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Interpretation of treatment changes in six-minute walk distance in patients with COPD

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Abstract

There is uncertainty about the interpretation of changes in the Six-minute walk distance (SMWD) in COPD patients and whether the minimal important difference (MID) for this useful outcome measure exists.

We used data from nine trials enrolling a wide spectrum of COPD patients with SMWD at baseline and follow-up and determined threshold values for important changes in SMWD using three distribution based methods. We also evaluated anchor-based methods to determine a MID.

We included data of 460 COPD patients with a mean FEV_1 of 39.2% predicted (SD 14.1) and a mean SMWD of 361 meters (112) at baseline. Threshold values for important effects in SMWD were between 29 and 42 meters, respectively, using the Empirical Rule Effect Size and the Standardized Response Mean. The threshold value was 35 meters (95% 30-42) based on the Standard Error of Measurement. Correlations of SMWD with patient reported anchors were too low to provide meaningful MID estimates.

SMWD should change by around 35 meters for patients with moderate to severe COPD to represent an important effect. This corresponds to about a 10% change of baseline SMWD. The low correlations of SMWD with patient reported anchors question whether a MID exists for the SMWD.

Background

The two most widely used outcomes in respiratory rehabilitation of patients with Chronic Obstructive Pulmonary Disease (COPD) are exercise capacity such as the Six-minute walk distance (SMWD) and heath-related quality of life (HRQL).[1] HRQL expresses the patient's perception of impairment and is, therefore, critical for decisions regarding health care interventions.[2, 3] SMWD is important for documenting changes during a physical exercise program[4], but it also has become an important measure in COPD because it is associated with patient-important outcomes such as activities of daily living, exacerbations and death.[5, 6]

To interpret the clinical relevance of changes in these outcomes induced by respiratory rehabilitation or other treatments, the minimal important difference (MID) has become the standard approach.[7, 8] The MID is “the smallest difference in the outcome of interest that informed patients perceive as important and which would lead the patient or informed proxies including physicians to consider a change in management”.[9] While HRQL and interpretation of its changes are arguably more important for COPD patients, many investigators use SMWD as the primary outcome as discussed above.[1] However, trial planning, in particular sample size calculations, and interpretation of trial result require knowledge of what constitutes an important change in SMWD.

Ten years ago, Redelmeier et al. determined that approximately 54 meters represent an important change in SMWD using a single methodological approach.[10] This approach relied on between-patient comparison and was based on cross-sectional correlations ($r = 0.59$) and longitudinal correlations ($r = 0.20$) of the SMWD with self-reported categorical scale anchors. Since then, numerous studies used this estimate for sample size calculations and interpretation of their trials.[1, 11, 12]

Despite agreement that a single approach is not sufficient to determine what constitutes an important effect and despite some scepticism that 54 meters might be too high as the SMWD, investigators have not applied other acceptable methods yet such as distribution based methods and within-patient anchor based approaches.[7, 13-15] Given the importance of an interpretation aid for the design and interpretation of studies in COPD[16], our aim was to provide more evidence regarding the MID or other interpretation support for the SMWD using various suggested methods in a large sample of COPD patients with varying degree of severity.

Methods

Studies and patients

We included all completed studies on which the authors of this article were principal or co-investigators and that fulfilled the following criteria: Prospectively planned longitudinal studies with approval from ethical committees; inclusion of COPD patients with any disease severity; at least one arm using effective treatment; at least one measurement of SMWD at baseline and follow-up; inclusion of patient-important outcomes for which the MID had been established such as the Chronic Respiratory Questionnaire (MID 0.5 point), St. Georges Respiratory Questionnaire (MID 4 points), Feeling Thermometer (6 points), or other COPD-specific instruments.

Measurement of SMWD and other outcomes used for anchor based method

In all included trials, patients who completed the SMWD followed standard protocols for this test [17] under supervision of qualified staff. Details about these tests were reported in previous papers.[11, 18-22] Briefly, in five trials, patients completed the SMWD at least twice also at follow-up.[18, 19, 22-24] For these analyses, we used the data of the best SMWD each at baseline and follow up.

