A frame of reference for assessing the intensity of exertional dyspnoea during incremental cycle ergometry

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Iso-power and iso-ventilation reference ranges for exertional dyspnoea were prospectively established in men and women aged 20 to 85. This is the first set of normative values to objectively assess the burden of dyspnoea during incremental cycle ergometry. https://bit.ly/2yfftY6

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ABSTRACT Assessment of dyspnoea severity during incremental cardiopulmonary exercise testing (CPET) has long been hampered by the lack of reference ranges as a function of work rate (WR) and ventilation (V'_E). This is particularly relevant to cycling, a testing modality which overtaxes the leg muscles leading to a heightened sensation of leg discomfort.

Reference ranges based on dyspnoea percentiles (0–10 Borg scale) at standardised work rates and V'_E were established in 275 apparently healthy subjects aged 20–85 years (131 men). They were compared with values recorded in a randomly selected "validation" sample (n=451; 224 men). Their usefulness in properly uncovering the severity of exertional dyspnoea were tested in 167 subjects under investigation for chronic dyspnoea ("testing sample") who terminated CPET due to leg discomfort (86 men).

Iso-work rate and, to a lesser extent, iso-V'_E reference ranges (5th–25th, 25th–50th, 50–75th and 75th–95th percentiles) increased as a function of age, being systematically higher in women ($p<0.01$). There were no significant differences in percentiles distribution between "reference" and "validation" samples ($p>0.05$). Submaximal dyspnoea-work rate scores fell within the 75th–95th or >95th percentiles in 108 out of 118 (91.5%) subjects of the "testing" sample who showed physiological abnormalities known to elicit exertional dyspnoea, *i.e.* ventilatory inefficiency and/or critical inspiratory constraints. In contrast, dyspnoea scores typically fell in the 5th–50th range in subjects without those abnormalities ($p<0.001$).

This frame of reference might prove useful to uncover the severity of exertional dyspnoea in subjects who otherwise would be labelled as "non-dyspnoeic" while providing mechanistic insights into the genesis of this distressing symptom.

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Introduction

Exertional dyspnoea is a key complaint of patients assessed by pulmonologists [1, 2]. If the cause(s) of the symptom is(are) not apparent from standard clinical investigations and/or patients' complaints are deemed out of proportion to resting findings, an incremental cardiopulmonary exercise testing (CPET) might be requested for further evaluation [3]. In most laboratories, cycling is the preferred testing modality as the work rate (power) can be reliably measured and the noise-to-signal ratio is lower compared with walking (treadmill) [4]. Cycling is also a safer testing strategy compared with treadmill exercise [4], an important advantage to those who are more likely to report disabling dyspnoea, *i.e.* the frail and elderly subject with multiple co-morbidities. As a relevant caveat; however, the leg muscles are more taxed on cycling and the locus of symptom limitation might shift "from the lungs" (dyspnoea) to the peripheral muscles (leg discomfort) [5].

In this context, it is rather axiomatic that any test focussed on a given sensory experience should have reference ranges to grade its severity relative to the magnitude of the concurrent stimuli [6]. Unfortunately, such a basic psychophysical construct remains largely ignored in practice: reference ranges for dynamic, submaximal dyspnoea scores during incremental cycling (*e.g.* 0–10 Borg category-ratio scale) [6] are not widely available. In fact, most laboratories restrain to record (if any) a single dyspnoea score at exercise termination. This strategy not only precludes the examiner to judge the cumulative burden of the symptom as power increases [7] but also overlooks the fact that dyspnoea severity might be obscured by the dominant sense of leg discomfort [8]. It follows that, despite dyspnoea investigation being universally cited as the main clinical indication of CPET, objective assessment of its burden throughout incremental cycling has been largely neglected [4, 9–11].

The present study, therefore, aimed at developing reference ranges for 0–10 Borg dyspnoea scores [6] at standardised work rates and V'_E during incremental cycle ergometry performed by a "reference sample" of men and women with a wide age range. In order to externally validate this frame of reference, we compared these intervals of severity with those obtained in a randomly selected sample of never smokers who have been assessed in a previous population-based study ("validation sample") [12]. Their usefulness in exposing the severity of exertional dyspnoea was examined in a group of subjects who had been referred for the investigation of chronic dyspnoea but terminated the exercise test primarily due to the complaint of leg discomfort ("testing sample").

Materials and methods

A detailed material and methods section is available in the supplementary material.

Subjects

275 apparently healthy, sedentary subjects aged 20 to 85 years (131 men) with normal spirometry and advanced pulmonary function tests comprised the "reference sample" (some of them participated on a randomised study which developed reference values for CPET [13]). The "validation sample" consisted of 451 never-smokers aged 40 and older (224 men) assessed in a prospective longitudinal cohort study (CanCOLD) [12]. The "testing sample" comprised of 171 subjects (86 males) with persistent dyspnoea (of at least three months duration) [14] of clinically significant severity (modified Medical Research Council Questionnaire (mMRC)$\geqslant$2) [15] who were referred to CPET for symptom investigation but terminated the test due to leg discomfort. They were part of a larger sample (n=284) which has been analysed to other outcomes [16]. A *post hoc* analysis was performed with the extant 113 subjects of this sample (65 males, aged 58–88 years) who terminated the test due to dyspnoea.

Procedures

Pulmonary function tests (spirometry, static lung volumes and lung diffusing capacity for carbon monoxide (D_{LCO})) were performed according to current guidelines [17, 18]: reference values for spirometry and D_{LCO} were those proposed by the Global Lung Initiative [18, 19] and Quanjer *et. al.* [20] (for lung volumes). CPET was conducted on electronically braked cycle ergometers: key measurements included standard breath-by-breath metabolic and cardiorespiratory parameters [4]. Dyspnoea and leg discomfort scores (modified 0–10-Borg scale) [6] were obtained in the last 30 s of each stage. Ventilatory inefficiency (lowest V'_E /carbon dioxide output (V'_{CO_2})>upper limit of normal for age and sex) [21], critically high inspiratory constraints (tidal volume/inspiratory capacity >0.7 and/or end-inspiratory lung volume/total lung capacity>0.8) [22], and exercise-related O_2 desaturation by pulse oximetry (S_{pO_2} decrease >4% and end-exercise S_{pO_2}<93%) [4] were assessed in the "testing" sample. In this sample, an upward shift in the dyspnoea-V'_E relationship was defined by a sudden increase in the ratings (by at least 2 points relative to the preceding V'_E) and they did not decrease afterwards.

