ and CAT scores were calculated using t-tests (normal distribution) or Mann Whitney U tests (not normal distribution).

Results

Participants

- The analyses included 1370 participants: 314 never smokers without COPD, 412 smokers at risk of COPD, and 644 participants with COPD (GOLD 1 [n=371]; GOLD 2+ [n=273]; **Table 1**). Most patients within the moderate COPD population were GOLD 2 (87.9%).

Table 1. Baseline demographics and clinical characteristics

	Never smokers without COPD (N=314)	Smokers at risk of COPD (N=412)	GOLD 1 COPD (N=371)	GOLD 2+ COPD (N=273)	P-value (between-group differences)
Age, years, mean (SD)	66.3 (9.8)	65.3 (9.4)	67.9 (9.8)	66.0 (10.3)	0.010
Male, n (%)	145 (46.2)	239 (58.0)	247 (66.6)	147 (53.8)	<0.001
BMI, kg/m ² , mean (SD)	27.0 (4.8)	27.9 (5.1)	26.7 (4.3)	27.5 (5.1)	0.011
Smoking status					
Never smoker, n (%)	314 (100.0)	0	124 (33.4)	60 (22.0)	<0.001
Former smoker, n (%)	0	323 (78.4)	198 (53.4)	147 (53.8)	<0.001
Current smoker, n (%)	0	89 (21.6)	49 (13.2)	66 (24.2)	<0.001
Pack-years, mean (SD)	0	18.8 (19.9)	17.3 (22.6)	27.7 (25.0)	<0.001
Self-reported comorbidities, n (%)					
Pneumonia	53 (16.9)	67 (16.3)	63 (17.0)	82 (30.0)	<0.001
Osteoporosis	29 (9.2)	42 (10.2)	44 (11.9)	35 (12.8)	0.478
Any musculoskeletal	87 (27.7)	126 (30.6)	123 (33.2)	80 (29.3)	0.463
Angina	11 (3.5)	17 (4.1)	8 (2.2)	20 (7.3)	0.011
Myocardial infarction	100 (31.8)	126 (30.6)	114 (30.7)	103 (37.7)	0.197
Hypertension	7 (2.2)	18 (4.4)	6 (1.6)	14 (5.1)	0.032
CVD excluding hypertension	86 (25.4)	97 (25.0)	93 (25.1)	99 (36.3)	0.004
Depression	10 (3.2)	17 (4.1)	16 (4.3)	23 (8.4)	0.017
Cataract	92 (28.9)	113 (27.4)	112 (30.2)	79 (28.9)	0.859
Glaucoma	13 (4.1)	18 (5.9)	22 (5.9)	16 (5.9)	0.441
Diabetes	25 (8.0)	42 (10.2)	24 (6.5)	33 (12.1)	0.067
Asthma	43 (13.7)	72 (17.5)	88 (23.7)	115 (42.1)	<0.001
Other respiratory comorbidities (excluding asthma)	102 (30.2)	117 (30.2)	86 (23.2)	90 (33.0)	0.034
Respiratory medications, n (%)					
Any	28 (8.9)	50 (12.1)	74 (19.9)	144 (52.7)	<0.001
LABA+SAMA/SABA	1 (0.2)	1 (0.3)	1 (0.3)	1 (0.4)	0.888
LAMA+SAMA/SABA	0	2 (0.5)	1 (0.3)	8 (2.9)	<0.001
LAMA+LABA+SAMA/SABA	0	0	0	2 (0.7)	0.040
LABA+ICS+SAMA/SABA	10 (3.2)	22 (5.3)	23 (6.2)	54 (19.8)	<0.001
LAMA+ICS+SAMA/SABA	0	0	1 (0.3)	3 (1.1)	0.033
ICS+SAMA/SABA	14 (4.5)	19 (4.6)	26 (7.0)	23 (8.4)	0.100
SAMA/SABA	4 (1.3)	5 (1.2)	20 (5.4)	22 (8.1)	<0.001
LAMA+LABA+ICS+SAMA/SABA	0	1 (0.2)	2 (0.5)	31 (11.4)	<0.001

