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Digital telemedicine interventions for patients with multimorbidity: a systematic review and meta-analysis

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ABSTRACT

Objective To determine the effectiveness of digital telemedicine interventions designed to improve outcomes in patients with multimorbidity.

Design Systematic review and meta-analysis of available literature.

Data sources MEDLINE, EMBASE, The Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the Database of Abstracts of Reviews of Effectiveness and hand searching. The search included articles from inception to 19 April 2019 without language restrictions. The search was updated on 7 June 2020 without additional findings.

Eligibility criteria Prospective interventional studies reporting multimorbid participants employing interventions with at least one digital telemedicine component were included. Primary outcomes were patient physical or mental health outcomes, health-related quality of life scores and the utilisation of health services.

Results Out of 5865 studies initially identified, 7 articles, reporting on 6 studies were retained (total of 699 participants). Four of these studies reported interventions including integration with usual care, two studies had interventions with no links to usual patient care. Follow-up periods lasted between 2 and 6 months. Among the studies with links to usual care, the primary outcomes were systolic blood pressure (SBP) (three studies), haemoglobin A1c (HbA1c) (three studies), total cholesterol (two studies) and self-perceived health status (one study). The evidence ranged from very low to moderate certainty. Meta-analysis showed a moderate decrease in SBP (8 mm Hg (95% CI 4.6 to 11.4)), a small to moderate decrease in HbA1c (0.46 mg/dL (95% CI 0.25 to 0.67)) and moderate decrease in total cholesterol (cholesterol 16.5 mg/dL (95% CI 8.1 to 25.0)) in the intervention groups. There was an absence of evidence for self-perceived health status. Among the studies with no links to usual care, time to hospitalisation (median time to hospitalisation 113.4 days intervention and 104.7 days control group, absolute difference 12.7 days) and the Minnesota Living with Heart Failure Questionnaire (intervention group 35.2 score points, control group 23.9 points, absolute difference 11.3, 95% CI 5.5 to 17.1) showed small reductions. The Personal Health Questionnaire (PHQ-8) showed no evidence of improvement (intervention 7.6 points, control 8.6 points, difference 1.0 points, 95% CI −22.9% to 11.9%).

Conclusion Digital telemedicine interventions provided moderate evidence of improvements in measures of disease control but little evidence and no demonstrated benefits on health status. Further research is needed with clear descriptions of conditions, interventions and outcomes based on patients' and healthcare providers' preferences.

PROSPERO registration number CRD42019134872.

Strengths and limitations of this study

- ► Multimorbidity is an increasing global challenge and digital health solutions could contribute to improving care.
- ► Despite the attention given to digital health, no systematic review of digital health interventions for multimorbidity has been conducted before.
- ► Our systematic review shows that evidence for the effectiveness of digital telemedicine interventions for multimorbidity is very limited.
- ► Further high-quality studies are needed to create the necessary evidence base to inform guidelines and policy makers.

INTRODUCTION

The number of patients with multimorbidity is increasing globally and there is a recognised need to improve healthcare and outcomes for patients with multimorbidity.[1] In Europe alone, more than 50 million people are affected, including 60% of those 65 years or older.[1 2] Patients with multimorbidity have complex healthcare needs and are 40% more likely to report problems with care coordination than non-multimorbid patients.[3] Digital telemedicine interventions have in recent years increasingly been recognised as a useful tool that could help integrate and improve care for the complex health and social needs of multimorbid patients, for example, by 'encouragement of a new relationship between patient and health professional, enabling standardised information exchange between providers, and extending the scope of healthcare in a geographical and conceptual sense'.[2] Most digital health research, however, has focused

on single chronic diseases, patients with multimorbidity are often excluded from studies and reviews, and to date no, systematic review of the effectiveness of digital health interventions for patients with multimorbidity exists.[4 5] In particular, a systematic review of the effectiveness on clinical and quality of life outcomes and the assessment of impact on use of healthcare systems is lacking. This is in particular reflected in the inadequacy of guidelines to support recommendations for managing multimorbid patients with digital telemedicine interventions.[6] The WHO's recommendations on digital interventions for health systems strengthening highlight the need to ensure integration with existing healthcare structures to not inappropriately divert resources from alternative, non-digital approaches.[7] Therefore, this review groups studies according to their integration with usual care.

Objectives

This study aimed to assess the effects of interventions with at least one digital telemedicine component designed to improve outcomes in patients with multimorbidity.

METHODS

Our systematic review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting of systematic reviews.[8] The protocol for this review has been registered in the PROSPERO network (registration number: PROSPERO 2019 CRD42019134872).

Patient and public involvement

There was no patient or public involvement as this is a review of already published studies.

Search strategy

The databases MEDLINE and EMBASE, The Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, and the Database of Abstracts of Reviews of Effectiveness were retrieved from inception to 19 April 2019 without language restrictions. The search was updated on 7 June 2020 without additional findings. In addition, reference lists of all papers and relevant reviews identified for relevant studies that the search might have missed were searched. The search strategy (see online supplemental appendix A) was developed based on the search terms for multimorbidity employed by the Cochrane review 'Interventions for improving outcomes in patients with multi-morbidity in primary care and community settings' and the search terms for e-health based on the Cochrane review 'eHealth interventions for people with chronic kidney disease'.[4 9] The rationale for employing the search strategies from the Cochrane review 'Interventions for improving outcomes in patients with multimorbidity in primary care and community settings' is that the definition of multimorbidity is identical to the one used in our review (coexistence of multiple chronic diseases and medical conditions in the same individual; where chronic disease are health problems that require ongoing management over a period of year or decades). The same rationale underlies the use of the strategy on e-health which reflects the definition of e-health described above (eg, Telehealth, mobile phone (including text messaging and the use of applications on mobile phones), internet and computer, electronic monitors, and wireless and Bluetooth enabled devices).

Study selection, inclusion and exclusion criteria

Types of studies

Randomised controlled trials (RCTs), controlled clinical trials, designs controlled before and after studies and interrupted time series analyses were included. Studies published in all languages published through 19 April 2019 were included (updated on 7 June 2020).

Types of participants

People or populations with multimorbidity receiving care in all settings were included. Multimorbidity was defined as the coexistence of at least two chronic physical diseases in the same individual. The 11th International Classification of Diseases (ICD-11) was used to define disease. For the purposes of this review, studies that reported interventions for people with a mental health condition comorbid with only one physical intervention were excluded. We postulate that interventions for somatic and mental conditions usually differ in nature and therefore are very likely similar or the same as in patients with monomorbidity. However, studies that targeted mental health in additional to those with at least two physical conditions were included.

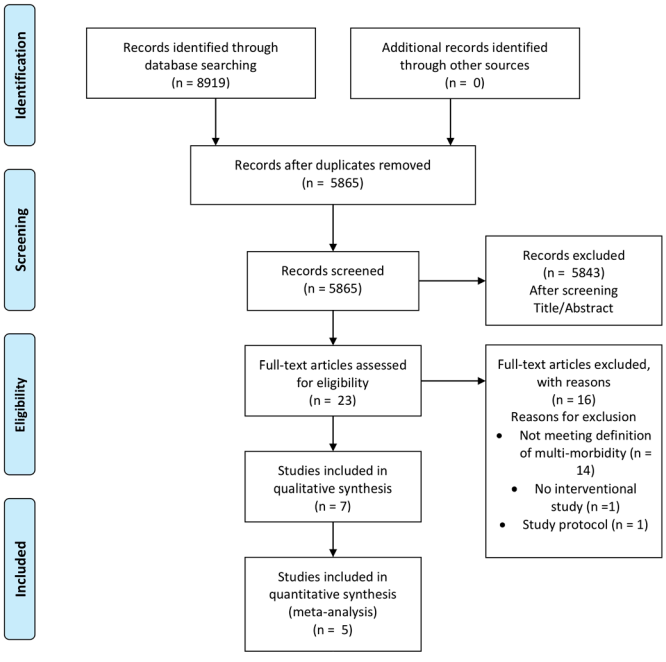

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The flow diagram depicts the flow of information through the different phases of a systematic review.

