Effects of pharmacological and non-pharmacological interventions on physical activity outcomes in COPD: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
Physical activity (PA) behavioural modification and pharmacological interventions lead to significant and clinically meaningful improvements in PA. Monitoring of PA outcomes in COPD may constitute a useful biomarker in research and medicine development. https://bit.ly/45pHGoX

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Abstract

Rationale The effect of pharmacological and non-pharmacological interventions on physical activity (PA) outcomes is not fully elucidated in patients with COPD. The objectives of the present study were to provide estimation of treatment effects of all available interventions on PA outcomes in patients with COPD and to provide recommendations regarding the future role of PA outcomes in pharmacological trials.

Materials and methods This review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions and reported in line with PRISMA. Records were identified through searches of 12 scientific databases; the most updated search was performed in January 2023.

Results 74 studies published from 2000 to 2021 were included, with a total of 8140 COPD patients. Forced expiratory volume in 1 s % predicted ranged between 31% and 74%, with a mean of 55%. Steps/day constituted the most frequently assessed PA outcome in interventional studies. Compared to usual care, PA behavioural modification interventions resulted in improvements in the mean (95% CI) steps/day when implemented alone (by 1035 (576–1493); p<0.00001) or alongside exercise training (by 679 (93–1266); p=0.02). Moreover, bronchodilator therapy yielded a favourable difference of 396 (125–668; p=0.004) steps/day, compared to placebo.

Conclusions PA behavioural modification and pharmacological interventions lead to significant improvements in steps/day, compared to control and placebo groups, respectively. Compared to bronchodilator therapy, PA behavioural modification interventions were associated with a 2-fold greater improvement in steps/day. Large-scale pharmacological studies are needed to establish an intervention-specific minimal clinically important difference for PA outcomes as well as their convergent validity to accelerate qualification as potential biomarkers and efficacy end-points for regulatory approval.

Introduction

In patients with COPD, limited physical activity (PA) levels have been associated with poor prognosis [1–8]. An Official Statement issued by the European Respiratory Society and recently a narrative review by the COPD Biomarker Qualification Consortium (CBQC) support the implementation of interventions to increase PA levels in patients with COPD [9, 10].

Currently, the effect of interventions on PA levels is not yet fully understood, with similar interventions eliciting variable effects on PA outcomes [10, 11]. Previous systematic reviews and meta-analyses did not establish a consistent and reproducible categorisation of interventions, thus precluding a conclusive estimation of treatment effects [10, 11]. This is due to PA being a complex health behaviour, affected and defined by several factors (*i.e.* physiological, environmental, regional, global and psychosocial) [12]. The necessity to accumulate sufficient evidence to clarify the impact of treatment interventions on PA was recently emphasised by the CBQC-launched international task force on PA, which explored whether measures of PA could qualify as efficacy end-points to support labelling claims around engagement in PA in COPD [13].

The aim of the present systematic review and meta-analysis was 2-fold. Firstly, to provide estimation of treatment effects of different types of pharmacological and non-pharmacological interventions for all available PA outcomes and secondly to provide recommendations for future study designs in patients with COPD. Some of the results of these studies have been previously reported in the form of abstracts [14, 15].

Methods

Identifying eligible studies

This review was registered in PROSPERO (CRD42021240146) and was conducted and reported in line with the Cochrane Handbook for Systematic Reviews of Interventions [16] and PRISMA guidelines [17]. Studies were originally obtained from a literature search performed up to November 2019 [18] and updated to identify published studies in July 2021 and January 2023. Records were identified through searches of 12 scientific databases. Eligibility was assessed through abstract and full-text screening. Only studies including people with COPD that used PA metrics as outcomes in controlled clinical studies were eligible. Records were included in full-text screening if a single reviewer deemed an abstract eligible, while rejection by two reviewers was required to exclude a study. The same protocol was followed during full-text screening. Additional methodological details are available in the supplementary material.

Data extraction

Data extraction was performed by a single author (D. Megaritis) using predesigned data extraction criteria. Two additional authors (N. Chynkiamis and E. Hume) checked extractions for accuracy. Disagreements were resolved through discussion or review by a third author (I. Vogiatzis). A list of extracted data is provided in the supplementary material.

Critical appraisal

The internal and external validity of the included studies was assessed by the PEDro scale (supplementary table S4) [19]. The certainty of evidence was assessed according to the GRADE approach (supplementary table S9). The risks of bias for all randomised controlled trials were assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (supplementary figure S1) [16]. Furthermore, the technical aspect of PA assessment was examined according to the latest recommendations [13] for the studies included in the meta-analyses.

