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Research letter

## **Minimal clinically important differences for Dyspnea-12 and MDP scores are similar at 2 weeks and 6 months: follow-up of a longitudinal clinical study**

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**Running head:** MCIDs for breathlessness at 2 weeks and 6 months

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To the editor,

Chronic breathlessness is a dominating symptom that restricts daily life for many people with cardiorespiratory disease [1]. Different dimensions of the symptom, such as the intensity, sensory qualities (SQs) and emotional responses, can be assessed using the instruments Dyspnea-12 (D-12) [2] and the Multidimensional Dyspnea Profile (MDP) [3], which share similarities in the underlying constructs of what is measured [4] and have emerged as widely used instruments for multi-dimensional measurement of breathlessness.

Dyspnea-12 and MDP are responsive to change and feasible to use as endpoints in clinical trials [5]. We recently published minimal clinically important differences (MCID) of the instruments in cardiorespiratory disease [5]. Data on MCIDs are fundamentally important to be able to evaluate the clinical significance of a change in breathlessness or a treatment effect. A recommended method to determine the MCID is to evaluate the mean change from the baseline score (over a time period) in people who experienced a clinically significant change in another relevant measure (anchor), compared to those who did not experience such a change [6]. However, a limitation in breathlessness research is that most datasets only have short-term data.

There is a need for longer-term trials of breathlessness, but MCIDs for D-12 and MDP to date have only been evaluated for up to a two-week period [5]. No study has reported MCIDs for MDP scores for individual SQs (descriptors) and emotional responses. It is not known if MCIDs – used to evaluate and compare effects – are stable or differ between short-term (two

weeks) and longer follow-up (such as six months). This knowledge is essential to be able to validly design, interpret and compare breathlessness trials of different durations.

We performed a six months follow-up of a longitudinal validation study of the Swedish versions of D-12 and MDP, which was previously used to determine MCIDs at two weeks [5]. We included a total 182 outpatients with cardiorespiratory disease (25% had chronic obstructive pulmonary disease, 21% asthma, 29% heart failure and 19% idiopathic pulmonary fibrosis), who reported breathlessness in their daily lives for the last two weeks or longer. They completed D-12 and MDP at a baseline clinical visit, and using a postal questionnaire at about two weeks (n=162 responses; 89%) and six months (n=145; 80%). The actual times to follow up were 14 days (interquartile range, 14 to 18) and six months (interquartile range, 5.4 to 7.2). The order of D-12 and MDP was randomized and the order was then the same at each time point for that participant, to facilitate unbiased comparison between the instruments. The focus period for the participants' breathlessness ratings was 'the last two weeks' [5].

Minimal clinically important differences were evaluated using an anchor-based method [6] as detailed elsewhere [5]: the MCID was estimated using linear regression as the mean change for each breathlessness score for one unit change on the Global Impression of Change (GIC) scale. The GIC is a seven point scale of the change in breathlessness from baseline (1='very much better'; 2='much better'; 3='minimally better'; 4='no change'; 5='minimally worse'; 6='much worse'; 7 = 'very much worse').[7] Mean differences in the breathlessness scores were similar between the different steps across the GIC scale [5]. The MCIDs were also quantified using distributional methods [6], defining a minimal to small effect size as a change of 0.25 standard deviation (SD) of the breathlessness score at each time point. MCIDs

were evaluated for all summary and sub-scores at two weeks and six months, respectively. Estimates were reported with 95% confidence intervals. Statistical analyses were conducted using the software package Matlab R2018b (Mathworks Natick, MA).

At six months, each tool had similar MCID scores to those measured at two weeks, as shown in Figure 1. The proportions of patients with worse/similar/improved breathlessness were 22% / 48% / 30% at two weeks and 32% / 25% / 43% at six months. The MCIDs were similar, with overlapping CIs, when analyzed using the anchor- and distribution-based methods, which support the validity of the estimates.

This study provides several novel findings. Firstly, it supports that the MCIDs of the instruments are stable when assessing changes in breathlessness over two weeks and six months, demonstrating that the same MCIDs can be used to evaluate and compare findings using these instruments across time periods. These MCIDs are also useful for sample size estimation in planning breathlessness trials. Secondly, this is the first comparison of short-term and longer-term use of the MDP and D-12. The findings are consistent with recently reported MCIDs for uni-dimensional scales of breathlessness intensity and unpleasantness for different recall periods (current and best, worst and average over the last 24 hours) [8, 9]. Thirdly, we report the first MCIDs for the intensity of individual SQ descriptors and emotional responses of breathlessness. We show that a change of 0.8 points is likely to be clinically significant both for overall unpleasantness (MDP A1 score) and across different sensations such as work/effort or air hunger, and that an even smaller difference can be clinically important for emotional responses such as anxiety, frustration or fright – which are likely to affect the person's wellbeing and behaviour.

