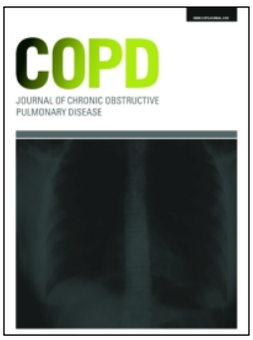

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Minimal Clinically Important Difference for Quadriceps Muscle Strength in People with COPD following Pulmonary Rehabilitation

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ABSTRACT

Quadriceps strength training is a key component of pulmonary rehabilitation (PR). Clinical interpretability of changes in muscle strength following PR is however limited due to the lack of cut-off values to define clinical improvement. This study estimated the minimal clinically important difference (MCID) for the isotonic and isometric quadriceps muscle strength assessed with the one-repetition maximum (1RM) and hand-held dynamometry (HHD) in people with chronic obstructive pulmonary disease (COPD) following PR.

A secondary analysis of a real life non-randomised controlled study was conducted in people with COPD enrolled in a 12-week community-based PR programme. Anchor and distribution-based methods were used to compute the MCIDs. The anchors explored were the St. George's respiratory questionnaire (SGRQ) and the six-minute walk test (6MWT) using Pearson's correlations. Pooled MCIDs were computed using the arithmetic weighted mean (2/3 anchor, 1/3 distribution-based methods) and reported as absolute and/or percentage of change values.

Eighty-nine people with COPD (84% male, 69.9 ± 7.9 years, FEV_1 49.9 ± 18.9% predicted) were included. No correlations were found between changes in 1RM and the SGRQ neither between changes in HHD and the SGRQ and 6MWT ($p > 0.05$). Thus, anchor-based methods were used only in the MCID of the 1RM with the 6MWT as the anchor. The pooled MCIDs were 5.7Kg and 26.9% of change for the isotonic quadriceps muscle strength with 1RM and 5.2KgF for isometric quadriceps muscle strength assessed with HHD.

The MCIDs found are estimates to improve interpretability of community-based PR effects on quadriceps muscle strength and may contribute to guide interventions.

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KEYWORDS
Quadriceps muscle strength; minimal important difference; hand held dynamometry; 1-repetition maximum

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition mainly characterised by persistent airflow limitation [1]. Extrapulmonary and systemic effects are also well recognised, including, but not limited, to nutritional deficits, weight loss, and skeletal muscle dysfunction [1].

Muscle dysfunction, often expressed as fatigue or weakness, can be defined as the situation where skeletal muscles are unable to perform their physiological tasks adequately [2]. Muscle dysfunction is heterogeneous with strength and endurance of the lower limbs being more impaired than those of the upper limbs [3]. A 20–30% reduction in quadriceps muscle strength has been reported in people with COPD when compared to healthy elderly volunteers [4]. These impairments have been attributed to structural and metabolic muscle adaptations that are seen in patients with COPD, namely decreased strength, atrophy, fiber-type distribution shifts, reduced oxidative capacity, mitochondrial dysfunction, and reduced capillarisation [5]. Thus, limb muscle dysfunction has been associated with reduced exercise capacity [6] and health-related quality of life [5], but also with increased morbidity, mortality and use of health care services [5].

Pulmonary rehabilitation (PR) is the cornerstone of the comprehensive care of people with COPD [7]. This and other exercise-based interventions have shown to produce significant increases in both isotonic, mean increase of 34%,

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and isometric, mean increase of 15%, quadriceps muscle strength [8]. Nevertheless, the interpretation of these improvements with PR remain difficult. This is mainly due to the lack of minimal clinically important differences (MCID) for outcome measures used to assess quadriceps muscle strength in routine clinical practice, such as repetition maximums (RM) or hand-held dynamometry (HHD). MCIDs establish thresholds for clinical meaningfulness, i.e. determine which is the smallest change in a measure that will be perceived as an important improvement for the patient [9]. MCIDs for muscle strength-related outcome measures will establish a therapeutic threshold for PR effectiveness and guide clinical decision-making in the management of people with COPD [10, 11]. One study has reported on the MCID of quadriceps muscle strength following PR [12], however MCID were only established using a fixed hand-held dynamometer which may not be widely available in clinical practice.

We aimed to determine the MCID for the isotonic and isometric quadriceps muscle strength assessed with the one-repetition maximum (1RM) and with a hand-held dynamometer, respectively.

Material and methods

Study design and participants

This was a secondary analysis of data from a real-world non-randomised controlled study to assess the cost-effectiveness of community-based PR [13]. Data was collected conducted between January 2018 and 2019. This study followed the guidelines for measurement properties studies proposed by the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN) initiative [14] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

People with COPD were recruited *via* clinicians at *Centro Hospitalar do Baixo Vouga* and at primary healthcare centres of the centre region of Portugal by a researcher not involved in patients' care and enrolled in a community-based PR programme. Individuals were considered eligible if diagnosed with COPD [1], and clinically stable for 1 month prior to the study (no hospital admissions or exacerbations, nor changes in medication, according to Global Initiative for Chronic Obstructive Lung Disease – GOLD report) [1]. Individuals were excluded if presenting other respiratory diseases or any clinical condition that precluded them from being involved in a community-based PR programme.

