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Do self-management interventions in COPD patients work and which patients benefit most? An individual patient data meta-analysis

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Background: Self-management interventions are considered effective in patients with COPD, but trials have shown inconsistent results and it is unknown which patients benefit most. This study aimed to summarize the evidence on effectiveness of self-management interventions and identify subgroups of COPD patients who benefit most.

Methods: Randomized trials of self-management interventions between 1985 and 2013 were identified through a systematic literature search. Individual patient data of selected studies were requested from principal investigators and analyzed in an individual patient data meta-analysis using generalized mixed effects models.

Results: Fourteen trials representing 3,282 patients were included. Self-management interventions improved health-related quality of life at 12 months (standardized mean difference 0.08, 95% confidence interval [CI] 0.00–0.16) and time to first respiratory-related hospitalization (hazard ratio 0.79, 95% CI 0.66–0.94) and all-cause hospitalization (hazard ratio 0.80, 95% CI 0.69–0.90), but had no effect on mortality. Prespecified subgroup analyses showed that interventions were more effective in males (6-month COPD-related hospitalization: interaction P=0.006), patients with severe lung function (6-month all-cause hospitalization: interaction P=0.016), moderate self-efficacy (12-month COPD-related hospitalization: interaction P=0.036), and high body mass index (6-month COPD-related hospitalization: interaction P=0.028 and 6-month mortality: interaction P=0.026). In none of these subgroups, a consistent effect was shown on all relevant outcomes.

Conclusion: Self-management interventions exert positive effects in patients with COPD on respiratory-related and all-cause hospitalizations and modest effects on 12-month health-related quality of life, supporting the implementation of self-management strategies in clinical practice. Benefits seem similar across the subgroups studied and limiting self-management interventions to specific patient subgroups cannot be recommended.

Keywords: chronic obstructive pulmonary disease, individual patient data meta-analysis, self-management, subgroup analysis

Introduction

With over 60 million people affected, COPD is a major global health problem leading to substantial morbidity and mortality.[1] In addition to the disease burden, COPD requires a major shift in patients' daily life as they need to adhere to drug treatment, implement lifestyle changes, monitor signs and symptoms, and apply decision making on early treatment of exacerbations to prevent complications.[2] Interventions to improve this self-management behavior in COPD patients have been receiving increasing attention and generally involve patient education and teaching skills to patients for monitoring their condition, carrying out medical regimens, and changing their health behavior.[3] A recent systematic review found positive effects on a range of outcomes, including health-related quality of life (HRQoL), dyspnea, and health care utilization.[4]

Although the evidence favors self-management interventions, there seems to be a large heterogeneity in the effects of these interventions. Findings from five randomized trials, all based on the self-management program Living Well With COPD,[5] were contradictory and have raised questions about large scale implementation of self-management interventions in COPD patients. The first two trials reported large positive effects on respiratory-related hospitalization[5] and the combined endpoint of respiratory-related hospitalization and emergency department visit,[6] but these promising findings could not be replicated in subsequent studies in the UK[7] and the Netherlands.[8] The fifth trial even reported higher mortality rates among patients in the self-management group and recruitment was terminated prematurely.[9]

Several researchers have postulated hypotheses in an attempt to explain the different outcomes of these five trials. The diversity among interventions, study populations, follow-up time, and outcome measures across these five trials compromise a generalization to real life. Patient factors might matter more than assumed to date and it has been suggested that adherence to and uptake of self-management interventions are better in specific subgroups of patients.[10] Currently, however, evidence on which subgroups are more likely to benefit from or respond negatively to self-management interventions is lacking. With this knowledge, clinicians might be able to target self-management interventions at those patients who benefit most.

Identification of such patient subgroups in individual trials is complicated, as these usually lack power. A meta-analysis of individual patient data (IPD) enables a more reliable subgroup analysis with sufficient power due to the large numbers of patients included and by allowing a similar definition of subgroups across studies.[11] Collecting the IPD from different trials also enables standardized statistical analyses and inclusion of data on available but unreported endpoints, which has additional advantages for analyzing the main effects of self-management interventions.

The present IPD meta-analysis aims to summarize the evidence on the effectiveness of COPD self-management interventions on relevant outcomes, including HRQoL, hospitalization, and mortality, with a particular focus on identifying subgroups of patients with COPD who are most likely to benefit from self-management interventions.

Methods

This IPD meta-analysis was conducted according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions[12] and followed a prespecified protocol.[13]

Search and selection of studies

We searched the electronic databases PubMed, EMBASE, Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL from January 1985 through June 2013 and scrutinized the reference lists of identified relevant systematic reviews.

