The modified Borg/6-min walk distance ratio: a method to assess exertional breathlessness and leg discomfort using the 6-min walk test

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Shareable abstract (@ERSpublications)
We present and validate a new method and normative reference equations to measure the breathlessness and leg discomfort response to a 6-min walk test that account for the level of exertion performed https://bit.ly/3OuU41A

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Abstract

Background The 6-min walk test (6MWT) is widely used to assess exercise capacity across chronic health conditions, but is currently not useful to assess symptoms, as the scores do not account for the 6-min walk distance (6MWD). We aimed to 1) develop normative reference equations for breathlessness and leg discomfort intensity expressed as modified Borg (mBorg)/6MWD ratios; and 2) validate the equations in people with COPD.

Methods Analysis of people aged ⩾40 years who performed two 6MWTs (on a 20-m course) in the Canadian Cohort Obstructive Lung Disease (CanCOLD) study: a healthy cohort (n=291; mean±SD age 67.5±9.4 years; 54% male) with normal 6MWD and lung function, and a COPD cohort (n=156; age 66.2±9.0 years; 56% male; forced expiratory volume in 1 s (FEV_1)/forced vital capacity 56.6±8.2%; FEV_1 74.4±18.6% pred). The mBorg score was calculated as the Borg 0–10 category ratio intensity rating of breathlessness or leg discomfort recorded at the end of the 6MWT +1 (range 1–11), to avoid zeros and yield ratios proportional to the symptom score and 6MWD−1.

Results Using data from the healthy cohort, sex-specific normative reference equations for breathlessness and leg discomfort mBorg/6MWD ratios were developed using multivariable linear regression, accounting for age, and body mass or body mass index. In the COPD cohort, abnormal breathlessness and leg discomfort (mBorg/6MWD>upper limit of normal) showed strong concurrent validity with worse airflow limitation, Medical Research Council breathlessness and COPD Assessment Test scores.

Conclusion Normative references for the mBorg/6MWD ratio are presented to assess breathlessness and leg discomfort responses to the 6MWT in COPD.

Introduction

Exertional breathlessness and impaired exercise capacity are leading causes of chronic suffering and disability in the general population [1, 2], and are cardinal symptoms in cardiorespiratory diseases, including COPD [3]. The trajectory of breathlessness is often progressive, leading to a vicious cycle of

impaired activity, deconditioning and worsening symptoms at low levels of exertion [4]. As people reduce their physical activity to avoid the symptom, the true severity of exertional breathlessness is often under-recognised. To appropriately assess and understand this debilitating symptom, exertional breathlessness should be measured in relation to a standardised level of exercise [5–7].

The 6-min walk test (6MWT) is widely used in research and clinical care to evaluate an individual's exercise capacity (assessed as the 6-min walk distance (6MWD)) [8, 9] and prognosis [10, 11]. The 6MWT is a standardised [12] and reproducible [13] self-paced exercise test where the participant is instructed to walk as far as possible during 6 min between two cones on a flat course [10]. The course length is most often 30 m, but a 20-m course is sometimes used due to space limitations [14, 15]. The 6MWT is recommended as an integral part of management across cardiorespiratory conditions such as COPD [8, 9, 16]. Intensity ratings of breathlessness and leg discomfort at completion of the 6MWT are often measured using Borg's 0–10 category ratio (CR10) scale [17].

Despite its widespread use, the 6MWT is currently not useful for measuring breathlessness or leg discomfort, as the test is self-paced [5, 7]. The symptom ratings at the end of test do not account for the walked distance (6MWD) [5], and are therefore not informative on the symptoms' severity, change with disease progression or response to treatment [5, 7]. We hypothesised that relating a modified Borg (mBorg) score to the 6MWD (expressed as a mBorg/6MWD ratio) could be useful for assessing the intensity of breathlessness and leg discomfort at the end of the 6MWT. Normative reference values would enable comparison of the severity of the symptoms at the end of a 6MWT for a given 6MWD compared to the predicted normal levels among healthy people, accounting for relevant participant-level characteristics such as age and body mass. This approach could have wide applicability to assess exertional breathlessness and leg discomfort in clinical care and interventional trials.

The aims of this study were to 1) develop normative reference equations for breathlessness and leg discomfort measured as mBorg/6MWD ratios at the end of a 6MWT in ostensibly healthy adults; and 2) validate the equations for assessment of exertional symptoms in people with COPD.

Material and methods

Study design and populations

This was an analysis of the Canadian Cohort Obstructive Lung Disease (CanCOLD) study [18], a prospective, population-based study conducted across nine sites in Canada (ClinicalTrials.gov identifier NCT00920348) of noninstitutionalised people aged ⩾40 years identified using random telephone digit dialling [18]. The data in the analyses are from CanCOLD visit 2 (hereafter called "baseline", which included data on 6MWTs and was conducted ∼18 months after the first visit), except for data on static lung volumes and diffusion lung capacity for carbon monoxide (D_{LCO}) which are from visit 1. All participants provided written informed consent prior to completing study assessments. The research ethics board for each participating institution approved the study protocol. The current study is reported in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis statement [19].