Ethical approval was obtained from the Ethics Committee for Health of the *Administração Regional de Saúde do Centro* (Ref. 73/2016; 85/2018) and from the National Committee for Data Protection (no. 7295/2016). Before enrolment and data collection, a written description of the study was provided to every participant and written informed consent was obtained.

Data collection

Sociodemographic, anthropometric, and general clinical data were first collected. Lung function values were obtained from participants' medical records and used to establish the severity of airway obstruction according to the GOLD report [1]. Physical activity was assessed with the Brief Physical Activity Assessment Tool [16]. The severity of comorbid diseases was recorded and scored according to the Charlson Comorbidity Index [17]. The modified British medical research council (mMRC) questionnaire was used to assess functional dyspnoea [18] and to classify participants according to the ABCD assessment tool [1]. These data were obtained to characterise the sample.

Other measures were collected before (T0) and after 12 weeks of PR (T1) by physiotherapists previously trained in the application of the selected outcome measures.

Health-related quality of life was measured with the St. George's respiratory questionnaire (SGRQ). Measurement properties of the SGRQ are well established in COPD [19] and a MCID of 4 units after PR has been recommended [20].

Exercise tolerance was measured with the distance walked in the 6-minute walk test, according to the American Thoracic Society (ATS) guidelines [21] and interpreted according to the reference equation proposed for the portuguese population [22]. Measurement properties of the 6-minute walk test are well established in COPD and a MCID of 25 m after PR has been recommended [23].

Isotonic and isometric muscle strength were measured with the 1RM and HHD, respectively. The 1RM aimed to determine the greatest amount of weight (in Kg) that the participant could move in a double leg extension manoeuvre. The 1RM strength test was performed using a weight-lifting multi-gym equipment (BH Fitness, G112X, Victoria, Spain). Before testing, participants were instructed on the proper technique (i.e. start from a sitting position with the knees flexed at 90° and extend both knees at the same time to a 180° extension using the same speed and range of motion in every repetition) and allowed performing 8-10 repetitions without load for familiarisation and warm up [24]. Then, 1RM was determined within four trials, with minimum rest periods of 3–5 min between trials, or as required for participants' recovery [24]. The initial weight was selected according to the participants' perceived capacity (∼50% − 70% of capacity) and progressively increased by 10%–20% until the repetition could not be completed [24]. Although no studies have explored the measurement properties of 1RM in people with COPD, this technique has shown high reliability in untrained healthy people ($ICC_{2,1}$=0.97) [25] and in people with chronic diseases, such as chronic heart failure ($ICC_{2,1}$=0.96) [26].

Quadriceps isometric strength at the dominant side was measured with a HDD (microFET2, Hoggan Health, The best Salt Lake City, Utah) in kilogram-force (KgF). Participants were seated on a raised plinth with the knee to be tested flexed at approximately 90° and resistance was applied to the anterior leg, 5 cm above the lateral malleolus [27]. Two practice repetitions were performed without

Table 1. Anchor and distribution-based methods to estimate the minimal important and detectable differences.

Method	Approach	Statistics
Mean change value	Mean difference ($\triangle$6MW$D > 25$m $\triangle$SGR$Q > 4$points)	T1 − T0
Anchor-based method	ROC curve	–
	Linear regression analysis	–
Distribution-based method	ES	$(mean_{T1} - mean_{T0})/\sqrt{(SD_{T1}^2 + SD_{T0}^2)/2}$
	0.5 times SD	$0.5 \times SD_{T0}$
	SEM	$SD_{T0}\ \sqrt{(1-r\ )}$
	MDC_{95}	$MDC_{95} = SEM \times 1.96 \times \sqrt{2}$

Legend: 6MWD, 6-minute walk distance; ES, effect size; MDC_{95}, minimal detectable change at the 95% level of confidence; r, test-retest reliability coefficient; ROC, receiver operator characteristics; SD, standard deviation; SEM, standard error of measurement, SGRQ, St. George's Respiratory Questionnaire.

resistance for familiarisation purposes. The best of 3 acceptable and reproducible manoeuvres (defined for this study as variations of less than 10% between the 2 highest values) was considered for analysis. Reliability of the microFET2 HDD has been previous established ($ICC_{2,1}$=0.87) [28].