With no general agreement on an operational definition of self-management interventions, an international group of self-management research experts set out to reach consensus on the criteria for defining self-management intervention. There is general agreement on the multifaceted nature of self-management interventions.[3,4,14] Therefore, self-management interventions were defined as interventions providing information to patients and including minimally two of the following components: 1) stimulation of sign/symptom monitoring, 2) education in problem solving skills (ie, stress/symptom management), enhancement of 3) medical treatment adherence, 4) physical activity, 5) smoking cessation, or 6) dietary intake. The emphasis for each component had to be on enhancing the patient's active role and responsibility. Therefore, interventions focusing on pulmonary rehabilitation were not considered eligible for this meta-analysis.

Studies were selected by two researchers working independently (NHJ and HW) and included if they 1) met the requirements of the definition of self-management intervention above, 2) had a randomized trial design with concealed allocation to treatment, 3) included patients with an established diagnosis of COPD, 4) compared the self-management intervention to usual care or another self-management intervention, 5) reported data on one or more of the selected outcomes, 6) followed patients for at least 6 months, and 7) were reported in English, Dutch, French, German, Italian, Portuguese, or Spanish.

Methodological quality was assessed by two researchers independently (NHJ and HW) using three relevant criteria from the "Risk of bias" tool from the Cochrane Collaboration:[12] 1) random concealed allocation to treatment, 2) intention-to-treat analysis, and 3) absence of other major sources of bias (eg, high drop-out rates, risk of contamination). Any discrepancies were solved through consensus with a third researcher (JCAT). Studies that scored a high risk of bias on one or more criteria were defined as "high risk of bias". Those studies were included, but their impact on the results was assessed in a sensitivity analysis.

Data collection

The principal investigators of selected studies were invited to participate in this IPD meta-analysis and share their de-identified trial data. Data from each trial were checked on range, extreme values, internal consistency, missing values, and consistency with published reports. Questions that arose during the data checking were discussed and resolved with principal investigators. Details on requested variables, data management, project management, and ethical considerations can be found in the published protocol.[13]

Outcomes

The main outcomes of this study included: HRQoL at 6 and 12 months (as measured with Chronic Respiratory Questionnaire[15] or St George Respiratory Questionnaire[16]), respiratory-related hospitalization (time-to-first-event, within 6 and 12 months), all-cause hospitalizations (time-to-first-event, within 6 and 12 months), and mortality (time-to-event, within 6 and 12 months). Additional outcomes analyzed were generic quality of life (QoL), as measured with the Short Form Health Survey,[17] and total days of respiratory-related and all-cause hospital stay since enrollment at 6 and 12 months.

Patient-specific effect modifiers

Clinically relevant potential effect modifiers (ie, variables, such as sex or age) were prespecified based on the self-management literature and availability of data across trials and presented in Table 1 (along with the baseline data). Based on teleconferences with the principal investigators, we decided to collect data on baseline exacerbation frequency, in addition to the potential effect modifiers prespecified in the protocol.[13]

Table 1 Baseline characteristics of COPD patients

Determinant	Categories	Control (n=1,492)	Intervention (n=1,790)	Total (N=3,282)
Sex	Male	999 (67.0)	1,151 (64.3)	2,150 (65.5)
	Female	492 (33.0)	639 (35.7)	1,131 (34.5)
Age	Mean (SD) years	68.3 (9.6)	67.9 (9.6)	68.1 (9.6)
	<65 years	487 (32.8)	619 (34.7)	1,106 (33.8)
	65–75 years	627 (42.2)	780 (43.7)	1,407 (43.0)
	>75 years	371 (25.0)	387 (21.7)	758 (23.2)
Airflow obstruction	Mean (SD) FEV_1 in % predicted	47.3 (18.8)	48.0 (18.9)	47.7 (18.9)
	≥50% FEV_1 in % of predicted	617 (42.1)	772 (43.5)	1,389 (42.9)
	<50% FEV_1 in % of predicted	847 (57.9)	1,001 (56.5)	1,848 (57.1)
Dyspnea[a]	Low level of breathlessness	151 (37.4)	275 (50.2)	426 (44.7)
	High level of breathlessness	253 (62.6)	273 (49.8)	526 (55.3)
Comorbidity index[b]	No comorbid conditions	366 (32.4)	428 (32.9)	794 (32.7)
	Comorbid conditions in one cluster	291 (25.8)	326 (25.0)	617 (25.4)
	Comorbid conditions in ≥2 clusters	471 (41.8)	548 (42.1)	1,019 (41.9)
Depression[c]	No/mild depression	414 (70.9)	546 (74.0)	960 (72.6)
	Moderate/severe depression	170 (29.1)	192 (26.0)	362 (27.4)
Level of education	Primary education or below	313 (39.6)	391 (38.3)	704 (38.9)
	Secondary education	351 (44.4)	456 (44.7)	807 (44.6)
	Higher education	127 (16.1)	173 (17.0)	300 (16.6)
Self-efficacy[d]	Low self-efficacy	185 (31.7)	290 (33.9)	475 (33.0)
	Moderate self-efficacy	216 (37.0)	268 (31.3)	484 (33.6)
	High self-efficacy	183 (31.3)	297 (34.7)	480 (33.4)
Living status	Living with others	548 (71.2)	572 (68.1)	1,120 (69.6)
	Living alone	222 (28.8)	268 (31.9)	490 (30.4)
Body mass index	Mean (SD)	27.2 (6.5)	27.1 (6.2)	27.1 (6.3)
	<25	539 (40.1)	641 (39.4)	1,180 (39.7)
	25–29.99	429 (31.9)	568 (34.9)	997 (33.6)
	≥30	376 (28.0)	418 (25.7)	794 (26.7)
Smoking status	Current nonsmoker	1,036 (71.8)	1,225 (71.1)	2,261 (71.4)
	Current smoker	407 (28.2)	499 (28.9)	906 (28.6)
Exacerbation frequency	0 exacerbations	188 (31.1)	194 (30.8)	382 (31.0)
	1 exacerbation	134 (22.2)	122 (19.4)	256 (20.7)
	≥2 exacerbations	282 (46.7)	314 (49.8)	596 (48.3)