Table 1 General characteristics of included studies

Author (country, year of publication)	No of participants	Population	Intervention group (for details, please refer to table 2)	Control group	Outcome measures	Duration of intervention	Links to usual care
Yoo *et al*[15] (South Korea, 2009)—RCT	123	Patients at a general hospital and public health centre with type 2 diabetes mellitus and hypertension	Combining telemonitoring and telecare	Usual care: clinic visits according to the routine schedule and usual outpatient treatment	Body weight, Body-mass-index (BMI) and waist circumference, systolic and diastolic office blood pressue (BP), right/left brachial-ankle pulse wave velocity (baPWV), HbA1c, fasting glucose, total cholesterol, High density lipoportein (HDL)-cholesterol, Low Density Lipoprotein (LDL)-cholesterol, triglyceride, adiponectin, high sensitivity-CRP, Interleukin-6	3 months	The usual physicians could follow trends in blood glucose, BP and body weight changes and sent individualised recommendations when needed
Wakefield *et al*[16] [17] (USA, 2011 and 2012)—RCT	302	Patients at veteran affairs primary care provider with type 2 diabetes mellitus and hypertension	Combining telemonitoring and telecare	Usual care: scheduled follow-up appointments with the primary care clinic in the usual manner and access to their nurse care manager employed by the medical centre	HbA1c and systolic BP, Geriatric Depression Scale (GDS) and patient adherence	6 months	The subject's primary care physician provided BP and blood glucose parameters and measurement intervals that should trigger changes in the treatment plan. Each weekday the study nurse decided if the treating physician should be involved.
Rifkin *et al*[20] (USA, 2013)—RCT	45	Patients at veteran affairs hospital ambulatory clinic with stage 3 chronic kidney disease and hypertension	Combining telemonitoring and telecare	Usual care: access to usual care and asked to measure and record their BP at home according to their physicians' instructions	Systolic and diastolic BP creatinine, eGFR, total number of medications, number of blood pressure medications, Morisky Medication Adherence Scale	6 months	Usual care physicians gave instructions for BP monitoring. Prior to scheduled appointments, the electronic medical record was updated with the full record of the telemonitoring results since the prior visit.
Mira *et al*[21] (Spain, 2014)—RCT	102	Patients at primary care health centres with multimorbidty	Self-management including telemonitoring (without telecare)	Usual care: clinic visits according to the routine schedule and usual outpatient treatment	Morisky Medication Adherence Scale (MMAS-4), number of missed doses, medication errors, self-perceived health status, HbA1c, cholesterol level, systolic and diastolic BP	3 months	The app stored patient's usual prescriptions. Monitoring of adherence to the prescriptions and medical advice of the healthcare provider.

Continued

Table 1 Continued

Author (country, year of publication)	No of participants	Population	Intervention group (for details, please refer to table 2)	Control group	Outcome measures	Duration of intervention	Links to usual care
Donesky *et al*[18] (USA, 2017)—RCT	15	Patients were at pulmonary rehabilitation programmes with COPD and heart failure	Videoconference-based telecare intervention	Usual care: clinic visits according to the routine schedule and usual outpatient treatment and educational material. The intervention nurse called each week for 15–30 min to discuss the educational information.	St. George's respiratory questionnaire, the Kansas City Cardiomyopathy Questionnaire (KCCQ), Personal Health Questionnaire, Dyspnea-12 Questionnaire, Borg scale at the end of the 6-minute walk test (6MWT), General Sleep Disturbance Scale	2 months	None
Bernocchi *et al*[19] (Italy, 2017)—RCT	112	Cardiology and Pulmonary Departments of three rehabilitation hospitals with patients with COPD and heart failure	Combining telemonitoring and telecare	Usual care: clinic visits according to the routine schedule and usual outpatient treatment, instructed in an educational session about the desirability of maintaining a healthy lifestyle	6MWT, reduction of hospitalisations, MLHFQ, COPD Assessment test (CAT), Barthel Index, MRC scale, Borg scale, Physical Activity Scale for the Elderly (PASE) questionnaire, daily steps reported by patients, improvement of oxygenation	4 months	None

BP, blood pressure; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; MLHFQ, Minnesota Living with Heart Failure Questionnaire; RCT, randomised controlled trial.

Table 2 Details of interventions following TIDieR

Name/Multimorbidity	Why? (rationale for the intervention)	What was delivered?	Who provided the intervention?	How was the intervention delivered?	Where was the intervention delivered?	When was the intervention delivered and how much?	How was the intervention tailored?
Yoo *et al*[15] (2009)—A ubiquitous chronic disease care (UCDC) system using cellular phones and the internet/diabetes mellitus (DM) type 2 and hypertension	To use the internet and cellular phones to improve multiple metabolic parameters in overweight patients with both type 2 diabetes and hypertension	Alarm on the cellular phone to remind the participant to measure their blood glucose and blood pressure; the device attached to their cellular phone conducted the glucose measurements and participant's exercise time; participants received information via short message service (SMS) three times a day regarding healthy diet and exercise methods	The algorithm was developed by endocrinologists, dieticians and nurses at Korea University; physicians followed trends in blood glucose levels, blood pressure and body weight changes	A cellular phone (LG-SV280; LG Electronics, Seoul, Korea) with a modular blood glucose measuring device (Anycheck; Insung Information, Seoul, Korea), strips and lancets; automatic blood pressure monitoring device (T5M; Omron, Kyoto, Japan), and body weight scales (HD308; Tanita, Tokyo, Japan)	Recruitment: university hospital and community healthcare centre in Korea Delivery: participants' homes	Blood glucose, blood pressure twice a day and body weight once a day; information via SMS three times a day Length: 3 months	Participant's exercise time using the SMS was predefined according to each patient's daily schedule
Wakefield *et al*[16 17] (2011 and 2012)—Home telehealth in comorbid diabetes and hypertension/DM type 2 and hypertension	To improve blood glucose and blood pressure through a nurse-managed home telehealth intervention blood pressure in veterans with comorbid diabetes mellitus and hypertension	Patients entered blood pressure and blood glucose measurements and responded to standardised questions, an algorithm delivered interactive advice (eg, diet, exercise, smoking cessation); the device automatically downloaded data each night, making the patient information available for the nurses to review the next day and allowed individualised messages to be transmitted to subjects	Nurses reviewed patient information, determined whether subjects needed follow-up and could send individualised messages	A home-telehealth device (Viterion-Bayer Panasonic) used a standard telephone line to enable data transmission between the patient's home and the study centre	Recruitment: Veterans affairs primary care clinic and Delivery: participants' homes	Blood pressure daily and blood glucose as before; daily review of parameters by nurse Length: 6 months	The subject's primary care physician was contacted for BP and blood glucose (BG) parameters that should trigger a call to the physician for changes in the treatment plan; personalised nurse intervention when parameters out of control
Rifkin *et al*[20] (2013)—A real-time, wireless blood pressure monitoring for older patients with kidney disease/chronic kidney disease (CKD) and hypertension	To record home blood pressure readings using home-based Bluetooth-enabled blood pressure monitoring device before the next clinic visit management for older adults with CKD	Patients measured and recorded their BP; physicians and pharmacist met to review BP logs of each participant; if a patient had consistently above-goal readings the physicians or pharmacists called to discuss the readings and adjust medications; prior to schedule in-person follow-up clinicians were invited to review telemonitoring results	Study physicians and pharmacists reviewed blood pressure logs of each participant and called participant if necessary	A A&D Medical UA-767PBT fully automated oscillometer BP unit (A&D Medical, San Jose, California, USA) and the home health hub (HHH). The HHH received BP and pulse data from the BP unit, and relayed the data through the internet to a secure website.	Recruitment: Veterans affairs clinic in San Diego and Delivery: participants' homes.	Measurement of BP to their physicians'; weekly review of study parameters Length: 6 months	Study physicians and pharmacist met to review BP logs, discuss the readings, provide counselling, or adjust medications
Mira *et al*[21] (2014)—A pillbox app for elderly patients taking multiple medications/ DM type 2 and several comorbidities	To increase adherence through a medication self-management application for elderly patients taking multiple medications	The application helps patients to remember to take all their medications correctly and provided doctors' recommendations for healthy habits, such as physical exercise and diet; monitoring of the level of adherence to the prescriptions and medical advice	Physician personalised recommendations and drugs; individual sessions of up to 2 hours to be shown how to use the app by investigators	An application (ALICE) on a tablet was a BQ Verne Plus 3G 7 inches with a touch screen	Recruitment: Primary care centres in Spain Delivery: participants' homes	Daily use length: 3 months	Works with personalised prescriptions and recommendations, customised system of alerts and reminders to remind patients when to take their medications and to put into practice healthy habits (eg, intake with meals).