Intervention

All participants completed a 12-week community-based PR programme at 7 locations: 6 primary health care centres and at a university centre (Respiratory Research and Rehabilitation Laboratory (Lab3R) of the School of Health Sciences of the University of Aveiro), all in the centre region of Portugal. The programme consisted of two weekly sessions of exercise training (i.e. warm up, aerobic and resistance exercises, balance training and cool down), one session of education and psychosocial support every two weeks and advice on exercises to perform at home in order to reach a total of 30′ of moderate physical activity during 5 days/week, according to the recommendation from the ATS/European Respiratory Society (ERS) [7]. Resistance training consisted of 8 exercises of the major upper and lower limb muscle groups, at 60 to 70% of 1RM, using the multi-gym and free weights for upper and lower limbs for 20–25 min [24]. A detailed description of the intervention has been published elsewhere [13].

Data analysis

Statistical analysis was performed using IBM SPSS Statistics, version 25 and plots created using GraphPad Prism, version 7 and MetaXL 5.3. Data were analysed only from participants who attended more than 65% of PR sessions, according to the international recommendations that 8 weeks of PR is needed to achieve substantial benefits [7]. The level of significance was set at 0.05.

The adequacy of the sample size was determined according to the quality criteria for measurement properties of health status measures, which establishes a sample size of at least 50 participants as adequate to compute the MCID [29]. Descriptive statistics were used to describe the sample. Differences between included participants and dropouts, baseline and post-PR and participants achieving and not achieving the established MCID were calculated with independent t-test/Mann–Whitney U test and paired t-test/Wilcoxon signed-rank tests, according to the normality of data distribution. The Cohen's d effect size (ES) was calculated and interpreted as small ($\geq$0.2), medium ($\geq$0.5) or large ($\geq$0.8) [30]. Percentage of change was calculated as (post – pre)/pre*100.

Minimal clinically important differences

MCIDs were calculated in the form of absolute and percentual change, whenever possible, using a combination of anchor-based and distribution-based methods [11, 31]. Anchor and distribution methods were weighted on a ratio of 2/3 (anchor methods) and 1/3 (distribution methods), according to the authors' best judgement and previous work [32]. The final MCID was calculated using an arithmetic weighted mean.

Anchor-Based methods

For anchor-based methods, the distance walked in the 6-minute walk test (6MWD) and the SGRQ were selected as possible anchors, which were interpreted according to the established MCID [31] (i.e. 25 m for the 6MWD [23] and 4 points for the SGRQ [20]). First, changes in 6MWD and in SGRQ were correlated with changes in quadriceps muscle strength, assessed with 1RM and HDD, using Pearson correlation coefficient, to determine suitability for its use as an anchor (i.e. $r \geq 0.3$ were required to proceed with the MCID calculation [31]).

The MCID of the 1RM and the isometric HDD were calculated through three different methods: i) the mean change value (i.e. the absolute difference between the mean scores of the quadriceps muscle strength tests at T1 and T0), of participants achieving the MCID established for the anchors; ii) receiver operating characteristic (ROC) curves (the area under the curve [AUC] > 0.7 was considered adequate); and iii) linear regression [11]. The anchor-based methods are summarised on Table 1.

Distribution-Based methods

Five distribution-based methods were calculated: i) 0.5 times standard deviation (SD);[9] ii) standard error of measurement (SEM) [33]; iii) 1.96 times SEM [9]; iv) minimal detectable change (MDC) [9] and v) ES [30] (Table 1). The intraclass correlation coefficient (ICC) used for the SEM