Data analyses

Meta-analyses of the studies were performed using the software Review Manager (RevMan v.5.4; Cochrane Collaboration, Oxford, UK). All outcomes were continuous; means and standard deviations of the change scores were used to obtain the overall effect size of the outcomes of interest. Detailed criteria regarding data analyses and categorisation of the interventions are presented in the supplementary material. The overall effect size was represented as mean difference (MD) with 95% confidence interval (CI) when a single variable was employed in the literature and as standard mean difference (SMD) with 95% CI when multiple variables were employed; a $p<0.05$ was considered significant [20]. The heterogeneity of studies was assessed by the I^2 value [16]. Meta-analyses were presented when two or more studies with methodological and clinical homogeneity were identified employing the same type of intervention [16]. Only studies with a "good" (6–8) or "excellent" (9–10) PEDro score were included in the meta-analyses [21]. A random effects model was used for the meta-analyses in order to allow generalisation inference [22]. Further details about heterogeneity and sensitivity analyses are presented in the supplementary material. For the purpose of this review, PA behavioural modification interventions were defined as those that employed a step counter to measure daily step counts during the intervention period, as well as implementation of dynamic target goal setting, based on the step counts of a previous period, according to the principles of goal-setting and goals implementation theory [23]. Additional techniques (such as motivational interviewing) could be integrated as part of counselling sessions [24]. Studies including interventions which employed only a counselling component (without assessing PA or providing a dynamic target goal setting) were classified as PA counselling and hence considered as a different type of

intervention. Moreover, exercise-based interventions were considered those that provided exercise training as part of 1) an outpatient pulmonary rehabilitation programme, 2) a community-based programme or 3) a home-based telerehabilitation programme. With exercise training we refer to prescribed exercise at appropriately titrated intensity and frequency, for a minimum duration of 8 weeks [7]. However, when exercise therapy was integrated as part of a pulmonary rehabilitation programme, we cannot exclude that PA counselling strategies were not included. Finally, pharmacological interventions were considered as interventions that employed any kind of prescription medication, excluding over-the-counter medication.

Results

74 studies were considered eligible for inclusion in the systematic review and meta-analysis. The PRISMA flow diagram of the database searches is presented in figure 1. 69 studies were randomised controlled trials and five were non-randomised controlled studies. The characteristics of the included studies are presented in supplementary table S2.

Reasons for exclusion from the database

Reasons for exclusion are presented in supplementary table S6.

