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The mMRC scale misclassifies exertional breathlessness among people referred for exercise testing

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INTRODUCTION

Exertional breathlessness is a cardinal symptom in people with cardiorespiratory disease [1], and is linked to impaired physical capacity [2] and activity [3], which can lead to downward spiral of deconditioning and further worsening of breathlessness [4]. High levels of exertional breathlessness in daily life are associated with impaired wellbeing [5], and an abnormally high risk of morbidity and mortality [4, 6]. Valid assessment of exertional breathlessness is important for clinical evaluation and management but is challenging [7]. In clinical practice and research, the individual is often asked to recall the level of breathlessness experienced during a time period using a questionnaire. The modified Medical Research Council (mMRC) breathlessness scale [8] is a widely used questionnaire to categorize the level of activity-related breathlessness and to determine eligibility for clinical trials [9, 10]. The mMRC is also used by the Global Initiative for chronic Obstructive Lung Disease (GOLD) to assess symptom burden of chronic obstructive pulmonary disease (COPD) [11]. The mMRC reflects the level of exertion (such as walking uphill) at which breathlessness limits physical activity [8], but does not measure the symptom intensity *per se*, and may be influenced by other factors such as the person’s cardiopulmonary fitness. [12]. An important limitation of the mMRC is that it does not assess breathlessness in relation to a standardized level of exertion, and therefore might underestimate exertional breathlessness and impaired exercise capacity in people who have decreased their physical activity levels to avoid the symptom [13]. Misclassification of exertional breathlessness using the mMRC can also arise as some people find the questionnaire illogical or confusing to use [14].

Following the basic principles of psychophysics, exertional breathlessness should be measured in relation to the magnitude of symptom stimulus, i.e., the level of exertion [15]. A
gold standard method to assess exertional breathlessness is using an incremental cycle exercise test (IET) [7, 16, 17]. Reference equations for the breathlessness intensity response (on the Borg 0-10 category-ratio [CR10] scale [18]) during cycle IET were recently published [19]. Using these reference equations, abnormally high exertional breathlessness can be defined as a Borg CR10 intensity rating above the predicted upper limit of normal (ULN). The ULN corresponds to the 95th percentile of breathlessness intensity ratings in the healthy reference population for a given age, sex, height, and power output (W) expressed as the percentage of the person’s predicted maximum power output (%predW_{max}) [19]. The reference values enable evaluation of exertional breathlessness in a more standardized way during a standardized IET.

No study has previously evaluated the ability of the mMRC scale to identify people with abnormally high exertional breathlessness or abnormally low exercise capacity assessed using a standardized IET. This is important to investigate as mMRC might underestimate the presence of abnormally high exertional breathlessness as people reduce their activity level to avoid the symptom, and as mMRC is widely used in clinical care [20]. Standardized exercise testing could potentially be used to unmask this otherwise hidden breathlessness burden [13]. An improved understanding of the measuring of breathlessness could have implications for how patients’ symptoms are assessed and managed across a wide range of conditions including cardiorespiratory diseases.

The aim of this study was to evaluate, among people referred for IET, the ability of the mMRC scale ratings to identify the presence of 1) abnormally high exertional breathlessness, and 2) abnormally low exercise capacity on standardized cycle IET. We were particularly interested in evaluating the rate of symptom unmasking; that is, the rate of abnormally high exertional breathlessness on IET among people with little to no self-rated breathlessness in daily life (mMRC 0-1).
METHODS

Design and population
This was a secondary analysis of data from a randomized controlled trial (RCT) of breathlessness during IET conducted at the Department of Clinical Physiology, Blekinge Hospital, Karlskrona, Sweden [21]. The trial included outpatients aged 18 years or older who were referred for cycle IET between March and December 2018. Reasons for referral were mostly suspected chronic coronary syndrome, as well as suspected exercise induced arrythmias, occupational health screening, and unexplained breathlessness [21]. The present analyses addressed de novo objectives independent of the original RCT that have not been presented previously.

Inclusion criteria for the present analysis were available self-reported data on the mMRC breathlessness scale before the IET and at least two Borg CR10 scale breathlessness intensity ratings at any time during the exercise part of the IET, including at peak exercise. In this analysis, only data from the start of the exercise phase to the symptom-limited peak of exercise were used. Breathlessness intensity ratings collected before and after IET were not included.