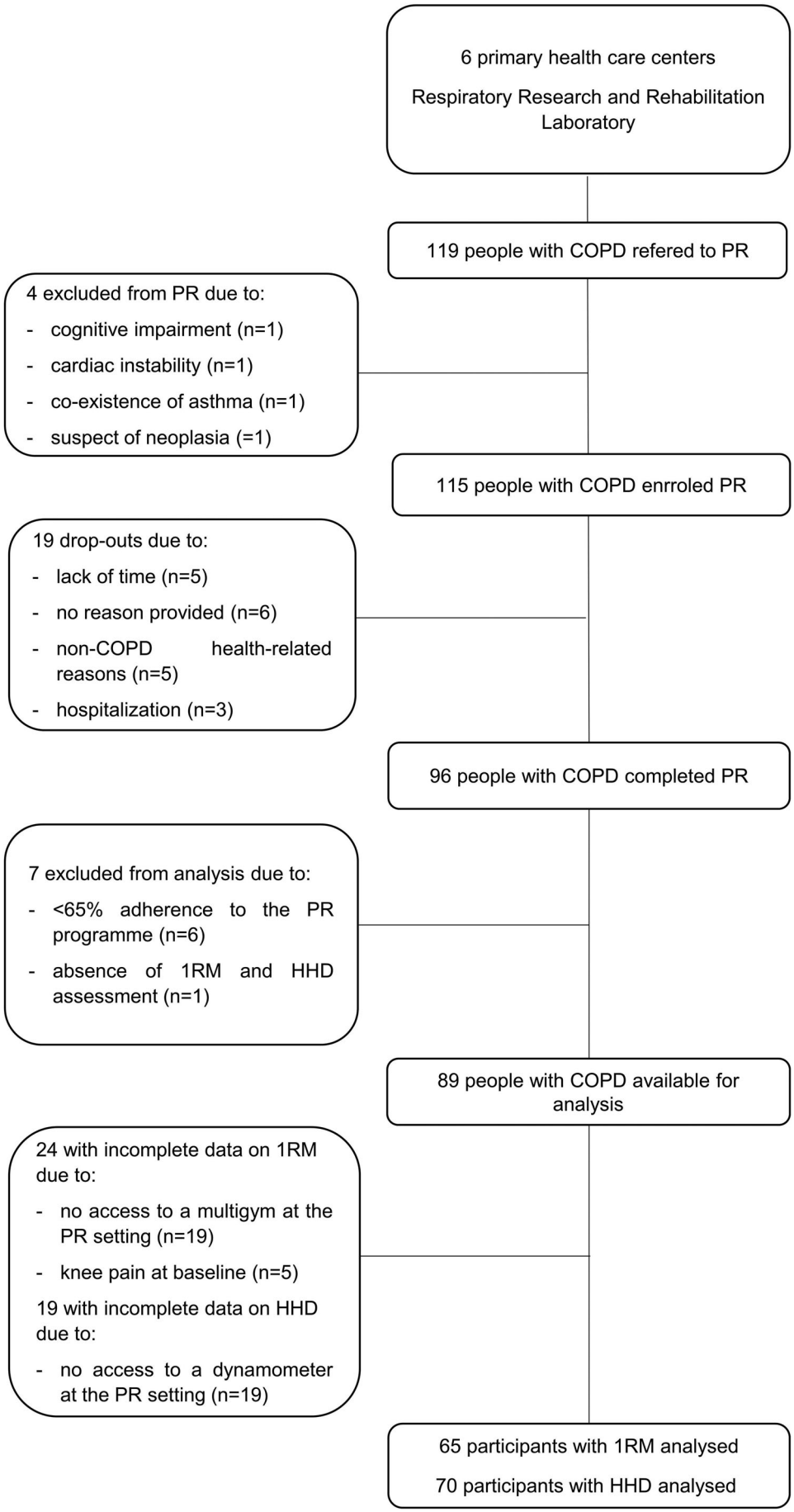

Figure 1. Flow diagram of people with chronic obstructive pulmonary disease included in the study. **Legend:** 1RM, 1 repetition maximum; COPD, chronic obstructive pulmonary disease; HHD, hand-held dynamometry; PR, pulmonary rehabilitation.

Table 2. Sample characterisation.

Characteristics	Participants included ($n = 89$)	Drop-outs ($n = 25$)	p-value
Age, years	69.9 ± 7.9	68.7 ± 10.9	0.542
Sex, male n (%)	75 (84)	19 (76)	0.247
BMI, kg/m^2	26.7 ± 5	25.9 ± 5.3	0.275
mMRC	2 [1-3]	2 [1-3]	0.286
Physical activity	0 [0-2]	0 [0-1]	0.433
Smoking status, n (%)	11 (12)	2 (8)	0.705
Current	62 (70)	17 (68)	
Former	16 (18)	6 (24)	
Never			
Packs/year	40 [24-69]	40 [15.6-58]	0.787
Exacerbations/year[1]	1 [0-1]	1 [0-3]	0.139
Lung function (post-bronchodilator)			
FEV_1, L	1.3 ± 0.6	1.3 ± 0.4	0.683
FEV_1, %predicted	49.9 ± 18.9	54.6 ± 20.1	0.264
GOLD stages, n (%)			
I	11 (12)	3 (12)	0.964
II	26 (29)	8 (32)	
III	42 (47)	10 (40)	
IV	9 (10)	2 (8)	
GOLD groups, n (%)			
A	28 (32)	9 (36)	0.194
B	41 (46)	6 (24)	
C	2 (2)	1 (4)	
D	18 (20)	9 (36)	
CCI, n (%)			
1-2	9 (10)	3 (12)	0.515
3-4	54 (61)	12 (48)	
≥5	26 (29)	10 (40)	
Medication, n (%)			
Bronchodilators			
SABA	8 (9)	0 (0)	0.172
SAMA	2 (2)	0 (0)	0.505
LABA	8 (9)	2 (8)	0.845
LAMA	25 (28)	6 (24)	0.805
LAMA/LABA combination	22 (25)	5 (20)	0.905
ICS	24 (27)	4 (16)	0.576
ICS/LABA combination	29 (33)	5 (20)	0.668
Xanthines	16 (18)	3 (212)	0.805
Expectorants	6 (7)	1 (4)	0.804
Antibiotics	3 (3)	0 (0)	0.402
1RM (leg extension, Kg)	37 ± 13.6	39.6 ± 15	0.442
HHD (leg extension, KgF)	31.3 ± 8.1	27.6 ± 7.4	0.055
6MWD, metres	411.1 ± 132	360.8 ± 119.2	0.076
6MWD, % predicted	85 ± 25.8	76.8 ± 22.3	0.153
SGRQ (total score)	45.6 ± 19.2	41 ± 20.2	0.297

Notes: Values are presented as mean ± standard deviation or median [interquartile range], unless otherwise stated. [1]past-year.