Data handling and statistical analysis

The statistical software package was IBM SPSS Statistics version 25. Before amalgamating the scores of dyspnoea from the different populations which comprised the "reference" sample, we tested for the presence of systematic bias in selected work rates and V'_{E}. As the mean bias was typically zero with a 95% confidence interval <2, the sub-populations were merged. Preceding the analysis of dyspnoea scores, we used Kolmogorov–Smirnov test to test their symmetry: scores at each work rate and V'_{E} were also tested for skewness and kurtosis. If differences were observed, Kruskal–Wallis or Bonferroni contrast testing was applied depending on variables distribution (asymmetric or symmetric, respectively). Unpaired t-test (or Mann–Whitney test when appropriated) were used to compare between-subject differences. One-way ANOVA (for more than two groups) followed by Bonferroni contrast testing were used to compare differences among groups. Chi-squared testing was used to compare frequencies. Generalised linear mixed model analysis was used to test the independent effects of sex, age and anthropometric attributes on dyspnoea ratings and their interactions with both work rate and V'_{E}. Owing to the fact that the median test only assesses the equality of a single percentile, the 50th, we also used the approach proposed by JOHNSON *et al.* [23] to simultaneously test multiple percentiles when comparing the "reference" and "validation" samples. The Bland–Altman procedure was applied to determine the limits of agreement between these two samples to indicate in which work rate selected dyspnoea scores were observed in different percentiles [24]. A p-value <0.05 level of significance was used for all analyses.

Results

"Reference" and "validation" samples' characteristics

Age, anthropometric attributes, resting lung function and CPET variables (including peak dyspnoea and leg discomfort scores) did not differ between reference and validation samples in men (table 1) and women (table 2) (p>0.05). The samples presented with similar age distribution (figure E1) within each age group (40–59 years, 60–69 years and ⩾70 years) in both sexes. As expected, maximal exercise capacity (either expressed as peak work rate or peak O_2 uptake ($V'_{\mathrm{O_2}}$)) declined with age in both sexes, being lower in women than men in each age group (tables 1 and 2).

TABLE 1 Resting and exercise data of the "reference" and "validation" samples in men

	20–39 years	40–59 years		60–69 years		⩾70 years	
	Reference	**Reference**	**Validation**	**Reference**	**Validation**	**Reference**	**Validation**
Demographic/anthropometric							
Subjects n	31	29	60	35	70	36	94
Age years	28.7±6.1*	50.8±5.2*	52.9±4.6*	64.8±3.0*	64.7±2.6*	74.0±3.5	75.9±5.1
Height m	1.73±0.07	1.71±0.07	1.77±0.07	1.71±0.06	1.75±0.06	1.71±0.07	1.72±0.07
Body mass index kg·m^{-2}	24.8±2.6	27.3±3.8	27.0±3.9	26.9±2.8	27.1±3.7	25.9±3.2	26.7±2.9
Lung function							
FVC % pred	99.7±11.2	99.2±12.6	100.7±14.1	103.0±14.0	105.4±16.1	108.5±16.8	106.7±21.5
FEV_1 % pred	96.3±11.1	97.5±12.5	93.5±16.9	101.3±13.7	97.7±15.4	100.5±17.2	97.8±21.3
FEV_1/FVC	0.81±0.06	0.75±0.04*	0.76±0.09*	0.73±0.06*	0.73±0.07*	0.71±0.05	0.69±0.09
TLC % pred	104.0±10.6	100.6±13.3	101.2±24.3	98.0±12.6	101.7±25.1	101.3±10.3	99.2±20.9
RV % pred	106.8±28.4	98.4±17.7	100.6±38.7	84.3±22.6	97.9±34.9	85.4±20.9	96.4±34.0
D_{LCO} % pred	125.7±20.2	116.4±35.8	107.2±27.7	104.9±31.4	99.3±27.8	98.0±27.2	97.9±26.8
Peak exercise							
Work rate W	187±29*	166±40*	174±47*	148±28*	152±40*	115±41	116±39
$V'_{\mathrm{O_2}}$ L·min^{-1}	2.82±0.38*	2.34±0.606*	2.48±0.64*	2.19±0.47*	2.22±0.48*	1.83±0.59	1.73±0.54
RER	1.33±0.12	1.26±0.17	1.18±0.09	1.15±0.14	1.11±0.07	1.15±0.12	1.12±0.09
HR % pred	97.7±5.8	97.4±7.7	98.1±6.4	94.7±11.6	96.6±10.3	97.4±10.4	96.1±9.9
V'_{E} L·min^{-1}	111.0±27.2*	83.7±22.1*	82.7±24.9*	75.7±18.3*	76.1±18. 7*	70.9±23.5	67.0±19.1
V'_{E}/eMVV	0.74±0.24	0.79±0.32*	0.76±0.20*	0.65±0.19	0.68±0.17	0.60±0.22	0.61±0.20
$S_{\mathrm{pO_2}}$ %	96±1	95±21	95±3	95±2	96±3*	95±3	96±2
Dyspnoea Borg units	3 (2–4) *	4.5 (2–5)	5 (4–8)	4 (2–5)	5 (3–8)	5 (3–6)	5 (3–7)
Leg effort Borg units	8 (7–9)	7 (6–8)	7 (5–9)	7 (5–8)	6 (4–9)	6 (3–7)	5 (4–7)

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; $V'_{\mathrm{O_2}}$: oxygen uptake; RER: respiratory exchange ratio; HR: heart rate; V'_{E}: ventilation; eMVV: estimated maximal voluntary ventilation; $S_{\mathrm{pO_2}}$: oxygen saturation by pulse oximetry. *: p<0.05 compared with the subsequent age group within a given sample (with exception of the 20–39 years group). No significant differences between reference and validation samples across age groups.