Notes: Values are expressed as mean (SD) or n (%). [a]Based on score modified Medical Research Council dyspnea scale[47] and categorized mMRC ≥3 or mMRC ≥2 as high level of breathlessness. [b]Based on clusters Cumulative Illness Rating Scale.[48] [c]Based on validated cutoff scores of instrument used in each specific study. [d]Categories based on tertile scores computed within each specific study.
Abbreviations: FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

Statistical analysis

The principal investigators of the individual trials were involved in the process of designing a detailed plan for statistical analysis and agreed upon this prior to data analysis. Missing values were imputed within studies only using multiple imputation by chained equations (overall 2.7% missing data, except 33.7% for HRQoL follow-up data).[18] For each study, 25 multiple imputed datasets were created and used for the primary analyses. Within these analyses, a one-stage approach was used, that is, simultaneously analyzing all observations while accounting for clustering of observations within studies.[19] Results of imputed datasets were pooled using Rubin's rules.[20]

All analyses were carried out according to the intention-to-treat principle. For time-to-event endpoints, effects of self-management were quantified by estimating hazard ratios using Cox proportional hazard models, including a frailty term to account for clustering within studies. The continuous outcomes (HRQoL and generic oL) were quantified by standardized mean differences (SMD) between intervention arms and analyzed using linear mixed effects models. Using the SMD, results are converted to a uniform scale representing the intervention effect relative to the observed variability in one study before pooling the results of different studies. Binary outcome data (mortality, respiratory-related, and all-cause hospitalization) were analyzed with log-binomial mixed effects models, which estimated risk ratios (RRs) or odds ratios (ORs) in case of nonconvergence of a model, respectively. To correctly model the presence of overdispersion in the count data of total days of hospital stay, negative binomial mixed effects models were used to estimate relative length of stay. All mixed effects models included a random intercept and a random slope for the treatment effect to take clustering at study level into account.

To assess whether the effect of self-management was modified by patient characteristics, the aforementioned models were extended with interaction terms for the patient characteristics included in Table 1. The independent variables in the models were random intercept, random slope, allocation to self-management, patient characteristic, and interaction term (treatment allocation*patient characteristic). This was performed for each patient characteristic separately. All effect modifiers with $P<0.10$ for the interaction (likelihood ratio test) in the univariable analysis were included in a multivariable model to estimate the effect of self-management within subgroups independent of other potential effect modifiers. Effect modification was considered significant if the interaction term showed $P<0.05$ in the final model.

As a sensitivity analysis, we investigated the potential of retrieval bias (ie, bias due to selective inclusion of studies in the IPD meta-analysis) by pooling the published main effects of studies for which IPD were unavailable with the main effects of included studies in a random effects meta-analysis. To assess the impact of studies of lower methodological quality on the main effects, an additional sensitivity analysis was performed, including only studies with a low risk of bias. Three additional sensitivity analyses were performed to assess the robustness of findings from the subgroup analyses: 1) a complete case analysis was carried out to assess the effect of imputing data, and analyses were repeated by 2) excluding older studies (recruitment before 2001) and 3) excluding the largest trial.[6] All analyses were performed in R for Windows version 3.1.1 (R Development Core Team. Released 2013. Vienna, Austria: R Foundation for Statistical Computing).

Results

Twenty-one studies met the inclusion criteria. Seven studies were not included in this IPD meta-analysis.[9,21–26] We could not contact the investigators of three studies;[21,23,24] for two studies, the investigators could not obtain approval from their local Institutional Review Board;[9,22] the data from one study were no longer available;[25] and investigators of one study could not participate due to time constraints.[26] The investigators of the other 14 studies participated in this IPD meta-analysis, resulting in the inclusion of data on 3,282 patients.