Based on the methodological framework for the MID, few outcomes fulfil the requirements as anchors to determine the MID of SMWD. We considered the Chronic Respiratory Questionnaire[2], the St. Georges Respiratory Questionnaire[3], the Feeling Thermometer[25, 26] and transition ratings as potential anchors because the MID has been established for these outcomes. [27],

Statistical analysis

We based the analyses on one combined data set generated from all included studies. Our primary aim was to use several approaches to determine the MID of SMWD including anchor and distribution based methods. We considered the anchor based method described previously[25] using the Chronic Respiratory Questionnaire or other COPD-specific instruments. However, correlations between the anchors and SMWD were low ($r<0.30$) and did not fulfill the methodological criteria ($r\geq0.5$) to provide meaningful estimates for the MID.[25]

As a consequence of the low correlations between SMWD and patient reported outcomes we do not refer to the threshold values that we derived in this study as MID. However, we based the analyses to help interpreting changes in SMWD on three distribution based methods. The most established method is the standard error of measurement (SEM) proposed by Wyrwich et al.[28, 29] The SEM is equal to the standard deviation (SD) x square root (1- a reliability coefficient (r)). We used the intraclass correlation coefficient from the two baseline SMWDs as a measure of test-retest reliability where between-person differences served as the signal (numerator) and within-person differences as the noise (denominator). In order to assess the variability of the SEM estimates, we used the non-parametric bootstrap for the generation of 95% confidence intervals.[30] These confidence intervals are not necessarily symmetric around the SEM estimates. Finally, we stratified the analysis for age, FEV_1 and gender to evaluate whether the threshold values for a relevant effect in SMWD differed between these subgroups.

We used another distribution-based method based on effect sizes.[31] We calculated the SD of SMWD change scores (difference between baseline and follow-up SMWD). We used the SD of SMWD change scores because respiratory rehabilitation has an established and patient-important effect on exercise capacity.[1] According to Cohen, 0.5 SD units represent a moderate effect size and investigators usually consider this estimate to correspond to an important effect.[31] Finally, we also determined an Empirical Rule Effect Size proposed by Sloan et al. that combines the Empirical theorem and Cohen's definition of small, moderate and large changes.[32] 99% of all observations fall, according to the empirical rule, within 6 SD. A change of 0.5 SDs (moderate effect according to Cohen) corresponding to an approximate 8% change represents an important effect. We determined that 8% of the empirically observed range (from the 0.5^{th} to the 99.5^{th} percentile) corresponds to a moderate effect or a relevant effect, respectively.

Finally, we compared the proportion of patients with change scores (between baseline and follow-up) exceeding the MID of patient reported outcomes (Chronic Respiratory Questionnaire, St. Georges Respiratory Questionnaire and Feeling Thermometer) with the proportion of patients with relevant effects in SMWD. Although this approach is also limited by low correlations between patient reported outcomes and SMWD and although it is influenced by the responsiveness of the measurements[11, 33] this analysis would provide some reassurance that the distribution based methods provided valid estimates of important changes. We conducted all analyses using the statistic software R.[34]

Results

We identified 9 trials that provided data for this analysis (table 1). In all trials, patients followed a respiratory rehabilitation program that included physical exercise as the main component but also patient education, breathing exercises or relaxation sessions. The 460 patients had a mean age of 68.9 years (SD 8.3), 71% were male, mean FEV_1 in percent predicted was 39.2 (SD 14.1) and mean SMWD at baseline was 361 meters (SD 112).

Seven studies with 305 patients provided sufficient data to calculate an intraclass correlation coefficient. Table 2 shows the intraclass correlation coefficients and SDs to derive the SEM. The overall SEM was 35 meters (95% CI: 30-42). Figure 1 shows that the SEMs were similar across studies with exception of one trial in which it was only 20 meters (95% CI: 16-26). Figure 2 demonstrates that in the stratified analysis for FEV_1, gender and age there were no significant differences between subgroups.

The other distribution based methods yielded similar estimates of what constitutes an important change in SMWD. These analyses were based on all 460 patients. The moderate effect size (0.5 of the SD of change scores) was 29 meters for all patients. Results for single studies were smaller (range from 18 to 32 meters) because of their inclusion and exclusion criteria. The Empirical Rule Effect Size for all patients was 42 meters. Within studies, single estimates of the Empirical Rule Effect Size were smaller (20 to 41 meters) because the range of SMWD was smaller as a consequence of more restricted patient groups as a result of restricted inclusion and exclusion criteria. Again, stratified analyses by FEV_1, gender and age did not show any significant differences between subgroups for these two distribution based methods.

60.4% and 57.3% of patients exceeded the MID of the Chronic Respiratory Questionnaire and the Feeling Thermometer, respectively. This was comparable to the proportion of patients with SMWD changes of at least 35 meters (50.7%), the average threshold for an important effect in SMWD in the present analysis. 24.4% of patients had changes scores exceeding the MID of the St. George's Respiratory Questionnaire.