Eligibility criteria for the present study are detailed in figure 1. All participants were required to have valid data on two 6MWTs and spirometry at baseline [18]. Participants were excluded if they stopped during any of the 6MWTs or were unable to perform the tests due to adverse events or condition(s) other than breathlessness. Participants meeting these criteria were divided into 1) a healthy cohort and 2) a COPD cohort based on additional eligibility criteria detailed in figure 1 and in the supplementary material (appendix 1).

Assessments and procedures

Participants self-reported baseline data on sociodemographics and health (*e.g.* smoking history, self-reported health conditions) *via* structured interview with a trained researcher. Body height and mass were measured. Assessments of pre- and post-bronchodilator spirometry, D_{LCO} and lung volumes measured by body plethysmography were performed using automated equipment in accordance with American Thoratic Society (ATS)/European Respiratory Society standards [18, 20, 21]. Predicted lung function values were calculated using Global Lung Function Initiative references [22–24].

6MWTs were performed in a corridor between two cones placed 20 m apart [18], using standardised instructions and procedures in accordance with ATS guidelines [12]. Participants were asked to walk as far as possible in 6 min by walking back and forth from one cone to another. A second 6MWT was performed 15 min after the first. Inhaled respiratory medications were withheld before the 6MWTs.

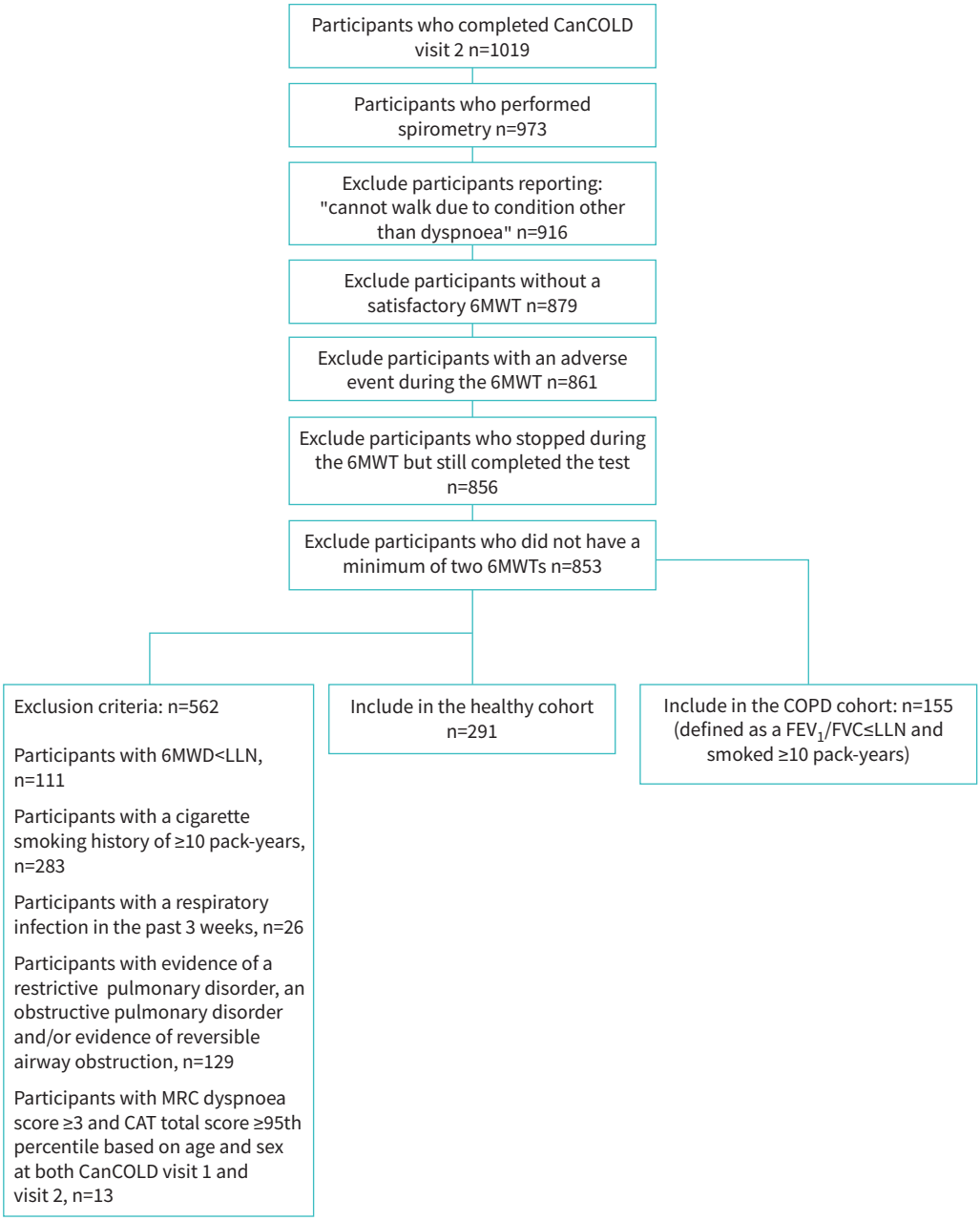

FIGURE 1 Participant flow. CanCOLD: Canadian Cohort Obstructive Lung Disease, 6MWT: 6-min walk test; 6MWD: 6-min walk distance; LLN: lower limit of normal; MRC: Medical Research Council; CAT: COPD Assessment Test; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Participants self-reported their intensity of breathlessness and leg discomfort at the end of each 6MWT using the 0–10 Borg CR10 scale [17] (see supplementary material, appendix 2 for detailed participant instructions). The 6MWT with the highest 6MWD for each participant was included in the analyses.