Patient characteristics are presented in Table 1. Not all studies measured the same baseline characteristics; only sex, age, and forced expiratory volume in 1 second in % of predicted were assessed in all studies. The majority of included patients were male (65.5%). Patients had a mean age of 68.1 years (±9.6) and a mean forced expiratory volume in 1 second in % of predicted of 47.7% (±18.9%). The majority of patients had high breathlessness scores (55.3%). Apart from dyspnea classification, all baseline variables were well balanced between control and intervention groups.

Table 2 presents the characteristics of included studies.[5–8,27–36] Seven studies recruited participants in a clinic or hospital setting,[5–7,27,29,30,32] five studies in general practice,[8,28,31,34,36] and two in both settings.[33,35] The sample size of studies ranged from 53[30] to 743 patients.[6] Self-management interventions varied across studies: a majority included an action plan and consisted of individual sessions with a nurse, and some involved group contacts. Duration of interventions ranged from 1 day[31] to 24 months.[8]

Table 2 Description of trials on self-management in COPD patients included in the individual patient data meta-analysis

Study	Country	Sample size	Setting	Intervention group	Control group	Duration intervention (months)
Bischoff et al[8] 2012	the Netherlands	165	General practice	A: Two to four individual sessions by nurse, action plan, follow-up six phone calls B: Two to four routine monitoring sessions by nurse	Usual care	24
Bourbeau et al[5] 2003	Canada	191	Clinic/hospital	Seven individual sessions by nurse/respiratory therapist/physiotherapist, one physical exercise session, workbook, action plan, follow-up monthly telephone calls	Usual care	12
Bucknall et al[7] 2012	UK	464	Clinic/hospital	Four individual home visits by nurse, action plan, follow-up by home visits at least every 6 weeks	Usual care	12
Casas et al[27] 2006	Belgium, Spain	155	Clinic/hospital	One individual session, minimally one home visit by nurse/physician, action plan, follow-up four telephone calls	Usual care	1
Coultas et al[28] 2005	US	217	General practice	A: One individual session by nurse, follow-up six telephone calls B: One individual session by nurse, follow-up seven telephone calls	Usual care	6
Effing et al[29] 2009	the Netherlands	153	Clinic/hospital	A: Four group sessions by nurse/physiotherapist, action plan, physical training for 11 months, follow-up three telephone calls B: Four group sessions by nurse/physiotherapist, action plan, follow-up three telephone calls C: Four group sessions by nurse/physiotherapist, 11 months physical training	Usual care + four group sessions on self-management	12
Gallefoss et al[30] 1999	Norway	53	Clinic/hospital	Two group sessions, minimally two individual sessions by multidisciplinary team, action plan	Usual care	0.5
McGeoch et al[31] 2006	New Zealand	161	General practice	One individual session by nurse, action plan	Usual care	1 day
Monninkhof et al[32] 2003	the Netherlands	248	Clinic/hospital	Five group sessions by nurse/physiotherapist, action plan, physical training program for 2 years	Usual care	4
Nguyen et al[33] 2013	US	125	Combination	A: One home visit, six group sessions by nurse, educational booklet, follow-up biweekly telephone calls B: Digital learning environment, one home visit, six chat sessions with nurse, follow-up biweekly e-mails	Usual care + home visit, monthly group sessions on health education, biweekly telephone calls	12
Rice et al[6] 2010	US	743	Clinic/hospital	One group session by respiratory therapist, individualized action plan, follow-up monthly telephone calls	Usual care + educational handout	12
Taylor et al[34] 2012	UK	116	General practice	Seven group sessions by two lay peer tutors, action plan	Usual care	1.6
Trappenburg et al[35] 2011	the Netherlands	233	Combination	One individual session by nurse, action plan, follow-up two telephone calls	Usual care + log s	4
Zwar et al[36] 2012	Australia	258	General practice	Two home visits by nurse, two visits to physician, action plan, follow-up five telephone calls	Usual care	6

Abbreviation: COPD, chronic obstructive pulmonary disease.

Main effects of self-management interventions

Self-management interventions improved HRQoL at 12 months (SMD 0.08, 95% confidence interval [CI] 0.00–0.16), but not at 6 months (SMD 0.05, 95% CI –0.05 to 0.15) (Table 3). The interventions improved time to first respiratory-related hospitalization (hazard ratio 0.79, 95% CI 0.66–0.94). Although there was no clear effect on respiratory-related hospitalization within 6 months, there was a significant risk reduction at 12 months (RR 0.77, 95% CI 0.64–0.93). Self-management interventions improved the time to first all-cause hospitalization (hazard ratio 0.80, 95% CI 0.69–0.90) and risk of hospitalization within 6 months (RR 0.81, 95% CI 0.67–0.97) and 12 months (RR 0.84, 95% CI 0.73–0.96). There was no effect of self-management on mortality. Figure 1 shows the effects across studies for HRQoL, respiratory-related and all-cause hospitalization, and mortality. Sensitivity analyses of including the published effects of studies for which no IPD were available resulted in similar effects of the self-management interventions (Supplementary material). No effects were observed on the additional outcomes of generic QoL or total days in hospital (Supplementary material).

