

## ON-LINE DATA SUPPLEMENT

### **MATERIALS AND METHODS**

#### **Subjects**

*“Reference” sample:* Two-hundred and seventy-five apparently healthy, never smokers and sedentary subjects aged 20 to 85 (131 men) with normal spirometry and advanced pulmonary function tests (lung volumes by body plethysmography and lung diffusing capacity for carbon monoxide ( $DL_{CO}$ )). They were prospectively recruited from the community to serve as controls for several ethically-approved studies previously performed in the Respiratory Investigation Unit, Kingston General Hospital, Kingston, ON, Canada (N= 100) and in the Laboratory of Pulmonary Function Tests in the Federal University of Rio Grande do Sul, Porto Alegre, RS, Brazil (N= 55). One-hundred and twenty subjects aged 40 and older were randomly selected from clerical and manual workers from the auxiliary staff of the Federal University of Sao Paulo, Sao Paulo, SP, Brazil in a prospective, ethically-approved study reported elsewhere (N= 120).[1] In this prospective study, subjects were carefully stratified by gender, age, height and weight. Data were amalgamated only after certification that there was no systematic bias as pertaining to population’s origin.

*“Validation sample”:* Four hundred and fifty-one apparently healthy subjects, never smokers and sedentary subjects aged 40 to 91 (224 men) with normal spirometry and advanced pulmonary function tests (lung volumes by body plethysmography and lung diffusing capacity for carbon monoxide ( $DL_{CO}$ )). They were assessed in a longitudinal cohort study in which subjects were split evenly between men and women. They were randomly selected from the community and contacted by phone in Calgary, Halifax, Kingston, Montreal, Ottawa, Quebec, Saskatoon, Toronto and Vancouver, Canada: ethical approved was granted in each of these centers. [2] They sampled the population living in a well-

defined area that had a total population of at least 250,000 people. The sample herein included consisted of all disease-free subjects who underwent CPET in the initial assessment.

*“Testing sample”*: One-hundred and seventy one subjects (86 males) with chronic persistent dyspnea (of at least three months duration)[3] of clinically significant severity (modified Medical Research Council Questionnaire (mMRC)  $\geq 2$ ) [4] who were referred to cycle ergometer CPET but terminated CPET due to leg discomfort. The tests were performed in three pulmonary function testing laboratories in Brazil (N= 41) and Canada (N= 130). Subjects were included if they endorsed a history of: a) exertional dyspnea despite only mild-moderate resting functional abnormalities which, in the opinion of the physician in charge, did not adequately explain the severity of the symptom (herein named “disproportionate dyspnea, N= 68), b) exertional dyspnea with complex combinations of respiratory, cardiac, metabolic, neuromuscular, hematological and other diseases in whom the referring physician expressed uncertainty regarding the main determinant of patients’ symptom (“dyspnea with multiple potential causes”, N: 72) and c) “dyspnea without an apparent cause” after a thorough clinical assessment, pulmonary function tests and a chest X-ray (N= 31). CPET results from part of this population (N= 102) have been described in a previous study: in that specific manuscript, however, sub-maximal dyspnea scores were not analyzed neither any specific association with coexistent physiological abnormalities was performed. A post-hoc analysis was performed with the extant 113 subjects of this sample (65 males, aged 58 to 88 years) who did terminate the test due to dyspnoea.

## **Procedures**

*Pulmonary function tests*: Spirometry (FVC: forced vital capacity (L); FEV<sub>1</sub>: forced expiratory volume in one second (L); FEV<sub>1</sub>/ FVC ratio), static lung volumes by body plethysmography (TLC: total lung

capacity (L); FRC: functional residual capacity (FRC); RV: residual volume (RV); and lung diffusing capacity ( $DL_{CO}$ : lung diffusing capacity: mL/min/mm Hg) were performed according to current guidelines [5] [6] : reference values were those proposed by the Global Lung Initiative [6] and Quanjer et. al. (for lung volumes) [7] .

*Incremental cardiopulmonary exercise testing:* CPET was conducted on an electronically-braked cycle ergometer in all laboratories. Standard breath-by-breath metabolic ( $\dot{V}O_2$ : oxygen uptake (L/min); carbon dioxide output:  $\dot{V}CO_2$  (L/min) RER: respiratory exchange ratio;) and cardiorespiratory parameters HR: heart rate (beats/min);  $\dot{V}_E$ : ventilation (L/min);  $V_T$  (L): tidal volume; eMVV: estimated maximal voluntary ventilation ( $FEV_1 \times 35$  L/min) [8];  $SpO_2$ : oxygen saturation by pulse oximetry (%)). The stepwise progressive CPET consisted of steady state rest, unloaded exercise (“0 W”) followed by 10-20 W increases in work rate (according to the estimated level of individual fitness aiming at 8 min or longer testing duration) [9] Subjects rated the intensity of their “breathing discomfort” (dyspnea) and “leg discomfort” at rest and in the last 30 seconds of each stage by pointing to a modified 10-point Borg scale. The scale's endpoints were anchored such that ‘0’ represented “no breathing/leg discomfort” and ‘10’ represented “the most severe breathing/leg discomfort ever experienced or imagined.” We herein report only peak (not submaximal) leg discomfort scores.

