Short/running title: PSYCHOSOCIAL INTERVENTIONS IN COPD

TITLE PAGE

Efficacy of psychosocial interventions on psychological and physical health outcomes in chronic obstructive pulmonary disease (COPD): A systematic review and meta-analysis

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ABSTRACT

Background: Psychosocial intervention has been suggested as a potentially effective supplement to medical treatment in COPD, but no reviews so far have quantified the existing research in terms of both psychological and physical health outcomes. We therefore conducted a systematic review and meta-analysis of controlled trials evaluating the effects of psychosocial interventions on psychological and physical health outcomes in COPD.

Methods: Two independent raters screened 1491 references for eligibility. Twenty independent studies investigating a total of 1361 patients were included, assessed for their methodological quality, and subjected to meta-analytic evaluation.

Results: After adjusting for potential publication bias, a statistically significant overall effect was found for psychological (Hedges' g=0.39, 95% CI: 0.19-0.58; p<0.001) outcomes. When analyzing individual intervention types, CBT appeared to be effective (g=0.39, CI: 0.15-0.62; p=0.001) for improving psychological outcomes. In contrast, for physical outcomes, only mind-body interventions (e.g. mindfulness-based therapy, yoga, and relaxation) revealed a statistically significant effect (g=0.40; CI: 0.01-0.79; p=0.042).

Conclusions: Taken together, the results lend support to psychosocial intervention as a tool in the management of COPD. However, due to indications of possible publication bias towards positive findings, the results should be interpreted with some caution, and more high quality research is needed.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) involves persistent obstruction of the airways and lung function impairment, and it affects up to about 10% of the population worldwide [1]. The most common physical symptoms of the disease are breathlessness (dyspnea), cough, and excessive sputum production [2], but many patients also experience extrapulmonary physical consequences such as systemic inflammation, nutritional abnormalities, and muscoloskeletal dysfunction, resulting in fatigue, low activity level, and poor exercise capacity [3]. In addition to these devastating physical problems, patients with COPD often experience psychological problems in the form of symptoms of anxiety and depression [4]. In the research literature, these symptoms are often combined as specific components of overall psychological distress or psychological impairment [5–7]. Furthermore, adding to the confusion, several studies focus on poor health-related quality of life (QoL), which is a multi-faceted construct including both physical, psychological, and social function and symptoms [8]. The physical and psychological effects of the disease appear to influence each other significantly, as exemplified by research reporting links between fatigue and QoL [9], psychological distress and exacerbation rates [5], as well as dyspnea and anxiety and depression [10–12]. Psychosocial intervention, defined as intervention programs with a psychosocial aim that does not include the prescription of medications or has a solely physical focus (e.g. acupuncture or massage therapy), could therefore serve as a potentially effective supplement to medical or physically oriented treatment initiatives in COPD.

So far, a number of reviews have summarized the effects of psychosocial interventions on psychological outcomes in COPD. In 2002, Rose and colleagues [13] published a narrative systematic review of six randomized controlled trials (RCTs) evaluating psychological interventions as a means of reducing anxiety and panic, and concluded that the evidence in the area was inconclusive. Later, Coventry and Gellatly [14] conducted a systematic review of four studies of cognitive behavioral

75 therapy (CBT) for COPD patients with mild-to-moderate anxiety and depression. They included
76 non-randomized (NRCT) as well as RCTs, but found no conclusive evidence of an effect. More
77 recently, in a comprehensive systematic review and meta-analysis of 9 studies (RCTs as well as
78 non-controlled studies) by Baraniak and Sheffield [15], the authors noted that psychologically ori-
79 ented interventions often included aims of improving physical outcomes such as physical function-
80 ing, dyspnea and exercise capacity. Despite this, their subsequent meta-analysis only included the
81 psychological outcomes of anxiety, depression, and QoL. Their analysis revealed a medium com-
82 bined effect size (r= -0.273, CI -0.419 to -0.141) on anxiety only, corresponding to a standardized
83 mean difference (Cohen's d) of 0.57. Clark and colleagues [16] have contributed with a broader
84 narrative review of non-systematic reviews, systematic reviews, and meta-analyses that included
85 clinical and educational as well as psychosocial interventions. They concluded that behaviorally
86 oriented interventions, in addition to improving psychological outcomes, also have the potential of
87 influencing physical outcomes such as pulmonary function and exercise capacity, but did not further
88 address the efficacy of psychosocial interventions on psychological and physical outcomes. Fur-
89 thermore, the available reviews generally note the relatively low methodological quality of studies
90 evaluating psychosocial interventions in COPD.

91 To the best of our knowledge, there has thus not yet been an attempt to systematically and quantita-
92 tively evaluate psychosocial interventions in terms of both psychological and physical outcomes in
93 COPD. The objective of the present study was therefore to contribute to the evidence base by con-
94 ducting a systematic review and meta-analysis of the efficacy of psychosocial interventions on rele-
95 vant psychological as well as physical outcomes in COPD. In addition, it was explored whether
96 some types of psychosocial interventions (e.g. CBT that focuses on altering maladaptive links be-
97 tween thinking and behavior patterns [17] or mind-body interventions that focus on the bidirectional
98 relationship of mind and body as the mediator of change such as for example mindfulness-based

99 therapy, meditative yoga or relaxation [18]) are more effective than other and to what degree the
100 effects are related to the methodological quality of the studies.

101 **METHODS**

102 The present study was protocol-based and conducted in accordance with the PICO-approach [19]
103 and the PRISMA recommendations for reporting systematic reviews and meta-analyses [20].

104 ***Search strategy***

105 We conducted a systematic review using a keyword-based search in the electronic databases of
106 PubMed, PsychINFO, Embase, Web of Science, Cochrane Library and CINAHL. Relevant MeSH
107 terms of all databases were included in the search. Keywords related to the population (COPD OR
108 "chronic obstructive pulmonary disease" OR "chronic obstructive lung disease" OR "chronic ob-
109 structive airway disease" OR "chronic obstructive respiratory disease" OR "chronic bronchitis" OR
110 emphysema) were combined with keywords related to the intervention ("psychological interven-
111 tion*" OR "psychosocial intervention*" OR psychotherap* OR psychoeducation* OR psycho-
112 education* OR "behavi*ral therap*" OR "cognitive therap*" OR mindfulness* OR relaxation* OR
113 meditation OR imagery OR hypnos*) and outcomes (depressi* OR anxiet* OR panic OR "quality
114 of life" OR "mental health" OR "health status" OR "physical activity" OR exercise OR "pulmonary
115 function" OR "lung function" OR "symptom level" OR breathlessness OR dyspnea OR fatigue).
116 The search was conducted independently by the first and the second author (IF and DJ) for the peri-
117 od from database inception to March 2014.