TABLE 2 Resting and exercise data of the "reference" and "validation samples" in women

	<40 years	**40–59 years**		**60–69 years**		**⩾70 years**	
	Reference	**Reference**	**Validation**	**Reference**	**Validation**	**Reference**	**Validation**
Demographic/anthropometric							
Subjects n	39	38	51	43	90	24	86
Age years	29.3±5.5*	50.7±6.3*	53.3±4.6*	64.5±2.9*	64.6±2.7*	74.4±3.0	76.6±4.9
Height m	1.61±0.07	1.59±0.06	1.62±0.07	1.60±0.06	1.61±15.2	1.59±0.08	1.63±0.10
Body mass index kg·m^{-2}	24.9±5.4	26.2±4.5	27.9±6.8	26.4±4.3	27.5±5.7	26.0±3.6	25.5±4.8
Lung function							
FVC % pred	99.4±9.3	105.7±13.9	99.3±13.6	106.8±13.6	97.1±25.9	110.0±13.8	102.6±22.3
FEV_1 % pred	97.1±12.9	95.3±13.9	94.4±15.3	96.8±12.5	92.7±15.7	94.1±17.2	95.6±21.8
FEV_1/FVC	0.80±0.03*	0.76±0.06*	0.76±0.04*	0.73±0.06*	0.74±0.05*	0.71±0.07	0.70±0.07
TLC % pred	100.3±12.5	101.5±14.3	105.6±15.1	103.3±11.5	107.3±14.3	101.3±12.6	102.9±14.7
RV % pred	109.5±12.9	109.5±24.5	107.6±29.9	108.6±11.4	107.6±30.5	105.8±8.5	98.5±69.6
D_{LCO} % pred	106.7±38.7	101.3±30.6*	99.1±24.7*	93.9±21.5*	95.4±21.1*	91.2±25.5	90.7±22.4
Peak exercise							
Work rate W	129±27 *	116±29*	114±27*	102±32*	96±29*	74±26	70±25
V'_{O_2} L·min^{-1}	1.69±0.26*	1.51±0.37	1.53±0.38	1.49±0.41*	1.44±0.38*	1.22±0.29	1.18±0.304
RER	1.23±0.21	1.29±0.14	1.14±0.09	1.19±0.13	1.14±0.10	1.19±0.11	1.19±0.12
HR % pred	92.7±7.2	99.5±8.0	98.5±7.3	97.1±10.7	98.6±11.1	100.7±14.9	99.3±11.2
V'_E L·min^{-1}	67.6±15.1*	55.2±13.9	53.2±13.5	58.3±15.6	51.6±14.9	51.7±11.9	49.7±12.9
V'_E/eMVV	0.55±0.16	0.62±0.18	0.60±0.14	0.65±0.17	0.61±0.15	0.61±0.18	0.59±0.14
S_{pO_2} %	97±2	96±4	97±3	95±3	97±2	95±2	96. 3
Dyspnoea Borg units	3.5 (2–4)	4 (3–6)	5 (3–5)	4 {3–6)	5 (4–7)	4 (2–6)	4 (3–6)
Leg effort Borg units	7 (6–9)	6 (4–8)	7 (4–89)	6 (4–7)	5 (4–7)	6 (3–7}	5 (4–7)

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. FVC: forced vital capacity; % pred: % predicted; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; RV: residual volume; D_{LCO}: diffusing capacity of the lung for carbon monoxide; V'_{O_2}: oxygen uptake; RER: respiratory exchange ratio; HR: heart rate; V'_E: ventilation; eMVV: estimated maximal voluntary ventilation; S_{pO_2}: oxygen saturation by pulse oximetry. *: $p<0.05$: compared with the subsequent age group within a given sample (with exception of the 20–39 years group). No significant differences between reference and validation samples across age groups.

Reference ranges for dyspnoea scores

Dyspnoea scores at a given work rate and V'_E presented with marked asymmetry in each age group in both men and women ($p<0.001$ for a non-symmetrical distribution). Generalised linear model analysis revealed an independent effect of sex and age (but not weight and height) and their interaction with exercise intensity (work rate and V'_E) on dyspnoea scores ($p<0.01$). Kruskal–Wallis test indicated higher dyspnoea scores in women than men across age groups in both sexes ($p<0.05$). The effect of age, however, was less pronounced: no significant differences were found in dyspnoea- V'_E between the 40–59 and 60–69 years groups in both men and women though they did differ from the other age groups ($p<0.05$).

The reference ranges for "mild", "moderate", "severe" and "very severe" dyspnoea burden were defined based on the following percentile intervals: 5th–25th, 25th–50th, 50–75th and 75th–95th (figures 1 and 2 for men and women, respectively). The individual dyspnoea percentiles by sex and age are provided in the supplementary material as Microsoft Excel files. Interestingly, subjects reporting dyspnoea scores in the "severe" to "very severe" range presented with lower peak work rate than their counterparts in both sexes despite non-significant differences in age (156±31 W *versus* 128±26 W and 137 W±24 W *versus* 108 ±29 W). We observed that dyspnoea-work rate occasionally increased in the work rate (but not V'_E) corresponding to the lactate threshold. Importantly, however, such changes never reached >2 ranges of dyspnoea severity. A *post hoc* analysis showed that the dyspnoea scores observed in the present study were typically lower than those predicted by regression equation established in the seminal work of KILLIAN *et al.* [7]: median (interquartile range) difference of 1.10 (0.5–2.0), 1.80 (0.8–2.6) and 2.5 (0.9–3.1) at 50 W, 100 W, and 150 W in men, respectively; and 0.80 (0.0–1.8), 1.5 (0.3–2.4) and 2.3 (1.1–3.0) at 25 W, 50 W and 100 W in women, respectively ($p<0.05$ for all comparisons).

Comparison of percentiles distribution: reference versus *validation samples*

Median and modified Pearson's chi-squared test for multiple percentiles [23] tests did not expose significant differences in percentiles distribution relative to dyspnoea-work rate and dyspnoea- V'_E when reference and validation samples were compared ($p>0.05$). As shown in table E1–E6, there was a remarkable similarity in the work rate associated with selected dyspnoea ratings across percentiles, a finding further confirmed in the Bland–Altman analysis (figures E2 and E3).