Legend: 1RM, 1 repetition maximum; 6MWD, 6-minute walk distance; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CCI, Charlson comorbidity index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD - Global Initiative for Chronic Obstructive Lung Disease; HHD, hand-held dynamometry; ICS, inhaled corticosteroids; LABA, long-acting beta-agonists; LAMA, long-acting muscarinic antagonist; LRTA, leukotriene receptor antagonist; mMRC, modified medical research council questionnaire; SABA, short-acting beta-agonists; SAMA, short-acting muscarinic antagonist; SGRQ, St. George's Respiratory Questionnaire.

calculation was based on the between-days reliability previously published for the 1RM ($ICC_{2,1}$=0.96) [26] and dynamometry ($ICC_{2,1}$=0.87) [28]. Since no reliability studies of the 1RM were found in COPD, the test-retest reliability coefficients derived from a similar clinical population (i.e. chronic heart failure) and of similar age as our sample [26].

After combining both anchor- and distribution-based methods using an arithmetic weighted mean, the pooled MCID value was used to compute the matching ES according to the formula: $MCID_{ES}=MCID_{pooled}/\sqrt{(SD^2_{T1}+SD^2_{T0})/2}$. [11] It has been recommended that a $MCID_{ES}$ should be between 0.3-0.5 [11].

Distribution-based methods and $MCID_{ES}$ were only computed for the absolute values obtained from 1RM and HHD, since they require the use of moment values (i.e. baseline and post intervention values not available as a percentage).

Results

Sample characterisation

One hundred and nineteen individuals with COPD were referred for PR, however after applying the study criteria and remove participants who droped-out, leg-extention strength assessed with 1RM and with the HHD were completed by sixty-five and seventy participants, respectively (Figure 1). Participants with complete (i.e. 1RM + HDD, $n = 46$) and incomplete data for the 1RM ($n = 24$) and HDD ($n = 19$) did not statistically differ in their sex (males 36 vs.

Table 3. Outcome measures before and after the 12-week community-based pulmonary rehabilitation programme in people with COPD.

Outcome measure	Baseline	Post-PR	△	% △	p-value	ES
1RM (leg extension, Kg) ($n = 65$)	37.2 ± 13.2	44.7 ± 17.9	7.5 ± 12.4	24.5 ± 42	<0.001*	0.5
HHD (leg extension, KgF) ($n = 70$)	31.7 ± 7.7	34.1 ± 8.2	2.1 ± 6.9	9.5 ± 26.5	0.015*	0.2
6MWD, metres ($n = 89$)	417.8 ± 127.5	460.2 ± 131.2	43.3 ± 63	15.5 ± 28.1	<0.001*	0.7
SGRQ (total score) ($n = 89$)	45.61 ± 19.2	38.5 ± 18.3	−7.9 ± 10.8	−16.2 ± 28.8	<0.001*	0.4

Notes: Values are presented as mean ± standard deviation. *$p < 0.05$.
Legend: △, mean change; 1RM, 1 repetition maximum; 6MWD, 6-minute walk distance; ES, Effect size; HHD, handheld dynamometry, PR, pulmonary rehabilitation; SGRQ, St. George's respiratory questionnaire.

21 vs. 18; $p = 0.222$), age (69.5 [65.8-77] vs. 71 [69-72.8] vs. 69 [64-76] years old; $p = 0.826$), severity of the airway obstruction (43.5 [34.5-54.3] vs. 46.5 [36.9-63] vs. 56.5 [37.8-84] FEV_1 percentage predicted; $p = 0.607$), dyspnoea (mMRC ≥ 2: 29 vs. 10 vs. 17; $p = 0.471$) and exacerbations in the past year (exacerbations ≥ 2: 10 vs. 5 vs. 3; $p = 0.828$). Participants adherent to the PR programme attended a median of 21 [IQR 18-22.5] out of 24 sessions. Table 2 shows the baseline characteristics of the 89 participants included in the analysis. No significant differences were observed between participants included and drop-outs.

After PR, participants increased their muscle strength in both 1RM (7.5 ± 12.4 Kg; $p < 0.001$) and HDD (2.1 ± 6.9 KgF; $p = 0.015$) assessments. Improvements were also noted in the 6MWD (43.3 ± 63 metres; $p < 0.001$) and SGRQ (-7.9 ± 10.8 points; $p < 0.001$) (Table 3).