118 ***Selection procedure and data extraction***

119 Only English-language reports published in peer-reviewed journals were considered eligible for the
120 present study. Eligible studies were those that evaluated individual-, or group-based psychosocial
121 interventions aimed at improving psychological and/or physical outcomes for adult patients with a

COPD diagnosis. Concerning study design and comparison, only trials with a control group were included. Papers were excluded if the focus was on patients with comorbid physical conditions or if the intervention did not involve a psychosocial component. For example, interventions in the form of pulmonary rehabilitation or self-management programs were excluded unless a substantial part of the program was explicitly characterized as being psychosocial, e.g. mind-body exercises such as meditative yoga, or counseling with elements of CBT or analytical therapy. In addition, reports focusing on interventions with a physical focus, such as acupuncture or massage therapy, or on complementary and alternative treatments, e.g. energy healing or music therapy, were generally excluded. However, certain complementary and alternative interventions were included if they primarily consisted of psychosocial components that had a broader biopsychosocial purpose, e.g. relaxation, guided imagery or meditation.

In the first round of assessment, the authors IF and DJ independently removed duplicates and screened the titles and abstracts of the identified references with the purpose of excluding irrelevant studies. In the second round of assessment, full-texts of the remaining references were read and ineligible reports were excluded on the basis of the criteria describe above and the reasons for exclusion registered. Disagreements and uncertainties were discussed with the third author (RZ) until a negotiated conclusion was reached.

Using the Microsoft Access software, a database was designed with the specific purpose of managing the data of the present study. Data from the included studies were extracted independently and cross-checked by IF and DJ. Any disagreements were resolved by negotiation with RZ. When there was disagreement on one or more of the criteria included in the quality assessment, the paper was re-examined closely, the initial reason for disagreement discussed, and a negotiated conclusion reached.

Quality assessment

Study quality was assessed using the Jadad criteria [21], a tool to evaluate methodological quality, e.g. use and description of randomization- and blinding procedures and description of dropout rates (score range: 0-13). Five additional quality criteria were specifically developed for the present study (inclusion of an active control group, pre-post data, any attempts of blinding of patients and/or researchers, use of standardized and reliable outcome measures), yielding a revised Jadad total quality score (range: 0-18). Quality ratings were not used as weights when calculating aggregated effect sizes (ES's), as this is discouraged due to risk of inducing bias [22]. Instead, associations between ES's and study quality were explored with meta-ANOVAs and meta-regression.

Heterogeneity

Heterogeneity was explored using Q and I^2 statistics. Heterogeneity tests are aimed at determining whether results reflect genuine between-study differences (heterogeneity), or whether the variation is due to random error (homogeneity) [23]. Due to the generally low statistical power of heterogeneity tests, a p-value ≤ 0.10 was used to determine significant heterogeneity [24]. The I^2 quantity provides a measure of the degree of inconsistency by estimating the amount of variance in a pooled ES that can be accounted for by heterogeneity in the sample of studies and is not influenced by the number of studies (K) [25]. An I^2 value of 0% indicates no observed heterogeneity. Values of 25%, 50%, and 75% are considered low, moderate, and high, respectively.

Computing effect sizes

Hedges' g was used as the standardized effect size. Hedges' g is a variation of Cohen's d [26] correcting for possible bias due to small sample size [27]. They both provide an estimate of the standardized mean difference, but whereas d pools the variances using n for each sample, g uses n–1 for each sample. ES's were computed using pre- and post-intervention means or medians and their standard deviations or ranges. In case of missing data, we attempted to contact the authors, asking

them to provide this information. Pooled ES's were weighted by the inverse standard error, taking into account the precision of each study. A random effects model was used in all analyses. For readers more familiar with *r* (the effect size correlation) as an indicator of effect, the corresponding *r* has also been included in the text.

Analytical strategy

First, pooled overall ES's for the effect of psychosocial interventions on psychological and physical outcomes were calculated. If the results indicated study heterogeneity, possible between-study differences in ES's were explored by comparing the ES's of studies according to the following study characteristics: active versus passive control, intervention type, methodological quality, treatment duration, number of sessions, age, gender, and lung function at baseline. This was done with either meta-ANOVA or meta-regression.

The calculations were conducted with Comprehensive Meta-Analysis, Version 2 (www.meta-analysis.com), SPSS-20 (www.ibm.com/software/analytics/spss/), and various formulas in Microsoft Excel.

Publication bias

Publication bias, a widespread problem when conducting meta-analyses [28], was evaluated with funnel plots, Egger's method, and by calculating fail-safe numbers [29,30]. A funnel plot is a graphic illustration of study ES's in relation to study size or precision. Egger's test provides a statistic for the skewness of results [31]. Calculation of fail-safe numbers is aimed at achieving an indication of the number of unpublished studies with null-findings that would reduce the result to statistical non-significance ($p>0.05$). It has been suggested that a reasonable level is achieved if the fail-safe number exceeds $5K+10$ (K = N studies in the meta-analysis) [32]. If the results were suggestive of pub-

lication bias, an adjusted ES was calculated using Duval and Tweedie's trim and fill method [33], which imputes ES's of missing studies and recalculates the ES accordingly.

RESULTS

The study selection process with reasons for exclusion is described in the PRISMA flow diagram shown in Figure 1. The initial search yielded 1491 articles, out of which 403 articles were read in full during the second round of assessment. The authors IF and DJ initially disagreed on 102 (25%) articles (inter-rater agreement: 0.50 (Kappa statistic)). Keeping in mind the broad and complex nature of the field of behavioral intervention, disagreements were most often a result of different initial assumptions of whether certain complex behavioral interventions could be classified as psychosocial intervention. The specific criteria and final inclusion of the individual studies were thus negotiated, and the third author, RZ, took part in the discussion concerning 58 of the articles selected in the first round. After excluding further 41 articles, 3 additional articles were included on the basis of a screening of other systematic reviews on the subject [13–15]. The authors of two papers with missing data (control group data and SDs, respectively) provided the requested data after they were contacted. The author of a third paper with missing data (means and SD for all outcomes relevant for the purpose of the present study) was unable to provide the data and the study was therefore excluded. A final total of 20 individual research papers describing results of 20 independent studies published from 1983 to 2012 were included in the study and subjected to meta-analytic evaluation.