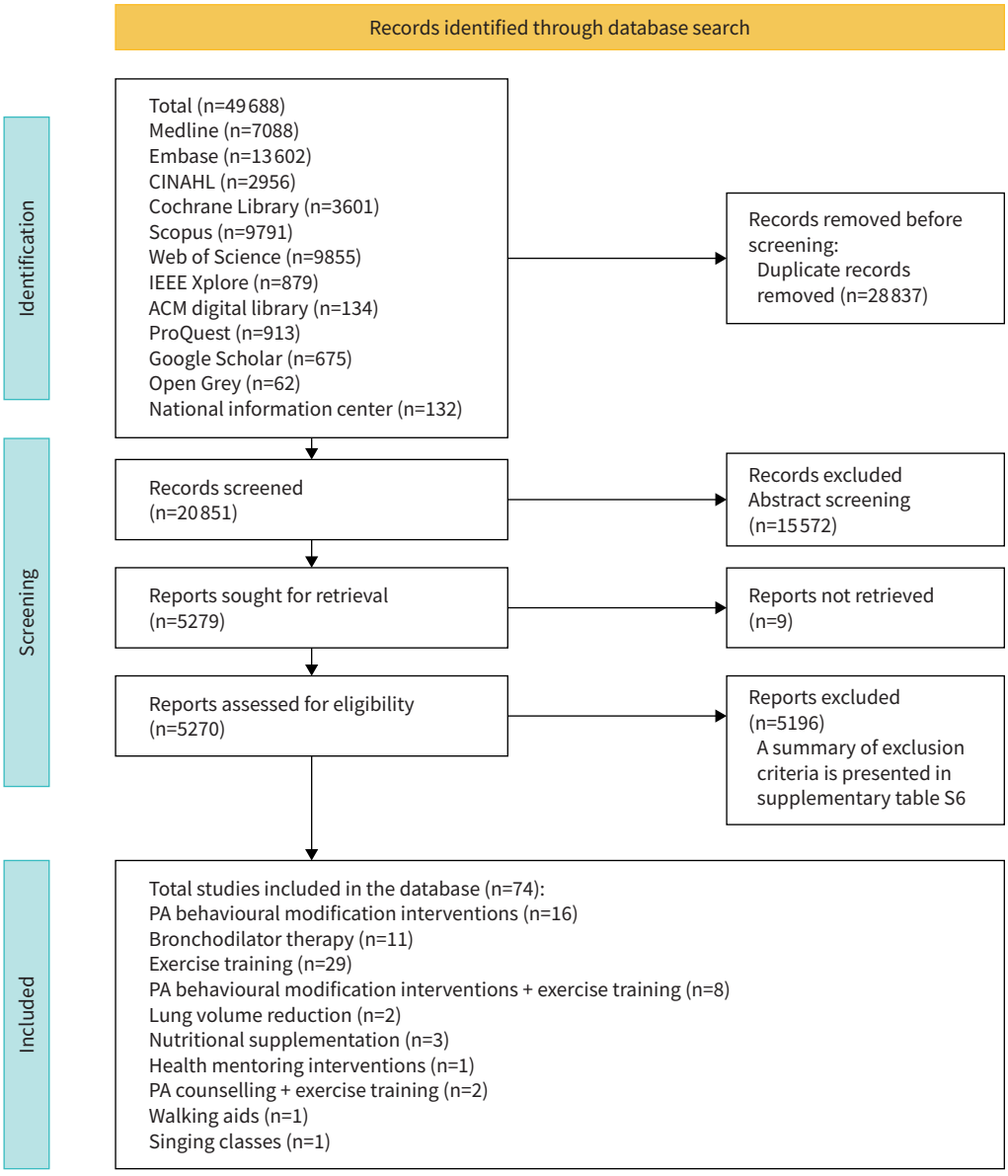

FIGURE 1 PRISMA 2020 flow diagram of the database. PA: physical activity.

Characteristics of the included participants and included studies

Although no type of prescribed drug was *a priori* excluded, only examples of pharmacotherapy with a known effect on lung function (*i.e.* bronchodilators) were found and included in the meta-analysis. Thus, pharmacological interventions included long-acting bronchodilators, namely long-acting muscarinic receptor antagonist (LAMA) and long-acting β-agonist (LABA)/LAMA fixed-dose combinations with an intervention duration ranging from 3 to 24 weeks. Non-pharmacological interventions included PA behavioural modification with an intervention duration from 4 to 24 weeks, exercise training with an intervention duration from 4 to 44 weeks and the addition of PA behavioural modification interventions to exercise training interventions with an intervention duration from 8 to 48 weeks, as well as single studies including PA counselling, lung volume reduction, nutritional supplementation and singing classes. The eligible studies included a total of 8140 patients (71% male); sample sizes ranged between 22 and 434 with a median of 53. The mean (range) age of the included patients was 66 (24–78) years. Predicted forced expiratory volume in 1 s (FEV_1 % predicted) ranged between 31% and 74%, with a mean of 55%. Disease severity ranged from Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I to GOLD stage IV, thus including all four GOLD stages [25]. Mean (range) of baseline steps/day was 4854 (1557–9186), categorising the population as sedentary [26]. All the included studies recruited patients with a minimum of 4 weeks of clinical stability, except for one study which enrolled patients immediately after hospitalisation for acute exacerbation of COPD (supplementary reference list: S28).

The database comprised individual interventions compared to usual care (UC), placebo or sham, as well as comparisons between different interventions (supplementary tables S2 and S8).

33 studies were included in the meta-analyses; all of the aforementioned studies comparing an intervention (namely PA behavioural modification, pharmacological, or exercise training interventions) with UC or placebo, and studies assessing the application of PA behavioural modification interventions alongside exercise training compared to exercise training alone were included in the meta-analyses.

Types of PA outcomes employed in interventional studies

The majority of interventional clinical trials assessing PA levels in COPD are limited to steps/day, daily walking time (DWT) and movement intensity (MI). Gait characteristics, such as stride length or frequency, and walking speed are scarce and were only assessed in one study alongside the use of walking aids (supplementary reference list: S95). 70 studies assessed steps/day, 13 studies assessed DWT, 11 studies assessed MI, eight studies assessed gait speed, one study assessed stride length and one study assessed stride frequency. As a result, only studies including steps/day, DWT and MI were included in the present meta-analyses. Furthermore, an explicit list of all the different types of PA outcomes is presented in supplementary table S2.