Statistical analyses

Breathlessness and leg discomfort mBorg intensity ratings were calculated as the observed Borg CR10 rating +1 (range 1–11), to avoid zeros and to make the ratio directly proportional to the modified Borg CR10 score and inversely proportional to the 6MWD (expressed in km). No data were imputed.

Participant characteristics of sex, age, height, body mass or body mass index (BMI) were evaluated as explanatory variables in the models. Reference equations were developed separately for healthy male and

female participants using the SAS procedures PROC REG, and explanatory variables to include in the final multivariable model was selected based on a combination of statistical significance ($p<0.05$) and fraction of explained variability (R^2), and lower-order polynomial (quadratic terms) for all these explanatory variables when significant ($p<0.05$). For each reference equation, the root mean square error (RMSE, corresponding to the standard deviation of the residuals) was calculated as an indication of the distribution of the data around the regression line. The upper limit of normal (ULN) was estimated as the predicted value plus 1.645 times the RMSE. The homogeneity of variance of residual was checked by PROC AUTOREG procedure in SAS and residuals of the normally distributed were also checked. The residuals of the these two variables were not normally distributed; thus, they were natural logarithm transformed (Ln(mBorg/6MWD ratio+0.5)) to reduce the skewness. Log-transformed data were used to build the final models.

The model performance was assessed using mean absolute error, RMSE and mean percentage error in the healthy cohort. A Pearson correlation coefficient was calculated to assess the association between the predicted and observed mBorg/6MWD ratios, and the 95% limits of agreement were evaluated using Bland–Altman plots.

In the COPD cohort, normal mBorg/6MWD ratios were predicted using the reference equations and were compared with the observed ratios for each person. An abnormal response was defined as a mBorg/6MWD ratio >ULN. The proportions of people with abnormal mBorg/6MWD ratios with increasing Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [16], Medical Research Council (MRC) breathlessness rating and COPD Assessment Test (CAT) total score, were analysed using Chi-squared or Fisher exact tests, and Cochran–Mantel–Haenszel analyses. Statistical analyses were conducted using SAS software (version 9.4, TS1M5; SAS Institute, Cary, NC, USA; 2016).

Results

The ratio and normative references

The healthy cohort comprised 291 participants (figure 1) aged a mean±SD 67.5±9.4 years, 54% male, with lung function and 6MWD within normal ranges (table 1). Participants were similar to the general Canadian population aged ⩾40 years [25] with regards to height (CanCOLD *versus* general population: male 174.6 *versus* 174.4 cm; female 160.7 *versus* 161.2 cm), but had slightly lower body mass (male 81.3 *versus* 86.5 kg; female 68.6 *versus* 73.7 kg). All variables were similar between the two 6MWTs performed (supplementary table S1), including the mean±SD mBorg/6MWD ratios for breathlessness (4.9±2.6 *versus* 4.9±2.7; p=0.71) and leg discomfort (4.3±2.7 *versus* 4.3±2.7; p=0.87). Data from the 6MWT with the longest 6MWD was used in all analyses.

Participants' mean±SD mBorg ratings (range 1–11) for breathlessness were 1.7±1.4, and for leg discomfort were 1.3±1.4 at the end of the 6MWT. The mean 6MWD was 578 m in males and 520 m in females, which was ∼100% of the normal predicted value for both sexes (table 1). Observed mBorg/6MWD ratios were similar between males and females (table 1 and supplementary figure S1).

The multivariable regression analysis of breathlessness and leg discomfort mBorg/6MWD ratios (and the RMSE of each model) in males and females are shown in supplementary table S2. The final normative reference equations are specified in table 2. Normative reference values for the breathlessness and leg discomfort mBorg/6MWD ratios by sex and age groups are shown in supplementary table S3.

The model performance and predictive ability of the normative reference equations were high (supplementary table S4). Agreement between observed and predicted mBorg/6MWD ratios are shown in supplementary figure S2. Overall, the predicted normal ratios were distributed approximately evenly between overestimation and underestimation. Lower ratios tended to be somewhat overestimated, whereas higher ratios tended to be somewhat underestimated. However, the systematic difference was very small, with <3% of the predicted ratios estimated outside the limits of agreement.