Study characteristics

The characteristics of the included studies are summarized in Table 1. The 20 studies had investigated a total of 1565 COPD-patients (mean % women: 35.1) and analyzed final data for 1361 participants. Six-hundred-eighty-three subjects received psychosocial intervention, 394 took part in an intervention that could not be classified as psychosocial (active control group), and 284 received care as usual (passive control group). Mean age ranged from 56.4 to 73.4 years and mean baseline

lung function varied from 34.0 to 60.5% predicted forced expiratory volume per second (FEV1% pred.). Study sample sizes ranged from 10 to 238 (mean N: 78.2). A total of 19 studies were RCTs with the remaining study presenting data from a NRCT. The majority of interventions could be classified as either CBT (10 studies) or mind-body interventions (8 studies) (e.g. mindfulness-based therapy, yoga, and relaxation). The two remaining interventions were analytical and behavioral therapy, respectively. The number of treatment sessions varied from 1 to 63 (mean: 12.0 sessions) and stretched over 1 to 12 weeks (mean: 7.3 weeks).

Three studies [34–36] included more than two group conditions, and data from conditions that made it impossible to isolate the effect of the psychosocial intervention (e.g. comprehensive pulmonary rehabilitation programs with psychosocial elements) were excluded. One study [37] included both an active and a passive control group, and only the active group was used as comparison.

Across the included studies, 14 studies reported data on the psychological outcomes of anxiety and depression, frequently assessed in parallel by the Hospital Anxiety and Depression Scale (HADS) or separately by the Spielberger Anxiety Inventory (SAI) or Beck Anxiety Inventory (BAI) to measure anxiety, and the Beck Depression Inventory (BDI) or the Center for Epidemiological Studies Depression (CES-D) scale to measure depression. Seventeen studies reported data on physical health outcomes such as lung function, dyspnea, exercise capacity and fatigue, most often assessed with spirometry (FEV1), visual analogue scales (VAS), the 6-Minutes Walking Test (6MWT), and the Pittsburgh Sleep Quality Index (PSQI), respectively. Sixteen studies reported data on QoL, most often measured with the disease-specific Saint George's Respiratory Questionnaire (SGRQ), the Chronic Respiratory Questionnaire (CRQ), or the generic instrument Short Form Health Survey (SF-36).

The Jadad quality score of the included studies ranged from 5-11 (mean score: 9.00; SD: 1.65), and the Jadad-revised score from 7-15 (mean score: 11.95; SD: 2.09). The inter-rater agreement ratio for the individual Jadad items ranged from 0.70 to 1 with Kappa scores (adjusting for chance agreement) ranging from 0.32 to 0.80.

Pooled ESs

The results of the meta-analyses are summarized in Table 2 and illustrated with Forrest plots (Figure 2). As the QoL construct includes both psychological and physical domains, a combined ES for QoL was calculated separately. Combining the ES's in the two overall categories of psychological and physical outcomes, regardless of individual study characteristics, yielded statistically significant ES's for both categories (psychological: Hedges' g=0.39 (corresponding to r=0.19), p<0.001; physical: g=0.30 (r=0.15), p=0.006), in both cases corresponding to a small effect [26]. The fail-safe number for psychological outcomes (K=90) exceeded the criterion (K=80) [32], suggesting a robust effect. This was not the case for the physical outcomes fail-safe number (K=64; criterion K=95). When exploring indicators of publication bias, the funnel plots for both outcome categories appeared skewed and Egger's test indicated the possibility of bias in favor of larger published positive ES's. When imputing missing ES's with the trim and fill method [33], the resulting adjusted pooled ES was smaller but remained statistically significant for the psychological outcome category. This was not the case for physical outcomes. With respect to specific outcomes, the combined ES's for anxiety, depression, dyspnea, and QoL (g=0.24-0.45 (r=0.12-0.22)) all reached statistical significance (p: 0.001-0.047). The combined ES (g=0.25 (r=0.12)) for exercise capacity was near-significant (p=0.069), whereas the combined ES's for fatigue and lung function did not reach statistical significance.

Associations between ES and study characteristics

As the *Q*-statistic for both psychological and physical outcomes were statistically significant (p=0.017, <0.001) and the I^2 statistic indicated low to moderate heterogeneity, we explored possible sources of heterogeneity and analyzed whether the ES's varied according to between-study differences in study design (active versus passive control), intervention type (CBT versus mind-body), sample characteristics (age; gender; lung function at baseline), intervention length (number of sessions; treatment duration) and methodological quality (quality scores).

Study design

The pooled ES's for the active and passive control group studies are shown in Table 2. With respect to psychological outcomes, the ES's were similar, and the between-group difference did not reach statistical significance. For the physical outcomes, the combined ES was smaller for passive control than active control studies, but again, the between-group difference did not reach statistical significance.

Intervention type

The combined ES's of studies examining the effects of CBT and mind-body interventions are shown in Table 2. For psychological outcomes, CBT and mind-body yielded similar ES's (g=0.39 (r=0.19) and g=0.38 (r=0.19)). However, only CBT reached statistical significance, whereas mind-body interventions were near-significant (p=0.081). For physical outcomes, only mind-body interventions yielded a statistical significant ES of g=0.40 (r=0.20). In comparison, the ES for CBT for physical outcomes was small (g=0.09 (r=0.05)) and statistically non-significant. The difference between the effects of CBT versus mind-body interventions, however, did not reach statistical significance. Insufficient power for tests of moderation is a well-known problem in meta-analysis [38]. Following the suggestions of Hedges & Pigott [38], we therefore conducted a post-hoc power analysis, revealing a statistical power of the between-group comparison of CBT and mind-body interventions for physical outcomes of only 0.30.

As only mind-body interventions appeared to be effective for the combined physical outcomes, the effects of mind-body intervention for each of the individual physical outcomes were analyzed. A statistically significant effect of mind-body intervention was found for dyspnea (g=0.38 (K=7) (CI: 0.04-0.71, p=0.028). The remaining effect sizes did not reach statistical significance (g= -0.02–0.33; K=3-6; p=0.146–0.951). No effects of CBT were found for any of the individual physical outcomes (no further data shown). When comparing effect sizes between mind-body therapies and CBT for the individual physical outcomes, mind-body therapies yielded larger effect sizes than CBT for dyspnea (g=0.38 vs. 0.01), lung function (0.15 vs. -0.24), and exercise capacity (0.33 vs. 0.08), whereas the results for fatigue appeared to favor CBT (-0.02 vs. 0.26). None of the differences reached statistical significance, however (no further data shown).