Continued

Table 2 Continued

Name/Multimorbidity	Why? (rationale for the intervention)	What was delivered?	Who provided the intervention?	How was the intervention delivered?	Where was the intervention delivered?	When was the intervention delivered and how much?	How was the intervention tailored?
Donesky *et al*[18] (2017)—A home-based tele yoga Intervention/ chronic obstructive pulmonary disease (COPD) and heart failure	To determine the clinical outcomes of an 8-week home-based yoga programme, conducted via multipoint videoconferencing for patients with COPD and heart failure	Tele yoga classes were offered using videoconferencing; Classes began with 10 min of relaxation followed by ca. 35 min of poses and concluded with 15 min of meditation and relaxation; patients were taking their own blood pressure, weight, heart rate and oxygen saturation levels before and after each class and reported them	A yoga teacher provided the intervention; a nurse called each participant on the telephone before and after each tele yoga session to assess symptoms of HF and COPD	A yoga mat, automatic blood pressure cuff, oximeter and scale; videoconferencing equipment was installed in the homes of the intervention group participants	Delivery: classes were provided at participants' homes.	Classes were offered twice weekly Length: 8 weeks	Participants received personalised instructions
Bernocchi *et al*[19] (2017)—Home-based telerehabilitation in older patients/COPD and heart failure	To investigate a telemonitoring programme integrated with rehabilitation in patients with COPD and heart failure	Mini-ergometer with incremental load, muscle reinforcement exercises using weights and pedometer-based walking; the nurse made a structured phone call to each participant collecting information about the disease status, offering advice regarding diet, lifestyle and medications.	Educational intervention delivered by nurse tutor (NT) and a physiotherapist tutor (PT); the NT made a weekly structured phone call to each participant.	A pulse oximeter (GIMA, Milan, Italy), and a portable one-lead electrocardiograph (Card Guard Scientific Survival, Rehovot, Israel) for real time monitoring; mini-ergometer, pedometer and diary	Recruitment: Rehabilitation centre Delivery: participants' homes	Real-time monitoring of vital signs Weekly structured phone call to participants Length: 4 months	Personalised exercise programme and advice The number/intensity of training sessions according to patients' progress were adjusted or in the case of problems

TIDieR, Template for Intervention Description and Replication.

Table 3 Overview of primary and secondary outcomes

Outcome category	Outcome (Study reporting this as primary outcome)	No of studies with this outcome
Primary outcomes	Blood pressure (systolic)	3
	HbA1c (Wakefield *et al*, 2011 and 2012)	3
	Cholesterol	2
	Depression score	1
	Health-related quality of life	2
	Reduction of hospitalisations	1
Secondary outcomes (details in online supplemental file A)	Physical functioning (Bernocchi *et al*, 2018)	2
	Self-efficacy	1
	Dyspnoea	2
	Medication adherence (Mira *et al*[21])	3
	Levels of adiponectin	1
	Creatinine/estimated glomerular filtration rate (eGFR)	1

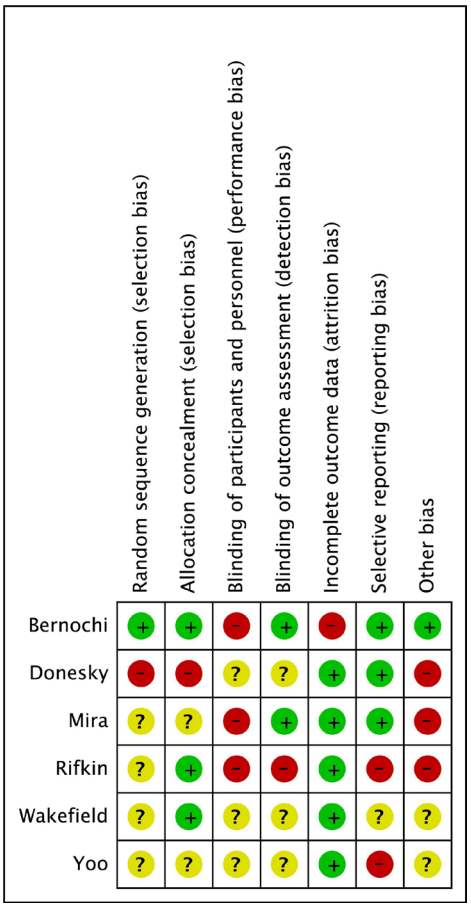

Figure 3 Risk of bias summary. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Types of interventions

This review focuses on digital telehealth interventions as defined below. Effective interventions are likely to be complex and can consist of elements such as telemonitoring, telecare and self-management elements.[4] Telemonitoring is defined as 'the remote monitoring of patients, including the use of audio, video, and other telecommunications and electronic information processing technologies to monitor patient status at a distance'.[10] Telecare is the use of those data to provide clinical care, education and prevention at a distance, including remote consultation (eg, videoconferencing).[11] Patient self-management is defined as 'any intervention which aims to empower patients to be active decision makers who deal with emotional, social or medical management of their illness with the aim of improving their independence and Quality of Life'.[12] Non-digital telemedicine interventions (ie, connections only based on telephone) will not be included in this review. All interventions specifically direct towards patients with multimorbidity that had at least one digital telemedicine component as described above were included. The following interventions were excluded: (1) interventions focusing on healthcare management (eg, electronic health records), (2) interventions solely based on health data analytics (eg, clinical decision support systems), (3) interventions in which patients were not