Validation in people with COPD

The COPD cohort comprised 156 participants (figure 1) aged a mean±SD 66.2±9 years; 56.4% were male; 39.1% were in GOLD stage 1, 49.4% GOLD stage 2, 9.6% GOLD stage 3 and 1.9% in GOLD stage 4 (table 3). Most participants had a MRC score of 1 (52.6%) or 2 (36.5%), and the mean±SD CAT total score was 9.2±7.4. Breathlessness and leg discomfort mBorg score ratings are shown in table 3. The mean±SD 6MWD was 474±96.6 m, corresponding to 87±16.7% of the predicted normal value. The COPD and healthy cohorts had similar median mBorg scores at the end of the 6MWT for breathlessness (COPD *versus* healthy 2.0 *versus* 2.0; p=0.071) and leg discomfort (1.0 *versus* 1.0; p=0.135), but the mean

TABLE 1 Healthy cohort characteristics

	All	Male	Female
Participants	291	157 (54)	134 (46)
Age, years	67.5±9.4	68.1±9.1	66.7±9.8
Age range, years	42.0–88.0	45.0–88.0	42.0–88.0
Height, cm	168.2±9.7	174.6±6.9	160.7±6.5
Body mass, kg	75.5±14.2	81.3±12.0	68.6±13.6
Body mass index, kg·m^{-2}	26.6±4.3	26.6±3.4	26.6±5.1
Cigarette smoking status			
Never	232 (79.7)	127 (80.9)	105 (78.4)
Former	54 (18.6)	26 (16.6)	28 (20.9)
Current	5 (1.7)	4 (2.5)	1 (0.7)
Pack-years of smoking	0.9±2.3	0.8±2.2	1.0±2.3
Hypertension	91 (31.3)	54 (34.4)	37 (27.6)
MRC breathlessness score			
1	229 (78.7)	131 (83.4)	98 (73.1)
2	62 (21.3)	26 (16.6)	36 (26.9)
CAT total score	4.0±3.3	3.7±3.0	4.4±3.5
Resting S_{pO_2}, %	96.9±1.6	96.9±1.5	97.0±1.8
Lung function			
FEV_1, % pred	102.4±14.0	102.8±12.9	102.0±15.3
FEV_1, z-score	0.2±0.9	0.2±0.8	0.1±1.0
FVC, % pred	108.2±13.5	109.2±13.2	106.9±13.7
FVC, z-score	0.5±0.9	0.6±0.9	0.4±0.8
FEV_1/FVC, %	73.3±7.4	72.1±7.0	74.7±7.7
FEV_1/FVC, z-score	−0.5±0.9	−0.6±0.9	−0.5±1.0
TLC, % pred	107.2±12.7	105.6±13.0	109.0±12.1
RV/TLC, % pred	104.6±16.5	102.3±15.3	107.3±17.4
D_{LCO}, % pred	103.4±17.1	104.4±16.7	102.2±17.5
6MWT			
Walk distance, m	554.0±95.2	579.1±95.2	524.6±86.6
Walk distance, % pred	101.1±13.3	100.7±13.3	101.5±13.4
Breathlessness, mBorg 1–11 score[#]	2.7±1.4	2.7±1.4	2.6±1.5
Median; IQR	2.0; 2.5	2.0; 2.5	2.5; 2.5
1	58 (19.9)	28 (17.8)	30 (22.4)
1.5	40 (13.7)	21 (13.4)	19 (14.2)
2	48 (16.5)	30 (19.1)	18 (13.4)
3	55 (18.9)	28 (17.8)	27 (20.1)
4	65 (22.3)	36 (22.9)	29 (21.6)
5	17 (5.8)	10 (6.4)	7 (5.2)
6	5 (1.7)	3 (1.9)	2 (1.5)
7	1 (0.3)	1 (0.6)	0 (0.0)
8	2 (0.7)	0 (0.0)	2 (1.5)
Leg discomfort, mBorg 1–11 score[#]	2.3±1.5	2.4±1.5	2.2±1.4
Median; IQR	2.0; 2.0	2.0; 2.0	1.8; 2.0
1	89 (30.6)	42 (26.8)	47 (35.1)
1.5	45 (15.5)	25 (15.9)	20 (14.9)
2	45 (15.5)	26 (16.6)	19 (14.2)
3	54 (18.6)	30 (19.1)	24 (17.9)
4	40 (13.7)	22 (14.0)	18 (13.4)
5	7 (2.4)	5 (3.2)	2 (1.5)
6	6 (2.1)	4 (2.5)	2 (1.5)
7	1 (0.3)	1 (0.6)	0 (0.0)
8	3 (1.0)	1 (0.6)	2 (1.5)
9	1 (0.3)	1 (0.6)	0 (0.0)
Breathlessness mBorg/6MWD ratio, units·km^{-1}	4.3 (2.6–6.8)	4.2 (2.7–6.1)	4.8 (2.5–7.2)
Leg discomfort mBorg/6MWD ratio, units·km^{-1}	3.4 (2.2–6.0)	3.4 (2.2–5.8)	3.5 (2.2–6.0)

Data are presented as n, n (%), mean±SD or median (interquartile range (IQR)), unless otherwise stated. MRC: Medical Research Council; CAT: COPD Assessment Test; S_{pO_2}: peripheral saturation of oxygen; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusion lung capacity for carbon monoxide; 6MWT: 6-min walk test; mBorg: modified Borg score; 6MWD: 6-min walk distance. [#]: mBorg scores are calculated as the reported symptom intensity on the Borg 0–10 category ratio scale+1 (range 1–11).

TABLE 2 Normative reference equations of breathlessness and leg discomfort modified (m)Borg/6-min walk distance (6MWD) ratios for healthy males and females

Male	
Breathlessness mBorg/6MWD	exp(0.28707+0.00921×Age+0.02343×Body mass index)−0.5
Leg discomfort mBorg/6MWD	exp(−55.11796−0.11987×Age+0.00092447×Age^2+0.69635×Height−0.00201×Height^2)−0.5
Female	
Breathlessness mBorg/6MWD	exp(−0. 37343+0.0201×Age+0.0092×Body mass)−0.5
Leg discomfort mBorg/6MWD	exp(0.04276+0.01082×Age+0.00971×Body mass)−0.5

The ratios are expressed as mBorg rating·km^{-1}. Age is expressed in years, body mass in kg and body mass index in kg·m^{-2}.