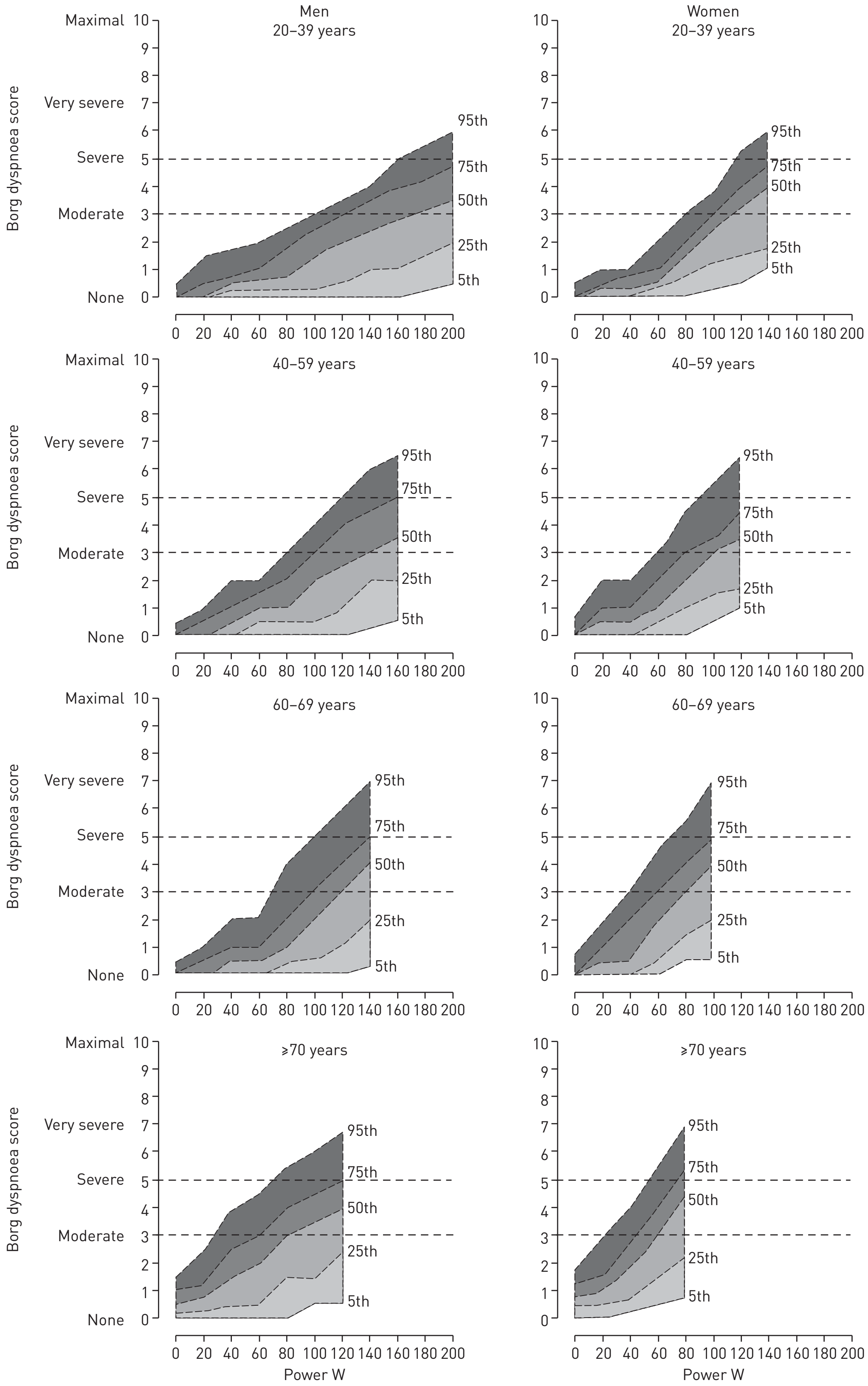

FIGURE 1 Submaximal dyspnoea-work rate scores as a function of age in men and women in the "reference" sample. Dyspnoea burden categorised as "mild" (5th–25th percentile), "moderate" (25th–50th percentile), "severe" (50th–75th percentile) and "very severe" (75th–95th percentile). Generalised lines model analysis indicated higher dyspnoea scores in women in each age group with progressively higher values as age increased in both sexes (p<0.01). Individual centiles are provided in the supplementary material.