Critical appraisal

Supplementary table S4 provides the critical appraisal score using the PEDro scale of the included studies. The quality of the included studies ranged from poor to excellent (mean (range) score: 6.3 (1–10)). The GRADE certainty of evidence is presented in supplementary table S9.

Pre and post intervention effects on PA

The effects of the interventions on PA are presented in supplementary table S3.

Meta-analyses

Steps/day

PA behavioural modification interventions

PA behavioural modification interventions exhibited a positive effect on steps/day compared to UC (n=13 studies, 1535 participants, MD 1035 steps/day, 95% CI 576–1493, p<0.00001) (supplementary reference list: S24, S26–S32, S34–S38) (figure 2). Heterogeneity was moderate (I^2=61).

Bronchodilator therapy

Bronchodilators led to significant improvements in steps/day compared to a placebo (n=4 studies, 1176 participants, MD 396 steps/day, 95% CI 125–668, p=0.004) (supplementary reference list: S59, S62–S64) (figure 3). Heterogeneity was not important (I^2=26).

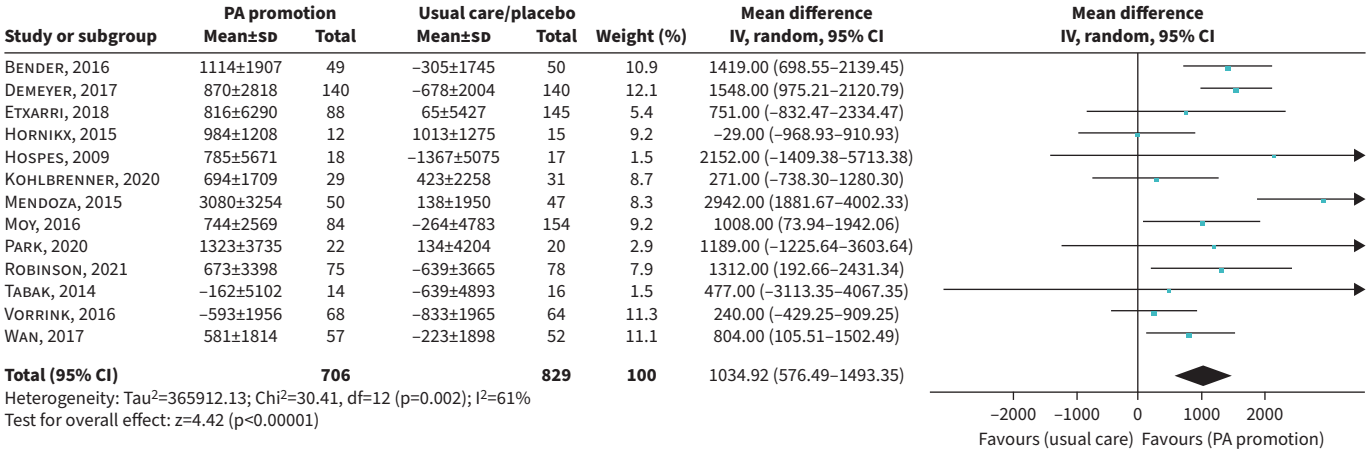

FIGURE 2 Effect size of physical activity (PA) behavioural modification interventions (PA promotion) *versus* usual care on steps/day.

Exercise training as part of a structured or a community-based pulmonary rehabilitation programme or telerehabilitation

Exercise training did not exhibit significant improvements on steps/day compared to UC (n=8 studies, 737 participants, MD 287 steps/day, 95% CI −254–827, p=0.30) (supplementary reference list: S41–S43, S47, S51, S53, S56, S57) (figure 4). Heterogeneity was moderate (I^2=60).

Application of PA behavioural modification alongside exercise training

PA behavioural modification strategies alongside exercise training showed significant improvements on steps/day compared to exercise training alone (n=6 studies, 659 participants, MD 679 steps/day, 95% CI 93–1266, p=0.02) (supplementary reference list: S68–S70, S73–S75) (figure 5). Heterogeneity was substantial (I^2=69).

Daily walking time

PA behavioural modification interventions

PA behavioural modification interventions exhibited a positive effect on DWT compared to UC (n=2 studies, 307 participants, MD 11.84 min, 95% CI 5.51–18.17, p=0.0002) (supplementary reference list: S26, S28; supplementary figure S2). Heterogeneity was substantial (I^2=83).