Sample characteristics, intervention length and study quality

As shown in Table 3, we conducted two meta-regression analyses (unrestricted maximum likelihood) with the Jadad quality score, the Jadad-revised quality score, treatment duration, number of sessions, mean age, percent women, and mean FEV1% pred. as the predictor variables and ES's for the combined psychological and physical outcome categories as dependent variables. In both analyses, only treatment duration reached near-significance (psychological: p=0.054; physical: p=0.066), with negative regression slopes (psychological: B=-0.06; physical: B=-0.05) indicating that longer treatment duration was associated with smaller ES's for psychological and physical outcomes. Furthermore we compared the average duration and number of sessions of CBT and mind-body interventions. The results indicated that mind-body intervention had longer duration (7.2 wks (SD: 3.9)) and included more sessions (18.8 (20.0)) than CBT (6.0 (3.0) and 10.5 (16.0)). However, the differences did not reach statistical significance (p=0.41 and 0.25).

DISCUSSION

307 The results initially revealed statistically significant effects of psychosocial interventions on both
308 psychological (g=0.39 (r=0.19)) and physical (g=0.30 (r=0.15)) outcomes in COPD patients when
309 compared with passive (care as usual) or active control groups. The effect size for psychological
310 outcomes remained relatively stable and statistically significant after adjusting for possible publica-
311 tion bias, whereas the effect size for physical outcomes was reduced (g=0.20 (r=0.10)) and became
312 only near-significant. Our findings are in contrast to the results of another relatively recent meta-
313 analysis by Baraniak and Sheffield [15], where only anxiety was improved by psychologically-
314 based interventions in COPD. A possible explanation for the inconsistent findings could be that the
315 quantity of published research in the area has grown over the years since Baraniak and Sheffield
316 conducted their review. Thus, coupled with the fact that we also included psychosocial mind-body
317 interventions, the results of the present study were based on data from a larger combined sample of
318 COPD-patients. Also, in the present study, we have statistically adjusted for possible publication
319 bias, which Baraniak and Sheffield reckoned was a problem for the interpretation of their results,
320 thereby giving way for a more precise effect size estimate.

321 As the construct of QoL is a multifaceted and relatively incongruently defined construct [39], we
322 found it inappropriate to include it in either the psychological or the physical overall outcome cate-
323 gory. The results revealed a statistically significant, but small, effect on QoL, giving further support
324 to the notion that psychosocial intervention may improve outcomes that involve both the psycholog-
325 ical and the physical domain of COPD. However, researchers conducting future meta-analyses
326 should be aware of the possible pitfalls of combining data from studies defining QoL differently.

327 Regarding the effects of the different types of psychosocial intervention being used with COPD
328 patients, the moderation analyses showed that only CBT, but not mind-body interventions, signifi-
329 cantly improved psychological outcomes. For the physical outcomes, the opposite result was found.
330 Here, only the results for mind-body interventions reached statistical significance. When exploring

effects on the individual types of physical outcomes, mind-body interventions had larger, albeit non-significant, effects on dyspnea, exercise capacity, and lung function, whereas the effect on fatigue was non-significant in the opposite direction. Our findings could be interpreted as supporting previous speculations [15,40] that ruminative thinking and avoidance, the primary focus of CBT, are often associated with the characteristic and noteworthy physical symptoms in COPD. Consequently, subjecting symptoms such as dyspnea to the exposure techniques often used in CBT could in the best case be ineffective and, in the worst case, harmful. In contrast, mind-body interventions explicitly take into account the co-influencing aspects of physical and psychological issues in COPD and hold a primary focus on physical sensations, rather than on psychological, i.e. cognitive and emotional, processes, as the therapeutic gateway towards change [41]. However, it should here be noted that the precision of the estimated effect sizes of interventions types in the present study may be limited, as indicated by the relatively broad confidence intervals. In addition, the results of our post-hoc power analysis suggest that more studies are needed to confirm this preliminary conclusion.

With the purpose of minimizing costs, psychosocial interventions are often delivered alongside other behavioral treatment initiatives such as pulmonary rehabilitation programs (most often including health education and physical exercise). Exploring directly whether this mode of delivery influences the effect of the psychosocial interventions lay outside the scope of the present study. However, the results failed to find any difference in ES's between the studies that included an active control group and those that did not (passive control group). This could indicate that receiving other behavioral treatments (e.g. disease-specific or general health education, breathing and walking exercise, and support groups) simultaneously does not compromise the effect of psychosocial intervention. On the other hand, whether psychosocial intervention moderates, e.g. boosts or reduces, the effects of other behavioral and medical treatment regimens still needs to be explored.

Surprisingly, the near-significant results of our meta-regression analysis indicated that overall, irrespective of the type of intervention, longer treatment duration may reduce the effect of psychological intervention. One possible explanation for this inverse relationship could be the natural deterioration of the chronic patients' psychological and physical condition over time – especially prevalent for smokers [42]. Another explanation could be the tedium of longer interventions or overstimulation, which are long-discussed challenges in the psychotherapy process [43,44]. However as a third possible explanation, the lesser effects of longer interventions could also be due to the relatively longer follow-up time, which might cause a loss of novelty and regression toward the mean. The finding that longer duration was associated with smaller, rather than larger, ES's, also suggest that the – non-significant – finding of longer duration of mind-body interventions compared to CBT's, does not explain the larger ES's found for physical outcomes for mind-body interventions compared to CBT. Further studies are needed to identify the optimal type and duration of psychosocial interventions for various outcomes in COPD.

The present study is the first to quantify the effect of psychosocial interventions on psychological as well as physical outcomes in COPD. It has several strengths in that it is based on rigorous methodological procedures and instruments (i.e. protocol-based inclusion with two independent reviewers, comprehensive methodological quality ratings and adjustment for publication bias) and includes only controlled studies, which substantially increases the likelihood that changes in post-intervention scores can be attributed to the intervention and not to other potentially confounding variables. Moreover, the present study includes mind-body interventions, which have generally been ignored in reviews of psychological intervention in COPD so far, even though they form a type of psychosocial intervention that has become a subject of increased popularity and evidence in healthcare research literature over the last few decades [41]. Among the limitations are that the available data do not allow for any conclusions as to the long-term maintenance of the effect, as the

majority of included studies did not present follow-up data in their analysis. Furthermore, not all included studies reported data on each outcome category of interest and the instruments used to measure psychological and physical outcomes were diverse. This was also the case for QoL instruments, with some studies using disease-specific and others using generic outcome measures.