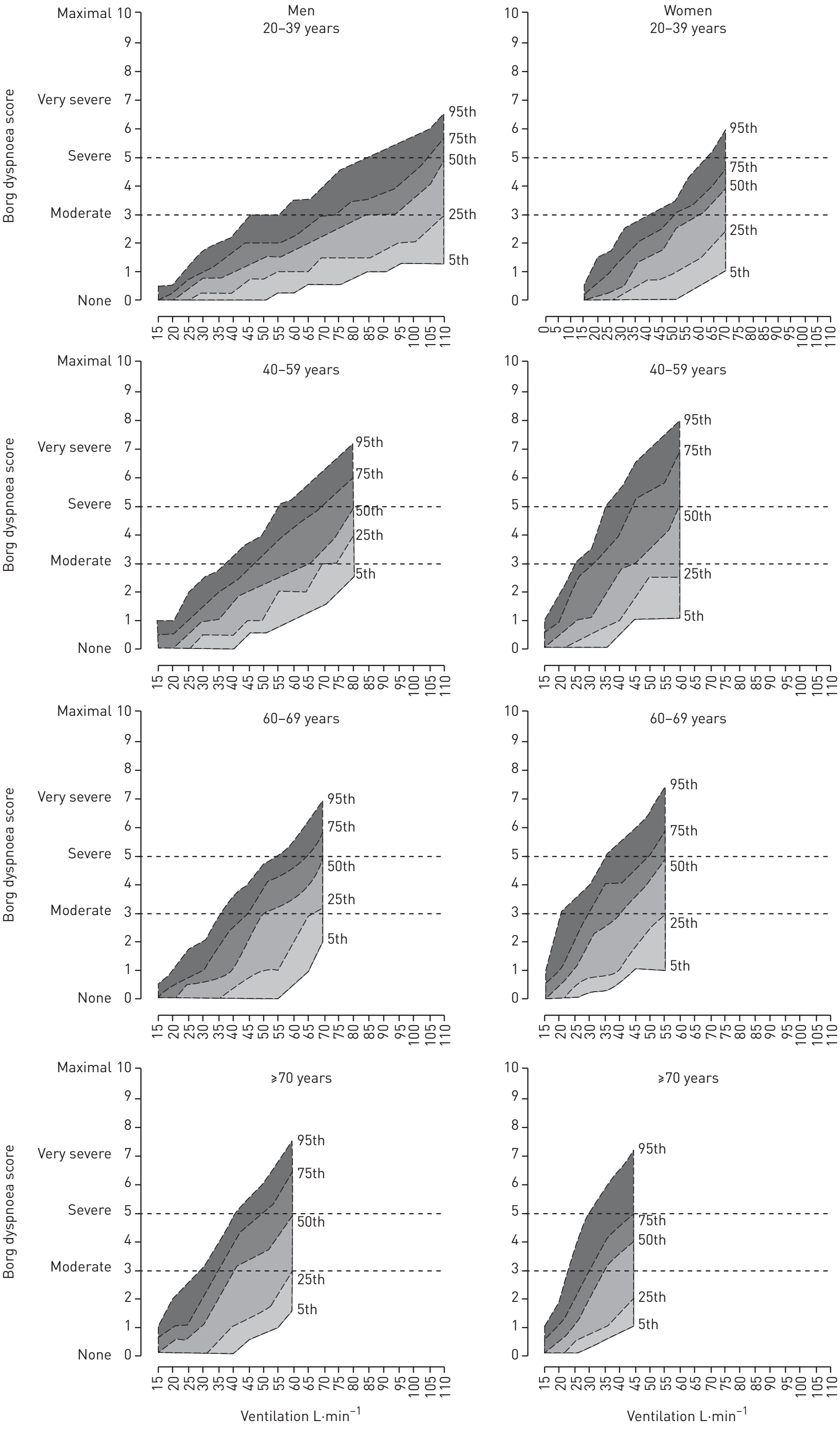

FIGURE 2 Submaximal dyspnoea-ventilation scores as a function of age in men and women in the "reference" sample. Dyspnoea burden categorised as "mild" (5th–25th percentile), "moderate" (25th–50th percentile), "severe" (50th–75th percentile) and "very severe" (75th–95th percentile). Generalised lines model analysis indicated higher dyspnoea scores in women than men across age groups ($p<0.05$). Differences between 40–59 years and 60–69 years subjects were not significant but they presented with intermediate values relative to younger and older subjects, respectively ($p<0.05$). Individual centiles are provided in the supplementary material.

Reference ranges applied to the "testing" sample

"Testing" sample characteristics are presented in table E7. Of note, 118 out of 167 (70.6%) subjects presented with key physiological abnormalities which have been causally related to exertional dyspnoea (ventilatory inefficiency, critical inspiratory constraints and exertional hypoxaemia) [25]. Of note, ∼80% of patients exhibiting key physiological abnormalities related to exertional dyspnoea reported dyspnoea-work rate scores above the 75th percentile, while <10% of those without these abnormalities endorsed such a level of submaximal dyspnoea (figure 3, right). Most patients who did not exhibit physiological abnormalities related to exertional dyspnoea reported dyspnoea score lying in the 5th–50th range ("mild" to "moderate" range) ($p< 0.001$ for between-group comparisons; figure 3, left).

We found an upward inflection in dyspnoea-V'_{E} in 56 out of 64 (87.5%) subjects who reached critical inspiratory constraints ($p<0.05$). Table 3 (and figure 4 for a representative subject) shows significant associations between a sudden upward shift in dyspnoea-V'_{E} scores and the attainment of critical inspiratory constraints in both sexes ($p<0.01$) with positive and negative predictive values of the later abnormality being consistently above 80%. The presence of ventilatory inefficiency in isolation was associated with high dyspnoea-work rate but preserved dyspnoea-V'_{E} scores (figure 5 for a representative subject). The *post hoc* analysis involving the subjects from the original population with dyspnoea on daily life [16] who reported dyspnoea as the limiting symptom at the end of CPET revealed that 54 out of 65 (86.4%) men and 39 out of 48 (82.1%) women showed dyspnoea-work rate scores above the 75th percentile ("very severe" dyspnoea) (figure E4).

Discussion

The present study provided a novel set of reference ranges to assess the severity of exertional dyspnoea during incremental cycle ergometry in men and women presenting with an age span of six decades (figures 1 and 2; and supplementary material). Age- and sex-specific reference intervals at standardised work rates and V'_{E} were externally validated in a larger sample of randomly selected subjects of both sexes (tables E1–E6; figures E2 and E3). Moreover, they properly uncovered the burden of dyspnoea in a group of subjects who had been referred for the investigation of chronic dyspnoea but stopped CPET due to leg discomfort (table 3, table E7 and figure 3). These reference ranges, therefore, are likely to enhance the yield of CPET in determining the severity of exertional breathlessness in individual patients whilst providing important mechanistic insights into the genesis of this distressing symptom [26].

Quantifying exertional dyspnoea during incremental exercise

The influential American Thoracic Society's statement on dyspnoea emphasised that the symptom should always be quantified in patients with cardiorespiratory disease [3]. The key anchoring point of the 0–10 Borg scale (score 10, the largest ever dyspnoea intensity felt by the subject) depends, of course, on subject's previous sensory-perceptual experiences, it is not surprising that there is a large between-subject variability on scores at a given external power output and V'_{E} [7, 27]. It is noteworthy that the dyspnoea-work rate scores herein provided were slightly (but consistently) lower than those described in the seminal study of Killian *et al.* [7]; the reasons are unclear. However, these authors retrospectively analysed data from a population under investigation of symptoms and/or presenting with suspected disorders of cardiorespiratory function. These subjects were mixed with a group of subjects likely to be motivated to endure high levels of sensory distress, *i.e.* those initiating exercise training and participants in research studies on healthy ageing and muscle strength [7] In contrast, our reference sample was part of prospective studies in which subjects with exercise-induced symptoms, cardio-respiratory diseases or those reporting regular physical activity were excluded. We also added to the study by Killian *et al.* [7] by showing dyspnoea as a function of its proximate physiological determinant, *i.e.* V'_{E} (figure 3).

In this context, the concept of dyspnoea burden based on symptom trajectory as exercise progresses (dynamic reference ranges) assumes a prominent role. We found that the majority of healthy individuals rated their dyspnoea within a given range for at least two-thirds of the test; moreover, the few exceptions changed their dyspnoea ratings only to the adjacent (higher) reference interval. It follows that different subjects were exposed to distinct (cumulative) burden of dyspnoea leading to earlier exercise cessation in those falling in the "severe" to "very severe range". Importantly, this was confirmed in an independent, randomly selected sample who also has never been exposed to the Borg scale (tables E1–E6; figures E2 and E3). Conversely, dyspnoea scores reported from chronically dyspnoeic subjects showing physiological abnormalities known to induce the symptom [25, 28] typically fell in the "very severe" range or above the 95th percentile (table E7 and figure 3). Similar findings were obtained in a *post hoc* analysis comparing the submaximal dyspnoea scores found in a group of subjects who reported dyspnoea as the main limiting symptom with the reference ranges herein proposed (figure E4). Collectively, therefore, these results indicate that the currently proposed reference ranges might provide clinically relevant information to be used in conjunction with objective findings (figures 4 and 5) [29].