Exercise training

Exercise training exhibited a non-significant effect on DWT compared to UC (n=2 studies, 120 participants, MD 3.56 min, 95% CI −16.13–23.25, p=0.72) (supplementary reference list: S42, S44; supplementary figure S3). Heterogeneity was substantial (I^2=74).

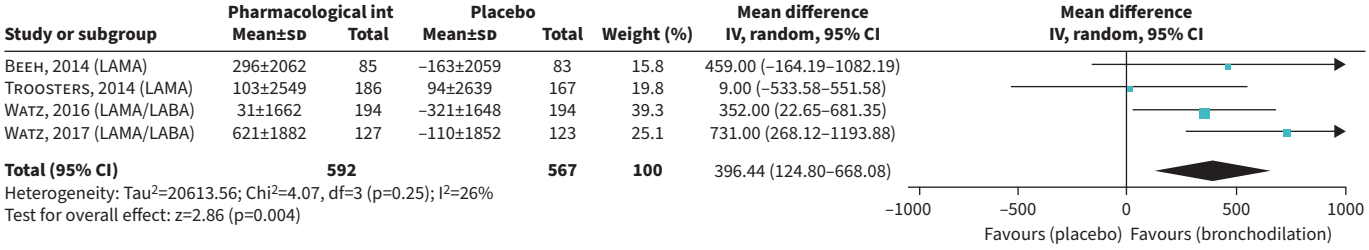

FIGURE 3 Effect size of pharmacological interventions *versus* placebo on steps/day. Long-acting bronchodilator type indicated next to the publication year. int: intervention; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting β-agonist.

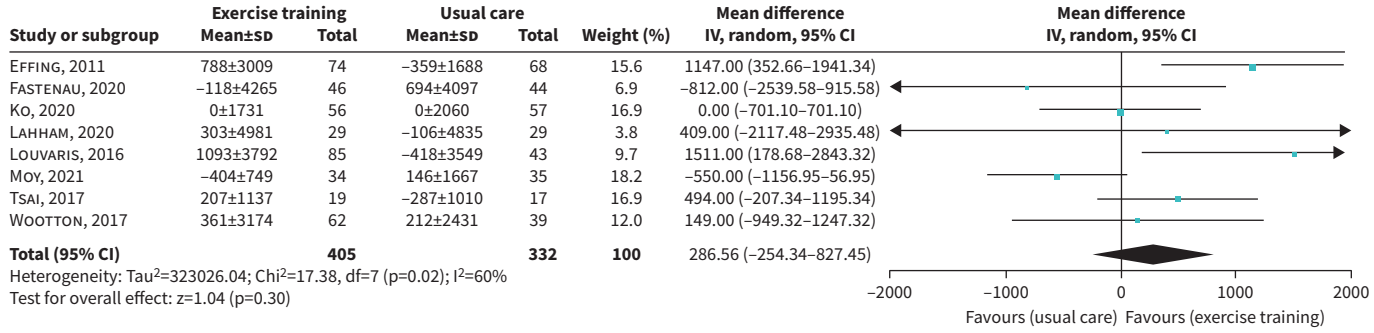

FIGURE 4 Effect size of exercise training (as part of an outpatient or community-based pulmonary rehabilitation programme or telerehabilitation) compared to usual care on steps/day.

Movement intensity

PA behavioural modification interventions

PA behavioural modification interventions exhibited a non-significant effect on MI compared to UC (n=2 studies, 307 participants, SMD 0.29, 95% CI −0.84–1.42, p=0.61) (supplementary reference list: S26, S28; supplementary figure S4). However, heterogeneity was substantial (I^2=88).

Exercise training

Exercise training exhibited a positive but non-significant effect on MI compared to UC (n=4 studies, 308 participants, SMD 0.49, 95% CI −0.03–1.00, p=0.07) (supplementary reference list: S40, S42, S44, S57; supplementary figure S5). However, heterogeneity was substantial (I^2=77).

Differences across interventions

PA behavioural modification interventions led to a 2-fold greater increase in steps/day compared to bronchodilator therapy (supplementary table S7).

Technical aspects of the PA assessment

The studies included in the present meta-analyses partly fulfilled the recommendations for PA assessment identified by Demeyer *et al.* [13]. The inclusion of at least 7 days of PA assessment was fulfilled in 62% of studies, and the requirement for included participants to have 4 days with at least 8 h of wearing time was fulfilled in 25% of studies. Supplementary table S5 provides information about the technical aspects of the PA outcomes according to the latest recommendations [13] for the studies included in the meta-analyses.

