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Objectively measured physical activity as a COPD clinical trial outcome

Short title: Objective PA as a COPD clinical trial outcome

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Summary conflict of interest statements

Chris Burtin has no conflict of interest.

Divya Mohan is a former employee and shareholder of GSK at the time the work was conducted; she is a current employee and shareholder of Genentech/Roche.

Thierry Troosters has no conflict of interest.

Henrik Watz has no conflict of interest.

Nicholas S Hopkinson has no conflict of interest.

Judith Garcia-Aymerich reports other from AstraZeneca, other from Esteve, other from Chiesi, other from Menarini, outside the submitted work.

Marilyn L Moy has no conflict of interest.

Ioannis Vogiatzis has no conflict of interest.

Harry B Rossiter has no conflict of interest.

Sally Singh has no conflict of interest.

Deborah D Merrill has no conflict of interest.

Alan Hamilton is an employee of Boehringer Ingelheim (Canada) Ltd.

Stephen I Rennard was an employee of AstraZeneca during the preparation of this manuscript and has since consulted with GSK and BerGenBio.

Malin Fageras is a full time employee of AstraZeneca.

Stefano Petruzzelli is an employee of Chiesi Farmaceutici S.p.A.

Ruth Tal-Singer is a former employee and current shareholder of GSK and reports consulting fees from Immunomet.

Erin Tomaszewski is a full time employee of AstraZeneca.

Solange Corriol-Rohou is an employee of AstraZeneca

Carolyn L Rochester is participating in a clinical trial for COPD treatment funded by Astra-Zeneca, Inc., and has participated previously in clinical COPD trials funded by GSK-Pharmaceuticals, Inc. and Boehringer Ingelheim Pharmaceuticals. She has also participated on COPS scientific advisory boards of GSK-Pharmaceuticals, Inc. and Boehringer Ingelheim in the past. She served as the chair of the American Thoracic Society on Pulmonary Rehabilitation from 2015-2017.

Frank C Sciurba has no conflict of interest.

Richard Casaburi has no conflict of interest.

William Man reports personal fees from Jazz Pharmaceuticals, personal fees from Mundipharma, personal fees from Novartis, grants from Pfizer, non-financial support from GSK, grants from National Institute for Health Research, grants from British Lung Foundation, outside the submitted work.

Rob Van Lummel is owner and chairman of McRoberts.

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Heleen Demeyer has no conflict of interest.

Martijn A Spruit has no conflict of interest.

Anouk Vaes has no conflict of interest.

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Abbreviation list

CBQC: COPD Biomarker Qualification Consortium

COPD: Chronic Obstructive Pulmonary Disease

DDT: Drug Development Tool

EMA: European Medicines Agency

FDA: Food and Drug Administration

IQR: Interquartile range

LABA: Long-acting beta-2 agonist

LAMA: Long-acting muscarinic antagonist

MID: Minimal important difference

MVPA: moderate to vigorous physical activity

PA: Physical activity

PAL: Physical activity level

PR: Pulmonary rehabilitation

RCT: Randomized Controlled Trial

Take-Home Point

Research Question
What is the available evidence on the efficacy and/or effectiveness of various interventions to enhance objectively measured physical activity in patients with COPD, taking into account minimal preferred methodological quality of physical activity assessment?

Results

37 of 110 (34%) identified studies fulfilled the methodological criteria; Few studies show an increase beyond the proposed minimal important change of 600-1100 daily steps, indicating that enhancing physical activity levels is a challenge.

Interpretation

Only a third of clinical trials measuring objective physical activity in people with COPD fulfilled the pre-set criteria regarding physical activity assessment; studies showed variable effects on physical activity even when investigating similar interventions.

Abstract

Background: Reduced physical activity is common in COPD and is associated with poor outcomes. Physical activity is therefore a worthy target for intervention in clinical trials, however, trials evaluating physical activity have used heterogeneous methodologies.

Research question: What is the available evidence on the efficacy and/or effectiveness of various interventions to enhance objectively measured physical activity in patients with COPD, taking into account minimal preferred methodological quality of physical activity assessment?

Study design and Methods: In this narrative review, the COPD Biomarker Qualification Consortium (CBQC) task force searched three scientific databases for articles that reported the effect of an intervention on objectively-measured physical activity in COPD. Based on scientific literature and expert consensus, only studies with ≥7 measurement days and ≥4 valid days of ≥8 hours of monitoring were included in the primary analysis.

Results: 37 of 110 (34%) identified studies fulfilled the criteria, investigating the efficacy and/or effectiveness of physical activity behavior change programs (n=7), mobile health or eHealth interventions (n=9), rehabilitative exercise (n=9), bronchodilation (n=6), lung volume reduction procedures (n=3) and other interventions (n=3). Results are generally variable, reflecting the large variation in study characteristics and outcomes. Few studies show an increase beyond the proposed minimal important change of 600-1100 daily steps, indicating that enhancing physical activity levels is a challenge.

Interpretation: Only a third of clinical trials measuring objective physical activity in people with COPD fulfilled the pre-set criteria regarding physical activity assessment. Studies showed variable effects on physical activity even when investigating similar interventions.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) are generally characterized by decreased physical activity (PA) and a more sedentary lifestyle compared with age-matched peers[1], which has been linked to multiple unfavorable health outcomes[2-6]. Therefore, the Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) states that home PA monitoring may be more relevant to prognosis than episodic in-clinic exercise capacity evaluation[7]. Additionally, PA is an important feature of daily life. It can be directly and unobtrusively measured during daily life and is a relevant patient-centered outcome[8].

PA is an increasingly used outcome measure in clinical trials, not only investigating interventions that directly target PA – e.g., PA coaching and pulmonary rehabilitation (PR) – but also bronchodilators, endoscopic lung volume reduction, nutritional interventions, long-term oxygen therapy and non-invasive ventilation, amongst others[9]. Regulatory agencies, including the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have accepted activity measures for approval of medicines across a range of diseases, for example time in moderate to vigorous physical activity (MVPA) for pulmonary arterial hypertension and 95th percentile of stride velocity in Duchenne muscular dystrophy. However, there is no objective PA measure qualified as Drug Development Tool (DDT) in COPD. The PROactive 'hybrid' tools (i.e., classical questionnaire items combined with activity monitor readouts) developed by the IMI PROactive consortium[8] is accepted by EMA to capture PA as a patient reported outcome; this is different from objectively assessed PA captured solely by an activity monitor.