Minimal clinically important differences

One repetition maximum

Significant and positive correlations, higher than 0.3, were found between absolute changes in the 1RM and changes in the 6MWD ($r = 0.394$; $p < 0.001$), as well as between the percentage of change in the 1RM and changes in the 6MWD ($r = 0.378$; $p = 0.002$). No correlations were found with changes in the SGRQ (r<-0.8; $p > 0.05$). The MCID established for the isotonic muscle strength with 1RM using the mean change according to the 6MWD was 6.4 kg (absolute value) and 33.7% (percentage of change). It was not possible to use ROC statistics to compute the MCID, since the AUC generated were not significant for absolute change (AUC= 0.627; $p = 0.09$) and below 0.7 for percentage of change values (AUC= 0.649; $p = 0.046$). Using linear regression, the estimated MCID was 5.9 kg (absolute value) and 19.2% (percentage of change) (Figure 2).

Distribution-based methods for the isometric muscle strength assessed with 1RM and the overall MCID pooled statistics are presented in Table 4. The pooled MCID for the isometric muscle strength was 5.7 kg (Figure 3) and 26.9%.

Hand-Held dynamometer

Absolute changes in the isometric quadriceps muscle strength assessed with the HHD (6MWD: $r = 0.02$; $p = 0.873$; SGRQ: r=-0.131; $p = 0.284$) and percentage of change (6MWD: r= −0.028; $p = 0.821$; SGRQ: r=-0.056; $p = 0.650$) did not correlate with the explored anchors thus, further analysis was not possible to be conducted. Distribution-based methods for the muscle strength assessed with the HHD and the overall MCID pooled statistics are presented in Table 4. Pooled MCID was 5.2 KgF (Figure 4).

When applying the determined MCID of 5.7 Kg and 26.9% for the isotonic quadriceps muscle strength assessed with the 1RM and 5.2 KgF for isometric quadriceps muscle strength to the results of the presented PR programme, clinically important improvements were observed in 32 (49%), 23 (35%) and 24 (34%) patients, respectively. Considering isotonic muscle strength, the group improving above the MCID established for 1RM presented a significantly higher proportion of men (94% vs. 75% male, $p = 0.025$). As for isometric muscle strength, participants improving above the established MCID presented significantly lower quadriceps isometric muscle strength at baseline than those not improving (28.3 ± 8 vs. 32.9 ± 7.8 KgF; $p = 0.026$). Further comparisons between groups can be found in the online supplementary material.

Discussion

This study found pooled MCIDs of 5.7 Kg and 26.9% for the isotonic quadriceps muscle strength assessed with the 1RM and 5.2 KgF for isometric quadriceps muscle strength assessed with HHD, in people with COPD following a community-based PR programme.

This is the first study to report on the MCID of isotonic muscle strength measured with 1RM and isometric muscle strength measured with HHD and to present the MCID as absolute and percentage of change values. The use of percentage change values in addition to absolute values has been suggested, as it allows adjusting for baseline scores and comparing across different instruments [9]. According to the ATS/ERS statement on limb muscle dysfunction in COPD [5], the use a strain gauge to measure isometric quadriceps peak torque is recommended, however, it is not clear to what extent this method is available and implemented in clinical practice. In fact, a recent systematic review including 70 studies that performed exercise-based interventions in people with COPD, has reported inconsistencies in the methodologies and equipment used to assess muscle strength [8]. Thus, adopting a percentage based MCID may be helpful in allowing comparisons among the clinically effects of different exercises protocols and different measures of muscle strength.

Considering previous published results [8], exercise-based interventions have reported isotonic quadriceps muscle strength improvements from 7.8 to 58.2% ($n = 8$/70; some studies presented more than one intervention) in people with COPD presenting severe airway obstruction

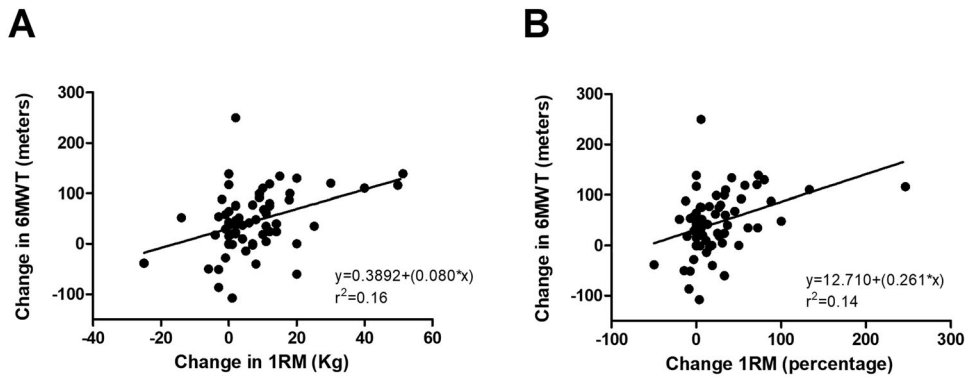

Figure 2. - Linear regression of A) changes in one-repetition maximum (1RM) of quadriceps muscle strength and changes in the six-minute walk test (6MWT) and B) percentage of changes in 1RM of quadriceps muscle strength and changes in the 6MWT.