Additional measurements herein reported only in the “testing sample” included: a) ventilatory inefficiency (the lowest (nadir)  $\dot{V}_E/\dot{V}CO_2$  ratio > upper limit of normal for age and gender);[10] and b) dynamic inspiratory capacity (IC, L/min) maneuvers before applying the Borg scale: from these measurements and  $V_T$  , we calculated end-inspiratory lung volume (EILV)/TLC ratio and  $V_T/IC$  ratio. We defined the presence of critically high inspiratory constraints using previously validated (against discrete dyspnea scores) thresholds [11] [12] :  $V_T/IC$  ratio > 0.7 [13] and/or EILV/TLC > 0.8)

reached at a work rate < lower limit of normal [14]. Exercise-related O<sub>2</sub> desaturation by pulse oximetry (SpO<sub>2</sub> decrease > 4% and end-exercise SpO<sub>2</sub> < 93%) [9]. In this sample, an upward shift in the dyspnea- $\dot{V}E$  relationship [15] was defined by a sudden increase in the ratings (by at least 2 points relative to the preceding  $\dot{V}E$ ) and they did not decrease afterwards.

### **Data Handling and Statistical Analysis**

The statistical software package used was IBM™ SPSS™ Statistics version 25. A  $P < 0.05$  level of significance was used for all analyses. 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  $\dot{V}E$ . As the mean bias was typically zero with a 95% confidence interval < 2, [16] the sub-populations were merged. Preceding the analysis of dyspnea scores, we used Kolmogorov-Smirnov test to test their symmetry: scores at each work rate and were also systematically 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).

#### *Comparing resting and exercise response: “reference”, “validation” and “testing” samples*

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 between- or among groups, respectively.  $\chi^2$  test was used to compare frequencies.

### *Testing for potential predictors of exertional dyspnea:*

Generalized 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 VE. Thus, we measure dyspnoea changes over progressive higher work rates and VE while accounting for relevant covariates.[17]

### *Comparing percentiles distribution*

We *a priori* opted to develop the reference ranges based on percentiles distribution: a subject was categorized to a given range of severity if at least two-thirds of his/her ratings lied within that specific range. 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. to simultaneously test multiple percentiles when comparing the “reference” and “validation” samples.[18] 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 by sex and age.[16].

## **References**

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**Table E1. Work rates (W) at which selected scores were reported at a given centile in the reference and validation samples in subjects 40-59 yrs old.**

|                                     | Men       |            | Women     |            |
|-------------------------------------|-----------|------------|-----------|------------|
|                                     | Reference | Validation | Reference | Validation |
| <b>Score 1 ("mild" dyspnea)</b>     |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | 120       | 120        |
| 25 <sup>th</sup> centile            | 120       | 120        | 80        | 100        |
| 50 <sup>th</sup> centile            | 60        | 80         | 60        | 60         |
| 75 <sup>th</sup> centile            | 40        | 40         | 40        | 40         |
| 95 <sup>th</sup> centile            | 20        | 20         | 0         | 0          |
| <b>Score 3 ("moderate" dyspnea)</b> |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | 140       | 120        | 100       | 100        |
| 75 <sup>th</sup> centile            | 100       | 100        | 80        | 80         |
| 95 <sup>th</sup> centile            | 80        | 80         | 60        | 60         |
| <b>Score 5 ("severe" dyspnea)</b>   |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | -         | -          | -         | -          |
| 75 <sup>th</sup> centile            | 160       | 140        | -         | -          |
| 95 <sup>th</sup> centile            | 120       | 120        | 100       | 100        |



Table E2. Ventilation (L/min) at which selected scores were reported at a given centile in men and women 40-59 yrs old.