Objective PA assessment is not subject to recall bias, a clear advantage over PA questionnaires[1,10], is more sensitive to change[11] and allows for collection of more granular data in a real-world setting providing insight into the extent to which people utilize their exercise capacity (typically assessed with a six-minute walk test or cardiopulmonary exercise test). However, objective PA assessment is

challenging since validity and reliability depend largely on the chosen monitoring device and the standardization of assessment..

This narrative review describes efficacy and/or effectiveness of various interventions to enhance different objectively measured endpoints that capture PA in COPD patients, based on a systematic literature search. It has specific attention to methodology used to assess PA, including only studies that prospectively accepted only PA measurements with at least four valid days of more than 8 hours of measurement within at least one week of measurement.

Methods

Consortium

Within the COPD Biomarker Qualification Consortium (CBQC) framework[12], a Task Force of experts in PA behavior was established, which aimed to explore the potential of objective PA assessment in daily life as DDT in trials evaluating novel therapies for COPD patients. Please see online supplement for details.

Search strategy

We searched PUBMED, Physiotherapy Evidence Database (PEDro) and The Cochrane Library for articles published from inception until September 25, 2020. The used search strategy is presented in the online supplement.

Inclusion and exclusion criteria

Based on currently available literature[13,14] and expert opinion, the Task Force reached consensus on minimal criteria to define minimal preferred methodological quality of objective PA assessment, regardless of device used. PA should be measured over ≥7 days, with ≥4 consecutive or nonconsecutive days meeting the criterion of a valid day. A measurement day is considered valid when ≥8 hours of measurement time is reached. Invalid days should be excluded from analysis.

English-language studies that reported any intervention's effect on objectively measured PA in COPD patients were identified. Included studies needed to report original data; randomized controlled trials (RCTs), controlled clinical trials as well as single-group intervention studies were eligible.

Studies that fulfilled these expert consensus-based criteria or studies that met these criteria in ≥80% of participants based on thorough description of wearing time are included in this manuscript.

Results of studies that investigated PA intervention effects but did not meet measurement criteria are presented in the online supplement.

Study selection

Two reviewers (CB and AWV) each performed half the title and abstract screening based on the listed criteria. Title and abstract were screened simultaneously to increase screening efficiency. Full-text screening was performed by the two reviewers for all papers. Any discrepancies were discussed and a consensus was reached to include or exclude a study.

Data extraction

Information on study design, sample size, patient characteristics, pulmonary function, details of PA assessment, intervention and PA outcomes were extracted from articles (see Table 1). Data are reported as mean ± standard deviation or mean (95% confidence interval), unless specified otherwise. Mean relative change (percentages of baseline) between pre and post measurements of PA outcomes were extracted or calculated by reviewers to construct eFigure 1.

Quality appraisal

Risk of bias of RCTs included in the primary analysis was assessed using the PEDro scale (Table 2) [15].

The ROBINS-I tool was used to assess bias risk of single group studies[16].

Results

We identified 6266 articles with our search strategy and removed 128 duplicates (Figure 1). Title and abstract screening identified 153 studies for full-text screening. After excluding 43 articles that did not measure PA in an objective manner, 110 were screened for PA assessment criteria. Thirty-seven studies fulfilled all criteria and were analyzed (Table 1).

Outcomes are described according to intervention type, i.e. activity monitor-based PA behavior change interventions (n=7), mobile health (mHealth) and electronic health (eHealth) interventions (n=9), exercise-based interventions (n=9), bronchodilator use (n=6), lung volume reduction procedures (n=3), singing classes (n=1), nutritional supplementation (n=1), elastic taping of the chest (n=1) and health monitoring intervention (n=1).

Methodological quality of RCTs was moderate to good (PEDro scale scores: 5 to 9). Items frequently unmet were subject blinding, therapist blinding, assessor blinding, concealed allocation and performance of intention to treat analysis. Overall, pharmaceutical trials showed higher scores than exercise or behavior change trials, as blinding of participants and therapists is inherently complex in the latter trials. Bias risk in single group studies ranged from low (n=3)[17-19] through moderate (n=3)[20-22] to serious (n=2)[23,24].

PA behavior change programs

Six RCTs[25-30] and one single group study[20] evaluated effects of PA behavior change programs on PA. PA was assessed using ActiGraph GT3+[20,25,30], Dynaport MoveMonitor[26,27], SenseWear Armband[26,28] and GENEactiv accelerometer[29]. PA was primary outcome in six studies[20,25-28,30].

Randomized controlled trials

Two studies adding a face-to-face behavior change intervention – mainly based on activity monitor feedback, goal setting, problem solving and action planning - to standard PR failed to demonstrate significant additional improvement in daily step counts[26,28], or time in MVPA[26,28]. Similarly, no effects were observed after 6-months of follow-up[28].

A randomized controlled feasibility study comparing a 12-week pedometer-based PA intervention – using a behavioral change model that included 20 behavior change strategies[31] - with standard PR reported no significant changes in either group[25]. Between-group analysis was not performed due to lack of power.

Another study evaluated efficacy of telephone health coaching based on the Social Cognitive Theory[32] to promote PA, including pedometer feedback[29]. In mild to moderate COPD patients, 4 telephone sessions over 11 weeks and postal information at weeks 16 and 24 did not improve time spent in MVPA compared to usual care after 12 months[29].

One study examining effects of pedometer feedback, goal setting and problem solving techniques in COPD participants after hospitalization for a severe exacerbation, showed no significantly higher PA increase compared to usual care[27].

One study demonstrated that a health mentoring intervention, consisting of 16 phone calls to support self-management in health behaviors (including PA), successfully improved PA compared to usual care, though only in COPD participants reporting lower anxiety or depression levels (no absolute data provided)[30].

Non-randomized studies

A feasibility study combining a behavior change intervention focused on activity monitor feedback and individual activity recommendations with conventional PR did not improve daily step counts or time spent in MVPA[20].

mHealth/eHealth interventions

Seven RCTs[33-39] and 2 single group studies[18,23] examined efficacy of internet- and computer-based (eHealth) and/or mobile phone based (mHealth) interventions to improve PA in COPD participants. Studies used SenseWear Armband[33], Actigraph GT3x[34,35,38] Dynaport MoveMonitor[34] or Omron HJ-720 ITC pedometer[18,23,36,37,39] to quantify PA. PA was included as primary outcome in three[18,33,34].