6MWD was significantly shorter in people with COPD *versus* the healthy cohort (474±97 m *versus* 554±95 m; p<0.001) (tables 1 and 3). In the COPD cohort, the prevalence of a reduced 6MWD (below lower limit of normal) was 25%.

The mBorg/6MWD ratios for breathlessness and leg discomfort for the population-based COPD cohort are shown in table 3, and were higher than the predicted normal values (figure 2). An abnormal mBorg/6MWD ratio (>ULN) for breathlessness was present in 34 (21.8%), and for leg discomfort in 36 (23.1%) of the participants with COPD.

The proportion of abnormal breathlessness and leg discomfort mBorg/6MWD ratios increased with increasing GOLD stage, MRC breathlessness ratings and CAT total scores (figure 3).

Discussion

Main findings

We present the first normative reference equations of the mBorg/6MWD ratio (performed using a 20-m walking course), to assess the presence and level of abnormal breathlessness and leg discomfort responses at the end of a 6MWT in people aged ⩾40 years. Importantly, the predicted normal symptom responses are standardised for the walk distance, and also account for the participant's age, sex, height, body mass and/or BMI. The equations predict the ULN, which can be used to define an abnormal symptom intensity relative to the distance walked at the end of the 6MWT (>95th percentile among the references). The mBorg/6MWD ratios for breathlessness and leg discomfort were validated in a sample of people with COPD from the general population, with mainly mild to moderate airflow limitation, of whom many were previously undiagnosed and did not have any respiratory medication. The prevalence of abnormal breathlessness (22%) and abnormal leg discomfort (23%) was similar to the prevalence of abnormally reduced 6MWD (25%) in this population. Symptom assessment using the mBorg/6MWD ratios showed concurrent validity with higher (worse) GOLD stage, MRC breathlessness ratings and CAT total scores.

These findings provide the first approach to measure the severity of exertional breathlessness and leg discomfort at the end of a 6MWT. This is important, as the 6MWT is widely available and used in everyday clinical management across cardiopulmonary conditions including COPD [9, 16], cystic fibrosis [26], interstitial lung disease [27], heart failure [28], pulmonary arterial hypertension [29, 30] and evaluation for lung transplantation [31]. The current approach is unique because it effectively standardises the symptom intensity ratings for the level of exertion. Compared to using the observed "raw" symptom ratings, the mBorg/6MWD ratios better meet the basic principle of psychophysics that the symptom level should be evaluated in relation to the level of stimuli (exertion) that was needed to elicit the symptom, which addresses a long-standing limitation of using the 6MWT for symptom assessment [5, 6, 32].

How to use the reference equations

Breathlessness and/or leg discomfort is measured at the end of the 6MWT using the 0–10 Borg CR10 scale. Importantly, people who stop during the test or are unable to complete the 6MWT were exluded from the present analysis (as the rest is likely to decrease their exertional symptoms) and may not be evaluated using the normative reference equations. However, people unable to complete six minutes of walking are likely to have abnormal symptoms or other reasons that mandate further clinical evaluation. In people who complete the 6MWT without stopping, the intensity ratings at the end of the test are converted (by adding 1 point) to the corresponding mBorg scores (range 1–11), to avoid zeros and make the mBorg/6MWD ratio directly proportional to the symptom score and inversely proportional to the walk distance. As an example, for a person with a breathlessness intensity rating of 2 on the Borg CR10 scale and a 6MWD of 300 m, the mBorg/6MWD ratio is (2+1)/300=0.01 units·m^{-1}. For a person performing two