CONCLUSIONS

The results of this methodologically thorough systematic review and meta-analysis suggest that psychosocial interventions, including physically oriented mind-body interventions, have the potential for improving both psychological and physical outcomes in COPD. It should be noted, however, that our findings of possible publication bias towards studies reporting larger and positive effect sizes may question the robustness of the effect found for physical outcomes. Despite this cautionary note, based on the overall results, it appears appropriate to recommend delivering psychosocial intervention alongside the already established medical treatment pathway. Concerning specific types of psychosocial intervention, clinicians could consider offering CBT if the primary purpose is to relieve psychological health outcomes, and mind-body interventions with the primary purpose of relieving physical health outcomes. However, clinicians, researchers, and policy makers should be aware that, due to statistical power issues and the possible tendency towards publishing positive and significant findings, the robustness of the results presented here cannot be fully ensured and should therefore be interpreted with some caution.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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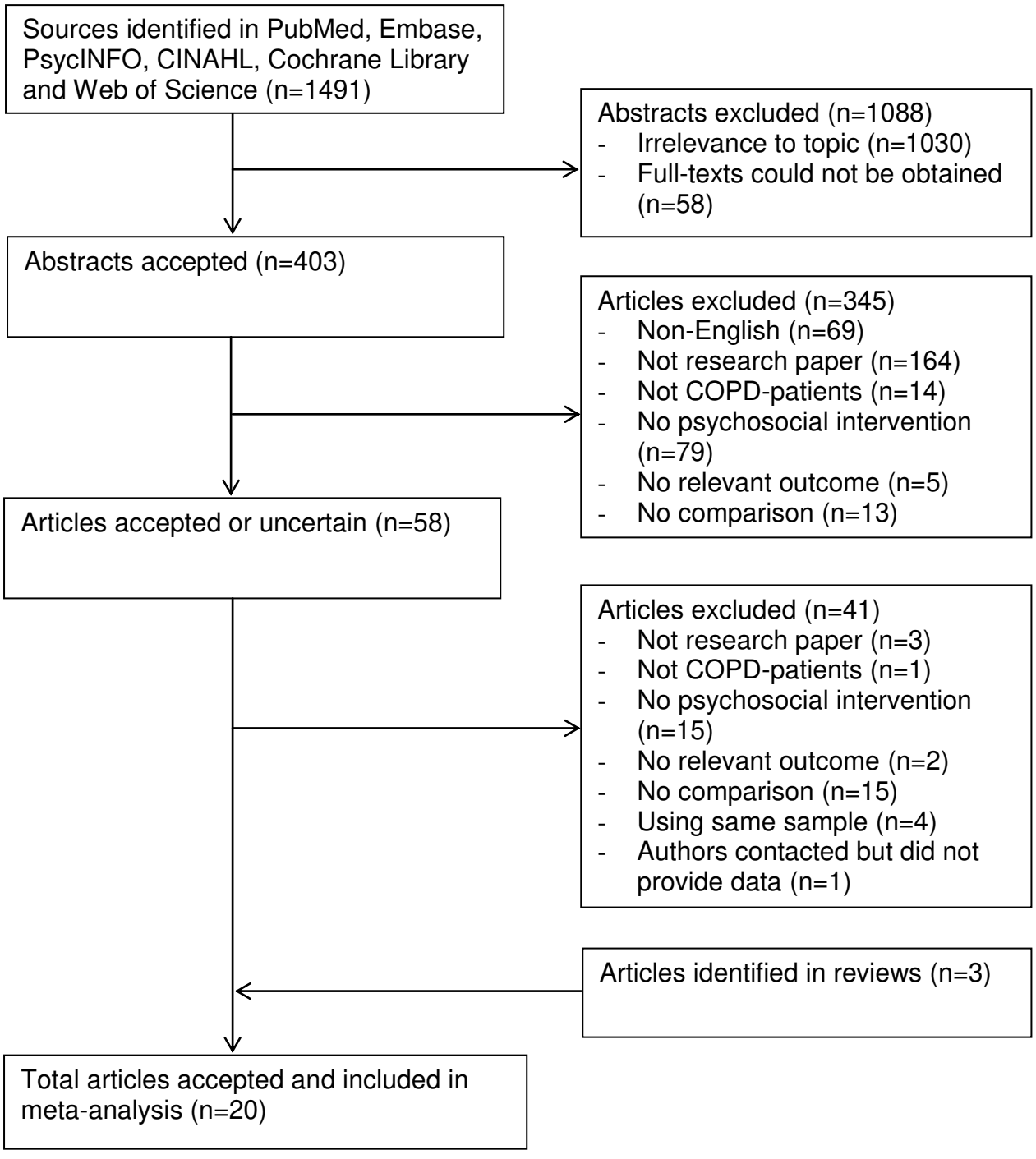
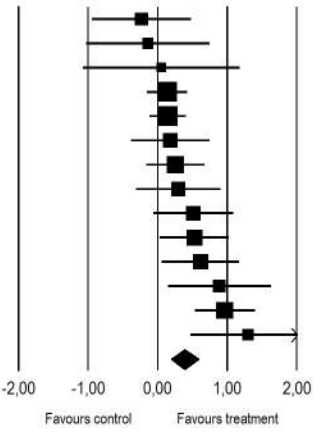
Figures and tables

Figure 1. PRISMA Flow-chart of selection procedure



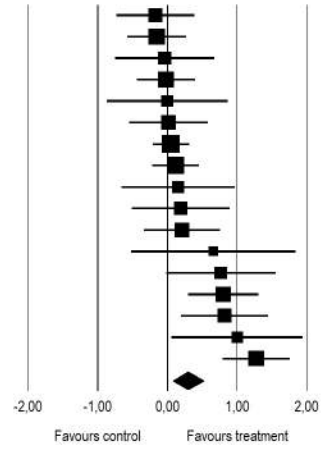
a) Psychological outcomes

Study name	Outcome	Hedges's g	p-Value	Total
Donesky-Cuenco et al., 2009	Combined	-0,233	0,520	29
Kapella et al., 2011	Combined	-0,139	0,757	18
Yeh et al., 2010	Depression	0,053	0,927	10
Lamers et al., 2010	Combined	0,137	0,348	187
Kunik et al., 2008	Combined	0,144	0,270	235
Emery et al., 1998	Combined	0,183	0,523	48
Sassi-Dambron et al., 1995	Combined	0,257	0,225	89
Livermore et al., 2010	Combined	0,296	0,337	41
Kunik et al., 2001	Combined	0,512	0,079	48
Singh, et al., 2009	Anxiety	0,527	0,036	64
Hynninen et al., 2010	Combined	0,616	0,029	51
de Godoy et al., 2005	Combined	0,888	0,018	30
Jiang et al., 2012	Combined	0,965	0,000	96
Gift et al., 1992	Anxiety	1,302	0,002	26
		0,385	0,000	972