Randomized controlled trials

RCTs concluded that telecoaching interventions, including real-time pedometer feedback, personalized goal setting and problem solving and motivational messages from a research teamresulted in significantly greater PA compared with a control group after 3-4 months, without[34] or with smartphone use[36]. After 12 weeks, Demeyer et al. reported a 1469 step between-group difference (973-1965 steps; 29% from baseline) – which is within or exceeds the proposed MID range of 600 to 1100 steps for this population – and a 10 minute increase (6-14 minutes; 44% from baseline) of MVPA per day in a semi-automated comprehensive smartphone-based telecoaching program compared to usual care[34]. After 4 months, Moy et al. found a between-group daily step count increase of 779 daily steps (241-1317 daily steps) of an internet-mediated pedometer-based walking program compared to usual care[36].

Another study investigated efficacy of a six-month smartphone-based self-management intervention – including pedometer feedback and self-monitoring of PA – added to a minimal control intervention, consisting of four education and four supervised exercise sessions in the first month and an individualized home exercise prescription[38]. The intervention showed significantly better activity counts per wear time improvement (216±103 to 275±100) and time spent in MVPA (3±2% to 5±3% of wear time), but not daily steps, inactive time and time spent in low-intense activities, compared to the control group (259±106 to 259±111; 4±2 to 4±3 respectively).

There were conflicting findings in studies on long term effects. One study showed no significant difference between 12-month home-based maintenance tele-rehabilitation – including an individualized action plan for walking, arm and leg exercises, remotely monitored exercise sessions and frequent health professional contact - and hospital-based outpatient maintenance PR in

preserving beneficial effects of an initial two-month rehabilitation program in time spent in sedentary, light, lifestyle and moderate intensity PA. The pattern of PA change parameters over 12 months was significantly better compared to usual care (no mean difference provided)[35]. In contrast, after a three/four month internet-mediated, pedometer-based walking intervention, increases in daily step count were not maintained compared to the control group 3-9 months after the intervention[37,39]. Similarly, a real-life study investigating a similar mHealth intervention performed by physiotherapists working in primary care did not show improvement in PA over 12-months in COPD participants who finished PR compared to usual care[33].

Non-randomized studies

Two single group trials – preceding an above-mentioned RCT from the same research team[36] – showed that telecoaching interventions based on real-time pedometer feedback[36], personalized goal setting and motivational messages significantly improved step count[18,23].

Exercise-based interventions

Six RCTs[40-45] and three single-group studies[19,21,24] determined efficacy of exercise-based interventions in enhancing PA in COPD participants. Three studies used SenseWear Armband[21,44,45], one used Dynaport Movemonitor[40], and two used Actigraph GT3X [41,42], while other studies used less known activity monitors, including the Personal Activity Monitor[43], RT3[46] and Ciro or MOX Activity Monitor[19]. PA was primary outcome in seven studies[19,21,24,40-43].

Randomized controlled trials

A walking program was evaluated in two RCTs[40,43]. A 10-week home-based walking program combined with center-based exercise training resulted in greater increase in time spent active (26 min/day, 7-45 min/day) and time spent in low intensity activities (19 min/day, 5-33 min/day), but not time spent in MVPA, compared with standard care[43]. An urban training program, combining behavioral strategies

with unsupervised outdoor walking, only improved daily step count at 12 months in a subsample of intervention-adherent participants (957 steps/day, 184-1137 steps/day compared to usual care), but was ineffective in the intention to treat sample[40].

In mild COPD patients, a home-based PR program consisting of walking exercise and resistance training using available equipment and telephonic exercise participation motivational support failed to enhance PA outcomes compared to usual care[45].

One study demonstrated that COPD participants performing high-intensity interval exercise training as part of PR significantly vs. usual care increased daily step count (from 4043±2484 to 5136±2866 steps/day versus from 3871±2526 to 3453±2493 in usual care) and time spent in light (from 135±62 to 160±67 min/day versus from 144±56 to 137±65 in usual care) and moderate intensity activities (from 13±15 to 20±19 min/day versus from 12±19 to 12±19 in usual care), which persisted for at least 12 weeks after rehabilitation[41].

Another study compared an eight-week home-based rehabilitation program –aerobic exercise (mainly walking), resistance training using available equipment and telephonic motivational support for exercise participation – with a standard outpatient program[44]. No between-group differences were found in sedentary behavior, MVPA, energy expenditure or daily steps.

An exercise-specific self-efficacy enhancing intervention with upper body resistance training resulted in a modest light PA increase after 4 months compared to a control group receiving health education with upper body resistance training or gentle chair exercises, though these changes were not sustained at 12-months and no significant changes were found in MVPA or sedentary time[42].

Non-randomized studies

A single group study found significant reduction in PA (from 3806±1596 to 2817±1968 steps per day, p=0.039) after a 12 months unsupervised, home-based treadmill walking program[21].

Two studies did not demonstrate significant PA increases after conventional PR[19,24], although one of these studies found that a participant subgroup (participants with higher body mass index and lower time spent in MVPA at baseline) significantly decreased sedentary time and increased time spent in light activities and MVPA[19].

Bronchodilators

The effect of bronchodilators on PA in COPD has been evaluated in six randomized, placebo-controlled studies[47-52]. PA was assessed using Sensewear Pro 3 Armband[47-50] or Dynaport MoveMonitor[51,52]. PA was primary outcome in one study[50].

Randomized controlled trials

In one study, inhaled aclidinium, a long-acting muscarinic antagonist (LAMA), resulted in increased MVPA time (10 min/day, 2-18 min/day) and daily active energy expenditure (55 kcal/day, 13-96 kcal/day) compared with placebo. However, step count and physical activity level (PAL) did not differ significantly from placebo[47]. Another study also failed to show significant differences in PA between LAMA therapy (tiotropium) and placebo in moderate COPD participants naive to maintenance therapy[48].