| Score 1 ("mild" dyspnea)            | Men       |            | Women     |            |
|-------------------------------------|-----------|------------|-----------|------------|
|                                     | Reference | Validation | Reference | Validation |
| 5 <sup>th</sup> centile             | 60        | 60         | 45        | 50         |
| 25 <sup>th</sup> centile            | 45        | 40         | 40        | 40         |
| 50 <sup>th</sup> centile            | 30        | 35         | 30        | 30         |
| 75 <sup>th</sup> centile            | 25        | 25         | 20        | 25         |
| 95 <sup>th</sup> centile            | 20        | 20         | 0         | 0          |
| <b>Score 3 ("moderate" dyspnea)</b> |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | 70        | 70         | -         | -          |
| 50 <sup>th</sup> centile            | 65        | 60         | 45        | 40         |
| 75 <sup>th</sup> centile            | 50        | 45         | 30        | 30         |
| 95 <sup>th</sup> centile            | 40        | 40         | 25        | 25         |
| <b>Score 5 ("severe" dyspnea)</b>   |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | -         | -          | 60        | 60         |
| 75 <sup>th</sup> centile            | 70        | 70         | 45        | 40         |
| 95 <sup>th</sup> centile            | 55        | 60         | 35        | 35         |

**Table E3. Work rates at which selected scores were reported at a given centile in the reference and validation samples in subjects 60-69 yrs old.**

|                                     | Men       |            | Women     |            |
|-------------------------------------|-----------|------------|-----------|------------|
|                                     | Reference | Validation | Reference | Validation |
| <b>Score 1 ("mild" dyspnea)</b>     |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | 120       | 120        | 60        | 70         |
| 50 <sup>th</sup> centile            | 80        | 100        | 40        | 40         |
| 75 <sup>th</sup> centile            | 40        | 40         | 20        | 20         |
| 95 <sup>th</sup> centile            | 20        | 20         | 0         | 0          |
| <b>Score 3 ("moderate" dyspnea)</b> |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | 120       | 140        | 80        | 70         |
| 75 <sup>th</sup> centile            | 100       | 100        | 50        | 60         |
| 95 <sup>th</sup> centile            | 60        | 60         | 40        | 40         |
| <b>Score 5 ("severe" dyspnea)</b>   |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | -         | -          | -         | -          |
| 75 <sup>th</sup> centile            | 140       | 140        | 100       | 100        |
| 95 <sup>th</sup> centile            | 80        | 100        | 80        | 80         |

**Table E4. Ventilation (L/min) at which selected scores were reported at a given centile in men and women 60-69 yrs old.**

|                                     | Men       |            | Women     |            |
|-------------------------------------|-----------|------------|-----------|------------|
|                                     | Reference | Validation | Reference | Validation |
| <b>Score 1 ("mild" dyspnea)</b>     |           |            |           |            |
| 5 <sup>th</sup> centile             | 65        | 60         | 45        | 45         |
| 25 <sup>th</sup> centile            | 50        | 45         | 40        | 40         |
| 50 <sup>th</sup> centile            | 40        | 35         | 25        | 30         |
| 75 <sup>th</sup> centile            | 30        | 30         | 20        | 20         |
| 95 <sup>th</sup> centile            | 20        | 20         | 0         | 0          |
| <b>Score 3 ("moderate" dyspnea)</b> |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | 65        | 70         | 55        | -          |
| 50 <sup>th</sup> centile            | 50        | 50         | 40        | 40         |
| 75 <sup>th</sup> centile            | 45        | 45         | 30        | 30         |
| 95 <sup>th</sup> centile            | 35        | 40         | 20        | 20         |
| <b>Score 5 ("severe" dyspnea)</b>   |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | 70        | -          | 55        | 60         |
| 75 <sup>th</sup> centile            | 65        | 70         | 50        | 45         |
| 95 <sup>th</sup> centile            | 55        | 60         | 35        | 35         |

**Table E5. Work rates at which selected scores were reported at a given centile in the reference and validation samples in subjects  $\geq 70$  yrs old.**

| Score 1 ("mild" dyspnea)     | Men       |            | Women     |            |
|------------------------------|-----------|------------|-----------|------------|
|                              | Reference | Validation | Reference | Validation |
| 5 <sup>th</sup> centile      | -         | -          | 80        | 70         |
| 25 <sup>th</sup> centile     | 70        | 70         | 50        | 50         |
| 50 <sup>th</sup> centile     | 30        | 30         | 20        | 30         |
| 75 <sup>th</sup> centile     | 10        | 20         | 0         | 0          |
| 95 <sup>th</sup> centile     | 0         | 0          | 0         | 0          |
| Score 3 ("moderate" dyspnea) |           |            |           |            |
| 5 <sup>th</sup> centile      | -         | -          | -         | -          |
| 25 <sup>th</sup> centile     | -         | -          | -         | -          |
| 50 <sup>th</sup> centile     | 90        | 80         | 60        | 60         |
| 75 <sup>th</sup> centile     | 60        | 60         | 40        | 30         |
| 95 <sup>th</sup> centile     | 30        | 30         | 20        | 20         |
| Score 5 ("severe" dyspnea)   |           |            |           |            |
| 5 <sup>th</sup> centile      | -         | -          | -         | -          |
| 25 <sup>th</sup> centile     | -         | -          | -         | -          |
| 50 <sup>th</sup> centile     | -         | -          | -         | -          |
| 75 <sup>th</sup> centile     | -         | -          | 70        | 70         |
| 95 <sup>th</sup> centile     | 80        | 70         | 50        | 50         |