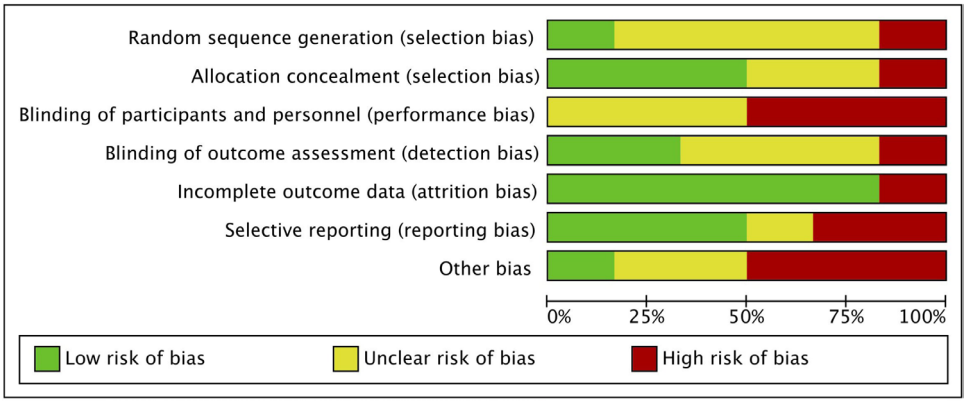

Figure 2 Risk of bias graph. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

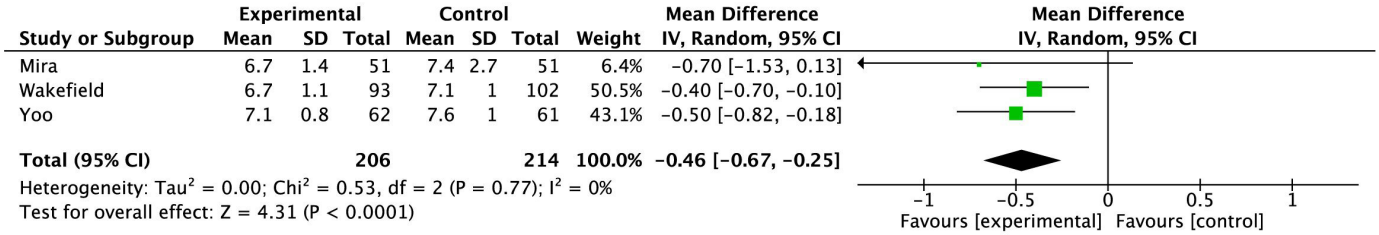

Figure 4 Meta-analysis for haemoglobin A1c (HbA1c) in mg/dL (including Wakefield high-intensity group). Forest plot of comparison: Digital telemedicine integrated with usual care compared with usual care, outcome: HbA1c in mg/dL.

multimorbid according to our definition (eg, based on age or composite scores). To systematically describe the nature of the interventions, the different elements were analysed using the Template for Intervention Description and Replication (TIDieR) checklist.[13]

Types of outcome measures

Different combinations of diseases, as is the norm in multimorbidity, pose the challenge to define outcomes that can be used across studies and that are relevant to patients and care providers. Currently, no agreed on generic outcome measures incorporating relevant clinical or mental health outcomes exist.[14] Therefore, important risk factors that are common to several prevalent diseases (blood pressure (BP), cholesterol and haemoglobin A1c (HbA1c)) were included as primary outcomes. As a major part of the burden of multimorbidity is caused by mental health problems (ie, depression), hospitalisations and reduced quality of life, these were also defined as primary outcomes. Secondary outcomes included self-efficacy, adherence to treatment and other psychosocial outcomes (see online supplemental appendix A).

Primary outcomes:

- Clinical outcomes (ie, BP, HbA1c, cholesterol).
- Mental health outcomes (depression scores).
- Health-related quality of life scores.
- Utilisation of health services (ie, hospitalisations).

Secondary outcomes:

- Patient psychosocial outcomes, including well-being and measures of disability or functional status.
- Patient behaviour including measures of medication adherence.
- Economic, including cost-effectiveness outcomes.

Attitude and knowledge outcomes were excluded.

Data collection and analysis

Potentially relevant studies were determined by concomitantly screening the titles and abstracts of search results by two authors. Full-text copies of all articles identified as potentially relevant were retrieved. Two review authors independently assessed each retrieved article for inclusion. There were no disagreements between the two authors. A flow diagram was developed using the PRISMA guidelines to display the search and selection process.

Data extraction and management

The following data were extracted for all included studies using a standardised form: a full description of the intervention including details regarding aims, evidence and/or theory on which the intervention was based, nature of multimorbidity, information on the provider of the intervention, clinical setting, study design, results and whether the intervention was modified during the study.

Risk of bias assessment

Bias was assessed for randomised studies using the Cochrane risk of bias in intervention trials checklist (covering sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting). A judgement of risk of bias on each of the tool's six domains was made from the extracted information, rated as 'high risk' or 'low risk'. If insufficient details were reported, the risk of bias was judged as 'unclear'.

Data analysis

Natural units were used for each study. Where outcomes were sufficiently clinically homogeneous (eg, systolic blood pressure (SBP) in mm Hg), a pooled meta-analysis was undertaken. A random-effects model was used to

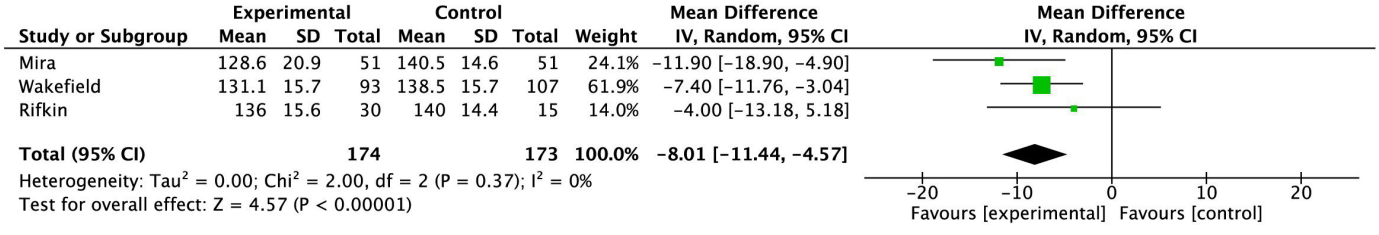

Figure 5 Meta-analysis for systolic blood pressure in mm Hg (including Wakefield high-intensity group). Forest plot of comparison: Digital telemedicine integrated with usual care compared with usual care, outcome: systolic blood pressure in mm Hg.

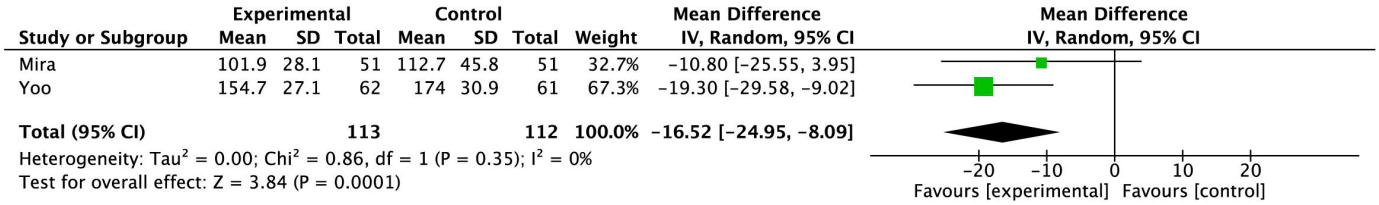

Figure 6 Meta-analysis for total cholesterol in mg/dL (including Wakefield high-intensity group). Forest plot of comparison: Digital telemedicine integrated with usual care compared with usual care, outcome: total cholesterol in mg/dL.

account for statistical heterogeneity that cannot be explained by subgroup analysis or meta-regression (eg, due to too few studies). We used standardised effect sizes (SES) following the Cochrane handbook where studies reported relevant data for their calculation. The general convention was used that an SES of more than 0.2 indicates a small, 0.5 a moderate and more than 0.8 a large effect size. The program RevMan V.5 was used for conducting meta-analyses.