Discussion

Three different distribution based methods showed that SMWD should change by around 35 meters for patients with moderate to severe COPD to represent an important effect. Since correlations of SMWD with patient reported anchors were low, anchor based methods were inappropriate and the interpretation aid for important effects derived from this study does not reflect the MID of a patient reported outcome. Our pooled analyses across several studies yielded greater estimates compared to those based on single studies as a result of widening the overall inclusion criteria for the study population. For example, one study included only GOLD stage III to IV patients.[11] Therefore, we consider the results based on the pooled data set to be more informative because they generalize better to COPD patients in general.

Our study has strengths and limitations. An advantage is that we included nine trials with patients from five countries. Thus, our population represented a broad COPD patient spectrum. This is particularly important when using distribution based methods to avoid underestimation of what constitutes an important effect. In more homogenous study populations, as it is generally the case in single studies, threshold values for important effects can be underestimated because distributions are narrower or SD smaller, respectively, as a consequence of stricter eligibility criteria.

Another advantage of including a broad patient spectrum to determine of what constitutes an important effect is that it can be used for any COPD population, also those included in pharmacological intervention trials. The distribution of SMWD of COPD patients enrolled in these trials is likely to be covered by the distribution observed in the present analysis. However, our threshold estimates might not apply to COPD patients that are minimally limited in their exercise capacity for whom the SMWD may not be a sensible test. Another strength is that all studies were methodologically sound studies following strict study protocols. A limitation is that we could not use the anchor based approach because correlations were too low (correlation coefficients <0.5) and thus we were unable to detect a solid MID for the SMWD.[25] Finally, we could not stratify the analyses for baseline SMWD because, by building subgroups, the SD would be unduly influenced. For example, if patients are stratified based on quartiles, the SD of patients in the two middle quartiles have much lower SDs than those in the lowest and highest quartile. Thus for distribution based methods we required a valid and “unrestricted” SD.

Our estimates to interpret effects in SMWD are lower than what Redelmeier reported (54 meters).[10] We do not believe that the difference between the results of the study by Redelmeier and our own study is due to differences in patient characteristics. In the study by Redelmeier patients also participated in a respiratory rehabilitation program and they appear to be similar to our patients. In addition, neither our stratified analyses nor those of Redelmeier indicated that the interpretation of effects differs between subgroups. Differences in the study design and statistical reasons could account for this difference. The sample size of the Redelmeier study was smaller and 95% confidence intervals around the 54 meters were wide (37-71 meters) with the lower boundary within our own estimates. Thus the estimate of 54 meters might differ from our results only by chance which we consider a likely reason. Another possibility for our lower estimates is that we used distribution based approaches whereas Redelmeier used an anchor based approach in which patients judged their own walking ability relative to that of other patients. It is possible that this approach leads to larger estimates of what constitute important effects in general but there are limited data supporting and refuting this hypothesis. However, it is likely that the stringent criteria for interpreting changes scores that we used in this study, would have not allowed Redelmeier et al. to develop an MID estimate as we will describe in the following paragraphs.

What evidence should future studies provide in order to further support the interpretation of effects in SMWD? To determine the MID of patient reported outcomes, anchor based methods are recommended as the preferred method.[14, 15] However, SMWD is not a patient reported outcome and, thus, these recommendations do not fully apply. They would only apply if the correlations with patient reported outcomes (such as the health related quality of life instruments we used here) were sufficiently high for the change scores. The reason is that change score correlations are required to be certain that the new measure for which one intends to determine an MID has indeed measured change related to a patient-important aspect. Redelmeier also considered within-patient anchor based approach but found that correlations with SMWD were too low for these anchors to provide meaningful estimates.[10] Only the cross-sectional but not the longitudinal between-patient anchor based approach was based on strong correlations that justify anchor based methods.[13, 14]

In agreement with those results, correlations of SMWD with patient reported outcomes were too low also in the present study. In our view, it is unlikely that appropriate anchors reflecting the patients' perspective exist for SMWD. However, investigators should not refrain from using anchor based methods with patient reported outcomes to explore if other anchors might fulfil these criteria. In particular, future studies should include a broad spectrum of COPD patients for the reasons discussed above and attempt to use distributions- and anchor-based methods if methodologically appropriate. Finally, only systematic reviews of these methodological studies may definitively inform clinicians and investigators about the interpretation of changes in SMWD to ensure that the limitations of single studies can be detected.