Effects in subgroups of patients

The final models in the prespecified subgroup analysis revealed no consistent effect modification by any patient characteristic across all relevant outcomes (Table 4), but the effect on specific outcomes differed according to some of the patient characteristics we studied. A positive effect of self-management interventions was observed in males (OR 0.61, 95% CI 0.41–0.90) compared to females on the outcome respiratory-related hospitalization within 6 months (OR 1.24, 95% CI 0.76–2.02; interaction *P*=0.006). Patients with severe airflow limitation showed a reduced risk on all-cause hospitalization within 6 months when allocated to the intervention (RR 0.71, 95% CI 0.58–0.88), while there was no treatment effect in patients with ≥50% forced expiratory volume in 1 second in % of predicted (RR 1.02, 95% CI 0.78–1.34; interaction *P*=0.016). Obese patients showed the most protective effects of self-management interventions on respiratory-related hospitalization within 6 months (OR 0.44, 95% CI 0.27–0.72; interaction *P*=0.038) and mortality within 6 months (OR 0.35, 95% CI 0.11–1.10; interaction *P*=0.026). Finally, patients with baseline moderate self-efficacy scores showed the largest reduction in risk on respiratory-related hospitalization within 12 months (OR 0.39, 95% CI 0.21–0.75) compared to patients with low (OR 0.85, 95% CI 0.46–1.59) or high levels of self-efficacy (OR 0.89, 95% CI 0.47–1.71; interaction *P*=0.036). Additional analyses for generic QoL and total days in hospital did not reveal different insights (Supplementary material). Subgroup analysis according to exacerbation frequency was impossible due to too diverse data collection at baseline and comparison of subgroups in individual trials did not reveal consistent effects across studies (Supplementary material). Sensitivity analyses to assess the robustness of the subgroup effects yielded similar findings to the primary analysis.

Discussion

This IPD meta-analysis of 14 randomized trials showed that self-management interventions exerted positive effects in COPD patients on respiratory-related and all-cause

Table 3 Effects of self-management interventions in patients with COPD

Outcome	N studies	n patients	Effect measure	Treatment effect	95% CI
Health-related quality of life					
At 6 months	9	1,876	SMD	0.05	(–0.05–0.15)
At 12 months	10	2,663	SMD	0.08	(0.00–0.16)
Respiratory-related hospitalization					
Time-to-first-event	6	1,872	HR	0.79	(0.66–0.94)
Within 6 months	8	2,347	RR	0.87	(0.69–1.09)
Within 12 months	9	2,426	RR	0.77	(0.64–0.93)
All-cause hospitalization					
Time-to-first-event	4	1,559	HR	0.80	(0.69–0.93)
Within 6 months	6	2,034	RR	0.81	(0.67–0.97)
Within 12 months	5	1,817	RR	0.84	(0.73–0.96)
Mortality					
Time-to-event	7	2,120	HR	1.02	(0.76–1.37)
Within 6 months	9	2,490	RR	1.06	(0.62–1.82)
Within 12 months	7	2,182	RR	1.04	(0.64–1.69)

Abbreviations: CI, confidence interval; HR, hazard ratio; RR, risk ratio; SMD, standardized mean difference.

Health-related quality of life at 12 months	Year	Sample size	SMD	95% CI
Bourbeau et al[5]	2003	191	0.10	(–0.13–0.33)
Monninkhof et al[32]	2003	248	–0.03	(–0.19–0.13)
McGeoch et al[31]	2006	161	0.10	(–0.13–0.32)
Casas et al[27]	2006	155	0.10	(–0.16–0.35)
Effing et al[29]	2009	153	0.20	(–0.08–0.48)
Rice et al[6]	2010	743	0.17	(0.03–0.30)
Bischoff et al[8]	2012	165	0.16	(–0.12–0.45)
Bucknall et al[7]	2012	464	0.08	(–0.14–0.31)
Nguyen et al[33]	2013	125	0.15	(–0.17–0.48)
Zwar et al[36]	2012	258	–0.12	(–0.34–0.10)
Overall			**0.08**	**(0.00–0.16)**