No unit of analysis error were found in the included studies. None of the included studies reported more than 15% of loss to follow-up or other sources of missing data. Therefore, no strategies for missing data were necessary. The evidence grade was determined using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

RESULTS

Search results

The electronic searches yielded 5865 articles after duplicates were removed (figure 1). A total of 5842 citations were excluded during screening of abstracts as they were not meeting the inclusion criteria. Full texts were retrieved for 23 studies. Of these, 16 studies were excluded during assessment of the full text and one was excluded during data extraction. Fourteen studies were excluded on the basis of not meeting the definition criteria for multimorbidity. One study was not an RCT and one was only published as a conference abstract of preliminary data (excluded studies in online supplemental appendix B). Seven articles from six studies were eligible for inclusion in this review.

Characteristics of included studies

We identified six RCTs eligible for inclusion in the review, reported in seven publications (Wakefield (2011)[1] and Wakefield (2012)[2] reported different outcomes of the same trial) (table 1). No other eligible study designs were identified (detailed characteristics of included studies in online supplemental appendix C). There was a total of 699 participants in the six included studies. Two studies involved participants with diabetes mellitus type 2 (DM type 2) and hypertension (Yoo *et al*[15] and Wakefield *et al*[16 17]), two studies patients with chronic obstructive pulmonary disease (COPD) comorbid with heart failure (Donesky *et al*[18] and Bernocchi *et al*[19]), one with chronic kidney disease (CKD) and heart failure (Rifkin *et al*[20]) and one with DM type 2 in combination with various other comorbidities (Mira *et al*[21]). Three studies were set in primary care or home settings (Mira *et al*,[21] Donesky *et al*[18] and Bernocchi *et al*[19], two studies were set at Veteran affairs hospital outpatient clinics (Wakefield *et al*[16 17] and Rifkin *et al*[20]) and one was set at a university hospital and community health centres (Yoo *et al*[15]). Three studies were conducted in the USA (Wakefield *et al*,[16 17] Rifkin *et al*[20] and Donesky *et al*[18]), one study in South Korea, Spain and Italy respectively (Yoo *et al*,[15] Mira *et al*[21] and Bernocchi *et al*[19]). All studies were funded by government or university grants. None were funded by industry. In all included studies, the control group received usual medical care (comparator). In two studies, the control group furthermore received education/educational material (Donesky *et al*[18] and Bernocchi *et al*[19]).

Assessment of interventions

All interventions are multifaceted and described in detail in table 2. All the interventions identified involved at least one element of digital telemedicine. The interventions lasted 2 months (Donesky *et al*[18]), 3 months (Yoo *et al*[15] and Mira *et al*[21]), 4 months (Bernocchi *et al*[19]) and 6 months (Wakefield *et al*[16 17] and Rifkin *et al*[20]). They could be divided into interventions combining telemonitoring and telecare (Yoo *et al*,[15] Wakefield *et al*,[16 17] Rifkin *et al*[20] and Bernocchi *et al*[19]), self-management including telemonitoring (without telecare) (Mira *et al*[21]), and a videoconference-based telecare intervention (Donesky *et al*[18]).

Four studies reported integration with usual care (Yoo *et al*,[15] Mira *et al*,[21] Rifkin *et al*[20] and Wakefield *et al*[16 17]). Two studies had no elements of integration with usual care (Bernocchi *et al*[19] and Donesky *et al*[18]). Table 1 shows how the interventions were integrated with the usual medical care of the participants.

Description of outcomes

Only three studies specifically defined and reported primary outcomes. HbA1c was reported in one study (Wakefield *et al*[16 17]), exercise tolerance improvement measured by difference in the metres walked in the 6-minute walk test(6MWT) (Bernocchi *et al*[19]) and adherence to treatment measured by the 4-item Morisky Medication Adherence Scale (MMAS-4) (Mira *et al*[21]) in the other studies. Without specifying primary or secondary outcome, three studies reported the outcome systolic blood pressure (Wakefield *et al*,[16 17] Rifkin *et al*[20] and Mira

et al[21]). Three studies reported the outcome HbA1c (Yoo *et al*,[15] Wakefield *et al*[16 17] and Rifkin *et al*[20]). Two studies reported the outcome total cholesterol (Mira *et al*[21] and Yoo *et al*[15]). Two studies reported health-related quality of life outcomes (Bernocchi *et al*[19] and Mira *et al*[21]). One study reported reduction of hospitalisations (Bernocchi *et al*[19]) and one study reported a depression score (Donesky *et al*[18]). For an overview of reported outcomes, please refer to table 3. All studies reported outcomes at immediate postintervention follow-up. In addition, Wakefield *et al*[16 17] also reported outcomes after 12 months and Bernocchi *et al*[19] after 3 months. No study reported proper economic outcomes or analysis.

Risk of bias across studies

Only one study reported all elements for the risk of bias domains. Four studies reported two or more domains with a high risk of bias. One study had four domains with a high risk of bias (figures 2 and 3). Four studies (Bernocchi *et al*,[19] Donesky *et al*,[18] Rifkin *et al*[20] and Wakefield *et al*[16 17]) reported information on allocation concealment. There was a high risk of bias in one study (Donesky *et al*[18]) due to open allocation of intervention and control groups. Baseline outcome measurements were conducted in all studies. Performance bias (blinding of participants and personnel) was unclear (not reported) in three studies (Donesky *et al*,[18] Wakefield *et al*,[16 17] Yoo *et al*[15]) and was judged as high risk in three studies (Bernocchi *et al*,[19] Mira *et al*,[21] Rifkin *et al*[20]) because participants could not be blinded due to the nature of the interventions. Detection bias was unclear in the same three studies (Donesky *et al*,[18] Wakefield *et al*[16 17] and Yoo *et al*[15]) and was judged as low risk in two studies (Bernocchi *et al*[19] and Mira *et al*[21]) and as high risk in one study (Rifkin *et al*[20]) as the assessors of the outcome were not blinded. All studies reported sufficient information to assess the risk of attrition bias. Five studies (Donesky *et al*,[18] Mira *et al*,[21] Rifkin *et al*,[20] Wakefield *et al*[16 17] and Yoo *et al*[15]) were judged as of low risk for attrition bias. One study (Bernocchi *et al*[19]) was rated as high risk of attrition bias due to high loss to follow-up unbalanced between the two groups. Five studies reported sufficient information to judge bias on selective reporting. Three (Bernocchi *et al*,[19] Donesky *et al*[18] and Mira *et al*[21]) were judged as low risk for selective reporting bias. One study was judged as unclear (Wakefield *et al*[16 17]) and one study (Rifkin *et al*[20]) was rated as of high risk of bias because of no prespecified outcome parameters; no prepublished protocol or prespecified outcomes described in the Methods section. Three studies reported high risk of other bias (Donesky *et al*,[18] Mira *et al*[21] and Rifkin *et al*[20]) due to further selection bias and unexplained elements for outcome reporting.