CVD, cardiovascular disease; ICS, inhaled corticosteroid; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting bronchodilator; SAMA, short-acting muscarinic antagonist. SD, standard deviation

MRC dyspnea scale

- The prevalence of dyspnea (MRC ≥2/5) at baseline increased progressively from never smokers without COPD to those with COPD GOLD stage 2 and above (**Figure 1A**).
- Adults with COPD were significantly more dyspneic than those without COPD (MRC2 vs MRC1 OR: 1.48, 95% confidence intervals [CI]: 1.08, 2.01); participants with mild COPD were significantly more dyspneic than never smokers (MRC2 vs MRC1 OR: 1.74, 95% CI: 1.07, 2.85; **Table 2**).
- Within the COPD population, physician-diagnosed versus undiagnosed and female versus male participants were more dyspneic (MRC2 vs MRC1). Participants with 1 versus 0 exacerbations and ≥2 versus 0 exacerbations were also significantly more dyspneic (MRC ≥3 vs MRC1; **Figure 1B**; **Table 2**).

SGRQ and CAT scores

- Generally, SGRQ total scores and CAT scores at baseline increased progressively from never smokers without COPD to those with moderate COPD, denoting worse HRQoL (**Figures 2 and 3**).
- Within the COPD population, significantly poorer HRQoL was shown in physician-diagnosed versus undiagnosed (SGRQ and CAT) and female versus male (SGRQ) participants, and in those with 1 versus 0 and ≥2 versus 0 exacerbations (SGRQ and CAT; **Figures 2 and 3**, **Table 2**).

Exertional dyspnea

- Within the overall study population, there were statistically significant differences in Δ Dyspnea/ Δ V_{O₂ and Δ Dyspnea/ Δ V^E between the GOLD 1 subgroup versus the never smokers without COPD and smokers at risk of COPD (**Table 2**).}
- In the overall COPD population, females versus males had significantly higher Δ Dyspnea/ Δ V_{O₂ and Δ Dyspnea/ Δ V^E, and physician-diagnosed versus undiagnosed patients had significantly higher Δ Dyspnea/ Δ V^E (**Table 2**).}
- In the mild COPD population (i.e. controlled for forced expiratory volume in 1 second (FEV₁) % predicted), females versus males and physician-diagnosed versus undiagnosed patients had significantly higher Δ Dyspnea/ Δ V_{O₂ and Δ Dyspnea/ Δ V^E (**Table 2**).}

Figure 1. Prevalence and severity of dyspnea at baseline in (A) overall population; (B) COPD population