Respiratory-related hospitalization	Year	Sample size	HR	95% CI
	Time-to-event			
McGeoch et al[31]	2006	161	0.60	(0.24–1.49)
Casa et al[27]	2007	155	0.60	(0.38–0.93)
Rice et al[6]	2010	743	0.67	(0.48–0.93)
Trappenburg et al[35]	2011	233	1.15	(0.55–2.42)
Bucknal et al[7]	2012	464	0.98	(0.74–1.28)
Taylor et al[34]	2012	116	0.83	(0.20–3.46)
Overall			**0.79**	**(0.66–0.94)**
All-cause hospitalization	**Time-to-event**			
Bourbeau et al[5]	2003	191	0.54	(0.36–0.83)
McGeoch et al[31]	2006	161	1.01	(0.55–1.84)
Rice et al[6]	2010	743	0.73	(0.57–0.93)
Bucknall et al[7]	2012	464	0.92	(0.74–1.14)
Overall			**0.80**	**(0.69–0.93)**
Mortality	**Time-to-event**			
Monninkhof et al[32]	2003	248	2.25	(0.43–11.61)
McGeoch et al[31]	2006	161	0.42	(0.04–4.61)
Casas et al[27]	2007	155	1.21	(0.56–2.61)
Rice et al[6]	2010	743	0.73	(0.47–1.13)
Trappenburg et al[35]	2011	233	1.11	(0.16–7.86)
Bucknall et al[7]	2012	464	1.39	(0.81–2.42)
Taylor et al[34]	2012	116	1.95	(0.22–17.47)
Overall			**1.02**	**(0.76–1.37)**

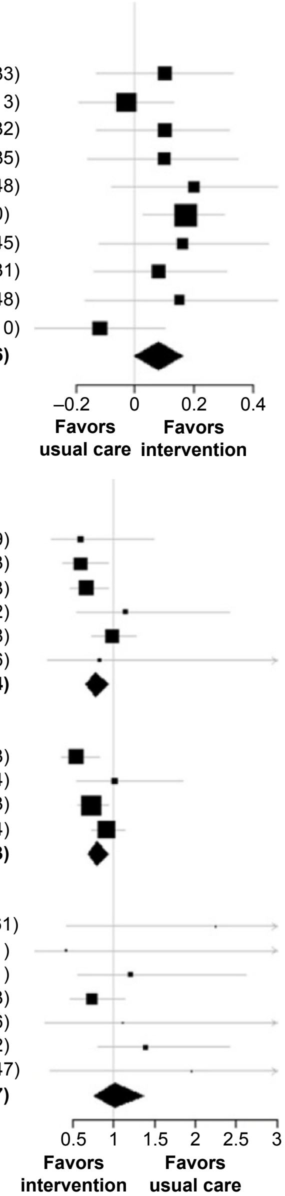

Figure 1 Forest plot of effects of self-management interventions on health-related quality of life, respiratory-related and all-cause hospitalization, and mortality in patients with COPD.
Abbreviations: CI, confidence interval; HR, hazard ratio, SMD, standardized mean difference.

hospitalization. Self-management interventions also resulted in small improvements on HRQoL at 12 months, but had no effect on HRQoL at 6 months or on mortality. One novel aspect from this study was the prespecified subgroup analyses, which did not show a consistent pattern across health outcomes of subgroups of patients benefiting most from the self-management interventions.

The main effects reported by the present study are in line with a recent Cochrane review on self-management trials in COPD patients.[4] Like the present study, the authors did not find an effect of self-management on mortality. However, the follow-up period of 12 months may have been too short to elicit an effect on this outcome. Although the Cochrane review applied a wider definition of "self-management interventions" and could include all eligible trials (N=23 vs N=14 in this IPD meta-analysis, respectively), we were able to include more recently conducted studies (N=6) of which some have cast doubts on the usefulness of self-management in COPD patients.[7,8] By including data from these recent studies as well as performing a sensitivity analysis, including the published results of the prematurely terminated trial,[9] the present study provides more extensive evidence that self-management interventions elicit positive effects in COPD patients and can be considered safe. However, the

Table 4 Effects of self-management interventions in subgroups of patients with COPD