Interventions not qualified for meta-analyses

Several studies reported on other interventions compared to UC (supplementary table S3). For example, surgical lung volume reduction (supplementary reference list: S84) did not exhibit significant effects on steps/day compared to UC; however, neuromuscular electrical stimulation (supplementary reference list: S45) did exhibit significant favourable effects. The addition of non-invasive ventilation (supplementary reference

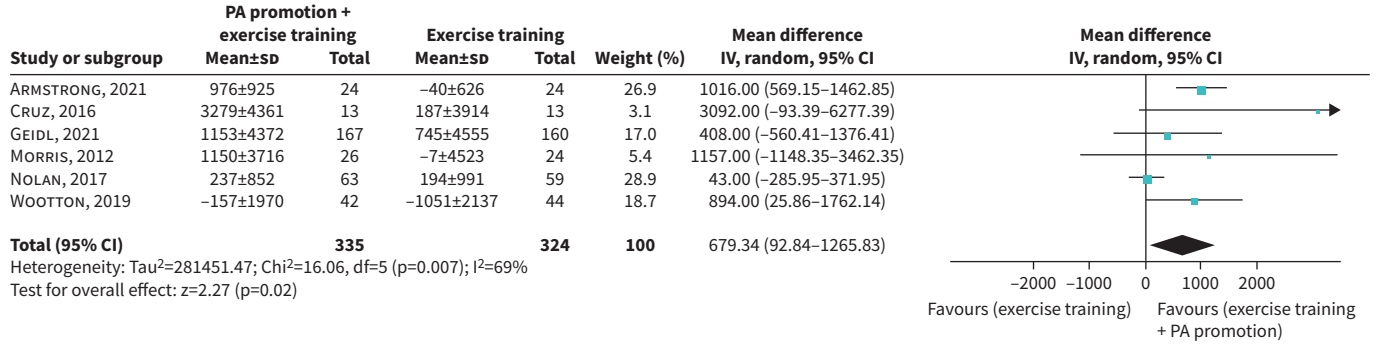

FIGURE 5 Effect size of application of physical activity (PA) behavioural modification alongside exercise training compared to exercise training alone on steps/day.

list: S89) and beetroot juice (supplementary reference list: S93) to exercise training exhibited significant improvements in PA. In contrast, the addition of PA counselling (without pedometer or goal setting) (supplementary reference list: S85, S86) to exercise training exhibited inconsistent effects across studies.

Discussion

Main findings

PA behavioural modification and pharmacological interventions lead to significant improvements in steps/day compared to a control group (UC or placebo), while exercise training interventions alone do not necessarily translate into significant improvements in PA outcomes. Compared to bronchodilator therapy, PA behavioural modification interventions induced a 2-fold greater increase in steps/day.

Novelties

The study incorporates new evidence on the pooled effects of pharmacological and non-pharmacological interventions on PA outcomes in patients with COPD, thereby refining the results of a previous meta-analysis which suggested that improvements in PA have not been systematically demonstrated following any type of intervention in COPD [11]. Furthermore, in light of the uncertainty communicated [10] regarding the effectiveness of interventions targeting PA as a COPD clinical trial outcome, the present meta-analysis supports the positive effects of PA behavioural modification interventions on specific PA metrics. Moreover, the "white paper" issued by the CBQC [13] highlighted the need to identify PA end-points for regulatory qualification; thus our meta-analysis provides an estimation of pharmacological treatment effects on steps/day in patients with COPD. This is particularly relevant as the Mobilise-D consortium, funded by the Innovative Medicines Initiative Joint Undertaking (a collaboration between the EU and European Federation of Pharmaceutical Industries and Associations (EFPIA)), has proposed a qualification strategy in consultation with the EMA for the use of mobility outcomes as biomarkers for monitoring mobility in clinical trials and for making marketing authorisation of drugs for different disease entities including COPD [27, 28]. Furthermore, our work shows that the mean effect of bronchodilator therapy compared to placebo (a difference of 396 steps/day) is within the reported minimal clinically important difference (MCID) (350–1100 steps/day) [29]; thus, this effect is not only statistically significant but likely clinically meaningful. In the context of pharmacological interventions lacking a validated specific MCID, we deemed that the MCID identified by Teylan *et al.* [29] (350–1100 steps/day) in response to a PA behavioural modification intervention would be more appropriate for assessing the effects of pharmacological interventions because this MCID was anchor-based and identified through medical events and deterioration in COPD. It is known that successful pharmacological interventions adjust/reduce clinical events [30, 31]. Thus, the pooled improvement in PA in the present meta-analysis can be considered clinically meaningful. In contrast, the MCID identified by Demeyer *et al.* [32] assessing the effect of pulmonary rehabilitation on steps/day was non-anchored potentially making it inapplicable to pharmacological interventions. Moreover, the present study provides methodological and clinical suggestions regarding the use of PA outcomes in clinical studies.