**Table E6. Ventilation (L/min) at which selected scores were reported at a given centile in men and women  $\geq$  70 yrs old.**

| Score 1 ("mild" dyspnea)            | Men       |            | Women     |            |
|-------------------------------------|-----------|------------|-----------|------------|
|                                     | Reference | Validation | Reference | Validation |
| 5 <sup>th</sup> centile             | 55        | 50         | -         | -          |
| 25 <sup>th</sup> centile            | 40        | 35         | 30        | 30         |
| 50 <sup>th</sup> centile            | 30        | 30         | 25        | 25         |
| 75 <sup>th</sup> centile            | 20        | 20         | 15        | 15         |
| 95 <sup>th</sup> centile            | 0         | 0          | 15        | 15         |
| <b>Score 3 ("moderate" dyspnea)</b> |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | 60        | 55         | -         | -          |
| 50 <sup>th</sup> centile            | 40        | 40         | 35        | 35         |
| 75 <sup>th</sup> centile            | 35        | 35         | 30        | 25         |
| 95 <sup>th</sup> centile            | 30        | 30         | 25        | 20         |
| <b>Score 5 ("severe" dyspnea)</b>   |           |            |           |            |
| 5 <sup>th</sup> centile             | -         | -          | -         | -          |
| 25 <sup>th</sup> centile            | -         | -          | -         | -          |
| 50 <sup>th</sup> centile            | 60        | 60         | 45        | 45         |
| 75 <sup>th</sup> centile            | 50        | 55         | 40        | 40         |
| 95 <sup>th</sup> centile            | 45        | 45         | 30        | 25         |

**Table E7.** Resting and exercise data of the testing sample. Subjects separated by age and the presence or absence of key physiological abnormalities known to induce exertional dyspnea (ventilatory inefficiency and/or critical inspiratory constraints (CIC) and/or exertional hypoxemia; N= 118 and N= 53, respectively).