Ethical considerations
This study was approved by the ethics committee of Lund University in Sweden (Dnr: 2017/310). All participants provided informed written consent. The trial was registered with ClinicalTrials.gov (NCT03468205) before recruitment of the first participant. The study is reported in accordance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines [22].
Assessments

Before the IET, participants completed the mMRC breathlessness scale (“mark the alternatives that applies to your situation in the last two weeks”), and questionnaires about their smoking status (current, former, never) and presence of physician-diagnosed health conditions and medical procedures (including COPD; asthma; and cardiovascular disease (CVD), which collectively defined in the present study as the participant having any one or combination of cardiovascular insult, myocardial infarction, angina, congestive heart failure, atrial fibrillation, prior invasive procedure against arterial stenosis, arterial aneurysm, bypass or balloon angioplasty of the coronary arteries).

A symptom-limited cycle IET was performed according to current Swedish guidelines [23]. The protocol was the same that was used in the cohort the normal range equations are based on. Initial work rate was usually 30W for women and 50W for men although higher (up to 90W) or lower values could be used depending on the participant’s expected exercise capacity, as judged by the responsible staff. Incremental increases were also based on the expected exercise capacity, with the aim to obtain an IET duration of about eight minutes. Increments of 10W/min, 15W/min or 20W/min were used for all participants, with 10W/min increments used for older and frail participants and 20W/min increments used for younger and more fit participants, as judged by the staff. Every 2 minutes during IET and at peak exercise, participants rated the intensity of their perceived breathlessness using the Borg CR10 scale [18]. Participants were asked “How strong is your breathlessness now?” and rated their breathlessness from 0 “nothing at all” to 10 “extremely strong”.

Statistical analyses

Abnormally high exertional breathlessness was defined as having a Borg CR10 scale breathlessness intensity rating > the predicted ULN at any point during exercise phase of the IET [24]. In addition, breathlessness was compared between participants by calculating each
breathlessness rating’s probability of normality, using the normative reference equations [24].

The probability of normality was defined as the probability of observing an equal or higher Borg CR10 scale breathlessness intensity rating among healthy people at a similar predicted maximal work capacity (W%pred_max), according to Swedish reference ranges [25], with a lower probability reflecting more abnormal (severe) exertional breathlessness [24]. The lowest probability of normality (reflecting the most severe exertional breathlessness) during the IET was plotted against the mMRC ratings. Abnormally low exercise capacity was defined as a peak exercise capacity < 75 %predW_max according to Swedish reference ranges [25]. Characteristics were tabulated by the presence of abnormally high exertional breathlessness and abnormally low exercise capacity using mean with standard deviation (SD) and median with range or interquartile range (IQR) for continuous variables with normal and skewed distribution, respectively.

Sensitivity, specificity, accuracy and discriminative ability (c-statistic) of each mMRC rating were calculated for detecting abnormally high exertional breathlessness and abnormally low exercise capacity, respectively. The c-statistic was analyzed using receiver operator characteristics (ROC) curves. Estimates were presented with 95% confidence intervals (CIs). Statistical significance was defined as two-sided p-value < 0.05. Statistical analyses were conducted using the software packages STATA version 17.0 (StataCorp LP; College Station, TX, USA).

RESULTS

Participants

A total of 92 participants were included with a mean age of 59 (SD 13.5) years, 61% were male, 20 (22%) had an mMRC rating of 0, 59 (64%) had a mMRC rating of 1, and 13 (14%) had an mMRC rating of ≥ 2 (Table 1). The proportion of participants who had abnormally high exertional breathlessness during the IET was 35%. The proportion of participants who
had abnormally low exercise capacity was also 35%. The proportion of participants who had both abnormally high exertional breathlessness and abnormally low exercise capacity was 22%. Compared to people whose exertional breathlessness was within the normal predicted range, people with abnormally high exertional breathlessness had significantly lower peak exercise capacity, were more likely to be current or former smokers, and to have a comorbid cardiovascular and/or pulmonary disease (Table 1).

**mMRC to identify abnormally high exertional breathlessness**

Although higher mMRC ratings were associated with abnormally high breathlessness during IET, people with mMRC 0-1 had variable breathlessness intensity ratings during IET – with some people having breathlessness intensity ratings well within normal predicted limits and some having abnormally high exertional breathlessness (Figure 1).