Watz et al. demonstrated benefits of the long-acting beta-2 agonist (LABA) indacaterol on PA[49]. Indacaterol significantly improved daily step count (722 steps/day, no confidence interval provided) and time spent in MVPA (28 min/day) compared to placebo.

In two studies investigating LABA/LAMA combination therapy, Watz et al. found significant benefits on PA[50,52]. Indacaterol/glycopyrronium significantly increased daily step count (358±2458 steps/day) but not daily time spent in MVPA, compared to placebo[50]. Aclidinium/formoterol significantly increased daily step count (731 steps/day, no confidence interval provided) and daily time spent in MVPA (10 min/day), compared to placebo[52]. Recently, among COPD patients participating in a self-

management behavior-modification program, addition of tiotropium or tiotropium/olodaterol, with or without exercise training, did not result in additional daily steps compared with placebo treatment[51].

Non-randomized studies

None

Lung volume reduction procedures

One study evaluated lung volume reduction surgery's impact on PA in COPD participants[17], and two studies evaluated effects of endoscopic lung volume reduction using endobronchial coils or valves[22,53]. PA was measured using Dynaport MoveMonitor[22,53] or SenseWear Armband[17]. All three used PA as primary outcome[17,22,53]

Randomized controlled trials

An RCT showed that endobronchial valve treatment significantly increased step count (+1252 vs. -148 steps/day; between group difference 1340±380 steps/day) and locomotion time (+17 vs. -2 min/day; between group difference not provided) compared to standard care[53].

Non-randomized studies

Two non-randomized studies reported no significant increase in steps/day following lung volume reduction surgery[17] or bronchoscopic lung volume reduction with coils[22].

Other interventions

Randomized controlled trials

One study investigated whether singing classes increased PA, assessed with SenseWear Armband, compared to a control group participating in a film club [54]. PA was the primary outcome. After 8 weeks, no significant between-group differences were shown in daily step count change[54].

In a double-blind placebo controlled RCT, dietary nitrate supplementation's effect (with beetroot juice) during PR on PAL, daily steps and time in MVPA was assessed with a Sensewear armband as secondary outcome[55]. Daily steps and time spent in MVPA increased in the supplement group (median 348 steps/day, interquartile range (IQR) -94; +1629 steps/day; median 2 min/day, IQR -4, +10 min/day) and decreased in the placebo group (median -329 steps/day, IQR -915; +640 steps/day; median -7 min/day, IQR -30, +6 min/day), with an estimated treatment effect of 748 steps/day (100-1471 steps/day) and 13 min/day (2-28 min/day) respectively.

A cross-over trial compared PA (as secondary outcome) during a week with and without thoraco-abdominal region elastic taping in non-obese male COPD patients[56]. During elastic taping patients spent more time in MVPA (117±75 vs 89 min/week; $p<0.05$) and a lower proportion of sedentary time (76±10 vs 80±9; $p<0.05$).

Non-randomized studies

None

Secondary analysis of papers not meeting the suggested minimal criteria of PA assessment

Results of these papers are in the online supplement (including eTable 1). eFigure 1 A-F shows the efficacy of interventions to increase PA.

Interpretation

This narrative review identified 110 interventional trials reporting objective PA outcomes, but only 37 of these papers used methodology that included ≥7 days of assessment and described valid measurement to include ≥4 days of ≥8 measurement hours. This poses a problem for generalizing conclusions from different studies.

Objective assessment of PA outcomes is typically very heterogeneous, characterized by use of different measurement devices, PA outcomes and methodological criteria. Consensus on minimal wearing time (both in hours/day and number of days) does not exist within the scientific community. Nevertheless, it makes sense that minimal wearing time is crucial to have a representative assessment of a patient's routine PA. Therefore, minimal criteria are proposed, based on published methodological papers[13,14] and expert opinion.

Even though papers not meeting the proposed criteria showed similar inconsistent effects on PA and would not have changed our main conclusions, we feel strongly that correct interpretation of results is only possible when methodology of PA assessment is rigorously described in papers. Therefore, we propose that these criteria - ≥7 days of assessment with ≥4 valid days of ≥8 measurement hours - are adopted in future COPD research to enhance PA assessment standardization and enable integration, analysis and comparison of data, with the aim of qualifying PA endpoints that can be used to develop and evaluate efficacy of new COPD therapies.

The Task Force does not recommend any particular device to objectively assess PA, but it is important that investigators are aware of accuracy and reliability of used devices. Measurement device choice should be based on these characteristics, also taking into account cost, user acceptance, assessment length and study design (e.g. PA measured as an outcome versus continuous PA monitoring as part of the intervention).

PA was most frequently used as primary outcome in studies assessing PA behavior change programs and/or mHealth/eHealth interventions. PA behavior change programs typically use a patient-centred approach and focus on action planning, goal setting, facilitating barrier identification, and relapse prevention. Ideally, techniques optimizing motivation and self-efficacy towards PA are incorporated[31]. These techniques could be facilitated by use of online platforms and/or smartphones.

Programs using PA behavior change techniques do not seem to enhance step count and time spent in moderate-to-severe intensity PA in patients recovering from a severe exacerbation[27] or when delivered as a PR adjunct in severely disabled patients [20,26,28]. This is consistent with the observation that, among patients with stable disease, patients with more symptoms and lower exercise capacity appear to have a less pronounced response to PA behavior change interventions[34].

Studies that incorporated behavior change and pedometer feedback interventions in stable patients more frequently reported enhanced PA. However, substantial variability in efficacy exists. Notably, these were typically provided as a stand-alone intervention – so the current literature does not allow us to conclude whether mHealth components are essential to obtain these benefits. Indeed, the only trial that investigated efficacy of PA behavior change in stable patients (outside the mHealth context) found it superior to PR in increasing PA[25]. Whether these interventions are specific for step counts, which is part of the training, or can be generalized to other activity forms, remains to be established.

Studies reporting long-term follow-up PA assessment showed mixed results in terms of preservation of benefits[33,35,37]. Interestingly, one study that investigated telehealth program effectiveness – including PA coaching – without real-life contact with primary and secondary health care providers found no effects on PA and reported a critically low Intervention adherence of both coaches and patients[57]. This suggests that healthcare providers have an active role in optimizing efficacy of mHealth interventions by providing motivational cues[58]. A qualitative study investigating components of an mHealth intervention corroborates these findings[59].