|                                    | 40-59 yrs         |                     | 60-69 yrs         |                     | ≥ 70 yrs          |                     |
|------------------------------------|-------------------|---------------------|-------------------|---------------------|-------------------|---------------------|
|                                    | Absence<br>(N=12) | Presence<br>(N= 26) | Absence<br>(N=19) | Presence<br>(N= 39) | Absence<br>(N=22) | Presence<br>(N= 53) |
| <b>General characteristics</b>     |                   |                     |                   |                     |                   |                     |
| Men/Women, N (%)                   | 8/4               | 11/15               | 10/9              | 19/20               | 10/12             | 27/26               |
| Age, years                         | 52.3 ± 6.5*       | 53.4 ± 5.9*         | 65.1 ± 4.3*       | 67.1 ± 3.2*         | 75.1 ± 3.1        | 74.2 ± 4.2          |
| Body mass index, kg/m <sup>2</sup> | 24.1 ± 5.5        | 25.6 ± 7.1          | 28.3 ± 3.7        | 29.1 ± 4.3          | 30.2 ± 4.6        | 31.1 ± 3.7          |
| CPET indication (dyspnea)          |                   |                     |                   |                     |                   |                     |
| Disproportionate, N (%)            | 3 (25)            | 8 (31)              | 6 (32)            | 14 (36)             | 8 (36)            | 31 (58)             |
| Multiple potential causes, N (%)   | 8 (67)            | 15 (58)             | 8 (42)            | 19 (49)             | 10 (45)           | 20 (38)             |
| Without apparent cause, N (%)      | 1 (8)             | 3 (11)              | 5 (26)            | 6 (15)              | 4 (19)            | 2 (4)               |
| Main underlying diagnosis †        |                   |                     |                   |                     |                   |                     |
| COPD, N (%)                        | 1 (8)             | 6 (23)              | 5 (27)            | 21 (56)             | 3 (14)            | 28 (53)             |
| ILD, N (%)                         | 1 (8)             | 0                   | 1 (5)             | 3 (7)               | 2 (8)             | 8 (16)              |
| Cardiovascular disease, N (%)      | 3 (8)             | 6 (23)              | 3 (15)            | 10 (25)             | 7 (32)            | 10 (19)             |
| Metabolic disease, N (%)           | 1 (8)             | 8 (31)              | 7 (38)            | 2 (5)               | 8 (38)            | 4 (8)               |
| None of above, N (%)               | 7 (68)            | 6 (23)              | 3 (15)            | 3 (7)               | 2 (8)             | 3 (4)               |
| <b>Lung Function</b>               |                   |                     |                   |                     |                   |                     |
| FEV <sub>1</sub> , % pred          | 88.5 ± 14.3       | 85.9 ± 18.6         | 87.3 ± 13.1       | 73.6 ± 10.9*        | 75.9 ± 16.3       | 68.1 ± 20.4*        |
| FEV <sub>1</sub> /FVC              | 0.70 ± 0.04       | 0.69 ± 0.06         | 0.67 ± 0.05       | 0.64 ± 0.03*        | 0.65 ± 0.04       | 0.60 ± 0.08*        |
| TLC, % pred                        | 93.2 ± 13.1       | 90.1 ± 14.7         | 95.4 ± 21.9       | 107.3 ± 14.3        | 90.8 ± 15.9       | 110.6 ± 14.3*       |
| RV, % pred                         | 103.6 ± 21.7      | 118.4 ± 26.5        | 97.2 ± 16.4       | 120.8 ± 22.4*       | 109.1 ± 12.6      | 124.95 ± 30.2       |
| DL <sub>CO</sub> , % pred          | 87.5 ± 28.1       | 78.4 ± 23.1*        | 85.1 ± 23.7       | 76.1 ± 26.9*        | 83.4 ± 30.3       | 71.6 ± 20.4*        |
| <b>CPET</b>                        |                   |                     |                   |                     |                   |                     |
| Work rate, W                       | 111 ± 14          | 92 ± 16*            | 100 ± 16          | 82 ± 19*            | 84 ± 17           | 66 ± 15*            |
| VO <sub>2</sub> , L/min            | 1.47 ± 0.20       | 1.29 ± 0.16*        | 1.31 ± 0.18       | 1.19 ± 0.22         | 1.16 ± 0.17       | 1.02 ± 0.14*        |
| HR, % pred                         | 94.3 ± 6.4        | 88.1 ± 7.1*         | 95.2 ± 5.9        | 84.2 ± 7.5          | 91.1 ± 9.3        | 80.6 ± 10.3*        |
| Ṁ <sub>E</sub> /eMVV               | 0.63 ± 0.12       | 0.69 ± 0.15         | 0.62 ± 0.11       | 0.70 ± 0.10*        | 0.71 ± 0.11       | 0.78 ± 0.13*        |
| CIC, N (%)                         | 0                 | 11 (42)             | 0                 | 23 (62)             | 0                 | 30 (57)             |
| Ventilatory inefficiency, N (%)    | 0                 | 17 (65)             | 0                 | 21 (54)             | 0                 | 28 (53)             |

|                                     |         |          |         |           |         |         |
|-------------------------------------|---------|----------|---------|-----------|---------|---------|
| SpO <sub>2</sub> , %                | 96 ± 3  | 94 ± 1   | 97 ± 2  | 93 ± 3 *  | 95 ± 3  | 90 ± 3* |
| O <sub>2</sub> desaturation, N (%)  | 0       | 4 (15)   | 0       | 10        | 0       | 14      |
| Dyspnea, Borg units                 | 6 (3-7) | 5 (3-7)  | 6 (5-7) | 5.5 (4-6) | 6 (5-7) | 5 (4-6) |
| Ranges of dyspnea severity          |         |          |         |           |         |         |
| < 5 <sup>th</sup> percentile, N (%) | 1 (8)   | 1 (4)    | 2 (11)  | 1 (3)     | 1 (5)   | 2 (4)   |
| "Mild", N (%)                       | 2 (16)  | 1 (4)    | 2 (11)  | 1 (3)     | 2 (10)  | 2 (4)   |
| "Moderate", N (%)                   | 4 (34)  | 2 (8)    | 10 (52) | 2 (6)     | 11 (50) | 2 (4)   |
| "Severe", N (%)                     | 4 (34)  | 2 (8)    | 3 (16)  | 1 (3)     | 6 (25)  | 3 (6)   |
| "Very severe", N (%)                | 1 (8)   | 8 (31)   | 1 (5)   | 14 (36)   | 1 (5)   | 15 (28) |
| >95 <sup>th</sup> percentile, N (%) | 0       | 12 (45)  | 1 (5)   | 20 (49)   | 1 (5)   | 29 (54) |
| Leg effort, Borg units              | 8 (5-8) | 8 (7-10) | 8 (6-9) | 9 (6-10)  | 8 (6-9) | 8 (6-9) |