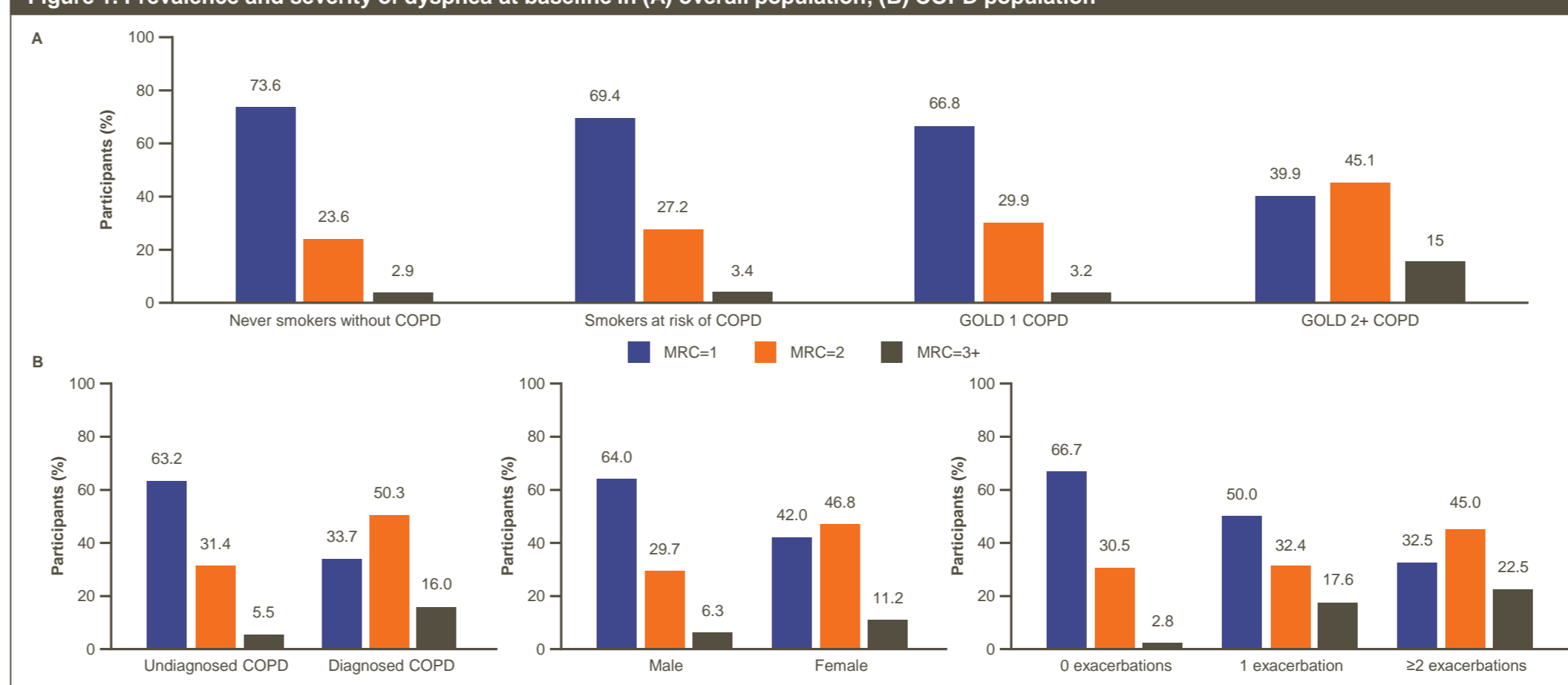


Table 2. Comparative MRC dyspnea scale, SGRQ total score, CAT score and exertional dyspnea by subgroup