Abnormally high exertional breathlessness was present in 69% of people with mMRC ≥2 vs. 29% of people with mMRC 0-1 (p=0.024) (Table 2). For identifying abnormally high exertional breathlessness during the IET: mMRC ≥1 had an accuracy of 50%, specificity of 91%, and sensitivity of 28%; and mMRC ≥2 had an accuracy of 71%, specificity of 93%, and sensitivity of 28%. The cut-off with the greatest discriminative ability was mMRC ≥2, with a c-statistic of 0.67 (Figure 2).

**mMRC to identify abnormally low exercise capacity**

Although higher mMRC ratings were associated with lower exercise capacity, a considerable proportion of people with higher mMRC ratings had normal exercise capacity, or vice versa. (Figure 1).

Abnormally low exercise capacity was present in 46% of people with mMRC ≥2 vs. 33% of people with mMRC 0-1 (p=0.14). For identifying abnormally low exercise capacity during
the IET, mMRC ≥1 had an accuracy of 50%, specificity of 28%, and sensitivity of 91%; and mMRC ≥2 had an accuracy of 64%, specificity of 88%, and sensitivity of 19%. The cut-off with the greatest discriminative ability was mMRC ≥2, with a c-statistic of 0.61 (Figure 2).

Unmasking of abnormal exertional breathlessness and exercise capacity
Among participants with mMRC 0 (n=20), three (15%) had abnormally high exertional breathlessness. Among the 59 participants with mMRC 1, 20 (34%) had abnormally high exertional breathlessness. Altogether, among the 79 participants with mMRC 0-1, 29% had abnormally high exertional breathlessness. The prevalence of abnormally low exercise capacity was 15% for participants with mMRC 0, 39% with mMRC 1, and 33% with mMRC 0-1 (Table 2).

DISCUSSION
Main findings and importance
The main findings are that 1) the mMRC breathlessness scale misclassifies abnormally high exertional breathlessness on IET among people referred for clinical exercise testing; and 2) IET can unmask abnormally high exertional breathlessness among individuals that present clinically with little to no self-reported burden of breathlessness (mMRC 0-1). We also found that, although a mMRC rating of ≥2 was the most accurate cut-point for identifying abnormally high exertional breathlessness or abnormally low exercise capacity, this cut-off had a sensitivity of only 28% and 19%, meaning that 72% and 81% of people who had abnormally high exertional breathlessness and abnormally low exercise capacity on IET were ‘false negative’ using mMRC, respectively. Thus, a mMRC rating of 0-1 does not preclude the presence of abnormally high exertional breathlessness or abnormally low exercise capacity, both of which can be unmasked using a standardized cycle IET.
This is the first study to assess the sensitivity and specificity of the mMRC scale for identifying people with abnormally high exertional breathlessness, evaluated using reference equations during cycle IET [24]. Even if this study was conducted in a relatively unselected sample of people referred for IET in clinical care, and not pertained to any specific disease group such as COPD, the current findings raise concerns regarding the use of mMRC to classify the respiratory symptom burden in clinical guidelines and care, such as in COPD [20] and heart failure (where an adapted version of the mMRC is used [26], the New York Heart Association (NYHA) scale [27]). The mMRC is also widely used in epidemiological studies [28] and for selecting people to participate in clinical trials on breathlessness [29]. The low sensitivity of mMRC for identifying people with abnormally high exertional breathlessness (and/or abnormally low exercise capacity) may contribute to delayed or insufficient identification and management of exertional breathlessness (and/or exercise intolerance) and the underlying condition(s) – which warrants further investigation.

**Strengths and limitations**

Strengths of the present study are the inclusion of a relatively unselected sample of people undergoing clinical cycle IET, who provided standardized self-ratings of breathlessness in daily life using the mMRC and during the IET using the Borg CR10 scale as part of a clinical trial. Breathlessness intensity and peak power output responses were evaluated using published normative reference equations for the present IET protocol in a large Swedish database [24, 25]. Limitations include that this was a single-center study with few participants with mMRC ratings of 3 or 4, and only one person with COPD.

**Implications**
For the clinician, the present findings suggest that: (1) the mMRC breathlessness scale is likely to misclassify the presence of abnormally high exertional breathlessness and/or abnormally low exercise capacity in patients – with a sensitivity of just 28% for detecting abnormally high exertional breathlessness and 19% for detecting abnormally low exercise capacity among people referred for clinical cycle IET; and (2) a standardized cycle IET can uncover ‘hidden’ exertional breathlessness and/or exercise intolerance in a substantial number of patients. However, given obvious differences in cost, time, equipment, resources and feasibility of people completing the mMRC breathlessness scale compared with a cycle IET, and given its high specificity, the mMRC could be useful as a first step to identify people with a rating ≥2, who are likely to have abnormally high exertional breathlessness, and/or abnormally exercise capacity, which is also in accordance with international clinical guidelines[30]. But importantly, a low mMRC breathlessness rating of 0-1 does not preclude the presence of abnormal ‘hidden’ exertional breathlessness and/or exercise intolerance, and a wider clinical evaluation including standardized exercise testing should be considered in people suspected to have abnormally high exertional breathlessness and/or abnormally low exercise capacity.