If threshold values for important effects in SMWD were in fact lower than previously assumed, this finding would have important implications for the design of studies. Randomised trials would need larger sample sizes to detect an effect of 35 meters instead of 54 meters, but they would be more likely to detect important changes if they were indeed sufficiently powered. Given that the SMWD is a continuous outcome the implications for sample size are not severe. Also, an increasing number of studies compare active treatments such as drugs or physical exercise to explore whether they are similarly effective in equivalence studies.[11] For the design of these studies it is essential to establish a priori a threshold for what constitutes an important effect. Taking equivalence boundaries of 35 meters (this is two interventions would be deemed equally effective if the difference and its 95% CI were within ±35 meters) is more conservative than equivalence boundaries of 54 meters and also has important implications for study design and patients.

On the other hand, knowledge of what constitutes an important effect informs the interpretation of clinical trials.[16], Consider randomised trials comparing respiratory rehabilitation and usual care. In 9 of 11 (81.8%) trials, effect estimates exceeded the MID of the Chronic Respiratory Questionnaire establishing large and patient important effects of this intervention.[21, 35-44] In contrast, assuming 54 meters for a relevant change in SMWD only three out of 19 (15.8%) trials showed effects above this threshold.[21, 35-43, 45-53] This inconsistency between the interpretation of effects on HRQL and SMWD may raise the suspicion that 54 meters may present an exceedingly high estimate for an important change. If the estimate of approximately 35 meters is considered for the SMWD, 12 out of the 19 trials (63.2%) showed patient important effects showing greater agreement with the interpretation of the effects of rehabilitation on HRQL. However, a note of caution is in order. Despite the validity of our results for the statistical approaches, the findings by Redelmeier and our observation of low correlations between patient reported outcomes and the SMWD cast doubt on the importance of the SMWD as a primary patient-important outcome.

In conclusion, our analysis of a large set of data across a broad spectrum of COPD patients suggests that an important effect in SMWD may be lower than previously assumed. Three distribution based methods showed that SMWD should change by around 35 meters for patients with moderate to severe COPD to represent a relevant effect. This corresponded to about a 10% change of the baseline SMWD (350 meters) in these patients.

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Legends for figures

Figure 1: Estimates for important effects in SMWD based on the standard error of measurement. Data come from 305 COPD patients enrolled in seven randomised trials of respiratory rehabilitation. The overall estimate is based on all patients whereas the results are also shown for the individual studies.

Figure 1

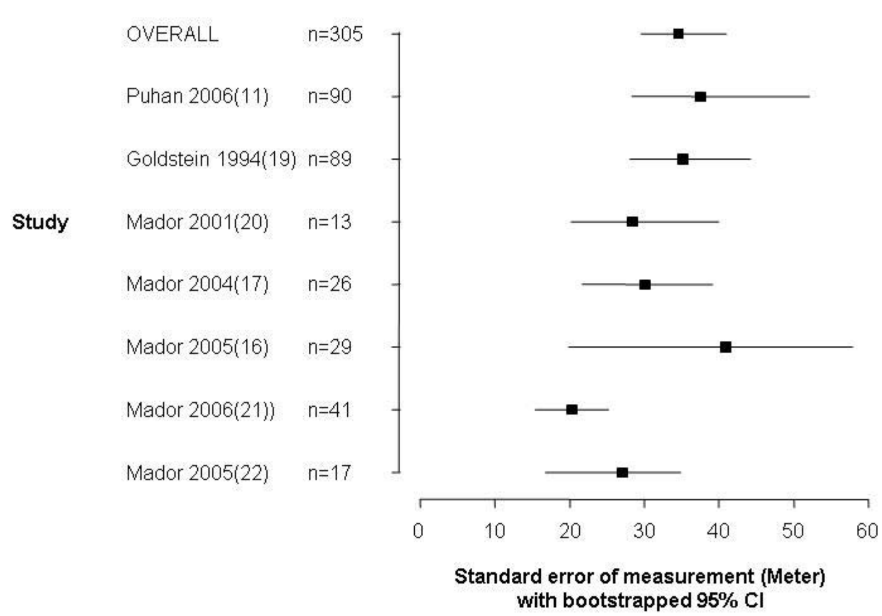

Figure 2: Estimates for important effects in SMWD based on the standard error of measurement stratified for FEV_1, gender and age.