TABLE 3 COPD cohort characteristics

	All	Male	Female
Participants	155	88 (56.8)	67 (43.2)
Age, years	66.2±9.0	66.1±9.7	66.3±8.1
Age range, years	44.0–91.0	44.0–90.0	51.0–91.0
Height, cm	168.6±9.8	174.6±6.8	160.7±7.2
Body mass, kg	79.6±16.1	84.7±14.3	72.9±16.0
Body mass index, kg·m^{-2}	28.0±5.1	27.7±4.1	28.3±6.3
Cigarette smoking status			
Former	109 (70.3)	64 (72.7)	45 (67.2)
Current	46 (29.7)	24 (27.3)	22 (32.8)
Pack-years of smoking	38.8±20.8	40.7±22.3	36.2±18.5
Hypertension	50 (32.3)	29 (33.0)	21 (31.3)
GOLD stage			
1	61 (39.4)	39 (44.3)	22 (32.8)
2	77 (49.7)	40 (45.5)	37 (55.2)
3	15 (9.7)	7 (8.0)	8 (11.9)
4	2 (1.3)	2 (2.3)	0 (0.0)
MRC breathlessness rating			
1	82 (52.9)	53 (60.2)	29 (43.3)
2	57 (36.8)	31 (35.2)	26 (38.8)
3	15 (9.7)	4 (4.5)	11 (16.4)
4	1 (0.6)	0 (0.0)	1 (1.5)
5	0 (0.0)	0 (0.0)	0 (0.0)
CAT total score	9.1±7.4	8.6±6.7	9.7±8.3
Resting S_{pO_2}, %	96.2±2.0	96.3±2.0	96.2±2.1
Lung function			
FEV_1, % pred	74.7±18.2	76.5±19.2	72.4±16.6
FEV_1, z-score	−1.6±1.1	−1.5±1.2	−1.7±1.0
FVC, % pred	101.4±19.6	104.0±20.3	98.1±18.2
FVC, z-score	0.1±1.3	0.2±1.3	−0.2±1.1
FEV_1/FVC	56.8±7.9	56.1±8.1	57.7±7.6
FEV_1/FVC, z-score	−2.5±0.7	−2.5±0.8	−2.5±0.7
TLC, % pred	110.2±18.0	108.8±15.5	112.2±21.0
RV/TLC, % pred	130.0±29.7	129.8±31.9	130.3±26.5
D_{LCO}, % pred	81.4±19.7	83.6±19.5	78.4±19.6
6MWT			
Walk distance, m	475.7±95.0	491.0±97.8	455.7±88.0
Walk distance, % pred	86.9±16.5	85.6±16.9	88.7±15.9
Reduced walk distance (<LLN)	39 (25.2)	24 (27.3)	15 (22.4)
Breathlessness mBorg 1–11 score	3.0±1.7	3.0±1.6	3.1±1.8
Median; IQR	3.0; 2.5	3.0; 2.0	3.0; 2.5
1	26 (16.8)	13 (14.8)	13 (19.4)
1.5	15 (9.7)	8 (9.1)	7 (10.4)
2	22 (14.2)	12 (13.6)	10 (14.9)
3	41 (26.5)	30 (34.1)	11 (16.4)
4	27 (17.4)	15 (17.0)	12 (17.9)
5	10 (6.5)	4 (4.5)	6 (9.0)
6	8 (5.2)	4 (4.5)	4 (6.0)
7	4 (2.6)	0 (0.0)	4 (6.0)
8	1 (0.6)	1 (1.1)	0 (0.0)
9	1 (0.6)	1 (1.1)	0 (0.0)
Leg discomfort mBorg 1–11 score	2.7±1.9	2.5±1.6	2.9±2.1
Median; IQR	2.0; 2.5	2.0; 1.5	2.0; 2.5
1	37 (23.9)	21 (23.9)	16 (23.9)
1.5	26 (16.8)	16 (18.2)	10 (14.9)
2	23 (14.8)	13 (14.8)	10 (14.9)
3	28 (18.1)	17 (19.3)	11 (16.4)
4	23 (14.8)	13 (14.8)	10 (14.9)
5	8 (5.2)	4 (4.5)	4 (6.0)
6	4 (2.6)	2 (2.3)	2 (3.0)
7	0 (0.0)	0 (0.0)	0 (0.0)

Continued

TABLE 3 Continued

	All	Male	Female
8	3 (1.9)	1 (1.1)	2 (3.0)
9	0 (0.0)	0 (0.0)	0 (0.0)
10	2 (1.3)	1 (1.1)	1 (1.5)
11	1 (0.6)	0 (0.0)	1 (1.5)
Breathlessness mBorg/6MWD ratio, units·km^{-1}	5.9 (3.6–8.0)	5.8 (3.6–7.5)	6.1 (3.6–9.4)
Leg discomfort mBorg/6MWD ratio, units·km^{-1}	4.4 (2.7–7.4)	4.0 (2.7–6.7)	5.1 (2.6–9.1)

Data are presented as n, n (%), mean±SD or median (interquartile range (IQR)), unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; MRC: Medical Research Council; CAT: COPD Assessment Test; S_{pO_2}: peripheral saturation of oxygen; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing lung capacity for carbon monoxide; 6MWT: 6-min walk test; LLN: lower limit of normal; mBorg: modified Borg score; 6MWD: 6-min walk distance.

6MWTs with a breathlessness Borg CR10 intensity rating of 0 after both tests, but who increases the 6MWD from 100 to 200 m, the improvement is captured as a proportional decrease in the mBorg/6MWD ratio from 0.01 (1/100) to 0.005 (1/200) units·m^{-1}. The achieved ratio compared to the predicted normal ratio is then evaluated by applying the normative reference equations for the person. The deviation of the symptom mBorg/6MWD from the predicted normal can be expressed as a z-score (observed − predicted/RMSE), where the predicted value and RMSE are obtained from the equations (supplementary table S2).