b) Physical outcomes

Study name	Outcome	Hedges's g	p-Value	Total
Emery et al., 1998	Lung Function	-0,168	0,555	48
Mularski et al., 2009	Combined	-0,150	0,486	86
Donesky-Cuenco et al., 2009	Combined	-0,035	0,924	29
Sassi-Dambron et al., 1995	Combined	-0,019	0,929	89
Eiser et al., 1997	Combined	0,003	0,995	20
Kunik et al., 2001	Exercise capacity	0,021	0,941	48
Kunik et al., 2008	Combined	0,055	0,674	235
Chan et al., 2011	Combined	0,123	0,469	139
Rosser et al., 1983	Lung Function	0,160	0,699	22
de Godoy et al., 2005	Exercise capacity	0,194	0,587	30
Hynninen et al., 2010	Fatigue	0,211	0,445	51
Yeh et al., 2010	Combined	0,665	0,268	10
Gift et al., 1992	Combined	0,772	0,053	26
Singh, et al., 2009	Combined	0,804	0,002	64
Kheirabadi et al., 2008	Lung Function	0,826	0,009	42
Kapella et al., 2011	Fatigue	1,008	0,036	18
Ng et al., 2011	Exercise capacity	1,280	0,000	80
		0,300	0,006	1037



c) Quality of Life (QoL) outcomes

Study name	Outcome	Hedges's g	p-Value	Total
Emery et al., 1998	QoL	-0,413	0,150	48
Sassi-Dambron et al., 1995	QoL	-0,252	0,233	89
Eiser et al., 1997	QoL	-0,163	0,710	20
Kapella et al., 2011	QoL	0,000	1,000	18
Donesky-Cuenco et al., 2009	QoL	0,011	0,976	29
Livermore et al., 2010	QoL	0,030	0,921	41
Kunik et al., 2008	QoL	0,116	0,371	235
Kunik et al., 2001	QoL	0,236	0,411	48
Mularski et al., 2009	QoL	0,241	0,261	86
Jiang et al., 2012	QoL	0,241	0,235	96
Hynninen et al., 2010	QoL	0,254	0,360	51
Lamers et al., 2010	QoL	0,285	0,051	187
de Godoy et al., 2005	QoL	0,567	0,119	30
Kheirabadi et al., 2008	QoL	0,626	0,044	42
Ng et al., 2011	QoL	1,126	0,000	80
Yeh et al., 2010	QoL	1,746	0,012	10
		0,235	0,018	1110

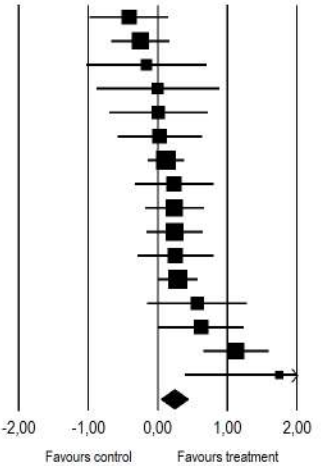


Table 1. Study characteristics

Author	Year	Study design [a]	N (N) [b] COPD severity at baseline (mean or proportion)	Mean age % women	Groups[c] (N assigned (N in final analysis))	Interven-tion type (category) [d]	No. of sessions (Treat-ment duration (weeks))	Physical outcome measure(s) [e]	Psychological outcome meas-ure(s)[f]	Quality of life outcome measure[g]	Jadad quality score, range: 0-13) [h]	Jadad-revised quality score, range: 0-18) [i]
1. Rosser et al. [36]	1983	RCT	65 (22) -	66 yrs. 33.8	1) PC (17(12)) 2) Analytic psycho-therapy(16(10))	Analytic	8 (8)	1) Lung function: Spirometry	-	-	9	12
2. Gift et al. [45]	1992	RCT	26 (26) Mean: 54.0	67 yrs. 69.2	1) AC (relaxation without guiding) (13(13)) 2) Guided relaxa-tion (13(13))	Mind-body	4 (4)	1) Lung function: Wright Peak Flow Meter 2) Dyspnea: VAS	1) Anxiety: SAI	-	6	9
3. Sassi-Dambron et al. [46]	1995	RCT	98 (89) Mean: 50.0	67.4 yrs. 44.9	1) AC (health edu-cation) (51(43)) 2) Health educa-tion, relaxation and stress management (47(46))	Mind-body	6 (6)	1) Dyspnea: VAS 2) Exercise capacity: 6MWT	1) Anxiety: SAI 2) Depression: CES-D	QWB	9	12
4. Eiser et al. [47]	1997	NRCT	20 (20) Prop.: 100% severe	72.2 yrs. 60.0	1) PC (8(8)) 2) CBT (12(12))	CBT	6 (6)	1) Lung function: Spirometry 2) Dyspnea: VAS 3) Execise capacity: 6MWT	-	SGRQ	5	7
5. Emery et al. [34]	1998	RCT	79 (48) Mean: 42.0	66.6 yrs. 53.2	1) PC (25(25)) 2) Stress manage-ment, CBT format (25(23))	CBT	63 (10)	1) Lung function: Spirometry	1) Anxiety: SAI 2) Depression: CES-D	SIP	9	11
6. Kunik et al. [48]	2001	RCT	56 (48) -	71.3 yrs. 17.0	1) AC (COPD edu-cation) (29(27)) 2) CBT (24(21))	CBT	1 (1)	1) Exercise capacity: 6MWT	1) Anxiety: BAI 2) Depression: GDS	SF-36	10	14

Author	Year	Study design [a]	N (N) [b] COPD severity at baseline (mean or proportion)	Mean age % women	Groups[c] (N assigned (N in final analysis))	Intervention type (category) [d]	No. of sessions (Treatment duration (weeks))	Physical outcome measure(s) [e]	Psychological outcome measure(s)[f]	Quality of life outcome measure[g]	Jadad quality score, range: 0-13) [h]	Jadad-revised quality score, range: 0-18) [i]
7. de Godoy et al. [35]	2005	RCT	49 (30) Mean: 34.0	- 27.0	1) PC (14(14)) 2) CBT and logotherapy techniques (16(16))	CBT	24 (12)	1) Exercise capacity: Distance walked-weight product	1) Anxiety: BAI 2) Depression: BDI	SGRQ	7	10
8. Kheirabadi et al. [49]	2008	RCT	42 (42) -	56.4 yrs. 31.0	1) PC (21(21)) 2) Psychoeducation and behaviour therapy (21(21))	Behavioral	8 (8)	1) Lung function: CCQ- symptoms subscale	-	CCQ	7	9
9. Kunik et al. [50]	2008	RCT	238 (235) Mean: 46.0	66.3 yrs. 3.8	1) AC (COPD education) (120(119)) 2) CBT (118(116))	CBT	8 (8)	1) Dyspnea: CRQ-Dyspnea subscale 2) Exercise capacity: 6MWT 3) Fatigue: CRQ-Fatigue subscale	1) Anxiety: BAI 2) Depression: BDI	SF-36	10	13
10. Donesky-Cuenco et al. [51]	2009	RCT	41 (29) Mean: 47.7	69.9 yrs. 72.4	1) PC (21(15)) 2) Yoga-meditation (20(14))	Mind-body	24 (12)	1) Dyspnea: CRQ-Dyspnea subscale 2) Lung function: Spirometry 3) Exercise capacity: 6MWT 4) Fatigue: CRQ-Fatigue subscale	1) Anxiety: SAI-State subscale 2) Depression: CES-D	SF-36	9	11
11. Mularski et al. [52]	2009	RCT	86 (86) Prop.: 64% severe	67.4 yrs. 0.0	1) AC (support groups) (42(42)) 2) Mindfulness-based breathing therapy (44(44))	Mind-body	8 (8)	1) Lung function: MSAS 2) Dyspnea: VAS 3) Exercise capacity: 6MWT	-	SGRQ	10	13