Figure 2

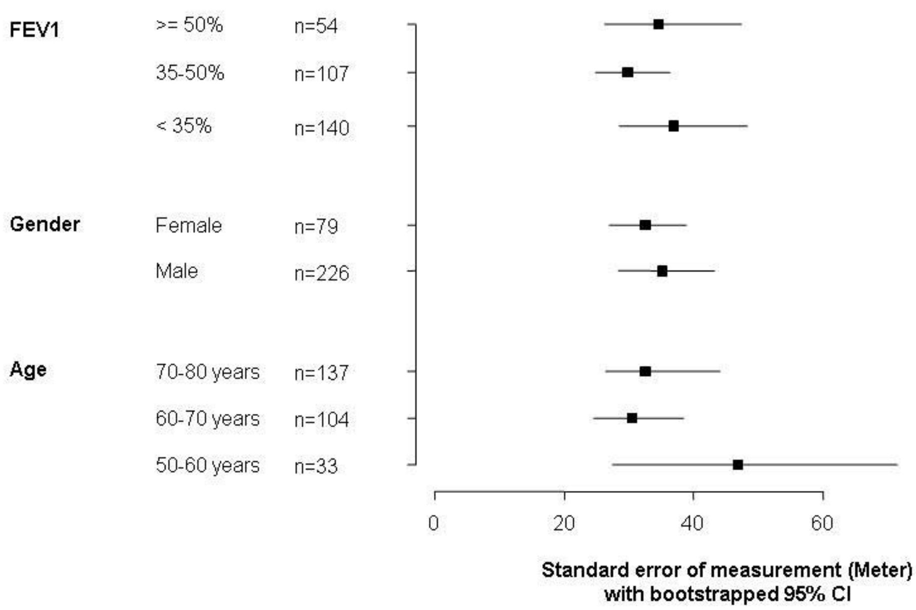
FEV1
>= 50%
n=54
35-50%
n=107
< 35%
n=140
Gender
Female
n=79
Male
n=226
Age
70-80 years
n=137
60-70 years
n=104
50-60 years
n=33
0
20
40
60
Standard error of measurement (Meter)
with bootstrapped 95% CI

Table 1: Characteristics of included trials

Study	Country	Intervention group 1	Intervention group 2	n	Age (SD)	Gender % males	Mean FEV1 (SD)	Baseline SMWD (SD)
Puhan 2006[11]	Switzerland	Respiratory rehabilitation (continuous exercise)	Respiratory rehabilitation (interval exercise)	98	68.9 (9.1)	67	34.3 (8.4)	323 (109)
Goldstein 1994[21]	Canada	Respiratory rehabilitation	Usual care	89	66.0 (7.2)	49	34.7 (13.2)	366 (99)
Puhan 2004[20]	Switzerland	Respiratory rehabilitation		71	67.5 (8.4)	66	45.1 (15.4)	360 (122)
Mador 2001[22]	USA	Respiratory rehabilitation		24	69.9 (9.5)	92	44.3 (17.1)	326 (105)
Mador 2004[19]	USA	Respiratory rehabilitation (endurance exercise)	Respiratory rehabilitation (strength exercise)	28	71.1 (6.1)	100	42.0 (14.7)	378 (119)
Mador 2005[18]	USA	Respiratory rehabilitation (endurance + hyperpnea)	Respiratory rehabilitation (endurance exercise)	29	70.3 (7.4)	100	44.8 (16.6)	435 (98)
Mador 2006[23]	USA	Respiratory rehabilitation (interval exercise)	Respiratory rehabilitation (continuous exercise)	41	71.1 (7.6)	98	43.1 (13.1)	431 (104)
Mador 2005[24]	USA	Respiratory rehabilitation (endurance + upper arm exercise)	Respiratory rehabilitation (endurance exercise)	17	73.9 (7.0)	100	36.7 (13.6)	383 (79)
Schunemann 2003[54]	Canada	Respiratory rehabilitation		63	69.8 (8.3)	54	38.9 (14.5)	334 (104)
All				460	68.9 (8.3)	71	39.2 (14.1)	361 (112)

Table 2: Standard error of measurement

Study	Number of patients with 2 SMWD at baseline	Intraclass correlation coefficient	Standard deviation (baseline SMWD)	Standard error of measurement (95% CI)
All studies	305	0.90	111	**35 (30-42)**
Puhan 2006[11]	90	0.89	111	37 (29-53)
Goldstein 1994[21]	89	0.88	99	35 (29-45)
Mador [22]	13	0.93	108	29 (21-41)
Mador 2004[19]	26	0.94	120	30 (22-40)
Mador 2005[18]	29	0.83	98	41 (21-59)
Mador 2006[23]	41	0.96	104	20 (16-26)
Mador 2005[24]	17	0.88	79	27 (17-35)