An important next research step is to evaluate the potential misclassification of using mMRC, compared with IET, in clinical populations, such as people with COPD, where mMRC is part of the GOLD management recommendations [20], and in people with heart failure where management is guided by the NYHA scale, which is an adapted version of the mMRC breathlessness scale [31]. Regarding the use of the normal range intervals and IET, it would be valuable to validate their use in the evaluation of treatment results, for instance though of intra-individual comparisons before and after exercise intervention used in cardiopulmonary rehabilitation.
Conclusion

Among people referred for clinical exercise testing, mMRC breathlessness ratings misclassified the presence of abnormally high exertional breathlessness and abnormally low exercise capacity assessed using a standardized cycle IET, with low sensitivity and frequent false negative results for people with mMRC 0-1.
## TABLES

### Table 1. Characteristics of participants

<table>
<thead>
<tr>
<th></th>
<th>All participants</th>
<th>With abnormally high exertional breathlessness during IET</th>
<th>With normal exertional breathlessness during IET</th>
<th>With abnormally low exercise capacity</th>
<th>With normal exercise capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>92</td>
<td>32</td>
<td>60</td>
<td>32</td>
<td>60</td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.0 (13.5)</td>
<td>60.4 (13.3)</td>
<td>58.3 (13.7)</td>
<td>57.9 (16.4)</td>
<td>59.9 (11.7)</td>
</tr>
<tr>
<td>Male</td>
<td>56 (61%)</td>
<td>17 (53%)</td>
<td>39 (65%)</td>
<td>18 (56%)</td>
<td>38 (63%)</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>14 (15%)</td>
<td>7 (22%)</td>
<td>7 (12%)</td>
<td>6 (19%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Former smoker</td>
<td>39 (42%)</td>
<td>13 (41%)</td>
<td>26 (43%)</td>
<td>11 (34%)</td>
<td>28 (47%)</td>
</tr>
<tr>
<td>Never smoker</td>
<td>38 (41%)</td>
<td>12 (38%)</td>
<td>26 (43%)</td>
<td>15 (47%)</td>
<td>23 (38%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Asthma</td>
<td>10 (11%)</td>
<td>5 (16%)</td>
<td>5 (8%)</td>
<td>4 (12%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>40 (43%)</td>
<td>19 (59%)</td>
<td>21 (35%)</td>
<td>15 (47%)</td>
<td>25 (42%)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>17 (18%)</td>
<td>10 (31%)</td>
<td>7 (12%)</td>
<td>9 (28%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>mMRC breathlessness rating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>20 (22%)</td>
<td>3 (9%)</td>
<td>17 (28%)</td>
<td>3 (9%)</td>
<td>17 (28%)</td>
</tr>
<tr>
<td>1</td>
<td>59 (64%)</td>
<td>20 (62%)</td>
<td>39 (65%)</td>
<td>23 (72%)</td>
<td>36 (60%)</td>
</tr>
<tr>
<td>2</td>
<td>11 (12%)</td>
<td>7 (22%)</td>
<td>4 (7%)</td>
<td>5 (16%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>0</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Referred for IET as part of occupational screening</td>
<td>12 (13%)</td>
<td>1 (3%)</td>
<td>11 (18%)</td>
<td>1 (3%)</td>
<td>11 (18%)</td>
</tr>
<tr>
<td>Peak power output (W)</td>
<td>158.9 (56.5)</td>
<td>126.4 (46.3)</td>
<td>176.3 (54.0)</td>
<td>121.4 (46.2)</td>
<td>178.9 (51.3)</td>
</tr>
<tr>
<td>Peak power output (W%pred)</td>
<td>80.8 (16.4)</td>
<td>69.3 (15.7)</td>
<td>87.0 (13.2)</td>
<td>63.0 (9.6)</td>
<td>90.3 (10.2)</td>
</tr>
<tr>
<td>Abnormally low exercise capacity (W &lt; 75%pred)</td>
<td>32 (35%)</td>
<td>20 (62%)</td>
<td>12 (20%)</td>
<td>32 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Abnormally high exertional breathlessness during IET</td>
<td>32 (35%)</td>
<td>32 (100%)</td>
<td>0</td>
<td>20 (62%)</td>
<td>12 (20%)</td>
</tr>
</tbody>
</table>

Data presented as mean (standard deviation) or frequency (percentage).