Table 4. Anchor and distribution-based methods used to compute the minimal clinically important difference of quadriceps muscle strength.

Anchor methods	1RM (leg extension, Kg)	1RM (% change)	HHD (leg extension, KgF)
Mean difference (6MWD)	6.4 (95%CI 0.1- 12.6)	33.7 (95%CI 18.4- 49)	–
Linear regression (6MWD)	5.9 (95%CI 1.2- 10.6)	19.2 (95%CI 3.1- 35.1)	–
Distribution methods			
0.5SD	6.6	–	4.1
SEM	2.6	–	2.9
1.96SEM	5.2	–	5.7
MDC	7.3	–	8.1
ES	0.5	–	0.2
Pooled MCID	5.7	26.9	5.2
MCID ES	0.5	–	0.9

Legend: 1RM, 1 repetition maximum; 6MWD, 6-minute walk distance; ES, Effect size; HHD, handheld dynamometer; MCID, minimal clinically important difference; PR, pulmonary rehabilitation; SD, standard deviation; SEM, standard error of the measurement.

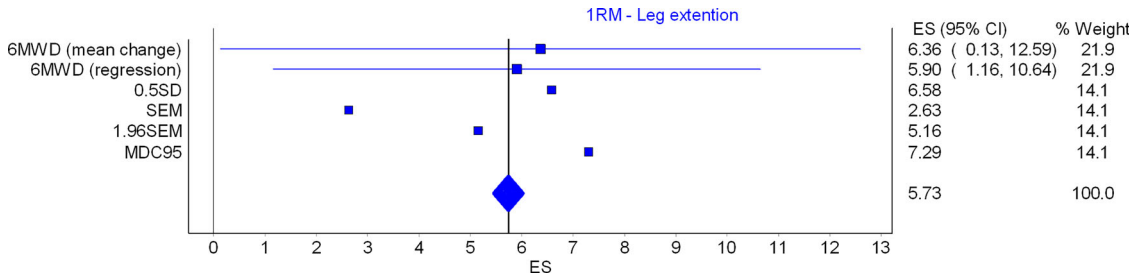

Figure 3. - Plot of the pooled MCID for one-repetition maximum (1RM) of quadriceps muscle strength. The plot represents the MCID estimates derived in this study, and where appropriate the estimates include the 95% confidence interval ($n = 65$). **Abbreviations**: 6MWD, distance performed on six-minute walk test; SD, standard deviation; SEM, standard error measurement; MDC, minimal detectable change.

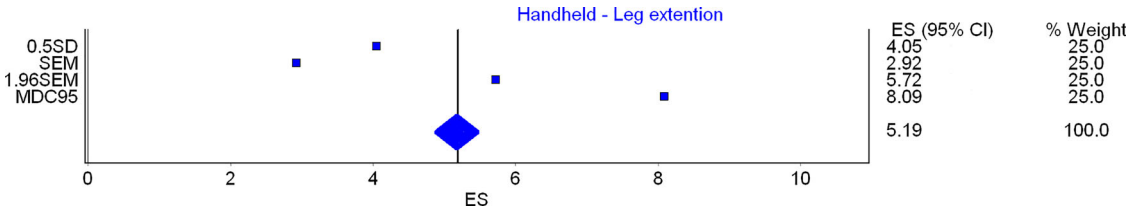

Figure 4. - Plot of the pooled MCID for quadriceps muscle strength assessed with hand-held dynamometer. The plot represents the MCID estimates derived in this study, and where appropriate the estimates include the 95% confidence interval ($n = 70$). **Abbreviations**: SD, standard deviation; SEM, standard error measurement; MDC, minimal detectable change.

(i.e. mean FEV1% predicted from 30 to 50%) [1] and using 1RM as an outcome measure [34–41]. In light of the new MCID determined, it is now possible to deduce that while most interventions presented statistically significant improvements, some may have failed to achieve clinical relevance ($n = 3/13$) [35–37]. Interventions improving the 1RM either above and below the established MCID presented similar programme lengths (8-12 weeks)

and intensities (2-4x/week; 30-60 min/session), and thus, it is not possible to infer about the most appropriate programme design to increase isotonic quadriceps muscle strength assessed with 1RM.