Efficacy of interventions

To compare the efficacy across different interventions in the meta-analyses, steps/day were used as this was the only outcome assessed across all types of interventions. Our finding that PA behavioural modification interventions increased steps/day compared to UC (by 1035 steps/day) is consistent with both MCIDs previously reported (600–1100 steps/day [32] or 350–1100 steps/day [29]). Moreover, bronchodilator therapy led to significantly increased steps/day in patients with COPD (by 396 steps/day) compared to a placebo, likely by reducing exertional breathlessness, improving lung function, decreasing dynamic hyperinflation and leading to lower exacerbation rate compared to placebo [33]. This reinforces the notion that there are significant (but limited) improvements in PA when lung function and symptoms are improved by pharmacological therapies. These findings further support our evidence that the amelioration of lung function facilitates improved PA. Therefore, a multimodal approach including both PA behavioural modification strategies and bronchodilators could constitute a more efficacious intervention in improving PA [33]. In contrast, exercise training interventions alone exhibit varying results and, thus, cannot be deemed optimal for improving PA outcomes in patients with COPD. Thus, pulmonary rehabilitation programmes combining exercise training interventions alongside PA behavioural modification strategies may optimise the effects of pulmonary rehabilitation on PA outcomes compared to pulmonary rehabilitation programmes featuring exercise training alone [34].

Critical appraisal (quality) of the studies

We used the 11-domain PEDro scale to rate the methodological quality of the included studies. The quality of the data ranged from very poor to excellent. The profound variability can be attributed to the inclusion of conference abstracts, which did not present adequate information and therefore scored poorly in the

PEDro scale. The studies included in the meta-analyses were those representing higher scores in the PEDro scale (either "good" (6–8) or "excellent" (9–10) PEDro scores), thereby presenting adequate quality/certainty of evidence. Variability could also be attributed to the nature of the different interventions, *i.e.* clinical trials employing pharmacological interventions compared to placebo are double or triple blinded, resulting in higher critical appraisal scores. Studies employing PA behaviour modification, counselling or exercise training could not be patient or therapist blinded, resulting in a lower score. In some cases, step counters were provided to the control group acting as placebo (supplementary reference list: S24, S38, S39), although patients were not formally blinded.

Furthermore, the certainty of evidence (*i.e.* records included in the meta-analyses) was assessed according to the GRADE approach. PA behavioural modification and pharmacological interventions exhibited high certainty due to significant and consistent responses across all studies, strong methodology and no evidence of risk of publication bias. Exercise training interventions exhibited low/moderate certainty due to inconsistent results and modes of delivery of the interventions, as well as suspected publication bias (supplementary table S9).

Limitations

Clinical and methodological heterogeneity identified in the literature was the most profound limitation. Despite both methodological and clinical heterogeneity, meta-analyses were undertaken in studies assessing identical variables and study designs. Search for MI did not include the intensity of PA measured by metabolic equivalents since there is no standardised categorisation for the intensity of PA; therefore, a meta-analysis would not be feasible for those variables.

Clinical and methodological gaps in the literature to optimise future study designs

Half of the studies included in the present review exhibited clinical heterogeneity in patient baseline characteristics, assessed by the PEDro score (supplementary table S4). Clinical heterogeneity between the different groups was mostly attributed to differences in steps/day within or exceeding the MCID (600–1100 steps/day) [32], potentially affecting the response to a given intervention. Thus, future studies should account/stratify for baseline PA levels amongst other variables, when randomising patients to intervention or UC groups. Furthermore, methodological heterogeneity was profound, as only a minority of studies included in the meta-analyses fulfilled the minimum number of days required for PA assessment, as per the latest recommendations [13]. In particular, the second criterion (*i.e.* a minimum of 4 valid days with >8 h of wearing time) was only fulfilled in a quarter of the studies included in the meta-analyses. Therefore, future studies should employ a more sophisticated data analysis plan incorporating the latter recommendations, to increase homogeneity and gain an extensive understanding of the effects of interventions on PA outcomes, to progress towards attainment of regulatory approval.