Author	Year	Study design [a]	N (N) [b] COPD severity at baseline (mean or proportion)	Mean age % women	Groups[c] (N assigned (N in final analysis))	Interven-tion type (category) [d]	No. of sessions (Treat-ment duration (weeks))	Physical outcome measure(s) [e]	Psychological outcome meas-ure(s)[f]	Quality of life outcome measure[g]	Jadad quality score, range: 0-13) [h]	Jadad-revised quality score, range: 0-18) [i]
12. Singh et al. [53]	2009	RCT	72 (64) Mean: 51.5	63.0 yrs. 30.0	1) AC (relaxation without music) (36(32)) 2) Music therapy and relaxation (36(32))	Mind-body	2 (1)	1) Lung function: Respiratory rate 2) Dyspnea: VAS	1) Anxiety: SAI-State subscale	-	9	13
13. Hynninen et al. [54]	2010	RCT	51 (51) Mean: 58.8	61.0 yrs. 51.0	1) PC (26(26)) 2) CBT (25(25))	CBT	7 (7)	1) Fatigue: PSQI	1) Anxiety: BAI 2) Depression: BDI	SGRQ	8	10
14. Lamers et al. [55]	2010	RCT	187 (187) -	71.0 yrs. 40.0	1) PC (91(91)) 2) CBT and self-management ele-ments (96(96))	CBT	4 (12)	-	1) Anxiety: SCL-90 Anxiety sub-scale 2) Depression: BDI	SGRQ	10	13
15. Liv-ermore et al. [56]	2010	RCT	41 (41) Mean: 54.1	73.4 yrs. 56.1	1) PC (20(20)) 2) CBT (21(21))	CBT	4 (4)	-	1) Anxiety: HADS- Anxiety subscale 2) Depression: HADS-Depression sub-scale	SGRQ	11	14
16. Yeh et al. [57]	2010	RCT	10 (10) Mean: 50.0	66.0 yrs. 40.0	1) PC (5(5)) 2) Tai chi meditative exercise (5(5))	Mind-body	24 (12)	1) Lung function: Spirometry 2) Dyspnea: CRQ-Dyspnea subscale 3) Exercise capacity: 6MWT 4) Fatigue: CRQ-Fatigue subscale	1) Depression: CES-D	CRQ	10	13

Author	Year	Study design [a]	N (N) [b] COPD severity at baseline (mean or proportion)	Mean age % women	Groups[c] (N assigned (N in final analysis))	Intervention type (category) [d]	No. of sessions (Treatment duration (weeks))	Physical outcome measure(s) [e]	Psychological outcome measure(s)[f]	Quality of life outcome measure[g]	Jadad quality score, range: 0-13) [h]	Jadad-revised quality score, range: 0-18) [i]
17. Chan et al. [37]	2011	RCT	206 (139) Prop.: 43% severe	73.0 yrs. 8.7	1) AC (breathing techniques and walking exercise) (69(69)) 2) Tai chi meditative exercise (70(70))	Mind-body	24 (12)	1) Lung function: Spirometry 2) Dyspnea: Borg scale 3) Exercise capacity: 6MWT 4) Fatigue: Borg scale	-	-	10	14
18. Kapella et al. [58]	2011	RCT	18 (18) Mean: 60.5	62.5 yrs. 22.2	1) AC (wellness education) (9(9)) 2) CBT for insomnia (9(9))	CBT	6 (6)	1) Fatigue: PSQI	1) Anxiety: POMS-Anxiety subscale 2) Depression: POMS-Depression subscale	FPI	9	12
19. Ng et al. [59]	2011	RCT	80 (80) Mean: 36.9	72.4 yrs. 11.2	1) AC (breathing techniques and walking exercise) (40(40)) 2) Qigong meditative exercise (40(40))	Mind-body	4 (4)	1) Exercise capacity: 6MWT	-	SF-36	11	15
20. Jiang et al. [60]	2012	RCT	100 (96) Prop.:39% severe	65.0 yrs. 30.2	1) PC (50(47)) 2) Uncertainty management, cognitive and behavioral strategies (50 (49))	CBT	4 (4)	-	1) Anxiety: SAI-State subscale 2) Depression: HADS- Depression subscale	SF-36	11	14

Notes: a) Abbreviations: NRCT (Non-randomized controlled trial), RCT (Randomized controlled trial); b) N (reported total sample size), (N) (Final sample size used in evaluation of effect on outcomes), COPD severity: % predicted forced expiratory volume per second (FEV1% pred.) reported as mean or percentage in the category "severe"; c) Abbreviations: AC (Active

control), CBT (Cognitive-behavioral therapy), PC (Passive control); d) CBT (Cognitive-behavioral therapy), Mind-body (Relaxation, Mindfulness, Meditative yoga, qigong or tai chi); e) Physical outcome measures: 6MWT (Six-Minute Walk Test [61]), Borg scale [62], CRQ (Chronic Respiratory Questionnaire [63]), MSAS (Memorial Symptom Assessment Scale [64]), PSQI (Pittsburgh Sleep Quality Index [65]), Respiratory rate (number of chest wall or abdomen rise and fall movements per minute [53]), Spirometry [66], VAS (Visual Analogue Scale [67]); f) Psychological outcome measures: BAI (Beck Anxiety Inventory [68]), BDI (Beck Depression Inventory [69]), CES-D (Center for Epidemiological Studies Depression scale [70]), GDS (Geriatric Depression Scale [71]), HADS (Hospital Anxiety and Depression Scale [72]), POMS (Profile of Mood States [73]), SAI (Spielberger Anxiety Inventory [74]), SCL-90 (Symptom Checklist-90 [75]), g) Quality of life outcome measures: CCQ (Clinical COPD Questionnaire [76]), CRQ (Chronic Respiratory Questionnaire [63]), FPI (Functional Performance Inventory [77]), SF-36 (the 36-item Short Form Health Survey [78]), SGRQ (Saint George´s Respiratory Questionnaire [79]), SIP (Sickness Impact Profile [80]), QWB (Quality of Well-Being scale [81]); h) Jadad study quality score (kilde); i) Total study quality score: modified Jadad score with additional study quality indicators.