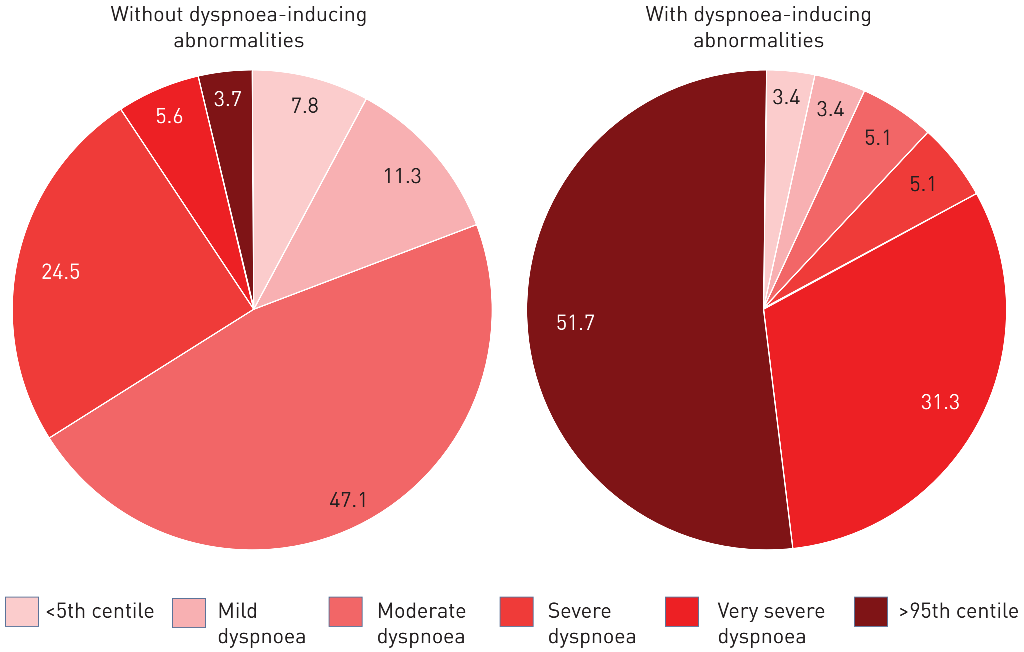

FIGURE 3 Percent distribution of submaximal dyspnoea-work rate scores in subjects of the testing sample presenting or not with physiological abnormalities known to elicit exertional dyspnoea (poor ventilatory efficiency and/or critical inspiratory constraints). "Mild", "moderate", "severe" and "very severe" ranges correspond to the following percentile intervals: 5th–25th, 25th–50th, 50–75th and 75th–95th, respectively.

TABLE 3 Contingency table showing the association between upward inflection of dyspnoea-V'_E relationship with the attainment of critical inspiratory constraints in men and women under investigation of undetermined dyspnoea

	Critical inspiratory constraints	
	Present	**Absent**
Men (n=69)		
Dyspnoea-V'_E upward inflection		
Present	32 (46.3%)	6 (8.7%)
Absent	5 (7.2%)	26 (37.8%)
Sensitivity	86.49%	71.23% to 95.46%
Specificity	81.25%	63.56% to 92.79%
Positive likelihood ratio	4.61	2.22 to 9.59
Negative likelihood ratio	0.17	0.07 to 0.38
Positive predictive value	84.21%	68.75% to 93.98%
Negative predictive value	83.87%	66.27% to 94.55%
Women (n=49)		
Dyspnoea-V'_E upward inflection		
Present	24 (48.9%)	4 (8.2%)
Absent	3 (6.2%)	18 (36.7%)
Sensitivity	88.89%	70.84% to 97.65%
Specificity	81.82%	59.72% to 94.81%
Positive likelihood ratio	4.89	1.99 to 11.98
Negative likelihood ratio	0.14	0.05 to 0.40
Positive predictive value	85.71%	67.33% to 95.97%
Negative predictive value	85.71%	63.66% to 96.95%
Total (n=118)	64 (54.2%)	54 (45.8%)

$p<0.05$ for both groups (Chi-squared test).