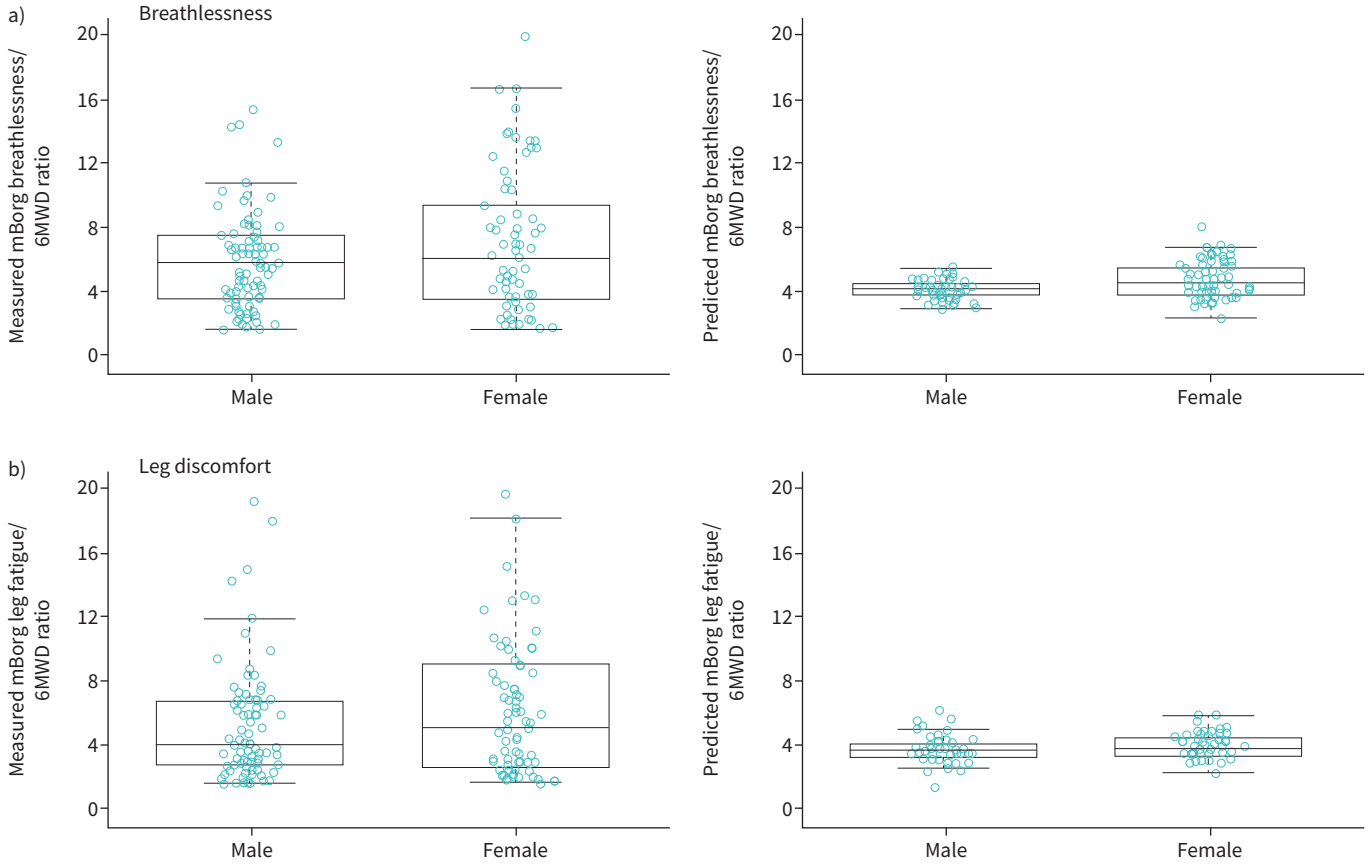

FIGURE 2 Predicted *versus* measured modified (m)Borg/6-min walk distance (6MWD) ratios for intensity ratings of a) breathlessness, and b) leg discomfort in participants with COPD. The mBorg score is calculated as the observed symptom score on the Borg 0–10 category ratio scale+1 (range 1–11). The mBorg/6MWD ratio is expressed as units·km^{-1}.