A strength of this study was the inclusion of a clinical cohort of patients with various forms of chronic cardiorespiratory disease and breathlessness in daily life, with longitudinal analysis of validated instruments and a high response rate at follow-up. Data collection was similar at the follow-up time points and MCIDs were estimated using both anchor-based and distribution-based methods. A limitation is that participants were too few to evaluate MCIDs for specific diagnostic groups. The present findings pertain to changes in breathlessness over time, and further data from RCTs would be valuable. Interventional trials are required to assess the MCIDs of the D-12 and MDP in response to an intervention. Further research is also needed on multi-dimensional measurement during even longer follow-up and on the impact of different aspects of breathlessness on the person's quality of life and function. Multi-dimensional measurements are important, given the complexity of the lived experiences of breathlessness which impacts important domains (including physical, psychological, social and sexual) of the person affected [10].

In conclusion, we report the first long-term follow-up MCIDs for multi-dimensional breathlessness instruments D-12 and MDP. The MCIDs were similar to those at short-term follow-up (two weeks). These findings inform trial design, evaluation of treatment effects in longer-term studies and comparisons between trials of different durations in chronic breathlessness.

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## TABLES

**Table 1.** Minimal clinically important differences (MCID) in the Dyspnea-12 and the Multidimensional Dyspnea Profile (MDP) assessed at two weeks and six months.

	MCID			
	Anchor-based mean (95% CI)		Distribution-based small effect size, 0.25 SD	
	2 weeks	6 months	2 weeks	6 months
<b>Dyspnea-12</b>				
Total	2.8 (2.0–3.7) n=133	2.9 (2.0-3.7) n=120	2.3 n=167	2.6 n=132
Physical	1.8 (1.3–2.3) n=142	1.9 (1.3-2.4) n=128	1.3 n=174	1.5 n=137
Affective	1.1 (0.6–1.5) n=144	1.1 (0.7-1.5) n=129	1.1 n=174	1.1 n=134
<b>MDP</b>				
A1 unpleasantness	0.8 (0.6–1.1) n=149	0.8 (0.6-1.1) n=132	0.7 n=157	0.7 n=137
Perception subdomain	4.6 (3.2–6.1) n= 123	5.1 (3.6-6.6) n=102	3.7 n=146	4.0 n=114
Emotional subdomain	2.4 (1.1–3.6) n=142	2.9 (1.6-4.2) n=125	3.3 n=158	3.2 n=129
<b>Sensory qualities (descriptors)</b>				
Muscle work or effort	0.8 (0.5-1.1) n=145	0.8 (0.6-1.1) n=123	0.7 n=158	0.7 n=128
Air hunger	0.7 (0.4-1.0) n=145	0.7 (0.4-1.0) n=127	0.8 n=158	0.8 n=132
Chest tightness	0.8 (0.5-1.1) n=146	0.9 (0.6-1.2) n=128	0.8 n=159	0.8 n=131
Mental effort	0.6 (0.3-1.0) n=142	0.6 (0.3-0.9) n=120	0.8 n=157	0.8 n=127
Breathing a lot	0.7 (0.3-1.1) n=140	0.9 (0.5-1.3) n=122	0.8 n=155	0.8 n=128
<b>Emotional responses</b>				
Depression	0.4 (0.1-0.7) n=151	0.3 (0.0-0.6) n=132	0.8 n=161	0.6 n=135
Anxiety	0.6 (0.3-0.9) n=150	0.7 (0.4-1.0) n=135	0.8 n=162	0.7 n=137
Frustration	0.4 (0.1-0.8) n=150	0.7 (0.4-1.0) n=129	0.8 n=159	0.8 n=132
Anger	0.3 (0.0-0.7) n=148	0.5 (0.2-0.9) n=129	0.8 n=159	0.8 n=134
Fright	0.5 (0.2-0.9) n=151	0.7 (0.4-1.1) n=129	0.8 n=160	0.8 n=133

MCIDs were estimated for change from baseline in each breathlessness score at two weeks and six months, respectively. A small effect size was defined as a change of 0.25 standard deviations (SD) of the score at each time point.