Comparing the MCID found for isometric muscle strength assessed with a hand-held dynamometer (i.e. 5.2KgF) with previous literature reporting on exercise interventions in people with COPD with severe airway obstruction (i.e. mean FEV1% predicted from 30 to 50%) [1] and using HHD as an outcome measure [8], we observe that exercise protocols reporting a combination of aerobic and resistance training (mean difference of 5.4kgF) [42] seem to improve isometric muscle strength above the MCID. On the other hand, programmes implementing resistance training only are just below the threshold of clinical significance (mean difference of 4.9kgF) [43]. Nevertheless, these results should be interpreted with caution, as the MCID for isometric muscle strength was established using distribution-based methods only, due to the lack of correlation with any of the anchors, and it is known that distribution-based methods yield large estimates and tend to overestimate MCIDs [10]. Lack of correlation between changes in SGRQ and 6MWD with muscle strength assessed with a HHD has been previously reported [12]. However, in our study, correlations between changes in 6MWD and muscle strength evaluated with 1RM were found. Medium effect sizes were found for improvements in isotonic muscle strength and in the 6MWD, while small effect sizes were found for isometric strength. This indicates that whereas isotonic muscle strength and the 6MWD improved at a similar rate, the isometric muscle strength assessed with HHD did not. Higher improvements in the muscle strength assessed with 1RM compared to improvements using the HHD were expected according to the principle of training specificity, since the assessment and training of isotonic muscle strength was performed using the same equipment and body movements (i.e. leg extension in the multi-gym). We also hypothesised that, by involving both limbs and generating more force, the 1RM recruited a higher number of muscle fibres and more muscular groups than the HHD, thus being more representative of the muscular force generated and used during the six-minute walk test.

It should be noted that all comparisons established using the defined MCIDs were performed with studies presenting similar populations, interventions, and outcome measures as the present one. It is known that several factors are likely to affect the MCID established [13]. Thus, healthcare professionals and researchers should be mindful of their population, programme and outcome measures when choosing the MCID that most applies to their context of practice.

Only one study has reported on the MCID of quadriceps muscle strength following a PR programme [12]. However, comparisons are not possible, since the methods for measuring muscle strength were significantly different [12]. In our study, isotonic and isometric muscle strength were assessed using 1RM and a HHD manipulated by an experienced assessor, respectively, while in Vaidya *et al.*, [12] a fixed HHD was used and the peak torque was reported. Nevertheless, the paucity of studies in the field is alarming considering the recommendations of the ERS and ATS to assess muscle strength and to include a resistance component as an essential exercise training component for people with COPD [5, 7]. Our study provides MCID to outcome measures that are widely used in clinical trials [8] and that can be easily implemented in clinical practice. We therefore believe, it represents a significant contribution for the clinical interpretation of changes in quadriceps muscle strength following PR.

Limitations and future work

This study presents some limitations that need be acknowledged. Firstly, we used the GOLD criterion of a fixed post-bronchodilator ratio of FEV1/FVC less than 0.7 as the primary indicator of COPD instead of the lower limit of normality (16% of our sample was above this limit). Despite the well known shortcomings of the fixed post-bronchodilator ratio [44, 45], this is currently the most used method to diagnose COPD clinically and it is also a widely used standard that can be readily compared with other published findings. Secondly, anchor-based methods were only possible to be used for establishing the MCID for 1RM and a patient reported outcome measure (PROM) could not be used for this purpose. Thirdly, as this was a secondary analysis of a real-word non-randomized controlled study, missing data for muscle strength was found for approximately 25% of the sample, the PR programme was delivered in a community setting and the sample was mainly composed of GOLD B male participants with high functional capacity as assessed by the six-minute walk test (mean sample $>$ 300m; 85% predicted). Thus, the external validity to other patients with COPD and PR programmes with different structures might be reduced. Forthly, in the absence of reliability studies for 1RMs in people with COPD, distribution-based methods, such as the SEM and the MDC, were calculated with ICC valued from a similar clinical population (i.e. chronic heart failure) and of similar age as our sample. Reliability studies for 1RM in people with COPD are warranted as this is a widely used method of muscle strength evaluation and prescription in PR programmes. Finally, MCIDs should correspond to an ES between 0.3 to 0.5 [11]. Although the MCID for 1RM is within this interval, the MCID found for the HHD corresponded to an ES of 0.9 thus, it may have been overestimated. This is consistent with the fact that only distribution-based methods were implemented, which tend to overestimate the MCID. Thus, further studies should explore other anchors to compute more accurate MCID for the quadriceps isometric muscle strength assessed with a HHD. Possible relevant tests may be the one-minute sit-to-stand test and the checklist of individual strength-fatigue subscale that has been previously validated and has an established MCID for people with COPD following PR programmes [46, 47].

Conclusion

This study suggests that improvements of 5.7 Kg and 26.9% for the isotonic quadriceps muscle strength with 1RM and 5.2KgF for isometric quadriceps muscle strength assessed with HHD, following a community PR programme in people with COPD are clinically relevant.

Declaration of interest statement

The authors declare no conflicts of interest.

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