Table 2. Effects of psychological intervention on psychological and physical outcomes in COPD patients.

	Sample size		Heterogeneity [a]				Global effect sizes			Failsafe N [c]	Criterion [d]
	K	**N**	**Q**	**df**	***p***	**I^2**	**Hedges *g*** [b]	**95% CI**	***p***		
A. Main effects											
Psychological (anxiety+depression)	14	972	26.0	13	0,017	49,9	0.39	0.19 – 0.58	**<0.001**	90	80
Psychological adj. for publication bias [e]	*(15)*	-	-	-	-	-	*0.38*	*0.19 – 0.58*	**-**	-	-
Physical (dyspnea+exercise capacity+fatigue+lung function)	17	1037	42.2	16	<0.001	62.1	0.30	0.08 – 0.52	**0.006**	64	95
Physical adj. for publication bias [e]	*(19)*	-	-	-	-	-	*0.20*	*-0.05– 0.44*	**-**	-	-
Anxiety	13	962	46.3	12	<0.000	74.1	0.45	0.18 – 0.72	**0.001**	108	75
Depression	12	882	13.1	11	0.286	16.2	0.26	0.11 – 0.42	**0.001**	30	70
Dyspnea	9	698	19.7	8	0.011	59.5	0.27	0.00 – 0.53	**0.047**	15	55
Dyspnea adj. for publication bias [e]	*(10)*	-	-	-	-	-	*0.20*	*-0.08– 0.48*	**-**	-	-
Exercise capacity	10	766	26.8	9	0.002	66.4	0.25	-0.02 – 0.52	*0.069*	-	-
Fatigue	6	482	9.7	5	0.083	48.7	0.13	-0.17 – 0.42	0.411	-	-
Lung function	10	486	19.9	9	0.018	54.9	0.14	-0.14 – 0.43	0.320	-	-
Quality of Life (QoL)	16	1110	34.3	15	0.003	56.3	0.24	0.04 – 0.43	**0.018**	42	90
B. Moderation analysis: Active versus passive control											
Psychological (active control)	6	480	9.5	5	0.092	47.1	0.37	0.09 – 0.65	**0.010**	15	40
Psychological (passive control)	8	492	16.2	7	0.023	56.8	0.39	0.09 – 0.69	**0.010**	24	50
Between groups [f]	14	972	0.09	1	0.928	-	-	-	-	-	-
Physical (active control)	9	785	35.3	8	0.001	77.3	0.37	0.05 – 0.69	**0.022**	35	55
Physical (passive control)	8	252	6.8	7	0.446	0.0	0.20	-0.04 – 0.45	0.105	-	50
Between groups [f]	17	1037	0.70	1	0.404	-	-	-	-	-	-

C.Moderation analysis: Intervention type (CBT vs. Mind-Body)											
Psychological (CBT)	9	754	17.2	8	0.028	53.6	0.39	0.15 – 0.62	**0.001**	43	55
Psychological (Mind-Body)	5	218	8.7	4	0.070	53.8	0.38	-0.05 – 0.81	*0.081*	-	-
Between groups [f]	14	972	0.0	1	0.971	-	-	-	**-**	-	-
Physical (CBT)	7	450	4.9	6	0.552	0.0	0.09	-0.10 – 0.27	0.345	-	45
Physical (Mind-Body)	8	523	30.4	7	0.001	77.0	0.40	0.01 – 0.79	**0.042**	26	50
Between groups [f]	15	973	2.0	1	0.153	-	-	-	-	-	-

Notes: a) Q-statistic: *p*-values < 0.1 taken to suggest heterogeneity. I^2 statistic: 0% (no heterogeneity), 25% (low heterogeneity), 50% (moderate heterogeneity), 75% (high heterogeneity); b) ES = Hedges g. Standardized mean difference, adjusting for small sample bias. A positive value indicates an effect size in the hypothesized direction, i.e. reduced distress or relative smaller increase in distress in the intervention group. To ensure independency, if a study reported results for more than one measure, the ES's were combined (mean), ensuring that only one ES per study was used in the calculation; c) Failsafe N = number of non-significant studies that would bring the p-value to non-significant ($p > 0.05$); d) A Failsafe N exceeding the criterion ($5 \times k + 10$) indicates a robust result [32]; e) If analyses indicated the possibility of publication bias, missing studies were imputed and an adjusted ESR calculated (italics) [33]. (K) indicates number of published studies + number of imputed studies; f) Meta-ANOVA (between-study comparisons)

Table 3. Moderation analyses: Results of meta-regression analyses

Dependent variable	Independent variable	K	Beta [a]	95% CI	p
Psychological (anxiety + depression)	Study quality (Jadad)	13	-0.10	-0.26 – 0.06	0.219
	Study quality (Revised Jadad)	13	-0.05	-0.70 – 2.59	0.491
	Treatment duration	13	-0.06	-0.12 – 0.00	*0.054* [b]
	Number of sessions	13	-0.00	-0.02 – 0.01	0.552
	Mean age	12	-0.03	-0.08 – 0.02	0.197
	Percent women	13	0.00	-0.01 – 0.01	0.873
	Mean FEV1%	10	0.01	-0.02 – 0.04	0.576
Physical (dyspnea + exercise capacity + fatigue + lung function)	Study quality (Jadad)	16	0.00	-0.15 – 0.15	0.972
	Study quality (Revised Jadad)	16	0.03	-0.09 – 0.14	0.655
	Treatment duration	16	-0.05	-0.11 – 0.00	*0.066* [c]
	Number of sessions	16	-0.01	-0.02 – 0.00	0.114
	Mean age	15	-0.02	-0.07 – 0.03	0.364
	Percent women	16	0.00	-0.01 – 0.01	0.819
	Mean FEV1%	10	0.01	-0.04 – 0.05	0.754

Notes: a) Mixed effects regression: unrestricted maximum likelihood; b) Near-significant ($p < 0.10$) in italics.