Studies integrated with usual care

Three studies reported HbA1c (Yoo *et al*[15], Wakefield *et al*[16 17] and Mira *et al*[21]) and systolic blood pressure (Rifkin *et al*[20], Wakefield *et al*[16 17] and Mira *et al*[21]) as outcomes, while two studies reported total cholesterol changes (Yoo *et al*[15] and Mira *et al*[21]). Meta-analysis showed a moderate decrease in SBP of 8 mm Hg (95% CI 4.6 to 11.4, test for overall effect p<0.0001, moderate certainty evidence) (figure 4), a small to moderate decrease in HbA1c of 0.46 mg/dL (95% CI 0.25 to 0.67, test for overall effect p<0.0001, moderate certainty evidence) (figure 5) and moderate decrease in total cholesterol of 16.5 mg/dL (95% CI 8.1 to 25.0, test for overall effect p<0.0001, moderate certainty evidence) (figure 6) in the intervention groups. No relevant heterogeneity was detected in the meta-analyses. Taking SBP as an example, we found the largest effect on the outcome in Mira *et al*[20] (absolute difference 12.1 mm Hg), followed by Wakefield *et al*[16 17] (absolute difference 7.4 mm Hg) and Rifkin *et al*[20] (absolute difference 4.0 mm Hg). The intervention in Mira *et al*[20] was a tablet-based application to increase adherence for medication self-management for elderly patients taking multiple medications while the control group received clinic visits according to the routine schedule and usual outpatient treatment. In Wakefield *et al*,[16 17] the intervention consisted of a nurse-managed home telehealth intervention where patients with hypertension and diabetes entered BP and blood glucose measurements regularly and responded to standardised questions. An algorithm delivered interactive advice (eg, diet, exercise, smoking cessation) and allowed individualised messages to be transmitted to subjects. The control group received scheduled follow-up appointments with the primary care clinic in the usual manner and access to their nurse care manager employed by the medical centre. The smallest effect size was observed in the study of Rifkin *et al*,[20] where the intervention consisted of a real-time, wireless blood pressure monitoring for patients with hypertension and chronic kidney disease and physicians and pharmacist that review BP logs of each participant to discuss the readings and adjust medications if necessary. The control grozp received access to usual care and BP measurements at home. All interventions had in common that they increased the frequency that patients were reminded of measuring or treating their BP. In the least effective study, the control group was also asked to measure their own BP more regularly, possibly this could have lead to a reduced difference in effect.

One study (Mira *et al*[21]) reported a quality of life outcome (self-perceived health status) with a small and non-significant standardised effect size (69.1% in control and 74.6% in intervention group, difference in proportions 5.4%, 95% CI −22.9% to 11.9%). Table 4 shows the details for clinical outcomes and table 5 shows the summary of findings for studies with links to usual care.

Studies not integrated with usual care

One study (Donesky *et al*[18]) reported a mental health outcome, the Personal Health Questionnaire-8 (PHQ-8), one study (Bernocchi *et al*[19]) reported reduction of hospitalisations and quality of life scores (Minnesota Living with Heart Failure Questionnaire (MLHFQ) score) as an outcome (8 and 12 weeks) (table 6). There was no

Table 4 Clinical outcomes in studies with links to usual care

Study	Multimorbidity	Outcomes	Intervention	Control	Results
Yoo *et al*[15]	DM type 2 and hypertension	HbA1c mg/dL (%) (3–6 months)	7.1 (SD 0.8)	7.6 (SD 1.0)	Absolute diff 0.5, relative % diff 7.0% 95% CI 0.2 to 0.8 p=0.001 SES=0.55
Wakefield *et al*[16]	DM type 2 and hypertension		Low: 6.8 (SD 0.99) High: 6.7 (SD 1.1)	7.1 (SD 1.0)	Absolute diff (0.33; 0.37), relative % diff 4.9%; 7.1% High intensity 95% CI 0.1 to 0.7 p=0.02 SES=0.33 Low intensity 95% CI 0.03 to 0.57 p=0.03 SES=0.31
Mira *et al*[21]	DM type 2 and several comorbidities		6.7 (SD 1.4)	7.4 (SD 2.7)	Absolute diff 0.7, relative % diff 9.5 95% CI −0.1 to 1.5 p=0.36 SES=0.33
Wakefield *et al*[16]	DM type 2 and hypertension	Systolic blood pressure (mm Hg) (SBP) (3–6 months)	High: 131.1 (SD 15.7) Low: 135.7 (SD 5,9)	138.5 (SD 15.7)	Absolute diff (2.77; 7.43), relative % diff (2.0; 5.7) High intensity 95% CI 3.1 to 11.7 p=0.001 SES=0.47 Low intensity 95% CI −0.5 to 6.1 p=0.06 SES=0.26
Rifkin *et al*[20]	CKD and heart failure		136 (SD 15.6)	140 (SD 14.4)	Absolute diff 4.0 Relative % diff 2.9 95% CI −6.9 to 14.9 p=0.32 SES=0.26
Mira *et al*[21]	DM type 2 and several comorbidities		128.6 (SD 20.9)	140.5 (SD 14.6)	Absolute diff 12.1 Relative % diff 8.5 95% CI 4.8 to 18.9 p=0.28 SES=0.66

Continued

Table 4 Continued

Study	Multimorbidity	Outcomes	Intervention	Control	Results
Mira *et al*[21]	DM type 2 and several comorbidities	Total cholesterol (mg/dL) (3 months)	101.9 (SD 28.1)	112.7 (SD 45.8)	Absolute diff 10.8 Relative % diff 9.6 95% CI −4.1 to 25.7 p=0.04 SES=0.28
Yoo *et al*[15]	DM type 2 and hypertension		154.7 (SD 27.1)	174.0 (SD 30.9)	Absolute diff 19.3, Relative % diff 9.8% 95% CI 8.9 to 29.7 p=0.011 SES=0.53
Mira *et al*[21]	DM type 2 and several comorbidities	Self-perceived health status, number (3 months)	74.6 (SD 17)	69.1 (SD 20)	Absolute diff 5.5 Relative % diff 7.4 95% CI −1.8 to 12.8 p=0.54 SES=0.3

CKD, chronic kidney disease; HbA1c, haemoglobin A1c; SES, standardised effect size.

significant effect size for the PHQ-8 outcome (intervention 7.6 points, control 8.6 points, difference 1.0 points, 95% CI −22.9% to 11.9%). Among the studies with no links to usual care hospitalisations (median time to hospitalisation 113.4 days intervention group vs 104.7 days control group, absolute difference=12.7 days, p=0.048, moderate certainty evidence), the MLHFQ (intervention group 35.2 score points, control group 23.9 points, absolute difference 11.3, 95% CI 5.5 to 17.1, p=0.007, moderate certainty evidence) showed a small reduction. The Personal Health Questionnaire (PHQ-8) showed no improvement (p=0.48, very low certainty evidence). Table 6 shows the details for primary outcomes, and table 7 shows the summary of findings table for studies without links to usual care. The certainty of the evidence for the depression score (PHQ-8) was downgraded to very low due to high risk of bias and imprecision (only 15 participants in the trial) (Donesky *et al*[18]). The certainty of the evidence for reduction of hospitalisations was moderate and downgraded due to serious risk of bias. The quality of life outcome (MLHFQ) had a moderate to large effect size and moderate certainty of the evidence due to serious risk of bias.