Trials investigating interventions aiming primarily to influence disease outcomes or parameters including pulmonary function (lung volume reduction), pulmonary function and dyspnea (bronchodilators) and dyspnea and exercise tolerance (exercise training), without specifically targeting behavioral change aimed at PA, largely did not affect PA. This suggests that physiologic functional improvement does not automatically translate to altered behavior. Whether such interventions impact on PA maintenance remains a research question with important clinical consequences. Additionally, bronchodilator trials typically used PA as a secondary or exploratory outcome. These trials are rarely powered to demonstrate PA change and may not pay attention to measurement methodology and quality as if this was a primary endpoint. Furthermore, where this is an interventional study exploratory endpoint, it is outside of reporting requirements, therefore there is likely under-reporting of studies with negative PA outcomes. Also, reported step count changes with bronchodilation generally do not exceed the proposed MID of 600-1100 steps/day, established both for daily steps increase observed with PR[60] and daily steps decrease resulting from an adverse medical event[61].

Even though decreased dyspnea symptoms during daily life activities and increased exercise capacity are possible facilitators of enhanced PA behavior[62], interventions that specifically target PA behavior may be needed to optimize lifestyle adaptations.

In contrast to our findings, Mantoani et al. found significant intervention effects on PA in over half of included COPD trials[9]. This discrepancy is likely explained by methodology differences, as they did not set PA assessment criteria and also included studies that used subjective PA reporting.

In a recent Cochrane review investigating effects of different interventions on objectively assessed PA, Burge et al.[63] suggested that small PA improvements can be found from a selection of

interventions, but emphasize that uncertainty exists surrounding methodological quality of the studies and firm conclusions cannot be made. Although we acknowledge that the authors mainly focus on bias risk in those studies, we feel that value will be added to future trials if criteria to harmonize assessment of PA are adopted.

We believe that inclusion of trials with consistent PA assessment methodology– based on consensus amongst an expert Task Force - is a strength of this study. A study limitation is that data extraction was only performed by one researcher for each study.

Interpretation

A systematic literature search identified 110 studies investigating the effect of any kind of intervention on objectively assessed PA in COPD patients. Of these, only 37 studies used methodology that met the proposed CBQC Task Force criteria, highlighting heterogeneity in clinical trials methodology measuring PA. The proposed guidance for trial design will allow for harmonized methodology, which will facilitate interpretation and pooling of PA data. Results are generally variable, reflecting large variation in patient characteristics, modalities, volume and duration of the intervention, control condition, follow-up time, PA parameters and assessment equipment, whether PA is a primary or secondary outcome, sample size and risk of bias. However, in terms of daily step count, few studies show increase beyond the proposed minimal important change of 600-1100 steps, indicating that enhancing PA levels is a challenge.

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Chris Burtin and Anouk Vaes took part in the conception of the work, performed the systematic literature search, analyzed and interpreted the data, drafted the report, approved the final version of the work, and agrees to be accountable for all aspects of the work he/she has done.

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Table 1. Study characteristics of studies used for primary analysis

Study	Study design	Subjects characteristics					Activity monitor Used PA outcome	Intervention		Findings
		N	Males (%)	Age (years)	FEV_1 (%pred)	BMI (kg/m^2)		Type	Frequency and Duration	
PA behavior change programs										
Burtin et al, 2015 [26]	RCT Primary outcome	I: 40 C: 40	I: 86 C: 79	I: 66±7 C: 67±8	I: 45±14 C: 45±18	I: 26±6 C: 25±6	Sensewear Pro Armband; Dynaport MiniMod Steps, MVPA, active time, walking time	Activity behavior change program, including goal setting, problem solving, action planning and feedback on activity behavior, during PR	6 months, 8 sessions of 20-30 min	No intervention*time interaction effect was found for daily walking time and MVPA when comparing the PA behavior change program + PR and the PR only group.
Cruz et al, 2014 [20]	Single group study Primary outcome	16	69	66±11	70±23	30±4	ActiGraph GT3+ Steps; PA Intensity; standing, sitting and lying time	Activity behavior change program, including goal setting and feedback on activity behavior, during PR using activity monitor	12 weeks, 3 feedback sessions throughout the program	Feedback on PA during PR improved daily steps and standing time, but not sitting or lying time nor time spent in light PA or MVPA.
Hornikx et al, 2015 [27]	RCT Primary outcome	I: 15 C: 15	I: 53 C: 60	I: 66±7 C: 68±6	I: 48±18 C: 38±17	I: 25±9 C: 29±5	Dynaport MoveMonitor Steps, walking time and intensity	Telephone-based activity behavior change program, including goal setting, problem solving, action planning and activity self-monitoring ,after exacerbation	1 month, 3 phone contacts per week	All PA measures improved in both groups (PA behavior change and usual care), no differences between groups were detected.
Jolly et al, 2018[29]	RCT Secondary outcome	I: 289 C: 288	I: 63 C: 64	I: 71±9 C: 70±8	I: 71±19 C: 72±19	I: 27±4 C: 27±5	GENEactiv accelerometer MVPA	Telephone-based general health behavior change program, including PA goal setting and activity self-	11 weeks; postal information at weeks 16 + 24	No between group difference in PA measures was observed between the telephone health coaching and a usual care group.