Outcome	n patients	Subgroup	Effect measure	Univariable analysis			Multivariable analysis		
				Treatment effect	95% CI	P-value for interaction	Treatment effect	95% CI	P-value for interaction
Health-related quality of life									
At 6 months		No subgroup effects							
At 12 months		No subgroup effects							
Respiratory-related hospitalization									
Time-to-first-event	1,214	Males	HR	0.68	(0.54–0.84)	0.022	0.78	(0.55–1.09)	0.130
	497	Females		1.05	(0.78–1.42)		1.07	(0.78–1.48)	
	549	No comorbidities	HR	0.93	(0.72–1.20)	0.073	0.78	(0.55–1.09)	0.206
	380	Comorbidities in one cluster		0.52	(0.33–0.80)		0.48	(0.31–0.76)	
	710	Comorbidities in >1 cluster		0.72	(0.52–1.00)		0.70	(0.50–0.97)	
6 months	1,544	Males	OR	0.67	(0.50–0.88)	0.005	0.61	(0.41–0.90)	0.006
	803	Females		1.36	(0.91–2.04)		1.24	(0.76–2.02)	
	835	BMI <25	OR	0.77	(0.54–1.11)	0.043	0.61	(0.41–0.90)	0.038
	636	BMI 25–29.99		1.23	(0.78–1.93)		1.01	(0.63–1.61)	
	618	BMI ≥30		0.55	(0.34–0.88)		0.44	(0.27–0.72)	
12 months	281	Low self-efficacy	OR	0.85	(0.46–1.59)	0.036	[a]		
	277	Moderate self-efficacy		0.39	(0.21–0.75)				
	250	High self-efficacy		0.89	(0.47–1.71)				
All-cause hospitalization									
Time-to-first-event	539	No comorbidities	HR	0.88	(0.71–1.09)	0.056	[a]		
	384	Comorbidities in one cluster		0.57	(0.41–0.78)				
	636	Comorbidities in >1 cluster		0.89	(0.68–1.15)				
6 months	698	≥50% FEV_1 % predicted	RR	1.02	(0.78–1.34)	0.016	[a]		
	1,336	<50% FEV_1 % predicted		0.71	(0.58–0.88)				
12 months	614	≥50% FEV_1 % predicted	OR	1.03	(0.73–1.46)	0.032	1.30	(0.54–3.12)	0.232
	1,203	<50% FEV_1 % predicted		0.63	(0.49–0.81)		0.82	(0.40–1.68)	
	222	Low self-efficacy	OR	0.93	(0.47–1.86)	0.047	1.30	(0.54–3.12)	0.062
	239	Moderate self-efficacy		0.35	(0.18–0.71)		0.52	(0.21–1.29)	
	195	High self-efficacy		0.92	(0.46–1.86)		1.31	(0.54–3.20)	
Mortality									
Time-to-event	549	No comorbidities	HR	1.56	(0.90–2.72)	0.075	[b]		
	380	Comorbidities in one cluster		0.66	(0.29–1.49)				
	710	Comorbidities in >1 cluster		0.77	(0.46–1.31)				
	140	Less breathlessness	HR	5.33	(0.69–40.91)	0.091	[b]		
	248	More breathlessness		0.83	(0.22–3.09)				
6 months	1,707	Males	OR	0.79	(0.42–1.49)	0.071	1.40	(0.64–3.05)	0.123
	783	Females		1.83	(0.82–4.11)		2.89	(1.19–7.02)	
	976	BMI <25	OR	1.83	(0.94–3.55)	0.016	1.40	(0.64–3.05)	0.026
	817	BMI 25–29.99		0.70	(0.33–1.51)		0.54	(0.23–1.26)	
	697	BMI ≥30		0.46	(0.15–1.35)		0.35	(0.11–1.10)	
12 months	1,557	Males	RR	0.85	(0.51–1.42)	0.092	1.18	(0.62–2.26)	0.445
	625	Females		1.59	(0.77–3.28)		1.57	(0.80–3.08)	

(Continued)

Table 4 (*Continued*)

Outcome	n patients	Subgroup	Effect measure	Univariable analysis			Multivariable analysis		
				Treatment effect	95% CI	*P*-value for interaction	Treatment effect	95% CI	*P*-value for interaction
	627	No Comorbidities	RR	1.37	(0.80–2.35)	0.074	1.18	(0.62–2.26)	0.213
	485	Comorbidities in 1 cluster		0.64	(0.31–1.30)		0.60	(0.30–1.25)	
	669	Comorbidities in >1 cluster		0.71	(0.43–1.16)		0.70	(0.43–1.15)	

Notes: Results of the subgroup analyses are only presented if a potential effect modifier showed an effect with $P<0.10$ in the univariable analysis. [a]Multivariable analysis was only performed if ≥2 potential effect modifiers in the univariable analysis to adjust for other potential effect modifiers. [b]Multivariable analysis not executed as this would result in N=1 study.

Abbreviations: BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; HR, hazard ratio; OR, odds ratio; RR, risk ratio.

positive effects observed for HRQoL at 12 months should be considered modest improvements, and no effects were observed at 6 months. It also remains questionable whether the statistical difference that we observed is a clinically important difference for COPD patients. Furthermore, it remains questionable whether our findings also apply to COPD patients recently discharged from hospital. A recently published systematic review on self-management interventions in this group of patients found that positive effects were limited to HRQoL,[37] but the authors applied rather wide inclusion criteria for the interventions, resulting in the inclusion of many interventions with only a limited self-management component compared to the present study.