	MRC 2 vs MRC 1		MRC ≥3 vs MRC 1		SGRQ total score		CAT score		Δ Dyspnea/ Δ V ^E		Δ Dyspnea/ Δ V _{O₂}	
	Adjusted OR* (95% CI)	P-value	Adjusted OR* (95% CI)	P-value	Adjusted β^{\dagger} (95% CI)	P-value	Adjusted β^{\dagger} (95% CI)	P-value	Adjusted β^{\dagger} (95% CI)	P-value	Adjusted β^{\dagger} (95% CI)	P-value
Overall study population (N=1370)												
COPD vs non-COPD	1.48 (1.08, 2.01)	0.014	1.66 (0.81, 3.42)	0.167	0.87 (-0.68, 2.42)	0.270	-0.33 (-0.97, 0.31)	0.314	-0.01 (-0.02, 0.00)	0.068	-0.57 (-1.10, -0.05)	0.033
GOLD 1 vs non-COPD	1.36 (0.96, 1.93)	0.079	0.77 (0.29, 2.06)	0.606	-0.48 (-1.93, 0.98)	0.521	-0.67 (-1.31, -0.03)	0.039	-0.01 (-0.02, 0.00)	0.008	-0.62 (-1.01, -0.23)	0.002
GOLD 1 vs never smokers	1.74 (1.07, 2.85)	0.026	0.81 (0.22, 2.91)	0.744	-0.67 (-3.15, 1.82)	0.598	-0.78 (-1.59, 0.03)	0.058	-0.02 (-0.03, 0.00)	0.021	-0.62 (-1.12, -0.12)	0.016
GOLD 1 vs smokers at risk of COPD	1.24 (0.84, 1.83)	0.270	0.95 (0.30, 3.01)	0.936	-0.29 (-1.84, 1.26)	0.713	-0.46 (-1.21, 0.29)	0.227	-0.01 (-0.02, 0.00)	0.021	-0.59 (-1.01, -0.18)	0.005
Overall COPD population (N=644)												
Diagnosed vs undiagnosed	1.71 (1.03, 2.83)	0.036	1.85 (0.76, 4.50)	0.173	4.95 (2.47, 7.43)	<0.001	3.05 (1.91, 4.18)	<0.001	0.02 (0.01, 0.04)	0.007	0.99 (-0.10, 2.09)	0.075
Female vs male	2.65 (1.72, 4.08)	<0.001	2.60 (1.18, 5.70)	0.018	2.31 (0.24, 4.37)	0.029	0.78 (-0.17, 1.73)	0.108	0.04 (0.02, 0.05)	<0.001	1.09 (0.17, 2.01)	0.020
1 vs 0 exacerbations [‡]	0.97 (0.50, 1.90)	0.940	6.66 (2.05, 21.70)	0.002	7.29 (4.19, 10.39)	<0.001	2.17 (0.63, 3.72)	0.006	-	-	-	-
≥2 vs 0 exacerbations [‡]	1.93 (0.81, 4.58)	0.137	10.67 (2.49, 45.64)	0.001	10.09 (6.09, 14.09)	<0.001	2.33 (0.33, 4.34)	0.023	-	-	-	-
Mild COPD population (N=371)												
Diagnosed vs undiagnosed	5.49 (2.08, 14.50)	<0.001	-	-	4.75 (0.93, 8.56)	0.015	2.75 (0.99, 4.52)	0.002	0.02 (0.00, 0.04)	0.018	0.81 (0.10, 1.52)	0.026
Female vs male	3.20 (1.76, 5.81)	<0.001	1.31 (0.21, 8.09)	0.770	2.08 (-0.18, 4.35)	0.071	0.55 (-0.51, 1.62)	0.306	0.04 (0.02, 0.05)	<0.001	1.20 (0.64, 1.76)	<0.001
1 vs 0 exacerbations [‡]	0.95 (0.36, 2.51)	0.916	27.32 (2.40, 311.11)	0.008	6.65 (2.81, 10.49)	<0.001	2.00 (0.02, 3.98)	0.047	-	-	-	-
≥2 vs 0 exacerbations [‡]	2.89 (0.67, 12.40)	0.153	10.67 (0.44, 328.02)	0.142	5.92 (-0.24, 12.08)	0.059	1.69 (-1.53, 4.90)	0.303	-	-	-	-
Moderate COPD population (N=273)												
Diagnosed vs undiagnosed	1.09 (0.54, 2.22)	0.804	1.78 (0.63, 5.01)	0.278	4.46 (0.46, 8.47)	0.029	3.04 (1.17, 4.91)	0.002	0.02 (0.00, 0.05)	0.103	1.19 (-1.09, 3.46)	0.305
Female vs male	2.27 (1.18, 4.38)	0.014	2.89 (1.08, 7.73)	0.035	1.76 (-1.88, 5.40)	0.343	0.85 (-0.85, 2.56)	0.326	0.04 (0.01, 0.06)	0.005	0.70 (-1.30, 2.71)	0.489
1 vs 0 exacerbations [‡]	0.87 (0.32, 2.34)	0.780	4.47 (0.92, 21.60)	0.063	7.63 (2.55, 12.71)	0.003	2.47 (-0.08, 5.01)	0.058	-	-	-	-
≥2 vs 0 exacerbations [‡]	1.62 (0.52, 5.03)	0.402	9.72 (1.55, 60.83)	0.015	10.83 (5.19, 16.46)	<0.001	2.32 (-0.50, 5.15)	0.106	-	-	-	-