								monitoring		
Nolan et al, 2017 [28]	RCT Primary outcome	I: 76 C: 76	I: 74 C: 71	I: 69±9 C: 68±8	I: 51±21 C: 50±22	I: 28±5 C: 29±7	SenseWear Armband Steps, PA intensity	Activity behavior change program, including goal setting and activity self-monitoring during PR	8 weeks, weekly meeting	No difference in PA measures was observed immediately and 6 months after the intervention between PA behavior change + PR and PR only group.
O'Neill et al, 2018 [25]	RCT Primary outcome	I: 23 C: 26	I: 57 C: 42	I: 61±9 C: 67±8	I: 54±23 C: 57±24	I: 27±7 C: 28±7	ActiGraph wGT3X-BT Steps, PA intensity	Activity behavior change program using 20 behaviour change techniques, including goal setting, problem solving, action planning and activity self-monitoring	12 weeks, weekly contact (6x face to face, 6x by phone)	PA behavior change was more efficacious than PR in improving daily steps.
Schüz et al. 2015 [30]	RCT Primary outcome	I: 90 C: 92	I: 49 C: 51	68±8	55±13		ActiGraph GT1M Steps	Telephone-based general health behavior change program, including goal setting, problem solving, action planning	12 months, 16 phone calls to increase self-management skills and behavior	A health mentoring intervention improved daily steps compared to usual care, but only in participants reporting lower levels of anxiety or depression
mHealth/eHealth interventions										
Demeyer et al, 2017 [34]*	RCT Primary outcome	I: 122 C: 122	C: 63% I: 61%	C: 67 (8) I: 66 (8)	C: 59 (20) I: 55 (21)	C: 26 (5) I: 27 (6)	Actigraph GT3x; Dynaport MoveMonitor Steps, PA intensity, Walking time and intensity	Smartphone-based Activity behavior change program including goal setting, problem solving, action planning, social support and activity self-monitoring	12 weeks	All PA outcomes measures improved more in the intervention group compared to the usual care group.
Moy et al, 2010 [23]	Single group study Primary outcome	24	54	56±7		35±7	Omron HJ-720 ITC Steps	Internet-mediated walking program, including goal setting, social support and	16 weeks	The walking program improved daily steps.

								activity self-monitoring		
Moy et al, 2012 [18]	Single group study Primary outcome	27	100	72±8	55±16		Omron HJ-720 ITC Steps	Internet-mediated walking program, including goal setting, social support and activity self-monitoring	90 days	The walking program improved daily steps.
Moy et al, 2015 [36]	RCT Secondary outcome	I: 154 C: 84	I: 95 C: 92	I: 67±9 C: 66±9			Omron HJ-720 ITC Steps	Internet-mediated walking program, including goal setting, social support and activity self-monitoring	4 months	The walking program improved daily steps compared to a wait-list control group that received a pedometer alone at 4 months
Moy et al, 2016 [37]	RCT Secondary outcome	I: 154 C: 84	I: 92 C: 95	I: 67±9 C: 66±9			Omron HJ-720 ITC Steps	Internet-mediated walking program, including goal setting, social support and activity self-monitoring	12 months	The walking program did not improve daily steps compared to a wait-list control group that received a pedometer alone at 12 months.
Park et al, 2020 [38]	RCT Secondary outcome	I: 22 C: 20	I: 86 C: 70	I: 70±9 C: 65±11	I: 61±19 C: 69±24		Actigraph wGT-3X-BT Steps, activity count per wear time, % of time spent inactive, in low intensity PA and MVPA	Smartphone app-based based activity behavior change program including goal setting, action planning and activity self-monitoring and social support; based on social cognitive theory and self-efficacy theory	6 months	Total activity count per wear time and % of time spent in MVPA, but not steps and time spent inactive or in light intense activities, improved in the intervention group compared to the control group
Vasilopoulou et al, 2017 [35]	RCT Secondary outcome	I1: 47 C1: 50 C2: 50	I1: 94 C1: 76 C2: 74	I1: 67±10 C1: 67±7 C2: 64±8	I1: 50±22 C1: 52±17 C2: 52±21	I1: 28±5 C1: 28±5 C2: 26±5	Actigraph GT3X PA intensity	Home-based (I1) maintenance tele-rehabilitation (including an individualized action plan) and outpatient maintenance rehabilitation (C1) after	12 months	Home-based and outpatient maintenance programs are equal and superior to usual care in terms of all PA outcome measures.

								initial PR		
Vorrink et al, 2016 [33]	RCT Primary outcome	I: 84 C: 73	I: 50 C: 49	I: 62±9 C: 63±8	I: 59±20 C: 53±15	I: 28±5 C: 29±7	SenseWear Pro; SenseWear MF-SW Steps, PAL	Smartphone-based activity behavior change program including goal setting and activity self-monitoring	6 months	The mHealth intervention did not change the PA outcome measures compared to usual care.
Wan et al, 2020 [39]	RCT Secondary	I: 57 C: 52	I: 98 C: 98	I: 68±9 C: 69±8	I: 60±21 C: 65±22		Omron HJ-720 ITC Steps	Internet-mediated walking program, including goal setting, social support and activity self-monitoring	3 months (9 months follow-up)	Steps increased significantly after the intervention, but effects disappeared at 3 and 9 months follow-up.
Exercise-based interventions										
Arbillaga-Etxarri et al, 2018 [40]	RCT Primary outcome	I: 132 C: 148	I: 86 C: 88	I: 68±9 C: 69±8	I: 56±17 C: 58±18		DynaPort MoveMonitor Steps	Urban Training combining behavioral strategies with unsupervised outdoor walking	12 months	Urban Training improved steps compared to usual care in adherent patients (per protocol analysis) but not in the intention-to-treat analysis.
de Roos et al, 2018 [43]	RCT Primary outcome	I: 26 C: 26	I: 31 C: 38	I: 69±10 C: 71±9	I: 65±10 C: 68±8	I: 28±6 C: 27±4	Personal Activity Monitor PA intensity, time spent active	Exercise training combined with home-based walking program	10 weeks, 3x/week 0.5-1 hour	Active time and time spent at light intensity PA, but not time spent at MVPA improved with the exercise intervention compared to a usual care group.
Holland et al, 2017 [44]	RCT (equivalence trial comparing home-based with center-based PR) Secondary outcome	I: 86 C: 80 PA data: I: 29 C: 38	I: 60 C: 59	I: 69±13 C: 69±10	I: 52±19 C: 49±19	I: 29±7 C: 28±6	SenseWear Armband Steps, PA intensity, TEE, PAL, sedentary time	Pulmonary rehabilitation (including aerobic exercise training, resistance training and self-management education) Home based (including one home visit and weekly phone calls) vs. center based	Home based: 8 weeks, at least 30 min on most days of the week Center based: 8 weeks, 2x/week	Intention-to-treat analysis showed no between-group differences for any PA variables. In the whole sample, sedentary time decreased, but this was not sustained at 12 months Time spent in bouts of MVPA of at least 10 min increased in the home-based