DISCUSSION

In light of the increasing role of digital health in the global health policy debate, we offer for the first time a systematic overview of interventional studies that assess digital telemedicine interventions for multimorbidity. Four studies had strong links to usual care. Among those studies, meta-analysis showed a moderate decrease in SBP of 8 mm Hg (moderate certainty evidence) in patients with diabetes mellitus and hypertension, a small to moderate decrease in HbA1c of 0.46 mg/dL (moderate certainty evidence) in patients with diabetes and chronic kidney disease as indicator diseases and moderate decrease in total cholesterol of 16.5 mg/dL (moderate certainty evidence) in the intervention groups in patients with diabetes and hypertension. However, there was an absence of evidence for self-perceived health status (low certainty evidence). Among the studies with no links to usual care hospitalisations (moderate certainty evidence), the MLHFQ (moderate certainty evidence) showed a small reduction. The Personal Health Questionnaire (PHQ-8) showed no evidence for improvement (very low certainty evidence). No evaluation of costs or cost-effectiveness was provided in the available articles. This is an important element for future studies as to determine the effectiveness of the interventions, costs are a necessary aspect to be in consideration.

Many studies reported a large number of outcomes, without clearly defining primary and secondary outcomes. There was only evidence for a very limited number of multimorbid diseases (diabetes mellitus, hypertension, COPD), leaving an evidence gap for most patients with other conditions. The definition of multimorbidity used in this review requires patients to have at least two physical diseases and does not include patients in which only one physical disease co-occurs with a diagnosed mental disease. This excludes a number of studies where multimorbidity is defined more broadly but for which interventions likely are very different. The lack of clearly defined primary outcomes in the included studies, together with the consistent lack of sample-size calculations and small numbers of participants across studies, leads to a very high risk of underpowered studies and false-positive observed effects. The short and varying follow-up times between 2 and 6 months may have implications as the measured

Table 5 Summary of findings table for studies with links to usual care

Summary of findings for the main comparison						
Patient or population: Patients with multimorbidity						
Setting: All settings/digital telemedicine with links to usual care						
Intervention: Digital telemedicine						
Comparison: Normal care						
Outcomes	**Anticipated absolute effects (95% CI)**		**Mean Standardised effect size**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with normal care	**Risk with digital telemedicine**				
Systolic blood pressure (SBP) follow-up: range 3–6 months	The mean systolic blood pressure was 139.7 mm Hg	MD 8 mm Hg lower (4.6 lower to 11.4 lower)	Moderate (0.5)	347 (3 RCTs)[16 20 21]	⊕⊕⊕◯ MODERATE† ‡ § ¶	Types of multimorbidity: diabetes mellitus and hypertension (2×) and diabetes mellitus and several other comorbidities
Haemoglobin A1c (HbA1c) assessed with: mg/dL (%) follow-up: range 3–6 months	The mean haemoglobin A1c was 6.8 mg/dL	MD 0.46 mg/dL lower (0.25 lower to 0.67 lower)	Small to moderate (0.41)	420 (3 RCTs)[16 20 21]	⊕⊕⊕◯ MODERATE‡ § ¶	Types of multimorbidity: diabetes mellitus and hypertension, diabetes mellitus and several other comorbidities, chronic kidney disease and heart failure
Total cholesterol assessed with: mg/dL follow-up: mean 3 months	The mean total cholesterol was 128.3 mg/dL	MD 16.5 mg/dL lower (8.1 lower to 25 lower)	Moderate (0.48)	225 (2 RCTs)[20 21]	⊕⊕⊕◯ MODERATE† ‡ ¶	Types of multimorbidity: diabetes mellitus and hypertension and diabetes mellitus and several other comorbidities
Self-perceived health status assessed with: proportion perceiving their health status as good or very good follow-up: mean 3 months	The mean self-perceived health status was 69.1%	Mean 74.6% higher	Small (0.3)	102 (1 RCT)[21]	⊕⊕◯◯ LOW§ ¶ **	Type of multimorbidity: diabetes mellitus and several other comorbidities

Wakefield *et al* (2012).
GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
*The risk in the intervention group (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).
†Risk of bias due to lack of blinding of outcome assessment (detection bias).
‡Risk of bias due to selective outcome reporting (reporting bias).
§Risk of bias due to lack of blinding of participants and personnel (performance bias).
¶Important biases were not adequately reported in the studies (unclear risk).
**Small number of participants and wide CIs.
MD, Mean difference.

outcomes can be transient and not sustainable in the longer term. A majority of studies had a serious risk of bias in at least two domains, in particular lack of blinding and selective outcome reporting. This is compounded by the small number of relevant randomised studies (n=6) with very few participants (n=699) that were not well conducted. An assessment of small study publication bias was not possible due to the heterogeneity of studies. In summary, the generalisability of our findings is limited. All of the studies in this review were published within the last 10 years, in high-income countries in privileged socioeconomic environments and with elderly patients, which is very likely due to the fact that digital technologies and e-Health interventions have only become more widespread and available recently. Increasingly, multimorbidity is becoming a problem of younger patients and people in low-income and middle-income countries which are currently not covered by the available evidence base.

It is difficult to examine the effect of the single elements of the interventions that contributed most to the pooled-effect sizes across studies. Interventions that included links to usual care reported larger benefits. This is consistent with our assumption at the outset that given that participants have multiple morbidity and more complex health needs, it seems highly likely that to be more effective in the long-term interventions would need to be linked to usual care (eg, through using electronic health records, involving physicians and nurses in goal setting, regular information exchange). We would also anticipate that links to usual care would be needed for interventions

Table 6 Primary outcomes in studies without links to usual care

Study	Multimorbidity	Outcomes	Intervention	Control	Results
Donesky *et al*[18]	COPD and heart failure	Personal Health Questionnaire-8 score (8 weeks)	7.2 (SD 6.3)	8.6 (SD 6.0)	Absolute diff 1.4 Relative % diff 16.3 95% CI −22.9% to 11.9% p=0.48 SES=0.22
Bernocchi *et al*[19]	COPD and heart failure	Reduction of hospitalisations—median time in days (12 weeks)	113.4	104.7	Absolute diff 12.7 Relative % diff 8.3 p=0.048 SES=0.38
Bernocchi *et al*[19]	COPD and heart failure	Minnesota Living with Heart Failure Questionnaire score (8 weeks)	23.9 (SD 14.2)	35.2 (SD 16.6)	Absolute diff 11.3 Relative % diff 47.3 95% CI 5.5 to 17.1 p=0.007 SES=0.73
		Minnesota Living with Heart Failure Questionnaire score (12 weeks)	32.8 (SD 14.2)	35.5 (SD 10.3)	Absolute diff 2.7 Relative % diff 7.6 95% CI −1.9 to 7.3 p=0.409 SES=0.22

COPD, chronic obstructive pulmonary disease; SES, standardised effect size.

to be safe, although we have no evidence from the systematic review regarding safety. However, for hypertension, the interventions that increased the frequency patients gave attention to measuring their BP or taking medication regularly showed the largest effect sizes. Therefore, we postulate that some of the observed effect of the digital telemedicine interventions might be due to reminding the patients of their disease and the respective treatment combined with increased self-monitoring. Self-monitoring has previously been shown to improve disease management for single diseases such as hypertension.[22] However, a plausible but undocumented side effect might include reduced quality of life due to an increased focus on morbidity.