*Odds ratio for participants having an MRC score of 2 or ≥3 versus an MRC score of 1. [†]Parameter estimate (slope) in linear regression model indicating the difference in score between the subgroups considered, significance is shown when 95% CI for the slope excludes 0. [‡]Comparison included all patients with COPD who attended the 3-year visit. Significant values are shown in bold.

Figure 2. SGRQ total score in (A) overall study population; (B) COPD population

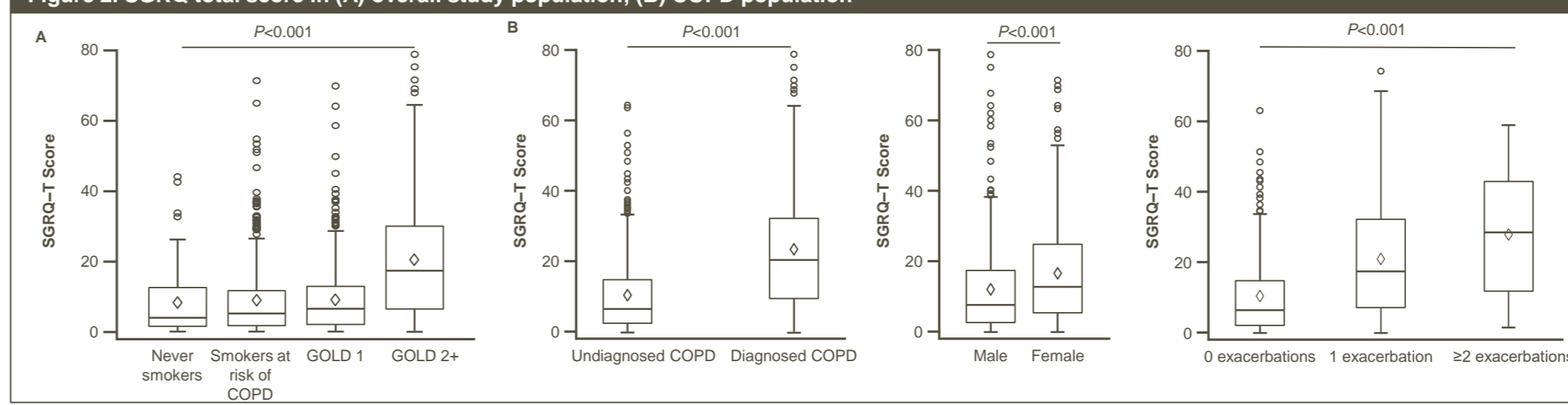
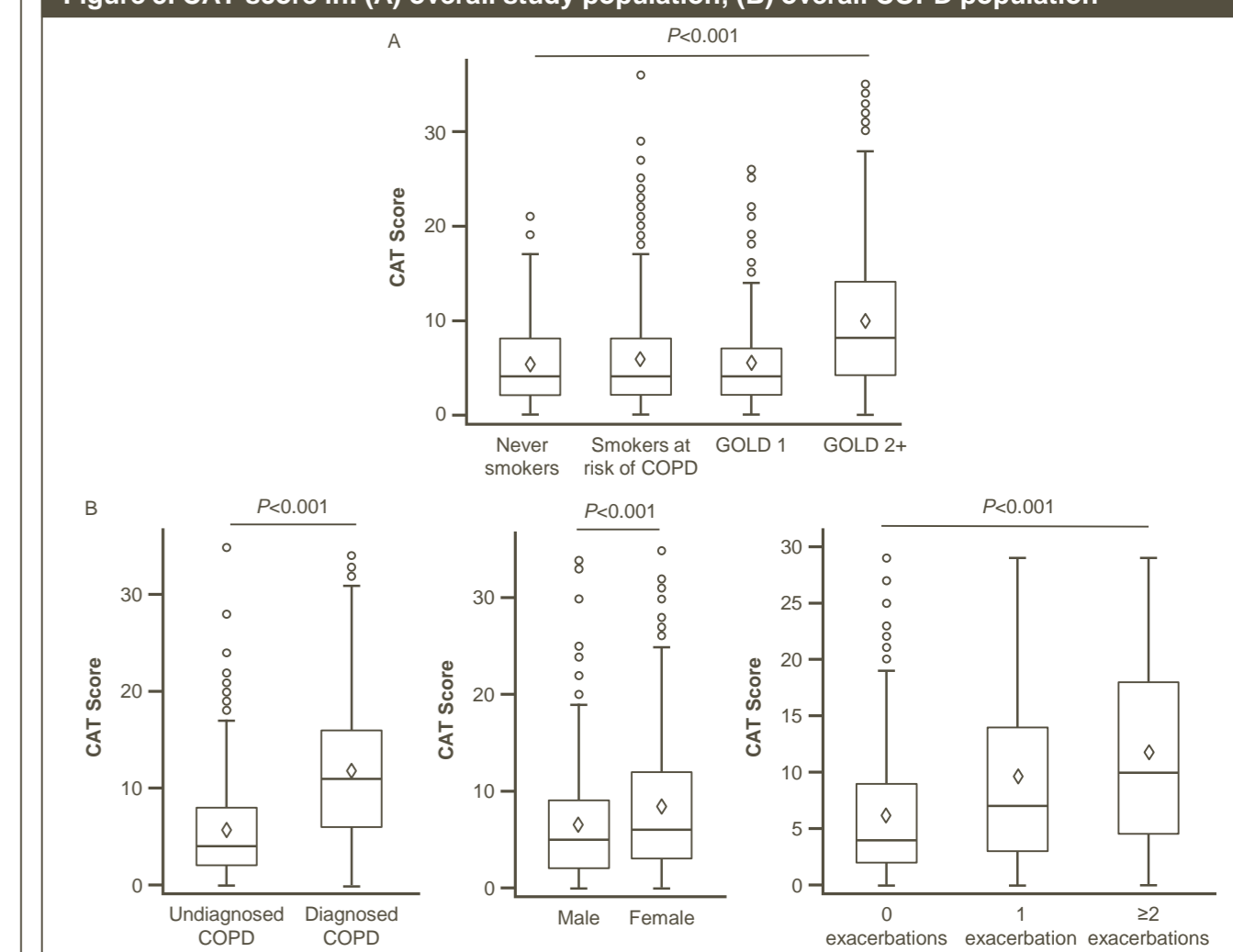


Figure 3. CAT score in: (A) overall study population; (B) overall COPD population



Conclusions

- Data from this population-based study indicate that adults with mild COPD were more dyspneic and had poorer HRQoL than never smoking control participants without COPD.
- In participants with COPD, dyspnea (MRC, Δ Dyspnea/ Δ V_{O₂ and Δ Dyspnea/ Δ V^E) and HRQoL were worse among physician-diagnosed versus undiagnosed participants and female versus male. In addition, frequent versus infrequent exacerbators had significantly worse dyspnea (MRC≥3 vs MRC1).}
- Among patients with mild COPD, self-reported dyspnea and exercise-induced dyspnea are worse among female versus male and among exacerbators versus non-exacerbators (MRC≥3 vs MRC1 only). These findings provide important clinical information that could assist physician-decision making in a personalized therapeutic approach.

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Disclosures

- ECG, GN, and SM are employees of GlaxoSmithKline (GSK) and hold stocks and shares. MC, DJ, WT, and JB are part of the CanCOLD team, who received funding from GSK to conduct the study.

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