										group.
Lahham et al, 2020 [45]	RCT Secondary outcome	I: 29 C: 29	I: 59 C: 59	I: 68±9 C: 67±10	I: 90±8 C: 92±7 (mild COPD)	I: 28±5 C: 28±4	Sensewear Armband Steps, PA intensity, TEE, PAL, sedentary time	Home-based Pulmonary rehabilitation (including walking training, resistance training and self-management education)	8 weeks, 5x/week, at least 30 min	No significant differences between or within groups for any PA outcome.
Larson et al, 2014 [42]	RCT Primary outcome	I: 15 C1: 20 C2: 14	84	I: 71±8 C1: 72±9 C2: 71±8	I: 61±20 C1: 54±17 C2: 56±17	I: 30±7 C1: 26±5 C2: 29±7	ActiGraph 7164 PA intensity	Exercise-specific self-efficacy enhancing intervention with upper body resistance training	4 months, 16 sessions + 3 booster sessions after 3, 6 and 9 months, 1x/week, 15 min	After the intervention, time spent at light intensity PA, but not sedentary time and time spent at MVPA, improved with the intervention of interest compared to two control groups with less extensive intervention (which did not improve PA measures).
Louvaris et al, 2016 [41]	RCT Primary outcome	I: 85 C: 43	I: 80 C: 84	I: 65±8 C: 67±8	I: 49±19 C: 45±19	I: 27±5 C: 28±5	Actigraph GT3X Steps, PA intensity, VMU	High-intensity interval exercise training program	12 weeks, 3x/week	Interval training improved all PA measures compared to usual care.
Hoaas et al, 2016 [21]	Single group study Primary outcome	9	56	58±6	42±20	26±5	SenseWear Armband Steps, PA intensity, TEE	Unsupervised home based treadmill training, as follow-up of a 2 year tele-rehabilitation program	12 months	Steps, TEE and time spent at light intensity PA, but not time spent at MVPA and sedentary time, decreased over the one year period.
Mador et al, 2011 [46]	Single group study Primary outcome	24		72±8	44±18	30±5	RT3 VMU	Pulmonary rehabilitation	8 weeks, 3x/week	Pulmonary rehabilitation did not increase PA outcome measures.
Mesquita et al, 2017 [19]	Single group study Primary outcome	90	60	67±8	47 (32-62)	26 (22-29)	CAM; MOX PA intensity	Pulmonary rehabilitation	8 weeks, 5x/week	Pulmonary rehabilitation did not increase PA outcome measures.
Bronchodilators										

Beeh/Watz et al, 2014 [47]	Crossover randomized trial Secondary outcome	112	68	60±8	57±12		Sensewear Pro 3 Armband Steps, PA intensity, PAL	Bronchodilator (Aclidinium)	3 weeks	Aclidinium improved time spent in MVPA and AEE, but not steps and PAL, compared to placebo.
Troosters et al, 2014 [48]	Randomized double-blind placebo-controlled trial Secondary outcome	I: 238 C: 219	I: 70 C: 67	I: 61±8 C: 62±9	I: 66±8 C: 66±8	I: 27±5 C: 29±6	SenseWear Armband Steps, PA intensity, EE	Bronchodilator (Tiotropium)	24 weeks	No between group differences in PA outcomes were found.
Troosters et al, 2018 [51]	Randomized, partially double-blind, placebo-controlled, parallel-group trial Secondary outcome	I1: 67 I2: 72 I3: 70 C: 65	I1: 76 I2: 63 I3: 60 C: 71	I1 65±6 I2: 65±7 I3: 65±7 C: 64±7	I1: 57±13 I2: 59±11 I3: 57±13 C: 56±14	I1: 29±5 I2: 27±5 I3: 28±6 C: 29±7	Dynaport MoveMonitor Steps, walking time and intensity	Self-management behavior-modification program combined with single (I1 - tiotropium) or combi (I2 – tiotropium+oldaterol) bronchodilation +/- exercise training (I3)	12 weeks; 8 weeks exercise training, 3x/week	PA measures improved with the self-management behavior-modification program, with no additional effect of the other interventions.
Watz et al. 2014 [49]	Randomized, placebo-controlled crossover trial Secondary outcome	129	67	61±9	64±9		SenseWear Armband Steps, MVPA, PAL	Bronchodilator (indacaterol)	21 days of treatment separated by wash-out period of 13 days	All physical activity measures improved with indacaterol compared to placebo.
Watz et al. 2016 [50]	Randomized crossover trial Primary outcome	194	66	63±8	62±11	27±5	SenseWear Armband Steps, MVPA, PAL	Bronchodilator (indacaterol and glycopyrronium)	21 days of treatment separated by a 14-day washout	PAL and daily steps, but not MVPA improved with indacaterol/glycopyrronium compared to placebo
Watz et al.	RCT	I: 134	I: 61	I: 63±8	I: 61±11		DynaPort MoveMonitor	Bronchodilator	8 weeks; week 1-4	All PA outcomes were improved with

2017 [52]	Secondary outcome	C: 133	C: 59	C: 62±8	C: 61±11		Steps, MVPA, AEE	(aclidinium/formoterol)	bronchodilator alone, week 5-8 bronchodilator + behavioral intervention	aclidinium/formoterol compared to placebo
Lung volume reduction procedures										
Hartman et al, 2012 [22]	Single group study Primary outcome	14	29	62.5 (median)	28 (median)		Dynaport MoveMonitor Steps, PAL, active time	Bronchoscopic lung volume reduction		No changes in PA outcome measures were observed after bronchoscopic lung volume reduction.
Hartman et al, 2016 [53]	RCT Primary outcome	I: 19 C: 24	I: 32 C: 17	I: 59±10 C: 59±7	I: 32±8 C: 30±7	I: 26±5 C: 24±4	Dynaport MoveMonitor Steps, walking time and intensity, sitting time, inactive time	Endobronchial valve treatment		Daily steps, walking time and walking intensity, but not sitting and inactive time, increased after endobronchial valve treatment compared to a control group.
Sievi et al, 2018 [17]	Prospective non-randomized trail Primary outcome	I: 19 C: 16	I: 58 C: 56	I: 65 (59-68) C: 64 (61-66)	I: 28 (21-33) C: 33 (29-50)	I: 22 (21-27) C: 26 (24-30)	SenseWear Pro Armband Steps, PA intensity	Lung volume reduction surgery		Physical activity outcomes were not different after lung volume reduction surgery compared to a control group.
Other interventions										
Lord et al, 2012 [54]	RCT Secondary outcome	I: 13 C: 11	NR	I: 69±11 C: 68±9	I: 44±14 C: 64±26		Sensewear Pro Armband Steps, AEE, active time, inactive time	Singing classes	8 weeks, 2x/week 1 hour	Singing classes did not improve PA outcome measures compared to a control group.
Pavitt et al, 2020 [55]	RCT Secondary outcome	I: 57 C: 65 PA data:	I: 58 C: 59	I: 70 [64, 78] C: 68 [62, 74)	I: 53 [37, 65] C: 48 [33, 63]	I: 27 [24-32] C: 26 [23, 31]	Sensewear Pro Armband Steps, PAL, MVPA, TEE	Dietary nitrate supplementation (beetroot juice) during pulmonary rehabilitation	3 hours prior to every exercise training session; 8 weeks, 2x/week	Step count and time spent in MVPA increased non-significantly in the intervention group and decreased non-significantly in the placebo group, leaving a significant treatment effect.