**Abbreviations:** COPD, Chronic Obstructive Lung Disease; IET, Incremental Exercise Test; mMRC, modified Medical Research Council breathlessness scale.
Table 2. Ability of mMRC to detect the presence of abnormally high exertional breathlessness and abnormally low exercise capacity identified using symptom-limited incremental cycle exercise testing.

<table>
<thead>
<tr>
<th>Abnormally high exertional breathlessness (Borg CR10 &gt; ULN)</th>
<th>mMRC cut-off rating</th>
<th>Prevalence, n (%)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Accuracy, %</th>
<th>C-statistic (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1</td>
<td>72 (78%)</td>
<td>91% (75-98%)</td>
<td>28% (18-41%)</td>
<td>50%</td>
<td>0.59</td>
<td>0.52-0.67</td>
</tr>
<tr>
<td>≥ 2</td>
<td>13 (14%)</td>
<td>28% (14-46%)</td>
<td>93% (84-98%)</td>
<td>71%</td>
<td>0.67</td>
<td>0.57-0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Abnormally low exercise capacity (W &lt; 75% predicted)</th>
<th>mMRC cut-off rating</th>
<th>Prevalence</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Accuracy, %</th>
<th>C-statistic (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1</td>
<td>72 (78%)</td>
<td>91% (75-98%)</td>
<td>28% (18-41%)</td>
<td>50%</td>
<td>0.59</td>
<td>0.52-0.67</td>
</tr>
<tr>
<td>≥ 2</td>
<td>13 (14%)</td>
<td>19% (7-36%)</td>
<td>88% (77-95%)</td>
<td>64%</td>
<td>0.61</td>
<td>0.51-0.71</td>
</tr>
</tbody>
</table>

The discriminative ability of mMRC cut-offs to identify the presence of abnormally high exertional breathlessness during a cycle IET. C-statistics were calculated using Receiver operating characteristics (ROC) analysis.

Abbreviations: CI, confidence interval; c-statistic, concordance statistic; mMRC, modified Medical Research Council breathlessness scale; ULN, upper limit of normal.

**FIGURE LEGENDS**

Figure 1.

a) Low mMRC ratings tends to have a higher probability of normality

Relationship between self-rated breathlessness before the test on the mMRC scale and the severity of exertional breathlessness during incremental cycle exercise testing (IET). The severity of exertional breathlessness during IET was expressed as the probability of normality (Y-axis), which is the predicted probability of having an equal of higher breathlessness (Borg
CR10) rating among healthy people calculated using normative reference equations[24]. A low probability reflects more abnormally high (severe) breathlessness. For each participant, the lowest probability of normality (the most abnormal breathlessness during the IET) was analyzed. The red line denotes the upper limit of normal breathlessness according to the reference equations (i.e. only 5% have an equal or higher breathlessness rating/the probability of normal is 5% or lower). The plot shows that participants with low mMRC ratings tend to have more normal breathlessness rating during IET, but with a high level of intra-individual variation. For instance, among the participants with an mMRC rating of 1, the lower quartile is below the 5% line - meaning that more than 25% of those participants experience abnormally high breathlessness at some point during cycle IET.

**b) High mMRC ratings tends to have lower exercise capacity**

Describes exercise capacity as a percentage of the predicted value according to the normal range interval. Reference line denotes the lower limit of normal (75% if predicted exercise capacity). The higher the mMRC score, the lower the exercise capacity is. The plot shows there is a connection between mMRC rating and exercise capacity, but among those with an mMRC rating of 3 or higher, more than 25% have normal exercise capacity whereas more than 25% of those with an mMRC rating of 1 have abnormally low exercise capacity.

**Figure 2.** Discriminative ability of the mMRC breathlessness ratings to predict the presence of a) abnormal breathlessness, and b) reduced exercise capacity, during a subsequent incremental cycle exercise test.

*Abbreviations:* ROC, receiver operating characteristics.

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Figure 1:

a) 

b)
Figure 2: