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REVIEW

Effectiveness of non-pharmacological COPD management on health-related quality of life - a systematic review

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ABSTRACT

Introduction: Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide. The chronic progressive disease is accompanied by a high loss of health-related quality of life (HRQoL). The available drugs usually only have symptomatic effects; therefore, non-pharmacological therapies are essential too.

Areas covered: This systematic review examines non-pharmacological interventions consisting of pulmonary rehabilitation, physical activity, and training versus usual care or no intervention in COPD using at least one of the following HRQoL measuring instruments: St. George's Respiratory Questionnaire, Clinical COPD Questionnaire, COPD Assessment Test, and EuroQol-5D. Of 1532 identified records from CENTRAL, MEDLINE, and EMBASE, 15 randomized controlled trials met the inclusion criteria. Pulmonary rehabilitation programs were investigated in nine studies, education and counseling-based training programs in three studies, and breathing exercises in three studies. Ten studies were found that investigated non-pharmacological treatment programs that led to a significant and clinically relevant improvement in HRQoL compared with usual care or no treatment.

Expert opinion: Non-pharmacological interventions consisting of pulmonary rehabilitation, education and counseling-based training programs, and breathing exercises can improve the HRQoL of COPD patients.

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COPD; non-pharmacological; review; lung disease; quality of life

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a serious public health problem globally. Worldwide, 328 million people are affected by the disease [1], and it is the third leading cause of death according to the WHO [2]. The disease is associated with early mortality, high death rates, and high treatment costs [3,4]. It is estimated that in 2010, COPD cost approximately 50 billion USD in the United States alone, consisting of 30 billion USD in direct medical costs and 20 billion USD in indirect costs [5]. COPD is characterized by a persistent and progressive obstruction of the respiratory tract, which restricts air flow and causes respiratory symptoms. This is usually due to respiratory and alveolar anomalies caused by contact with harmful particles or gases [6]. Tobacco smoking is the main cause of COPD, although burning solid fuels for cooking and heating indoors is another major risk [7].

Spirometry is required to diagnose COPD [6]. The presence of persistent air flow limitation is confirmed by measuring a post-bronchodilator forced expiratory volume in 1 s (FEV_1) /forced vital capacity of <0.70 [8]. To classify the air flow limitation, COPD is divided into four degrees of severity: mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), severe ($30\% \leq FEV_1 < 50\%$ predicted), and very severe ($FEV_1 < 30\%$ predicted) [6]. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendation [6], pharmacotherapy should be based exclusively on patients' symptoms and history of exacerbation. Patients are divided into groups A, B, C, or D according to the frequency of exacerbations in the past 12 months and the individual severity of symptoms, measured by the COPD Assessment Test (CAT) [9] or modified Medical Research Council scale [10]. In the early stages of COPD, the loss of lung function is faster, and thus more important, than in the late stages [11]. Consequently, it is crucial to diagnose and treat COPD in the early stages to avoid rapid deterioration of health.

The disease has a major impact on the lives of patients and their families, particularly the occurrence of exacerbations, which are acute deterioration and disease progression associated with specific symptoms, such as changes in initial dyspnea, cough and/or expectoration, lung function, significantly impaired pulmonary function [12], health status [13], and health-related quality of life (HRQoL) [6,14,15].

Pharmacological therapies for COPD usually have only symptomatic effects [16]. Therefore, non-pharmacological therapies

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Supplemental data for this article can be accessed here.

Article Highlights

- Chronic obstructive pulmonary disease (COPD) is the third leading cause of mortality worldwide. The chronic progressive disease is associated with high loss of health-related quality of life (HRQoL).
- Drugs usually only have symptomatic effects; thus, non-pharmacological therapies are essential too.
- We examine non-pharmacological programs consisting of pulmonary rehabilitation, physical activity, education or counselling-based training programs, and breathing exercises compared with usual care.
- The following studies showed significant and clinically relevant improvements in HRQoL compared with usual care:
  - five of nine studies with pulmonary rehabilitation as the main component,
  - two of three studies with education and counselling-based training programs,
  - three of three studies with breathing exercises as the main components.
- To improve COPD care, further measures are needed to increase the accessibility and applicability of non-pharmacological treatment programs. In addition, non-pharmacological treatments should be tailored to the needs of the patient to achieve high HRQoL.

should become an essential part in the management of COPD to prevent deterioration and to promote self-efficacy [6,17].

2. Objectives

The aim of this systematic review is to compile the current evidence on the HRQoL effects of non-pharmacological interventions consisting of pulmonary rehabilitation, physical activity, and training compared with usual care or no intervention in COPD according to the main components of the intervention and their intensity.

3. Methods

3.1. Data sources and searches

In this review, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instructions were followed [18]. This list serves as a structural guide for systematic reviews and is available in Appendix 1.

The databases MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library were searched for publications suitable for this systematic review. Specific MeSH headings and additional keywords were used to locate all relevant randomized controlled trials (RCTs) (Appendix 2).

In addition, the Cochrane Highly Sensitive Search Strategy for identifying RCTs in the MEDLINE and EMBASE databases was used [19] to ensure that all relevant RCTs were found and no bias occurred. RCTs are the gold standard for comparing a new therapy with a standard therapy. Studies in which the control group received significantly more than usual care, such as weekly training, were excluded. Including such studies in this review would only measure the impact of comprehensive rehabilitation in addition to training, and thus obscure some of the positive effects of rehabilitation over usual care.

The search was conducted on 2 October 2019. After removing duplicates, the titles and abstracts were screened. The eligibility of each reference was examined based on the following a priori defined criteria.

(i) Patients whose main disease was COPD.
(ii) Pulmonary rehabilitation, physical activity, exercises, or training was used.
(iii) Control group received usual care (e.g. conventional drug treatment) or no intervention. Patients in a usual care group could have received simple instructions for certain exercises. If the instructions included keeping a diary or video material, the study was excluded.
(iv) HRQoL was considered using questionnaires that are quality standards and have been tested for their sensitivity, validity, and reliability (i.e. St. George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ), CAT, or EuroQol-5D (EQ5D)) [20–23].
(v) Studies that were RCTs.
(vi) German or English language of publication.
(vii) Published in the years 2008–2019.

3.2. Data extraction

For the data extraction, the Cochrane Collaboration Checklist was used [24], which included i) characteristics of participants (i.e. age, gender, and COPD severity); ii) interventions (i.e. components, duration, and intensity); and iii) effects on HRQoL (SGRQ, CCQ, CAT, or EQ5D).

One of the aims of this review was to compare the intensities of the interventions. There is no suitably validated approach for assessing the intensities of non-pharmacological interventions for COPD in the literature. To make a standardized assessment, the number of sessions and the duration of the interventions was examined for 1 week. Thus, the interventions were divided into three categories (Appendix 4). The time the patient spent each week to perform the intervention was also divided into three intensity levels. The intensity of the intervention was classified as low for less than 120 minutes per week, medium for between 120 and 300 minutes per week, and high for more than 300 minutes per week. The classification was based on the main components of the intervention.

3.3. Quality of life instruments

If the studies did not have a direct comparison of HRQoL between the intervention group and the control group, the comparison was performed by a difference-in-differences approach, which included the differences between the baseline and the end of study between the intervention and control groups.

The SGRQ is a validated, disease-specific questionnaire with a scale from 0 (best possible health status) to 100 (worst health status). The questionnaire is standardized with 76 items and three domains, and can be used to compare the HRQOL outcomes of studies with different interventions. An improvement in the HRQoL is indicated by an average decrease in the SGRQ score. The SGRQ calculates three components (symptom, activity, impact) and a total score, which provides information about the effects of the disease on the general state of health [20]. The minimum clinically important

difference (MCID) is 4 points [25,26] and represents the smallest difference in the score that corresponds to the smallest perceived difference of an average patient and would justify a change in patient management [20,27].

The CCQ contains 10 questions divided into the domains symptoms, mental state, and functional state. A scale from 0–6 is used to answer the questions. The CCQ total is the most important results measure, calculated as the average of the sum of all items [28]. A low state of health is expressed by a high value. The MCID of the CCQ total score is 0.44 [29].

The CAT contains eight questions, which can be answered on a scale of 0–5. The minimum score with complete freedom from symptoms is 0 and the maximum score is 40. A score of less than 10 means few symptoms [30]. The MCID of the CAT is 2 points [31].

The EQ-5D questionnaire consists of five dimensions for which three (EQ-5D-3L) or five (EQ-5D-5L) levels of disease severity can be reported. A summary score of health perception is reported by respondents on a visual analogue scale (VAS), ranging from 0 (worst) to 100 (best health condition) [32]. In addition, there are value sets that reflect national population preferences and provide a utility value. For COPD patients, minimum clinical important differences for the VAS have been reported for both the 3L and 5L versions [33,34].

3.4. Assessment of risk of bias in studies

The quality of the studies was evaluated using the Cochrane Collaboration risk of bias tool for RCTs [35]. Each study was evaluated considering random sequence generation, allocation concealment, selective reporting, blinding of participants, personnel and outcomes, incomplete outcome data, and the analysis of other potential risk of biases. Each domain was assessed with either low, high, or unclear risk. For clarity, two figures were created with Review Manager Version 5.3 (Appendix 5) [36].

4. Results

4.1. Literature search

The systematic literature search revealed 1532 citations from all three data-bases. After removing 535 duplicates, 997 titles and abstracts were screened based on the pre-defined inclusion criteria. During the screening, 948 articles were excluded with reasons. This resulted in 49 potentially relevant articles. After examination of the full texts, 15 RCTs remained, which were included in the qualitative synthesis. The process for including or excluding articles is shown in the PRISMA flowchart (Figure 1).

4.2. Overview of studies

The study characteristics of the RCTs are presented in Table 1, sorted by type of intervention. All the studies were published between 2008 and 2016, and the sample sizes ranged from 30 [37] to 155 participants [38]. A total of 1059 patients were randomized in the studies. The studies were conducted in Brazil [37,39], the Netherlands [38,40], France [41], Egypt [42], Turkey [43], China [44–46], Taiwan [47], Poland [48], Denmark [49], and the UK [50]. In 13 studies, outpatient programs were examined. Two studies [39,44] examined the effectiveness of programs for patients hospitalized due to acute exacerbations of chronic obstructive pulmonary disease (AECOPD). The average age of patients in the intervention groups was between 58.0 [42] and 74.1 years [49], and patients in the control groups were between 58.08 [43] and 73.09 [44] years old on average. The proportion of male patients in the intervention group ranged from 26.67% [37] to 100% [45], whereas that in the control group ranged from 35.00% [49] to 90.0% [47].

Thirteen studies used the SGRQ [37,39–43,45–51], CCQ was used twice [38,40], CAT was used once [44], and Hospes et al. [40] used CCQ and SGRQ. No trials using an EQ5D version as an outcome measure were found. The studies dealt with mild [38,40,43] to very severe stages of COPD, including exacerbations [39,44,45,50]. Fourteen studies examined several COPD severity degrees, and only Barakat et al. [41] considered patients of severity grade III.

4.3. Types of interventions

Nine studies investigated pulmonary rehabilitation, which is defined by the American Thoracic Society as 'a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy' [52]. Rehabilitation could also include education and counseling. Because the nature and extent of the interventions overlapped and pulmonary rehabilitation programs have different components, the individual components of the programs were identified and presented in detail (Appendix 3).

The pulmonary rehabilitation programs in this review mainly deal with physical activity through exercises and training [39,42–45,47,49–51]. Furthermore, the studies examine various programs, which may also include small individual components, such as education and counseling [38,40,41]. In addition, breathing exercises were performed to contribute to the function of the respiratory muscles and lungs [37,46,47]. The program durations varied between 8 days [39,44] and 14 weeks [41]. Differences in the intensities related to the number of minutes per week required for the implementation of the programs were observed. Of the pulmonary rehabilitation studies, one study with a low-intensity intervention [49], five studies [41,42,48,50,51] with medium-intensity interventions, and three studies [39,44,45] with high-intensity interventions were found. The three education and counseling-based studies all had low-intensity interventions [38,40,43], and of the breathing exercise studies, two studies [46,47] had high-intensity interventions and one study had a medium-intensity intervention [37]. The calculation of the intensities of the interventions in each study are provided in Appendix 4.

4.4. Effects on HRQoL

In the following subsections, the effects on HRQoL alone are examined. HRQoL could be measured as a primary or secondary outcome and there are individual components of the interventions that overlap across studies. Nevertheless, we structure the studies according to the type of intervention. For each study, we give the duration and main program components and their effects on the HRQoL.

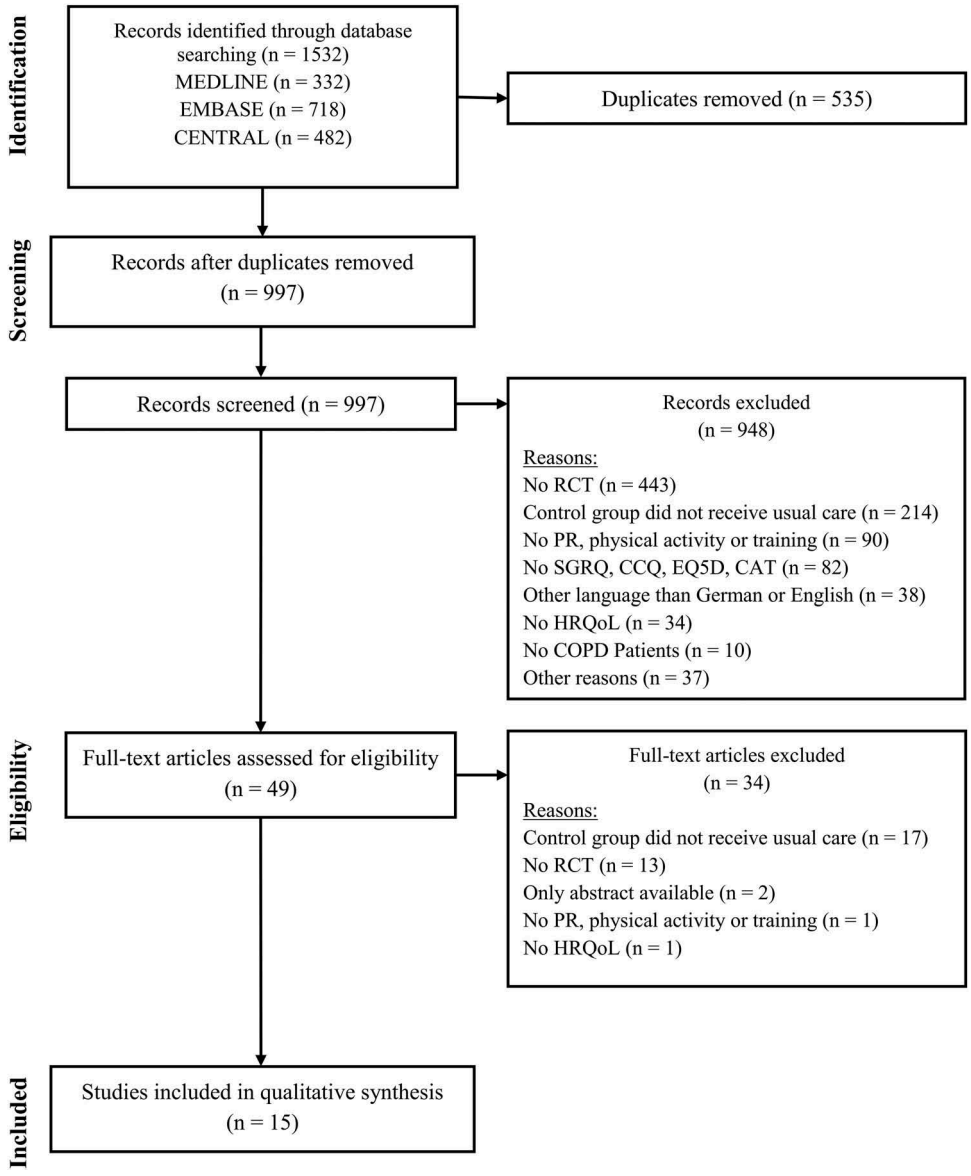

Figure 1. PRISMA flowchart for including or excluding articles.

HRQoL, health-related quality of life; *n*, number; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RCT, randomized controlled trial

4.4.1. Pulmonary rehabilitation programs

One of the studies [41] showed that a 14-week exercise program for strengthening the muscles of the lower extremities by using a bicycle improved the HRQoL in patients with moderate COPD. The SGRQ total score of the intervention group after 14 weeks of pulmonary rehabilitation was reduced by 12.3 points compared with the baseline. After completing the study, the intervention group showed a statistically significant difference of 10.8 points ($p < 0.05$) in the SGRQ total score compared with the control group, which was more than the MCID. There was no significant difference between the control group and the baseline.

Borges et al. [39] investigated the effects of whole-body resistance training on the HRQoL in COPD patients hospitalized due to acute exacerbation. The intervention group started performing weightlifting exercises for the upper and lower limbs on the third day of hospitalization. Patients were examined on the second day of hospitalization, at discharge, and 30 days after discharge. In the intervention group and the control group, no significant differences in HRQoL were measured at discharge from hospital compared with the second day of hospitalization. One month after hospital discharge, the clinically relevant decrease in the SGRQ total score in the intervention group was 17.4 compared with the baseline. The clinically relevant decrease in the SGRQ total score in the control group was 11.9 points compared with the baseline. Compared with the control group, the intervention group showed a statistically significant decrease in the SGRQ impact domain ($p < 0.05$).

Daabis et al. [42] showed that two 8-week training modalities in pulmonary rehabilitation had positive and significant effects on HRQoL in patients who have had an exacerbation. The first group performed endurance training alone and had an clinically relevant SGRQ total score decrease of 18.8, whereas the second group performed combined training in the form of endurance plus strength training and had a clinically relevant SGRQ total score decrease of 18.1 between the end of program and the baseline. In the control group,

Table 1. Study characteristics.

Author, country, follow-up	Participants (Randomized, completed, GOLD / severity stages)	Intervention [a] setting	HRQoL Outcome (mean ± SD) Active group	HRQoL Outcome (mean ± SD) Control group	HRQoL, IG vs. CG, difference in differences, end of study
Pulmonary rehabilitation programs					
Barakat, 2008, France Follow-up 14 weeks	Randomized: 80, completed: 71, IG: 40 (34 male, mean age 63.7), CG: 40 (33 male, mean age 65.9), FEV_1, % predicted, IG: 41.9 ± 2.6 (III) CG: 43.33 ± 3.6 (III)	Exercises, cycling Outpatient clinic	SGRQ total score Baseline 59.6 ± 3.2 Follow-up 47.3 ± 2.3	SGRQ total score Baseline 58.5 ± 3.7 Follow-up 57.0 ± 3.0	IG vs. CG: 10.8, $p < 0.05$* Bicycle exercises can improve HRQoL
Borges, 2014, Brazil Follow-up4 weeks	Randomized: 46, completed: 39, IG: 15 (8 male, mean age 68), CG: 14 (10 male, mean age 64), FEV_1, % predicted, IG: 41.7 ± 13.6 CG: 39.1 ± 15.5	Whole body resistance training Hospital	SGRQ total score baseline 71.6 ± 15.3 Change to baseline -24.3% (17.4 points)	SGRQ total score baseline 63.5 ± 18.6 Change to baseline -18.8% (11.9 points)	IG vs. CG: 5.5 Significant differences between the groups only in impact domain
Daabis, 2017, Egypt Follow-up 8 weeks	Randomized and completed: 45 (Sex unknown) IG1: 15 (mean age 61), IG2: 15 (mean age 58), CG: 15 (mean age 60) GOLD combined, Endurance training: B = 2; C = 6; D = 7; Combined IG: B = 3; C = 6; D = 6CG: B = 1; C = 6; D = 8	IG1: Endurance training IG2: Endurance/ strength training) Hospital	SGRQ total Score IG1: Baseline 68.2 ± 18.6 After training 49.4 ± 17.7 IG2: Baseline 64.45 ± 20.1 After training 46.4 ± 17.7	SGRQ total Score Baseline 66.9 ± 17.6 Follow-up 63 ± 14.6	IG1 vs. CG: 12.3 IG2 vs. CG: 14.15 No significant intergroup differences
Gottlieb, 2011, Denmark Follow-up 18 months	Randomized: 61, completed: 34 IG: 22 (7 male, mean age 74.1), CG: 20 (7 male, mean age 73.2), moderate COPD	Physical training Education GP practice	SGRQ total score Baseline 27.35 Follow-up 26.88	SGRQ total score Baseline 25.75 Follow-up 19.82	IG vs. CG: -5.46 No significant differences
He, 2014, China Follow-up 9–10 days	Randomized and completed: 94 IG: 66 (60 male, mean age 69.2), CG: 28 (23 male, mean age 73.9) IG: III = 28, IV = 38 CG: II = 1, III = 15, IV = 13	Endurance and strength, respiratory training, education Hospital	CAT scores not reported IG before vs. after: significant ($p < 0.001$)	CAT scores not reported Control before vs. after: significant ($p < 0.001$)	Statements about the inter group differences not possible
Ko, 2011, China Follow-up 12 months	Randomized: 60, completed: 45 IG: 30 (30 male, mean age 73.47), CG: 30 (29 male, mean age 73.80) FEV_1% mean IG: 46.19 ± 19.71 CG: mean 40.79 ± 17.54	Supervised training Outpatient after hospital discharge	SGRQ total score Baseline 61.09 ± 15.76 6 months 42.3 ± 20.06 12 months 51.98 ± 23.98	SGRQ total score Baseline 57.17 ± 16.94 6 months 51.44 ± 18.98 12 months 53.79 ± 20.26	IG vs. CG: 5.73 $p = 0.01$* up to six months, but not at 12 months
Majewska-Pulsakowska, 2015, Poland Follow-up 8 weeks	Randomized and completed: 43 IG1: 8 (2 male, mean age 63.4), IG2: 9 (6 male, mean age 62.3), IG3: 9 (10 male, mean age 61.5), CG: 13 (7 male, mean age 65.5), GOLD stage II, III	IG1: Inspiratory muscle training IG2: Cycle ergometer IG3: I1 + I2	SGRQ (Initial, final) total score IG1: 47.5 ± 16.9, 47.2 ± 16.0 ($p = 0.92$) IG2: 52.4 ± 15.5, 50.6 ± 12.6 ($p = 0.56$), IG3: 57.7 ± 19.0, 48.2 ± 17.1 ($p = 0.02$*)	SGRQ total score Initial 47.2 ± 16.0, final 47.5 ± 19.4 (Initial vs. Final p = 0.87)	IG1 vs. CG: 0.6 IG2 vs. CG: 2.1 IG3 vs. CG: 9.8 Inter group *p*-values not reported
Seymour, 2010,UK Follow-up 12 weeks	Randomized: 60, completed: 49 IG: 30 (13 male, mean age 67), CG: 30 (14 male, mean age 65) FEV_1 (% predicted) mean (SD) IG:: 52 (20), CG: 52 (22)	Exercise and education Outpatient	SGRQ total score Baseline: 64.1 (16.9) Follow-up 56.5 (13.7)	SGRQ total score Baseline 57.4 (16.8) Follow-up 61.4 (14.7)	IG vs. CG: 11.6 $p = 0.02$* Post-exacerbation rehabilitation in COPD improves HRQoL
Wootton, 2014, Australia Follow-up 10 weeks	Randomized: 143, completed: 130 IG: 95 (56 male, mean age 69), CG: 48 (28 male, mean age 68) IG: II 40, III 42, IV 13 CG: II 22, III 21, IV 5	Ground-based walking training Outpatient program	SGRQ total score Baseline: 47 ± 17 Follow-up 41 ± 14	SGRQ total score Baseline 47 ± 16 Follow-up 47 ± 16	IG vs. CG: 6 $p = 0.003$* Ground-based walking training improves HRQoL
Education and counseling based training programs					
Altenburg, 2015, Netherlands Follow-up 3 months	Randomized: 155, (102 male, median age 62); IG 78, CG 77; GP, Total: I 32, II 65, III 38, IV 20 Primary care (PC): I 22, II 23, III 3, IV 0 Secondary care (SC): I 7, II 23, III 15, IV 1PR: I 3, II 19, III 29, IV 19	Physical activity counseling Outpatient clinics, PR center	CCQ (Baseline) PC: 0.80 (0.20–1.30) SC: 1.40 (0.90–2.10) PR: 2.15 (1.28–3.23) CCQ (15 months) PC: 0.50 (0.30–0.75) SC: 1.20 (0.70–1.80) PR: 3.10 (2.15–3.55)	CCQ (Baseline) PC: 0.70 (0.40–1.20) SC: 1.20 (0.80–1.70) PR: 2.30 (1.45–2.90) CCQ (Follow-up) PC: 0.50 (0.40–1.3) SC: 1.30 (0.90–2.08) PR: 2.30 (1.60–2.90)	No significant differences

(*Continued*)

Table 1. (Continued).

Author, country, follow-up	Participants (Randomized, completed, GOLD / severity stages)	Intervention [a] setting	HRQoL Outcome (mean ± SD) Active group	HRQoL Outcome (mean ± SD) Control group	HRQoL, IG vs. CG, difference in differences, end of study
Elci, 2008,Turkey Follow-up 12 weeks	Randomized and completed: 78 IG: 39 (33 male, mean age 59.67), CG: 39 (33 male, mean age 58.08), IG (%): I = 7.7, II = 30.8 III = 51.3, IV = 10.3CG (%): I = 7.7, II = 30.8, III = 51.3, IV = 10.3	Education, training Outpatient programme in hospital	SGRQ total Score Baseline 60.27 ± 18.20 Follow-up 45.88 ± 11.61	SGRQ total Score Baseline 61.66 ± 19.90 Follow-up 65.47 ± 17.38	IG vs. CG: 18.2; $p = 0.001$* PR without specialist team can improve HRQoL
Hospes, 2009, Netherlands Follow-up 12 weeks	Randomized: 39, completed: 35 IG: 18 (10 male, mean age 63.1), CG: 17 (11 male, mean age 61.2) IG: I = 4, II = 11, III = 3 CG: I = 1, II = 12, III = 4	Exercise counseling program Outpatient clinic	SGRQ total score Baseline 37.7 (12.4) Follow-up 34.2 (13.5) CCQ Total Baseline 1.6 (0.6) Follow-up 1.5 (0.8)	SGRQ total score Baseline 35.2 (18.7) Follow-up 38.3 (16.8) CCQ Total Baseline 1.8 (1.2) Follow-up 1.9 (0.9)	IC vs. CG: 6.6 $p = 0.05$* Exercise counseling can improve the HRQoL of outpatients with COPD
Breathing exercises					
Gu, 2018, China Follow-up 8 weeks	Randomized: 81, completed: 65 IG1: 22 (21 male, mean age 65), IG2: 23 (23 male, mean age 66), CG: 20 (19 male, mean age 68) FEV_1, % predicted I1: 36.31 ± 13.37, I2: 37.91 ± 12.84, CG: 37.41 ± 12.41	Novel breathing training (NBT) Diaphragmatic breathing (DB) Outpatient clinic hospital	SGRQ total score Baseline NBT: 47.81 ± 14.09 DB: 44.56 ± 12.42 Follow-up NBT: 35.40 ± 12.98 (< 0.001) DB: 32.04 ± 14.09 (< 0.001)	SGRQ total score Baseline 48.35 ± 19.05 Follow-up 47.95 ± 18.68 (0.779)	IG1 vs. CG 12.01, $p < 0.001$* I2 vs. CG 12.12, $p < 0.001$* NBT and DB can improve HRQoL
Lin, 2012, Taiwan Follow-up 12 weeks	Randomized: 44, completed: 40 IG: 20 (15 male, mean age 67.95), CG: 20 (18 male, mean age 69.45) IG: II = 6 III = 11 IV = 3 CG: II = 11 III = 5 IV = 4	Pursed lip breathing Outpatient department	Baseline to follow-up changes SGRQ total score −9.39 ± 15.67	Baseline to follow-up changes SGRQ total score 0.16 ± 8.73	IG vs. CG: $p < 0.024$* Respiratory training can improve the HRQoL.
Yamaguti, 2012, Brazil Follow-up 4 weeks	Randomized: 30, completed: 30, IG: 15 (11 male, mean age 66.5), CG: 15 (11 male, mean age 66.4), IG: I 0, II 3, III 8, IV 4CG: I 0, II 4, III 7, IV 4	DB, Academic medical center	SGRQ total score Baseline: 53.6 (23.9–77.5) Follow-up 43.9 (19.0–72.1)	SGRQ total score Baseline 54.0 (25.9–84.6) Follow-up 54.8 (26.1–74.9)	TG vs CG: 10.5 $p = 0.004$* DB can improve HRQoL

Notes: 6MWT 6 Minute Walking Test, CAT COPD assessment test, CCQ Clinical COPD Questionnaire, CG Control group, COPD Chronic obstructive pulmonary disease, DB Diaphragmatic breathing, FEV1 Forced expiratory volume in 1 second, FVC Forced vital capacity, GOLD Global Initiative for Chronic Obstructive Lung Disease, HRQoL Health-related quality of life, IG Intervention group, MCID Minimal clinically important difference, NR not reported, PEPR post-exacerbation pulmonary rehabilitation, n number, RCT Randomized controlled trial, SD standard deviation, SGRQ St. George's Respiratory Questionnaire, TG Trainings group, UC Usual care, UK United Kingdom, vs. versus

* Significant; a more detailed information and individual components of the interventions can be found in the Appendix

there was no significant decrease in SGRQ total score. After completing the study, the difference-in-differences was 12.3 points in the SGRQ total score compared with the control group, which is more than the MCID. No intergroup *p*-value was reported between the intervention group and the control group.

Gottlieb et al. [49] investigated the effects of a pulmonary rehabilitation program on the HRQoL of moderate COPD patients. The 7-week program included endurance training, static circuit training, walking, and breathing techniques. A 6-month follow-up showed a decrease of 6.4 (±11.3) points in the intervention group in the total SGRQ score, but this temporary improvement was not statistically significant ($p = 0.73$). The change was greater than the MCID of 4 points. There were no statistically significant differences in the SGRQ total score ($p = 0.77$) of the control group. At the 18-month follow-up, no statistically significant differences between the groups were observed ($p = 0.14$). The difference-in-differences in the SGRQ total score was −5.46 in favor of the usual care group, which is more than the MCID. No reason for the improvement in the control group was reported.

He et al. [44] showed that early pulmonary rehabilitation can improve the HRQoL in stationary COPD patients with acute exacerbation. The interventional group underwent pulmonary rehabilitation, which included exercise training, relaxation, and respiratory training. The exercises lasted between 9 and 10 days. The study did not report exact CAT scores, although the graph suggested that a clinically relevant decrease of more than 2 points was achieved in both groups. For the pulmonary rehabilitation group and control group, a statistically significant decrease in the CAT score from baseline to post-pulmonary rehabilitation was reported. The absolute SGRQ scores were not reported; thus, we cannot make a statement about the inter-group differences.

Ko et al. [45] reported that the intervention group in their study received an 8-week rehabilitation program 2 to 3 weeks after the hospital stay due to exacerbation. The program included supervised exercise training by a physiotherapist, with use of a treadmill, arm cycling, and arm and leg weight training. Patients were also recommended to do the exercises at home. The rehabilitation program led to a clinically and statistically significant decrease in SGRQ total score of 10.68 points ($p = 0.01$) after 3 months and 13.06 points ($p = 0.01$) after 6 months compared with usual care. After 12 months, the decrease was 5.73 points, but not statistically significant.

Another study [48] showed an improvement in HRQoL through an 8-week ergometer training program in hospital with inspiratory muscle training at home. At the end of the study, the SGRQ total score of the intervention group showed a statistically significant decrease of 9.5 points ($p = 0.02$) and exceeded the MCID compared with the initial score. The control group score decreased by 0.3 and the change was not significant compared with the baseline score. The difference-in-differences between the intervention group and control group was 9.8 points, but no intergroup *p*-values were reported.

Seymour et al. [50] showed that outpatient pulmonary rehabilitation following acute exacerbations in COPD patients was associated with an improved SGRQ total score. After being discharged from hospital, patients in the intervention group performed aerobic activities and exercises to strengthen the limbs twice a week for 8 weeks. At the 3-month follow-up, the SGRQ total score showed a statistically significant decrease of 8.2 points in the intervention group compared with the control group ($p = 0.02$), which is more than the MCID. The SGRQ total score in the control group improved by 7.6 points compared with the baseline.

According to Wootton et al. [51], ground-based walking training conducted three times a week for 8–10 weeks supervised by physiotherapists with experience in pulmonary rehabilitation improved the HRQoL in COPD patients. After the study was completed, the intervention group showed a statistically significant decrease of 6 points ($p = 0.003$) in the SGRQ total score compared with the control group, which was more than the MCID. The activity limitations ($p = 0.003$) and impact of disease ($p = 0.01$) domains showed statistically significant improvements of 7 and 6 points, respectively, compared with the control group.

4.4.2. Education and counseling-based training programs

Altenburg et al. [38] investigated the effects of a 12-week counseling program to increase physical activity of COPD patients from general practice, outpatient clinics, and pulmonary rehabilitation. The intervention included motivational interviews, wearing step counters, and keeping a diary. The usual care group wore a pedometer and received care appropriate for their health status. The CCQ score of the counseling group with patients of the pulmonary rehabilitation center deteriorated by 0.95 after 15 months compared with the baseline, which is more than the MCID of 0.44 [29]. The CCQ score of the usual care group remained unchanged. The difference between the counseling group with patients of the pulmonary rehabilitation center and the usual care group exceeded the MCID, but was not statistically significant.

One study [43] investigated the effectiveness of a program in a secondary care hospital that included information from a nurse about the disease, nutrition, medication, and sports activities. The patients were told that they should perform lower limb endurance exercises and lift weights to strengthen their muscles. The control group did not participate in the pulmonary rehabilitation program. Statistically significant differences in SGRQ total scores were measured between the intervention and control groups after the second ($p = 0.001$) and third month ($p = 0.001$) of the pulmonary rehabilitation program. The SGRQ total score of the rehabilitation group decreased by 14.39 points at the third visit compared with the first visit, which exceeded the MCID. There was a statistically significant ($p = 0.001$) difference between the rehabilitation group and control group of 18.2 points, which also exceeded the MCID.

Hospes et al. [40] showed that pedometer-based training counseling increased the HRQoL of stable COPD patients. In 12 weeks, five 30 minute sessions were held. Pedometers were used to motivate the participants during the study. The counseling program consisted of motivating interview techniques delivered by a trained counselor. After the intervention, there was a statistically significant decrease in the SGRQ total score in the exercise counseling group compared with the control

group ($p < 0.05$). The SGRQ total score of the exercise counseling group decreased by 3.5 points after 12 weeks compared with the baseline. The SGRQ total score of the control group increased by 3.1 points. No statistically significant differences between the intervention and control group were found in the CCQ.

4.4.3. Breathing exercises

Gu et al. [46] showed that a new breathing technique and diaphragmatic breathing training increased HRQoL in patients with moderate to severe COPD. The training in the new breathing technique group included quick and powerful inhalation exercises monitored by researchers in a hospital. The patients in the diaphragmatic breathing group performed diaphragmatic breathing training. Patients performed the exercises three times daily at home for 15 minutes over a period of 8 weeks. After 8 weeks, statistically significant and clinically relevant decreases in the SGRQ total score of 12.41 and 12.52 in both intervention groups compared with the baseline were found. No significant changes were observed in the control group. The decreases in SGRQ total scores of both intervention groups group exceeded the MCID and were statistically significant ($p < 0.001$) compared with the control group.

Lin et al. [47] presented the effects of respiratory training for COPD patients. The exercises were explained by medical specialists in a hospital and included pursed-lip breathing, abdominal breathing, and upper extremity exercises. Based on the SGRQ total score before and after the intervention, breathing training resulted in a clinically and statistically significant increase in the HRQoL of 9.39 points ($p = 0.018$). The control group received conventional care and had a decrease in HRQoL of 0.16 points. The difference between the groups was clinically and statistically significant ($p < 0.024$).

Yamaguti et al. [37] demonstrated that diaphragmatic breathing training increased the HRQoL of COPD patients. Patients in the intervention group completed the 4-week program, consisting of three 45-minute weekly sessions. The training was supervised by a physiotherapist who gave instructions for inhaling and exhaling in different positions. In the intervention group, a significant reduction of 10 points in the SGRQ total score was observed. The decreases in the SGRQ domains symptom and impact were statistically significant compared with the control group and exceeded the MCID (p-value of the overall intergroup difference = 0.004).

4.5. Risk of bias in the studies

Details of the risk of bias tool [35] and an overview of the detailed assessments for each risk domain of every study are given in Appendix 5. The information available on the assignment of treatment groups and the allocation concealment indicates a low risk of selection bias in the majority of studies. For most studies, no registration protocol was found; thus, there was no way to examine whether all predefined results were included in the articles. In one study, bias by selective reporting was assumed [44] because the results of the Chronic Respiratory Disease Questionnaire (CRQ) domain and the registration number of the study were not reported. Due to the nature of the interventions, we assumed that it was not possible to blind the participants in the studies. Accordingly, the risk of performance bias was high in all studies. Thirteen [37–43,45–48,50,51] of the studies were judged to have a low attrition risk caused by incomplete outcome data. There were low and balanced dropout rates across the groups or study authors performed an intention-to-treat analysis. Three of the 15 studies [44,46,49] probably had a high risk of bias owing to incomplete outcome data, and one of these studies had a high dropout rate of 31% [49]. The most frequent reason for dropouts in these three studies was a lack of motivation. Another of the three studies had no information about the causes of follow-up losses and had an unbalanced number of patients in the groups at the end of the study [44]. No sources of bias other than those described above were found.

5. Discussion

This systematic review synthesized the results of 15 RCTs investigating non-pharmacological COPD treatment compared with usual care or no treatment in terms of HRQoL. This included pulmonary rehabilitation, breathing exercises, and education and counseling-based programs. There is a multitude of different non-pharmacological therapies, and thus there are various possible combinations. Supervised training [45] and resistance training for hospitalized COPD patients [39] and ambulatory interventions, such as bicycle exercises [41], endurance and strength training [44], education [50], or ground-based walking training [51], showed positive effects on the health status and HRQoL of COPD patients. Most studies were conducted in stable, ambulatory COPD patients, although studies with small sample sizes also suggested that pulmonary rehabilitation is feasible and effective in patients with exacerbations of COPD and can improve HRQoL [42,44,45,50,51]. The main components of pulmonary rehabilitation are based on exercises for physical activity [39,41,45,48–51]. Some studies investigated integrative approaches in multidisciplinary programs, which were partly similar in their components. The primary goal of the programs should be to avoid the occurrence or recurrence of exacerbations [53,54] and the associated hospital admissions, which often have a significant negative effect on HRQoL [13,55]. In addition, patient education or counseling can be effective interventions to improve HRQoL [40,43]. Furthermore, breathing exercises were reported to improve HRQoL significantly [37,46,47].

In the studies, severity of airflow limitation (spirometric classification) was assessed using FEV_1. However, there is ample evidence that FEV_1 has a weak correlation with symptoms and impairment of a patient's health status [9,56,57]. According to the GOLD recommendation, the ABCD assessment is also required, which is based on patient-reported symptom burden assessment and history of exacerbations [6].

In this review, five out of nine studies [39,41,44,45,50,51] investigating pulmonary rehabilitation including physical activity as the main component reported significant and clinically relevant HRQoL improvements compared with usual care or no treatment. Four studies [38,39,45,49] were identified in which more than two measurement points were reported. Three of these studies had follow-up measurements beyond

the duration of the programs. In these studies, decreased HRQoL effects of the programs were reported from the end of the program [38], 4 months [45] and 1 year [49] after the end of the programs, which may be due to lack of motivation or compliance [47]. There are further studies in which declining effects were observed after the end of the rehabilitation program [58–60]. Longer-term effects could be achieved through more feedback after pulmonary rehabilitation, including telephone calls and home visits [61], as well as through family support [47]. Further research is needed to determine which non-pharmacological interventions can contribute to long-term effects. Studies investigating pharmacological therapies have shown that an early initiation of treatment, prolonged therapy and maintenance therapy with long-acting bronchodilators can significantly improve the long-term health status of patients and achieve long-term benefits [62,63]. In three studies [42,44,48], no statement on the statistical significance of HRQoL compared with the control group was possible because no intergroup comparisons were made for HRQoL. In the counseling-based training programs, two of the three studies showed significant improvements [40,43] compared with usual care. In the study by Altenburg et al. [38], no significant improvements and no intergroup *p*-values were reported. The dropout rates for interventions and control groups were relatively high at 29.9%, and the most frequent reason was lack of motivation. Possible causes might have been the underlying more severe stages of COPD, often associated with more frequent exacerbations affecting the physical activity of the patients. All three studies with breathing exercises as the intervention showed significant and clinically relevant improvements in HRQoL [37,46,47]. This type of intervention is easier to carry out in patients' daily lives than training programs that require bicycles or treadmills [48,51]. The ease of the intervention can also have a positive effect on the motivation and compliance of the participants. Gottlieb et al. [49] and Ko et al. [45] mainly investigated older people compared with the other studies. The high dropout rates and the lack of significant long-term effects in these studies may indicate that the programs are not suitable for people with moderate COPD [49] or for older people who are physically impaired and unable to perform certain exercises. In the two studies [38,49] without significant improvements, the high dropout rates of 30 [49] and 39 [38] patients may indicate a mismatch between the offered intervention and the needs of the patients. With the exception of Borges et al. [39] and He et al. [44], only outpatient programs were examined in the studies. However, recent results also showed the effectiveness of pulmonary rehabilitation programs for severe hospitalized AECOPD patients [64–67]. The literature on the feasibility and effectiveness of the programs demonstrates that programs can even be implemented during hospitalization because of AECOPD. Future research should focus more on the timely application of rehabilitation in AECOPD patients, considering the specific and preferred modalities and duration of programs. In this context, it is important that the programs are tailored to the physical and psychological conditions of the patient.

For clinical practice, the results of the studies demonstrated that non-pharmacological interventions can be useful in various settings as they can be integrated for less severe COPD patients, and also in regular pulmonary rehabilitation programs with multidisciplinary approaches for severe COPD grades. The results also showed that HRQoL improvement effects can be achieved with different types of exercise training programs. Interdisciplinary disease management in COPD can be complemented by non-pharmacological programs and should evolve toward a personalized medical approach, where programs are adapted to the individual characteristics of patients and active patient participation is encouraged. This means that not only the variation of the components of the program should be varied, but also that the intervention within the components should be flexible. In personalized medicine, self-management is an important factor in managing behavioral risk factors, coping with symptoms in everyday life, and adherence to treatment [68]. Depending on the complexity and burden of the disease, the symptoms, and the degree of disability [69], additional individual non-pharmacological interventions can be monodisciplinary, such as nutritional supplementation, or multidisciplinary, such as pulmonary rehabilitation [70].

Furthermore, some of the studies in this review excluded patients who had comorbidities. An observational study showed that more than half of the patients undergoing pulmonary rehabilitation had at least one comorbidity and this had an negative effect on HRQoL [71]. Consequently, the effects in the studies may be overestimated and the true effect of the programs on HRQoL may be weaker. In the studies, the socioeconomic status of the patient groups was not considered. However, according to an observational study [72], socioeconomic deprivation is associated with impaired HRQoL in pulmonary rehabilitation.

In this review, the overall risk of bias in the studies was low (Appendix 5), except in the domain of blinding, which was not possible due to the nature of the intervention. Ten of the 15 studies showed a significant improvement in HRQoL compared with usual care [37,39–41,43,45–47,50,51].

6. Comparison with literature

The existing systematic literature reviews in the field of non-pharmacological treatment of COPD and HRQoL focus on pulmonary rehabilitation, including physical activity. In addition to the uses of medication, guidelines highlight the important role of pulmonary rehabilitation in the management of COPD [6,8,13,17,60,73–75]. Compared with other reviews in the area of non-pharmacological interventions for COPD versus usual care, only the HRQoL effects of the interventions were considered in this review and the significance of the interventions was assessed based on a difference-in-differences approach between the active and the usual care groups of each study. In addition, the differences were compared with the MCID of each questionnaire.

In the Cochrane review by McCarthy et al. [76], only pulmonary rehabilitation was considered. According to the review, pulmonary rehabilitation is one of the most effective therapeutic strategies for improving exercise tolerance, health, and shortness of breath. The study focused not only on HRQoL, but also on the effect of pulmonary rehabilitation on

exercise capacity compared with usual care in COPD patients. Sixty-five RCTs and a total of 3822 participants were included. There were no limitations on the year of publication and studies were considered that used the CRQ and SGRQ. The meta-analysis included 19 studies in which the SGRQ was used. Nine of these studies showed significant decreases in SGRQ total score. The results support pulmonary rehabilitation, including at least 4 weeks of exercise training, as a useful intervention to improve HRQoL in COPD. The follow-up times of the studies were different and the majority were not aimed at long-term effects. The most frequent study lengths of 8 to 12 weeks were similar to the studies in the present review. The search period of McCarthy et al. was until 2014, whereas in this review, the search period was until 2019. McCarthy et al. excluded studies in which the control group received education or any form of additional intervention. The present study included studies in which the control group could receive short instructions and standard health education, for example, on the use of standard medicine for the respiratory tract.

The Cochrane review of Lacasse et al. [77] considered pulmonary rehabilitation as an important component in the treatment of COPD. The review examined 31 RCTs that compared pulmonary rehabilitation with conventional community care or no intervention using the CRQ and SGRQ. Six studies using the SGRQ and five studies using the CRQ were included in the meta-analysis. There was no limitation on the publication date of the trials included. Statistically significant improvements were observed in both questionnaires. For each of the CRQ domains, the lower limit of the confidence interval around the common treatment effect exceeded the MCID, which indicates the statistical and clinical significance of pulmonary rehabilitation. In the analysis of the studies with the SGRQ, the combined effect of all studies exceeded the MCID. All results were statistically significant, except for the symptom domain. In addition, the literature shows that the care of COPD patients requires different health professionals from different fields, such as physiotherapists, general practitioners, and nurses, to offer different components and improve HRQoL.

The results of the present review are consistent with the results of Vieira et al. [78], who demonstrated the positive HRQoL effects of pulmonary rehabilitation compared with standard care. The review included 12 randomized clinical studies that were conducted between 1990 and 2009 and mainly examined home-based pulmonary rehabilitation programs with durations of at least 8 weeks. Eight of the studies compared home-based pulmonary rehabilitation with standard care as the control group, of which three used the CRQ and three used the SGRQ. Significant intergroup differences were only reported in three studies, but these were not compared with the MCID. There were no significant changes in the standard care group. However, because the evidence was poor to average according to the PEDro quality assessment in the study [79], the results should be treated with caution.

The present systematic review has three strengths. First, non-pharmacological interventions and their effects on HRQoL in individuals with COPD were studied comprehensively and systematically, and the PRISMA statement instructions were followed (Appendix 1). Second, only RCTs were included, which represent a gold standard in research. Planning, execution, and evaluation influences the quality of an RCT. Thirdly, to verify the quality of the studies, a comprehensive quality assessment was independently carried out by two reviewers using the Cochrane risk of bias tool [35].

Our review also has limitations. Only studies from the last 10 years in German and English were considered. The search was limited to the databases EMBASE, MEDLINE, and CENTRAL. Literature screening and data extraction were performed by only one reviewer. Only the results of the HRQoL questionnaires SGRQ, CCQ, and CAT were considered. The approach for evaluating the intensities was based on a self-designed scheme and on the main components of the intervention (Appendix 3). A meta-analysis could not be conducted due to the heterogeneity of the data (Table 1). There are some differences between the studies in terms of patient populations. The HRQoL baseline values of the patients vary greatly and the programs were conducted in patients in stable condition as well as after acute exacerbations and hospitalization. In addition, there were differences in the duration of the individual programs. The classification of patients by severity (GOLD I–IV) is mainly based on FEV_1. This does not include the symptom severity of COPD, which has a much stronger effect on HRQoL than FEV_1 [80,81]. Blinding of the patients and mostly also of assessors was not possible due to the nature of the non-pharmacological interventions, which could have biased the results.

7. Conclusion

The results of this systematic review included 15 RCTs. The studies strongly support the positive effects on HRQoL of non-pharmacological programs in COPD, which mainly include pulmonary rehabilitation with components of physical activity, education or counseling-based training programs, or breathing exercises. To improve COPD care, further measures are needed to increase the accessibility and applicability of non-pharmacological treatment programs. In addition, non-pharmacological treatments should be tailored to the needs of the patient to best improve their HRQoL.

8. Expert opinion

COPD has a huge impact on the lives of patients. In particular, exacerbations resulting from the decrease in FEV_1 and the progressive course of the disease have a negative effect on the HRQoL of patients [82]. To counteract this, it is important that the physical activity of the patients is rebuilt and maintained. In addition to symptomatic pharmacological therapy [17], non-pharmacological treatment of COPD can be a good option for managing COPD patients in terms of HRQoL. The results of our review support non-pharmacological therapies, such as pulmonary rehabilitation, including physical activity and supervised exercises or breathing exercises. Among the studies, interventions were identified that showed clinically relevant and statistically significant improvements in HRQoL. These treatments can be performed in stable and acute COPD. Non-

pharmacological treatment of COPD patients is diverse and requires a multidisciplinary approach and management of treatment pathways. This requires a good cooperation between general practitioners and specialists. The aim should be to avoid the progression of disease and exacerbation. In addition, it is important to reduce disease-related impairment of physical and social activity, for which the programs in the studies in this review are well suited, as they can be integrated into the patient's daily routine and continued easily [83]. In the case of breathing difficulties and comorbidities, it is important to determine which activities can be performed and which are too risky.

To develop healthcare for COPD patients further, more attention should be paid to treatment programs that contribute to improving patients' HRQoL. For future practice, this means that the availability of effective non-pharmacological treatment, such as pulmonary rehabilitation including cycling [41] and strengthening exercises [50], walking training [51], education and counseling-based programs [40,43], or breathing training [37,46,47], must be expanded to best treat every COPD patient.

Further measures are needed to improve the accessibility and applicability of non-pharmacological therapies. Interventions should be as close as possible to the patient's needs. To counteract high dropout rates and lack of motivation, intensive supervision during the programs could help. In addition, long-term studies are needed to determine the optimal duration of interventions and the long-term effects of non-pharmacological COPD treatment.

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Declaration of Interest

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