		I: 28 C: 37								There was no difference in PAL between groups.
Pinto et al, 2020 [56]	Cross-over RCT Secondary outcome	10	100	66±7	41±12	23±3	Actigraph GT3X MVPA, inactive time	Elastic tape on the trunk	One week with compared to one week without taping	While wearing the tape, participants had a higher duration of MVPA and lower sedentary time.
Data are shown as mean ± standard deviation or median [quartile 1, quartile 3]. RCT=randomized controlled trial; I=intervention; C=control; PA=physical activity; PR=pulmonary rehabilitation; PA intensity=time spent at different intensities of physical activity; METs=metabolic equivalents; PAL=physical activity level; EE=energy expenditure; AEE=active energy expenditure; VMU=vector magnitude units. * Data extraction from Demeyer et al 2017 [34] is based on a sensitivity analysis within the published online supplement, including fewer participants than the main manuscript.										

Table 2. PEDro scale scores of randomized controlled trials included in primary analysis

	Eligibility criteria specified*	Random allocation	Concealed allocation	Baseline comparability	Subject blinding	Therapist blinding	Assessor blinding	Completeness of follow-up	Intention-to-treat analysis	Between-group statistical comparison	Point measures and variability	Score
PA behavior change programs												
Burtin et al, 2015 [26]	X	X	X	X	-	-	X	-	-	X	X	6
Hornikx et al, 2015 [27]	X	X	-/?	X	-	-	-	X	-	X	X	5
Jolly et al, 2018[29]	X	X	X	X	-	-	-	X	X	X	X	7
Nolan et al, 2017 [28]	X	X	X/?	X	-	-	X	-	X	X	X	7
O'Neill et al, 2018 [25]	X	X	X	X	-	-	X	-	-	X	X	6
Schüz et al. 2015 [30]	X	X	X	X/?	-	-	-	-	-	X	X	5
mHealth/eHealth interventions												
Demeyer et al, 2017 [34]*	X	X	X	X	-	-	-	X	X	X	X	7
Moy et al, 2015 [36]	X	X	-	X	-	-	-	X	X	X	X	6
Moy et al, 2016 [37]	-	X	-	X	-	-	-	X	X	X	X	6
Park et al, 2020 [38]	X	X	-	X	-	-	-	X	X	X	X	6
Vasilopoulou et al, 2017 [35]	X	X	-	X/?	-	-	-	X	-	X	X	5
Vorrink et al, 2016 [33]	X	X	-	X	-	-	X	-	-	X	X	6
Wan et al, 2020 [39]	X	X	-/?	X	-	-	-	X	-	X	X	5
Exercise-based interventions												
Arbillaga-Etxarri et al. 2018 [40]	X	X	-	X	-	-	X	-	X	X	X	6
de Roos et al, 2018 [43]	X	X	X	X	-	-	-	X	X	X	X	7
Holland et al, 2017 [44]	X	X	X	X	-	-	X	X	X	X	X	8
Lahham et al, 2020 [45]	X	X	X	X	-	-	X	X	X	X	X	8
Larson et al. 2014 [42]	X	X	X	X	-	-	X	-	-	X	X	6
Louvaris et al, 2016 [41]	-	X	X	X	-	-	X	X	-	X	X	7
Bronchodilators												
Beeh/Watz et al, 2014 [47]	X	X	X	X	X	X	?	X	X	X	X	9
Troosters et al, 2014 [48]	X	X	-/?	X	X	X	-/?	X	-	X	X	7
Troosters et al, 2018 [51]	X	X	-	X	-	-	-	X	-	X	X	5
Watz et al. 2014 [49]	X	X	-/?	X	X	X	-/?	X	-	X	X	7
Watz et al. 2016 [50]	X	X	-	X	X	X	X	X	X	X	X	9
Watz et al. 2017 [52]	X	X	-	X	X	X	?	X	X	X	X	8
Lung volume reduction procedures												
Hartman et al, 2016 [53]	X	X	-	X	-	-	X	-	-	X	X	5
Other interventions												
Lord et al, 2012 [54]	-	X	X	X	-	-	X	-	-	X	X	6

Pavitt et al, 2020 [55]	X	X	-	X	X	X	X	-	X	X	X	8
Pinto et al, 2020 [56]	X	X	X	-/?	-	-	X	X	X	X	X	7

Table 3. ROBINS-I scores of non-randomized studies included in primary analysis

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement outcomes
PA behavior change programs						
Cruz et al, 2014[20]	Low	Low	Low	Low	Moderate	Low
mHealth/eHealth interventions						
Moy et al, 2010[23]	Serious	Low	Low	Low	Moderate	Low
Moy et al, 2012[18]	Low	Low	Low	Low	Low	Low
Exercise-based interventions						
Hoaas et al, 2016[21]	Low	No information	Low	No information	Moderate	Low
Mador et al, 2011[24]	Low	Moderate	Low	Low	Low	Low
Mesquita et al, 2017[19]	Low	Low	Low	Low	Low	Low
Lung volume reduction procedures						
Hartman et al, 2012[22]	Low	Moderate	Low	No information	Low	Low
Sievi et al, 2018[17]	Low	Low	Low	No information	Low	Low

Figure legends

Figure 1. Flow chart of screening process. PA = physical activity