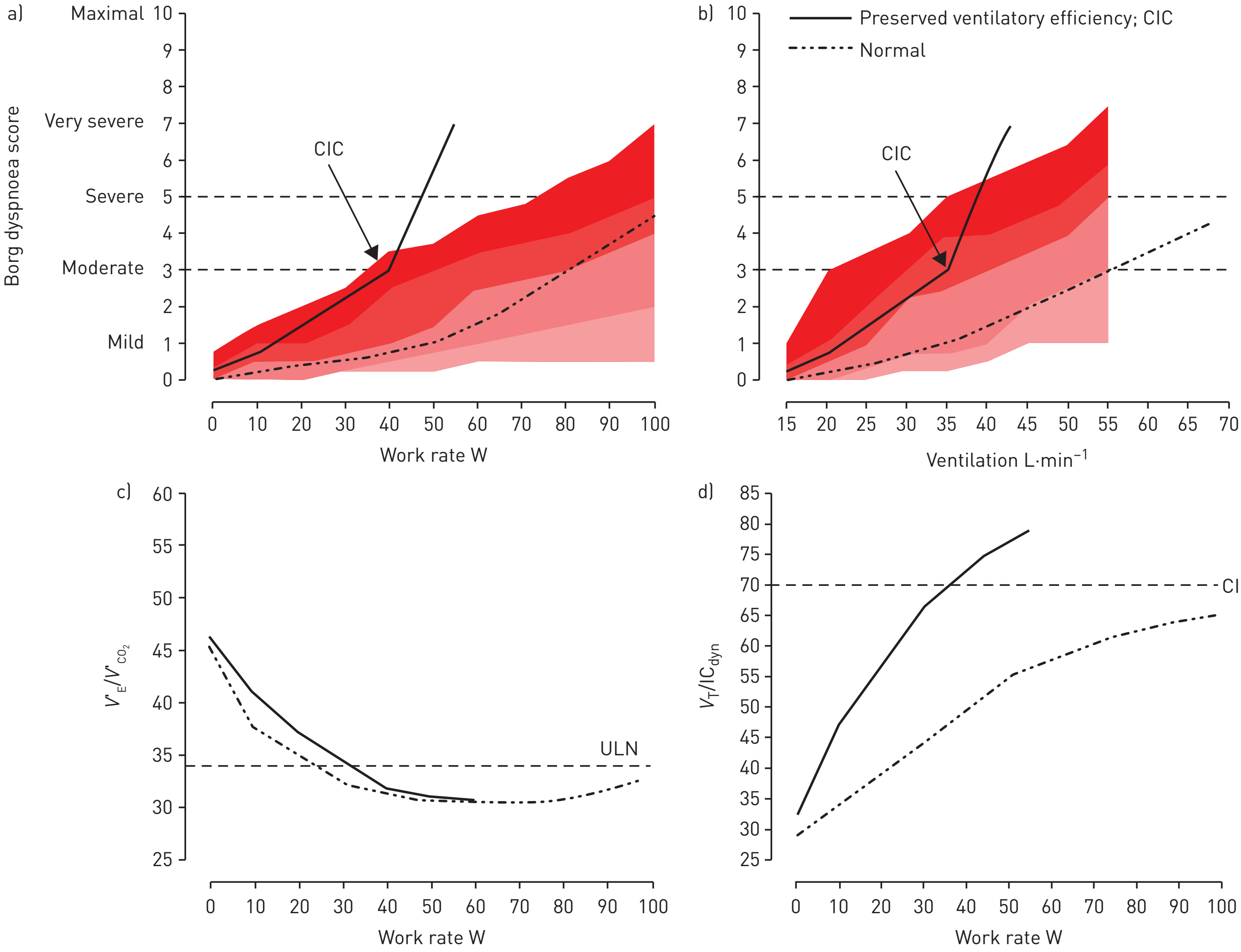

FIGURE 4 Representative subject from the “testing sample” (woman, aged 64) who presented with a sudden upward inflection in dyspnoea-work rate (a) and dyspnoea-ventilation (V'_E) (b). Note the simultaneous attainment of critical inspiratory constraints (CIC (tidal volume (V_T)/dynamic inspiratory capacity (IC_{dyn}) >0.7; d) without any increase in V'_E as a function of metabolic demand (carbon dioxide output (V'_{CO_2}) *i.e.*, ventilatory inefficiency (V'_E/V'_{CO_2}) below the upper limit of normal) (c). Thus, dyspnoea increased out or proportion to V'_E because the CIC (“neuromechanical dissociation”) precluded further increases in V'_E The dotted line represents the ratings endorsed by a woman aged 66 years from the “testing sample” who did not reach the CIC.

The effect of age and sex on exertional breathlessness

There is a sound physiological rationale to explain the significant effect of age and sex on exertional dyspnoea (figures 1 and 2). Briefly, progressive decrease in the ability to maintain sufficiently high muscle O_2 delivery on exercise (both due to central and peripheral haemodynamic alterations) and lower mitochondria density may prompt elderly subjects to an earlier lactate threshold thereby increasing V'_E at a given work rate [30]. Senescence is also associated with poorer ventilatory efficiency (both due to higher dead space and lower tidal volume), particularly in women [21, 31]. Lower chest compliance is characteristically seen in the elderly: higher work of breathing coupled with weaker respiratory muscles may contribute to higher dyspnoea-V'_E relationship in subjects aged 70 years and older [32]. However, despite presenting with poorer ventilatory efficiency than younger subjects, older subjects did increase similarly their V'_E when additional dead space was added [33]. In other words, they were not mechanically limited otherwise further increase in V'_E would not be tenable [34].

It is also noteworthy that women have smaller airways, lung volumes and weaker respiratory musculature but a higher mechanical work of breathing during exercise compared with age-matched men (as reviewed in [35]). This is likely to put women at greater risk of being mechanically limited. In fact, we found that sex had a larger effect on dyspnoea-V'_E than ageing (figures 1 and 2). Overall, it seems that the quantity, rather than the quality, of V'_E seems an important determinant of dyspnoea as age progresses [36].