Outcomes such as steps/day and DWT (*i.e.* volume of PA) might be better suited to reflect improvements following PA behavioural modification interventions, as the primary aim of these interventions is to increase steps/day (a measure of volume of PA rather than its intensity). Additionally, PA performed during the intervention period is performed at an intensity resembling community walking and not necessarily during aerobic high-intensity activity [35].

Our meta-analysis on four pharmacological interventions *versus* placebo provides an estimation of a significant treatment effect, equivalent to 396 (125–668) steps/day, alongside the improvement of lung function in all four studies (supplementary reference list: S59, S62–S64). Thus, steps/day as a primary or secondary outcome appears to exhibit high sensitivity and convergent validity [13, 36]. Consequently, steps/day capturing a crucial and patient-centred outcome could be used to power future pharmacological trials.

Furthermore, future pharmacological studies are needed to establish an intervention-specific MCID for PA outcomes anchored against: 1) improvement in lung function with bronchodilator therapy compared to placebo and 2) clinical events (exacerbations, hospitalisations, clinical deterioration). Moreover, the convergent validity of PA outcomes needs to be assessed on a patient level in future pharmacological trials. This can be accomplished by assessing the effect of the intervention on the primary outcome (*e.g.* lung function, exercise tolerance) in relation to the effect on PA outcomes (*e.g.* steps/day). Finally, assessing the sensitivity of PA outcomes following pharmacological interventions across different sub-types of COPD patients would be desirable [37], since comorbidities are becoming increasingly recognised as substantial causes of adverse clinical events in COPD. Thus, novel PA biomarkers may be qualified to identify the course of disease progression *via* a responder analysis (improvement or deterioration of PA) [38]. Following the above recommendations, PA outcomes might receive favourable consideration to support labelling claims [13] and the marketing authorisation of drugs [27].

Novel PA outcomes related to pace and rhythm [18] should be validated, especially against pharmacological interventions, which have been shown to successfully and consistently improve PA without primarily aiming to improve this outcome. Whether pharmacological targets beyond the pulmonary system (*i.e.* muscle function) may lead to enhanced PA remains to be further investigated. A recent study employing Selective Androgen Receptor Modulation (SARM) failed to exhibit significant improvements in objectively measured PA and experience of PA [39]. Additionally, results regarding improvements in PA following exercise training interventions, as reported by commonly implemented PA outcomes such as steps/day or DWT, are not consistent, exhibiting variable effects. This may be due to limitations of the aforementioned outcomes not capturing the full spectrum of mobility/PA. Novel PA outcomes may complement the suite of objectively assessed outcome measures to capture PA and mobility and may be more sensitive to change and better suited to detect improvements in PA following exercise training interventions which are known to improve functional capacity.

Conclusions

In patients with COPD, PA behavioural modification and pharmacological interventions lead to significant improvements in steps/day compared to control and placebo groups, respectively. In light of a biomarker qualification process, steps/day could potentially be a useful biomarker for research and medicine development, as this meta-analysis found steps/day to be a sensitive variable in response to pharmacological interventions. Additionally, PA outcomes are needed to capture patient-centred effects following an intervention and assess an outcome that is independent of performance in a clinical visit (*e.g.* 6-min walk test or spirometry). Finally, assessing the MCID of PA outcomes in response to pharmacological interventions (anchored against clinical events/deterioration) in large-scale clinical trials, as well as the convergent validity of PA outcomes, may accelerate qualification as potential biomarkers and efficacy end-points for regulatory approval.

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Author contributions: D. Megaritis and I. Vogiatzis led the systematic review and meta-analysis. D. Megaritis, A.M. Polhemus, H. Watz, T. Troosters and I. Vogiatzis developed the study protocol. D. Megaritis and A.M. Polhemus conducted the electronic database searches and the additional searches. D. Megaritis, E. Hume, N. Chynkiamis, A.M. Polhemus and the Mobilise-D COPD Review group screened titles, abstracts and full texts. D. Megaritis extracted the relevant data. E. Hume and N. Chynkiamis performed the quality assessment of the extracted data. D. Megaritis performed the meta-analyses. D. Megaritis and I. Vogiatzis drafted the manuscript. All authors contributed to revising the manuscript and approved the final version. The Mobilise-D consortium approved the manuscript.

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