\* p<0.05: compared to the subsequent age group. No significant differences between reference and validation samples across age groups. †: as established by the referring physician. Systemic arterial hypertension and/or diastolic dysfunction and/or heart failure with preserved ejection fraction and/or coronary artery disease were the commonest cardiovascular diagnoses. Non-insulin dependent diabetes mellitus and/or, hypercholesterolemia and/or hypothyroidism or another endocrine disease were the commonest metabolic diseases. *Definition of abbreviations:* CPET: cardiopulmonary exercise testing; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; FVC= forced vital capacity; FEV<sub>1</sub>, %: forced expiratory volume in one second; TLC: total lung capacity; RV: residual volume; DL<sub>CO</sub>: lung diffusing capacity;  $\dot{V}O_2$ = oxygen uptake; HR: heart rate;  $\dot{V}_E$ : ventilation; eMVV: estimated maximal voluntary ventilation;; SpO<sub>2</sub>= oxygen saturation by pulse oximetry. .

Figure E1. Age distribution in men and women in the “reference” (*panel A*), “validation” (*panel B*) and “testing” (*panel C*) samples: note the differences in the range of values y values across samples.

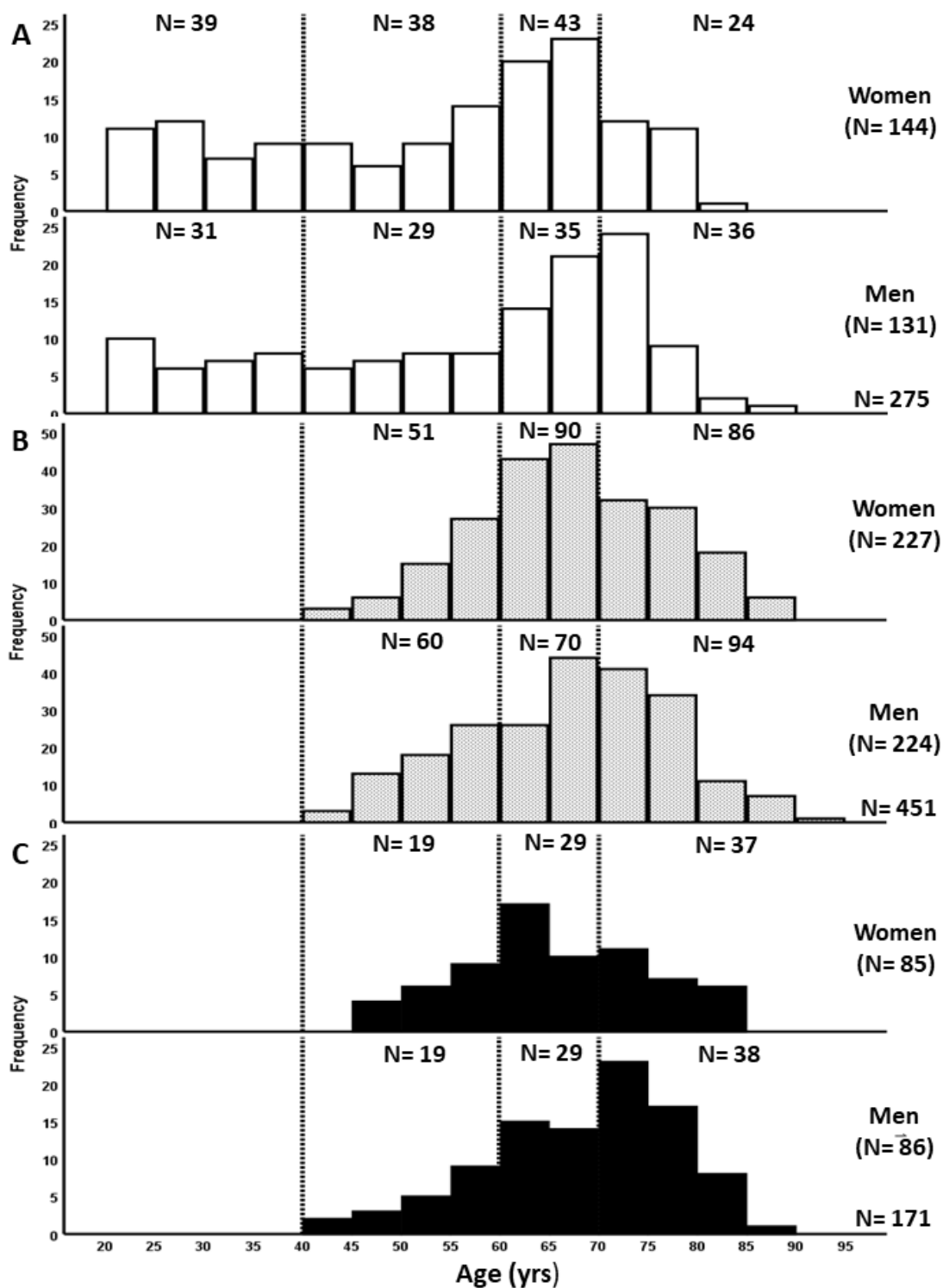




Figure E2. Mean bias (solid line) and 95% confidence limits (dashed lines) for the work rate at which selected Borg dyspnea scores ("1", "3" and "5") were reported across percentiles in the reference and validation samples in men and women 40 and older.

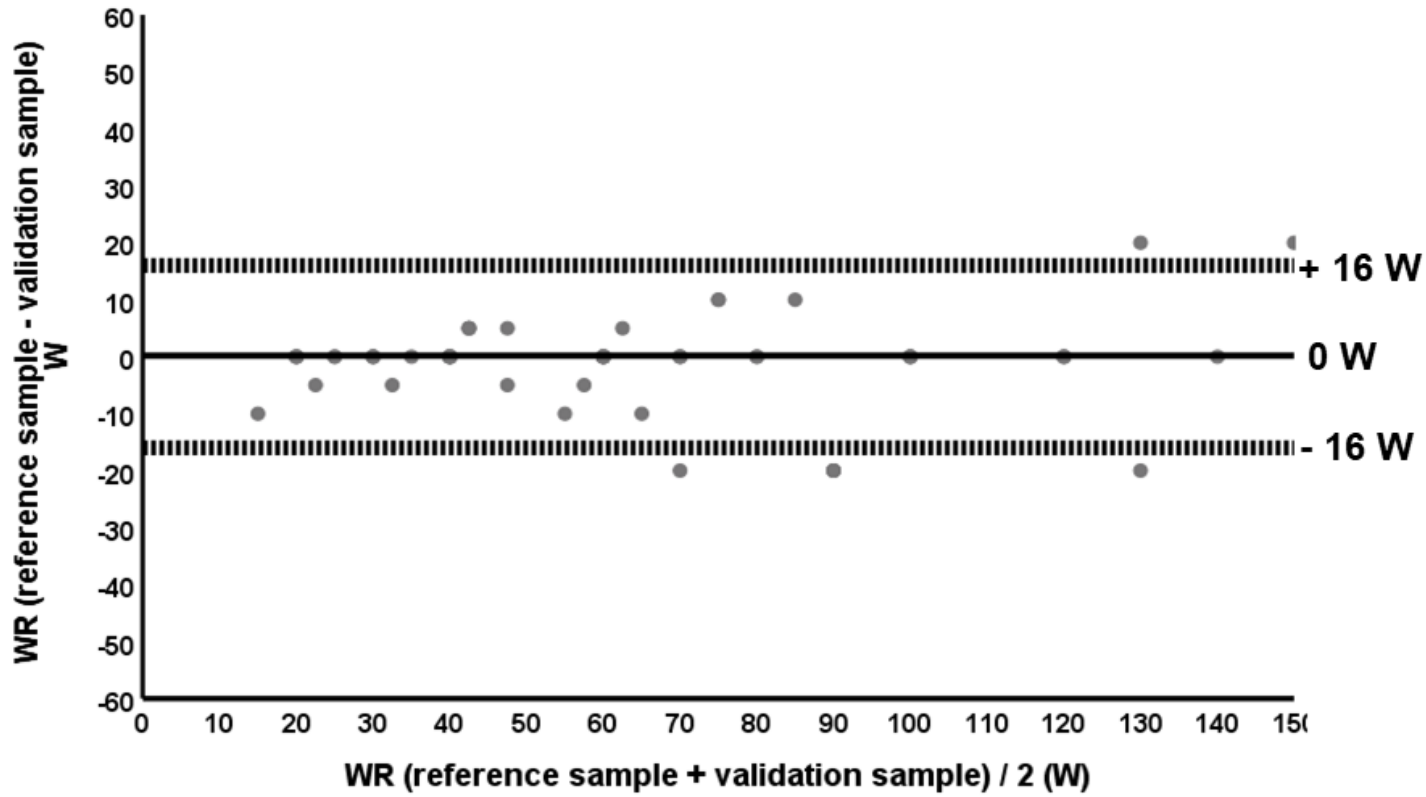


Figure E3. Mean bias (solid line) and 95% confidence limits (dashed lines) for the ventilation ( $\dot{V}_E$  at which selected Borg dyspnea scores ("1", "3" and "5") were reported across percentiles in the reference and validation samples in men and women 40 and older.