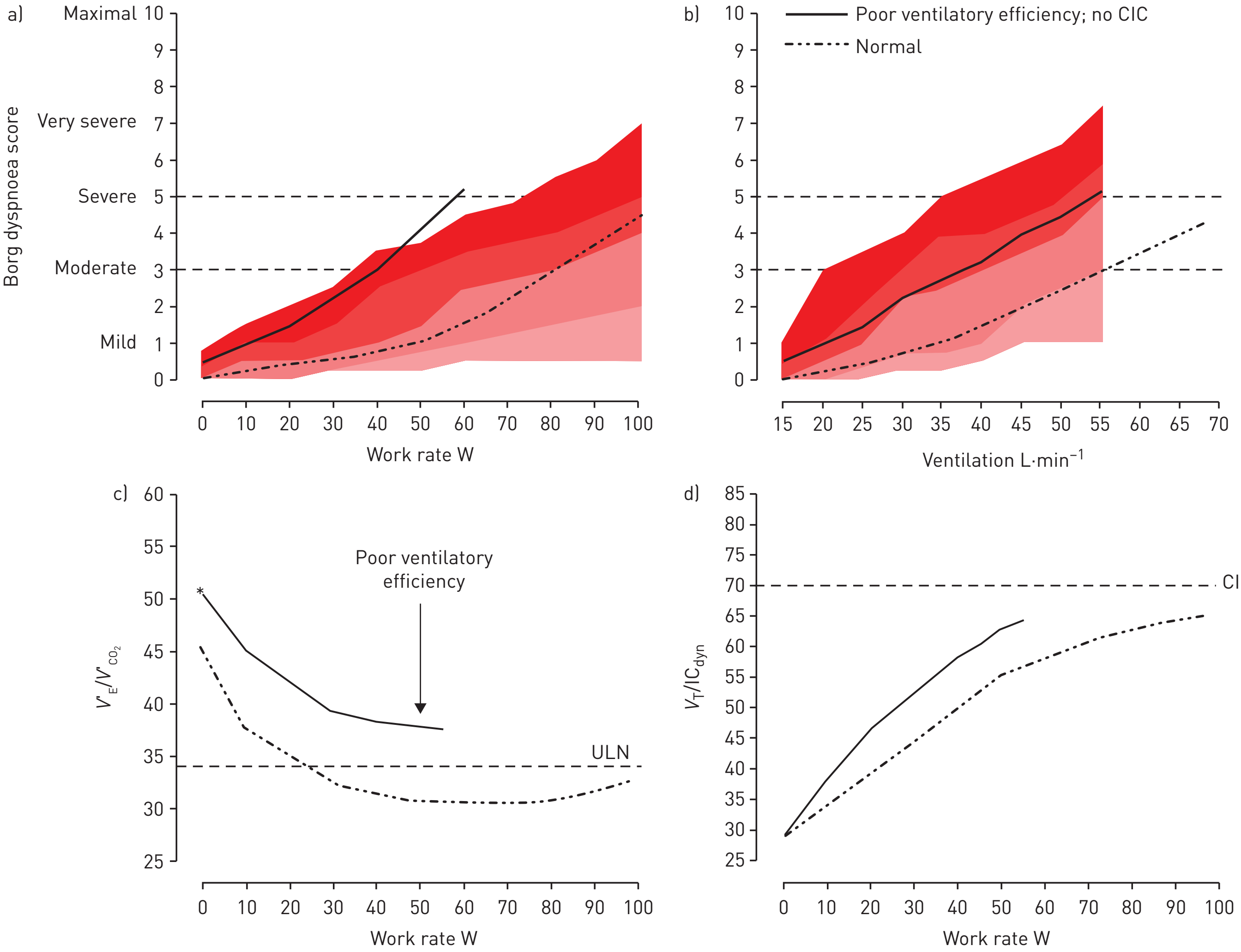

FIGURE 5 Representative subject from the "testing sample" (woman, aged 62) who presented with ventilatory inefficiency (ventilation (V'_E)/carbon dioxide output (V'_{CO_2}) consistently above the upper limit of normal) (c) but did not reach critical inspiratory constraints (CIC (tidal volume (V_T)/dynamic inspiratory capacity (IC_{dyn}) $\leqslant 0.7$; d). Note the lack of upward inflections in dyspnoea-V'_E (c), indicating that her high dyspnoea burden (dyspnoea-work rate in the "very severe" range) (a) was secondary to increased ventilatory demands rather than mechanical constraints. The dotted line represents the ratings endorsed by a woman aged 66 from the "testing sample" who did not present with ventilatory inefficiency.

Conversely, the mechanical constraints seem to assume a more prominent role to explain higher exertional dyspnoea in women than men [35].

Incorporating dyspnoea burden in the clinical interpretation of CPET

What are the clinical scenarios in which the submaximal dyspnoea ranges might impact on the interpretation of incremental CPET? We chose to focus our primary analysis in a population in which the actual burden of dyspnoea may have been overshadowed by heightened leg discomfort at exercise termination. By uncovering the severity of submaximal dyspnoea in these subjects, unique information could be obtained from the sub-maximal dyspnoea scores. The files provided in the supplementary material can be uploaded by individual laboratories and/or added to currently available software for CPET interpretation. It seems particularly important, however, to depict dyspnoea-work rate and dyspnoea-V'_E plots in the same page of traditional physiological responses; thus, the reader can promptly related subjective to objective findings (*e.g.* figures 4 and 5) [37]. Once the submaximal dyspnoea-work rate scores lie below the "severe" range there is a lower likelihood of physiological abnormalities; conversely, if they are above the "moderate" range the reader should carefully look for a sound physiological explanation, *i.e.* increased ventilatory demand and/or altered ventilatory mechanics (figure 3). In the later scenario, complementary information can be obtained from the dyspnoea-V'_E relationship: whereas a sudden upward shift strongly suggests the attainment of critically high inspiratory constraints (table 3 and figure 4), lack of changes in dyspnoea-V'_E are more consistent with increased ventilatory requirements, *e.g.* poor ventilatory efficiency (figure 5) or the ventilatory threshold [38]. Thus, the importance of systematically relate the sensory experience with objective findings: in similarity with any other CPET variable [4, 9–11], dyspnoea scores, in isolation, do not present with discriminative properties.

There are other specific scenarios in which assessment of submaximal dyspnoea burden might prove particularly useful. For instance, the effect of interventions aimed at decreasing ventilatory demands and/or improving lung mechanics [1] might be better exposed compared to peak scores in isolation. Exertional dyspnoea has long been associated with negative clinical outcomes (including survival) [1]: instead of relying in a single discrete value, assessing the overall burden is prone to more relevant to daily functioning. Additional studies are warranted to test these premises.

Study limitations

Our study has, naturally, some limitations. As a single centre study, it is unclear whether our results could be unrestrictedly applied to other populations; nevertheless, this concern applies to the KILLIAN *et al.* [7] study which also analysed data from a single laboratory. Larger multi-centre (ideally multi-national) study would be valuable to develop more representative reference ranges. Meanwhile, it is advisable that the validity of the reference ranges herein proposed be tested against the dyspnoea scores reported by a group of normal men and women who are representative of the local population. An important dimension of exertional dyspnoea (dyspnoea quality) was not determined [39]. It remains unclear whether slowing or speeding the rate of work rate increment changes appreciably dyspnoea-V'_{E} and, particularly, dyspnoea-work rate. In keeping with current recommendations, most of our tests lasted between 8 and 12 min [4]; thus, care should be taken in analysing dyspnoea elicited by shorter or longer tests. We were unable to test the validity of dyspnoea scores in subjects younger than 40 though it could be argued that this population is less likely to be referred to clinical exercise testing. Similar concerns might be raised to subjects aged 80 years and older (figure E1); again, in practice, this is a not a frequent population seen in CPET laboratories. Our sample does not have a large number of overtly obese subjects (tables 1 and 2); thus, care should be taken to extrapolate our findings to a population which characteristically presents with higher V'_{E} at a given work rate [40] and increased work of breathing at a given V'_{E} [32]. Finally, the reference ranges herein presented should not be applied to physically active subjects who might report lower dyspnoea-work rate and dyspnoea-V'_{E} ratings.

Conclusions

The present study provided a novel frame of reference to assess the severity (and the cumulative burden) of dyspnoea throughout incremental cycle ergometry in men and women presenting with a large age span. Owing to the fact that these reference ranges were externally validated in an independent healthy population and able to uncover the severity of dyspnoea in subjects who otherwise would be labelled as "non-dyspnoeic", they might prove valuable to enhance the clinical usefulness of CPET.

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