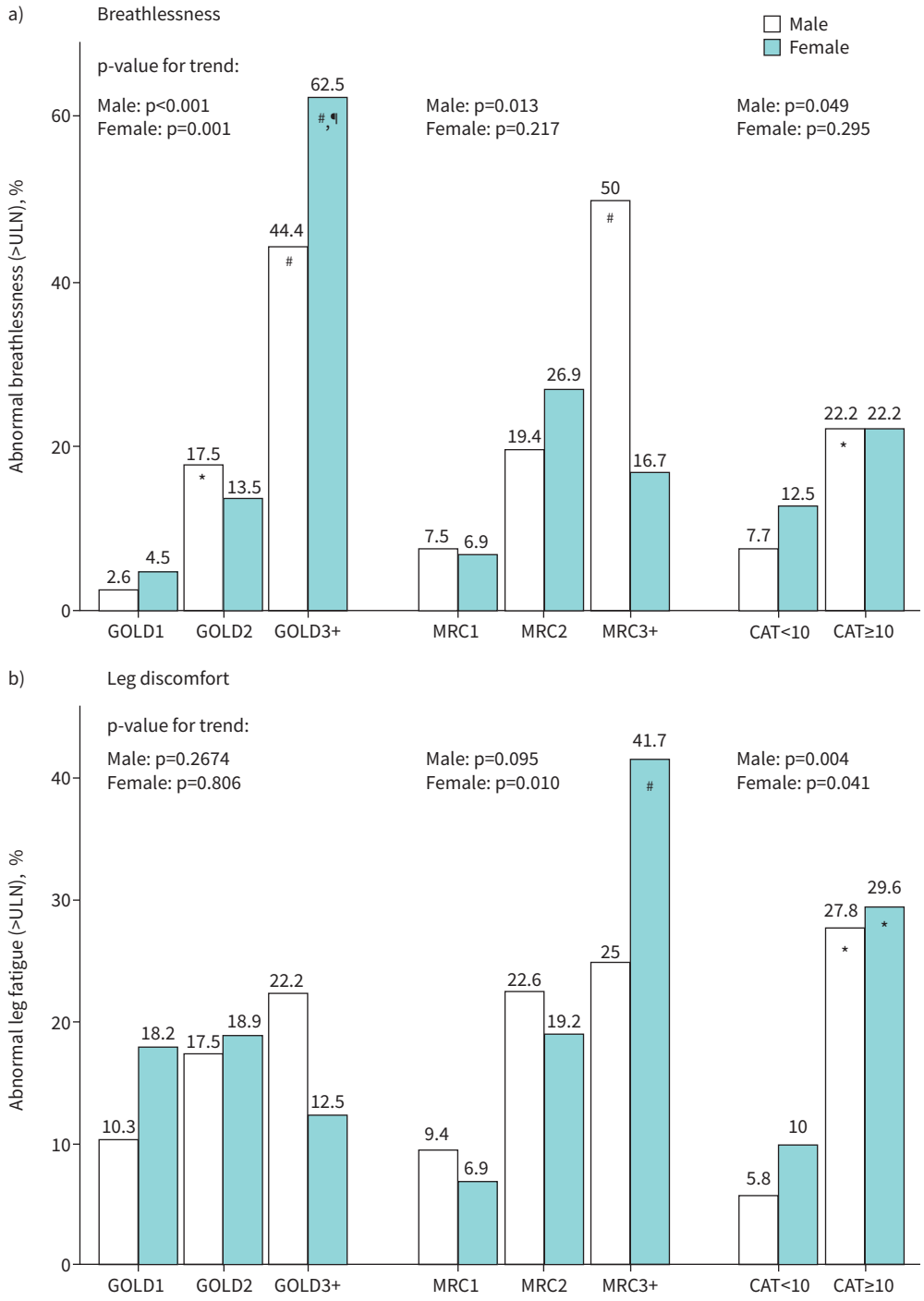

FIGURE 3 Prevalence of a) abnormal breathlessness and b) leg discomfort modified (m)Borg/6-min walk distance (6MWD) ratios, in men and women with COPD by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, Medical Research Council (MRC) breathlessness rating and COPD Assessment Test (CAT) total score. ULN: upper limit of normal. *: p<0.05 by comparing GOLD1 *versus* GOLD2 or MRC1 *versus* MRC2 or CAT <10 *versus* CAT ⩾10; #: p<0.05 by comparing GOLD1 *versus* GOLD3+ or MRC1 *versus* MRC3+; ¶: p<0.05 by comparing GOLD2 *versus* GOLD3+ or MRC2 *versus* MRC3+.

Furthermore, mBorg/6MWD ratios >ULN can be categorised as representing abnormally high exertional breathlessness and/or leg discomfort. This approach is similar to the use of normative references for interpreting spirometry values [21].

Strengths and limitations

Strengths of the present study include the use of the well-characterised, multicentre CanCOLD database, and the relatively large healthy sample. The mBorg/6MWD normative references were validated in a population-based sample of people with mostly mild-moderate COPD. This is a relevant study population as it pertains to the large majority of people with COPD, where symptom assessment is important for earlier detection of disease and need for clinical evaluation and follow-up [33]. Validity of the mBorg/6MWD references was evaluated against established measures of respiratory symptom burden (MRC and CAT questionnaires) [16]. Procedures and measurements were similar between the development and clinical validation cohorts.

A limitation is that the findings pertain to 6MWTs performed using a 20-m course instead of the 30-m course recommended by the ATS [12]. A 20-m course was used in CanCOLD study for feasibility across all nine participating sites [18]. Data on differences when using a 20-m course compared with a 30-m course are conflicting, with some studies reporting a lower 6WMD (possibly due to more frequent turns) [15, 34–36], whereas other studies report no difference in 6MWD between the different course lengths [14, 37, 38]. Symptom intensity ratings at the end of the 6MWT were reported to be similar between using a 20-m and 30-m walking course [15, 34–38]. The current methodology should be extended to validate normative references for 6MWT using a 30-m walk course. In addition, the present equations pertain to people who completed the 6MWT without stopping during the test, and to people with mostly mild to moderate airflow limitation.

Implications for clinical care and research

The normative reference equations provide a novel method to evaluate the severity of breathlessness and/or leg discomfort using the 6MWT, a test already widely used across different settings. Next research steps include evaluation of normative reference equations in other populations, including people with conditions other than COPD, people with more severe illness (such as people with moderate to severe airflow limitation, and undergoing pulmonary rehabilitation), and people aged <40 years; relationships of each mBorg/6MWD ratio to clinical outcomes and prognosis; responsiveness to change and minimal clinically important differences, to measure change over time and in response to interventions (such as rehabilitation training) and for use as end-points in clinical trials. Data on breathlessness and/or leg discomfort from previous 6MWT trials could be re-evaluated using the present normative reference equations to explore potential treatment effects on exertional symptoms.

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