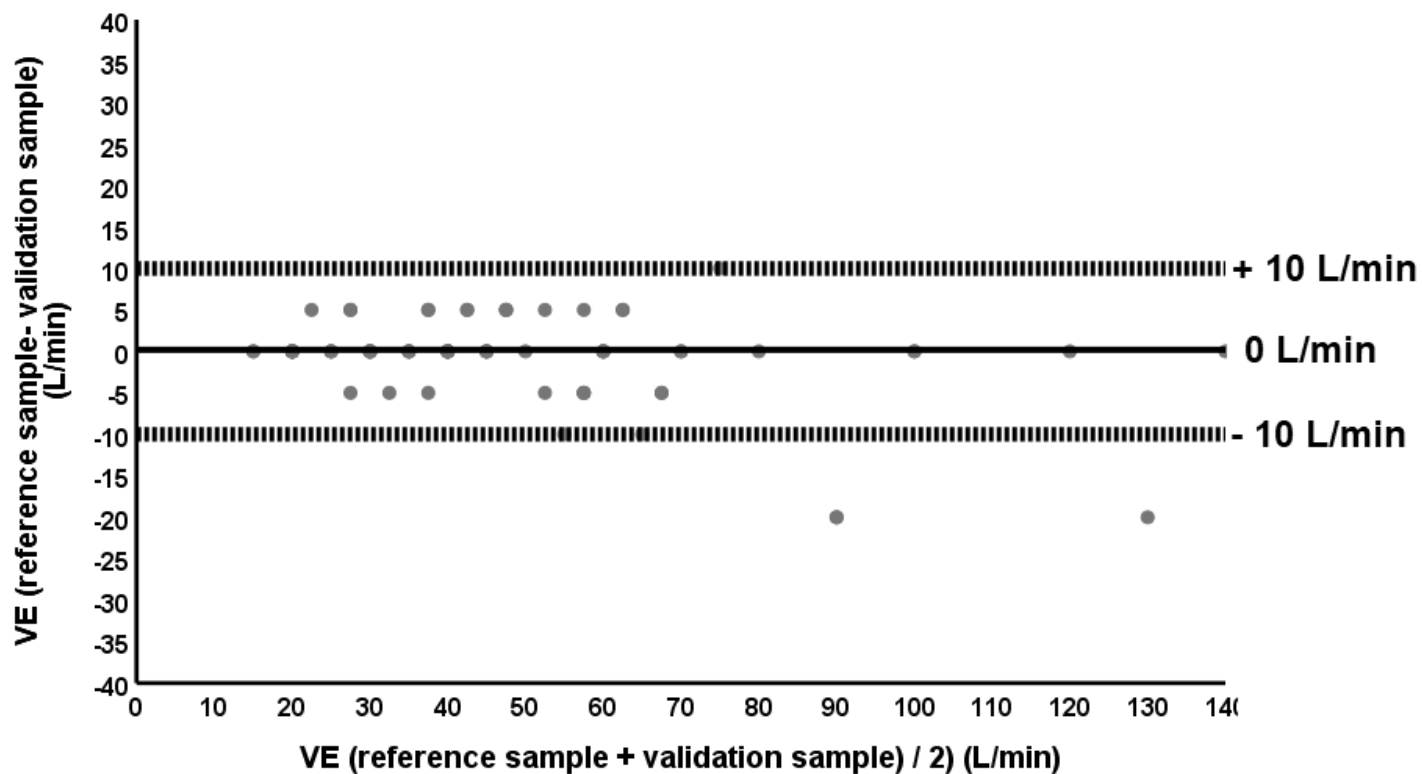


Figure E4. Percent distribution of submaximal dyspnoea-work rate scores in a group of 113 subjects who were referred for cardiopulmonary exercise testing and reported dyspnea as the limiting symptom at the termination of the test. "Mild", "moderate", "severe" and "very severe" ranges correspond to the following percentile intervals: 5<sup>th</sup>-25<sup>th</sup>, 25<sup>th</sup>-50<sup>th</sup>, 50-75<sup>th</sup> and 75<sup>th</sup>-95<sup>th</sup>. In both groups, there was a significant association between poor exercise tolerance (peak work rate < lower limit of normal) with dyspnoea scores above the 75<sup>th</sup> percentile ( $p < 0.01$ ;  $\chi^2$  test).