The novel aspect of the present study compared to the previously conducted systematic reviews was the prespecified subgroup analysis. This subgroup analysis revealed larger effects of self-management interventions in males, patients with more severe airflow limitation, patients with moderate levels of self-efficacy, and obese patients, but only on some outcomes. To date, differential effects of self-management interventions in subgroups of COPD patients have scarcely been examined. One study included in this IPD meta-analysis analyzed response of subgroups of COPD patients to the self-management intervention on hospitalization or death.[7] The preplanned subgroup analyses did not show any evidence of differential effects, but the authors found that only 42% of intervention group subjects learnt to self-manage successfully. The successful self-managing patients had significantly reduced hospitalization rate.[7] The present IPD meta-analysis, with more power to perform subgroup analyses, suggested larger effects of self-management interventions on respiratory-related hospitalization as well as mortality at 6 months in obese patients. Although effect modification by body mass index has not yet been analyzed in COPD patients in the context of self-management interventions, evidence is starting to emerge that overweight or obese patients encompass a specific phenotype of COPD patients.[38] It is possible that this particular phenotype of COPD patients responds differently to self-management interventions. Our analyses only revealed differential effects of obesity on the outcomes respiratory-related hospitalization at 6 months and mortality at 6 months. Effects at 12 months were in a similar direction, but these were not statistically significant. Previous efforts to assess the influence of body mass index on effectiveness of pulmonary rehabilitation have also yielded inconsistent results.[39,40] Although our subgroup analysis was prespecified[13] and yielded several statistically significant findings, the high number of analyses increases the chance of false-positive findings. With no consistent pattern across multiple health outcomes, the subgroup results should be interpreted with caution.[41] Limiting self-management support to specific patient subgroups cannot be recommended at this stage and further research is therefore needed to confirm the observed subgroup effects for other health outcomes. Reassuringly, there were no indications in our analyses that certain subgroups of patients responded in a negative way to the self-management interventions.

To our knowledge, the present study is the first to pool and reanalyze the original data of a large number of randomized trials on self-management interventions in patients with COPD and transcends the previously conducted systematic reviews.[4,37] An IPD meta-analysis is a resource intensive approach, given the time and efforts needed for collecting and merging the raw patient data.[42] As a result, no articles published after June 2013 were included for analysis. The high response rate of principal investigators (66.7%), large number of patients included (n=3,282), prespecified statistical plan, and close collaboration with the principal investigators through regular teleconferences contribute to the robustness of our findings. There are several methodological limitations worth considering. First, in spite of numerous efforts to contact and convince the principal investigators of all eligible studies, we could not obtain the data of seven randomized trials, including the prematurely aborted trial.[9] However, the sensitivity analysis of pooling the published results of those trials with the main effects of included studies showed that this did not alter our findings (Supplementary material).

Second, we assumed all interventions to be homogeneous self-management interventions in our analyses, but the included self-management intervention designs differed from each other in terms of dose, mode, and content. Without consistent evidence for subgroups of patients benefiting across various health outcomes, we could hypothesize that specific subgroups of patients only respond better to particular components of interventions (ie, action plans in self-management interventions). Future research addressing various interventions is needed to identify what type of intervention works for whom. Nevertheless, the reported main effects on HRQoL at 12 months, and respiratory-related and all-cause hospitalization were consistent across cultures and health care settings. This indicates that, despite their diversity, self-management interventions exert positive effects, even in different formats and differing patient populations.

Third, this IPD meta-analysis was highly dependent on data that were previously collected. This seriously limited our choice of potential effect modifiers. Exacerbation frequency has attracted considerable attention in recent years,[43] but due to the diverse data collection across studies, the quality of available data on baseline exacerbation rate was too low to enable a pooled analysis of this patient characteristic. This emphasizes the urgent need for a uniform operational definition of exacerbations within the field of COPD research.[44] For similar reasons, we could not study other potentially relevant variables, such as Global initiative for chronic Obstructive Lung Disease stage, coping style, disease perception, and adherence. Previous studies have shown that even though adherence to self-management treatment is a challenge for a majority of patients enrolled in randomized trials, the patients who actually applied those new self-management skills showed better outcomes.[7,45] This suggests that emphasis should be placed on patients' ability to apply self-management guidelines and subsequently change their behavior as this is a prerequisite for better outcomes. Collection of data on intervention delivery, treatment adherence, and behavior change in randomized trials, particularly on complex interventions, such as self-management, is indispensable to identify patients most likely to adhere to the self-management interventions and in whom these interventions may improve prognosis.[46]

Conclusion

Self-management interventions exert positive effects in patients with COPD on respiratory-related and all-cause hospitalization and modest improvement of HRQoL at 12 months, but do not show an effect on mortality. These benefits seem similar across the subgroups of patients studied as subgroup analysis did not reveal a consistent pattern across different health outcomes. Our findings support implementation of self-management strategies in practice, but targeting self-management interventions at specific subgroups of patients cannot be recommended based on the current evidence.

Author contributions

NHJ, HW, JCAT, RHHG, JB, TWE, JvdP, TT, AWH, and MJS participated in the design of the study. JCAT, EWMAB, JB, CEB, DC, TWE, ME, FG, JG-A, EMM, HQN, KLR, MS, SJCT, and NAZ contributed data to this study. NHJ and HW collected and merged the data. NHJ, HW, JCAT, RHHG, AWH, and MJS wrote the statistical analysis plan. NHJ and RHHG carried out the statistical analysis. All authors reviewed and approved the statistical plan and contributed to the interpretation of the statistical analysis. NHJ wrote the draft of the manuscript. All authors contributed to the critical revision of the manuscript. All authors contributed toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

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