A recent Cochrane review of interventions for improving outcomes in patients with multimorbidity in primary care and community settings similar to this review also only found a small number of relevant studies.[4] The authors concluded that interventions need to target specific risk factors in order to be effective. These findings are in line with the findings of this review that the effective interventions target specific common risk factors of many multimorbid diseases such as BP or cholesterol. The results of this review are also in agreement with studies of telemedicine interventions targeting specific individual risk factors such as BP where 'several randomised studies have documented a significant BP reduction with regular BPT compared with usual care and where additional benefits are observed when BPT is offered under the supervision of a team of healthcare professionals' (the mean systolic reduction was larger in the telemonitoring group by 5 mm Hg, compared with 8 mm Hg in our review).[23] Similar positive effects were observed for the effect of e-health and m-health interventions on HbA1c (pooled difference in HbA1c means= −0.37 mg/dL for e-health and −0.27 mg/dL for mobile phone, compared with −0.46 mg/dL in our review).[24 25] Two further Cochrane reviews of e-health interventions for anxiety and depression in children and adolescents with long-term physical conditions and of eHealth interventions for people with chronic kidney disease concluded that the evidence for e-health intervention was of low quality, with randomised trials with uncertain effects due to the heterogeneity of interventions and outcomes.[9 26] This supports an important conclusion of this review that future research needs to identify outcomes that are relevant to patients and needs to investigate which individual elements of interventions are effective.

Usually the management of multimorbidity is defined by multiple appointments, potentially competing treatment goals, and non-integrated care services for patients and multiple guidelines, challenges of prioritisation coordination with other professionals.[27] In summary, digital telemedicine interventions could improve the management of multimorbidity. However, overall, our findings suggest that current evidence for the use of digital

Table 7 Summary of findings table for studies without links to usual care

Digital telemedicine compared with normal care in multimorbidity care						
Patient or population: Patients with multimorbidity						
Setting: All settings—digital telemedicine without links to usual care						
Intervention: Digital telemedicine						
Comparison: Normal care						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Mean standardised effect size**	**No of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with normal care	**Risk with digital telemedicine**				
Personal Health Questionnaire-8 score (PHQ-8 score) assessed with: score follow-up: mean 8 weeks	The mean Personal Health Questionnaire-8 score was **8.6** score points	Mean **7.6 score points**	Small (0.22)	15 (1 RCT)[18]	⊕◯◯◯ VERY LOW† ‡ § ¶	Type of multimorbidity: chronic obstructive pulmonary disease (COPD) and heart failure
Reduction of hospitalisations assessed with: median time in days follow-up: mean 12 weeks	Median time until hospitalisation in the intervention group: 113.4 days control group: 104.7 days		Small (0.38)	112 (1 RCT)[19]	⊕⊕⊕◯ MODERATE** ††	Type of multimorbidity: COPD and heart failure
Minnesota Living with Heart Failure Questionnaire score assessed with: score (number) follow-up: mean 8 weeks	The mean Minnesota Living with Heart Failure Questionnaire score was **35.2** score points	Mean **23.9 score points**	Moderate to large (0.73)	112 (1 RCT)[19]	⊕⊕⊕◯ MODERATE** ††	Type of multimorbidity: COPD and heart failure

GRADE Working Group grades of evidence.
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
*The risk in the intervention group (with 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (with 95% CI).
†Important biases were not adequately reported in the studies (unclear risk).
‡Risk of bias due to lack of random sequence generation (selection bias).
§Risk of bias due to lack of allocation concealment (selection bias).
¶Small number of participants and wide confidence intervals.
**Risk of bias due to lack of blinding of participants and personnel (performance bias).
††Risk of bias due to incomplete outcome data (attrition bias).

telemedicine in multimorbidity is limited and interventions have rarely been evaluated in a systematic fashion. In spite of the considerable role digital telemedicine has taken in public and professional debates in healthcare over the last 15 years, the implementation of digital telemedicine interventions for patients with multimorbidity cannot be recommended because of the weak evidence. Where health services are implementing, it seems sensible to integrate interventions with usual care and adapt them to the local context to not inappropriately divert resources from alternative, non-digital approaches. After implementation, continuous evaluation will help improve practice and also add to the still small evidence base for digital telemedicine for multimorbidity. It is important to ensure interventions are implemented with relevant outcome parameters, determined ideally by taking into account the preferences of patients and healthcare providers and in the best interest of society and the overall health systems and not just as assumed progressive prestige projects. Future high-quality interventional research is needed that includes longer periods of follow-up and should investigate which components of

telemedicine are most effective and how usual care, in and across sectors, can best be integrated avoid inappropriately diverting resources from alternative, non-digital approaches. It should be considered to include realistic evaluation approaches because of the importance that particular contextual factors could have on the implementation effectiveness of the interventions of interest. We anticipate that more evidence will become available in the future requiring updates of this review to inform policy makers and research appropriately.

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Appendix A – Search terms

Search Strategy: Database: Ovid MEDLINE(R) <1900 to April Week 2 2019>
1 Comorbidity/
2 (comorbid* or co-morbid*)
3 (multimorbid*)
4 (multidisease? or (multiple adj (ill* or disease? or condition? or syndrom* or disorder?)))
5 or/1-4
6 Chronic disease/
7 (chronic* adj3 (disease? or ill* or care or condition? or disorder* or health* or medication* or syndrom* or symptom*))
8 or/6-7
9 5 or 8
10 diabetes mellitus/ or diabet*
11 hypertension/ or (hypertens* or "high blood pressure?")
12 heart diseases/ or (((heart or cardiac or cardiovascular or coronary) adj (disease? or disorder? or failure)) or arrythmia?)
13 cerebrovascular disorders/ or ((cerebrovascular or vascular or carotoid* or arter*) adj (disorder? or disease?))
14 asthma/ or asthma*
15 pulmonary disease chronic obstructive/ or (copd or (pulmonary adj2 (disease? or disorder?)))
16 hyperlipidemia/ or (hyperlipidem* or Hypercholesterolemia* or hypertriglyceridemia*)
17 Thyroid diseases/ or ((thyroid adj (disease? or disorder)) or hyperthyroid* or hypothyroid*)
18 arthritis rheumatoid/ or rheumatoid arthritis
19 mental disorders/ or (((mental or anxiety or mood or psychological or sleep) adj (disease? or disorder?)) or ((substance or drug or marijuana or cocaine or Amphetamine) adj2 abuse) or depression or schizophren* or psychos* or "substance abuse" or addiction?)
20 epilepsy/ or (epileps* or seizure?)
21 hiv infections/ or (HIV or acquired immune* deficiency syndrome? or (aids adj (associated or related or arteritis)))
22 neoplasms/ or (neoplasm? or cancer?)
23 kidney diseases/ or (kidney adj (disease? or disorder?))
24 liver diseases/ or (liver adj (disease? or disorder?))
25 osteoporosis/ or osteoporosis
26 or/11-25
27 ((coocur* or co-ocur* or coexist* or co-exist* or multipl*) adj3 (disease? or ill* or care or condition? or disorder* or health* or medication* or symptom* or syndrom*))
28 chronic*,hw.
29 27 or 28
30 26 and 29
31 Telemedicine/
32 Internet/
33 communications media/
34 Programmed Instruction as Topic/
35 Computers, Handheld/
36 Mobile Applications/
37 Cell Phones/
38 ((sms or mms) and messag*).tw.
39 apps.tw.

40 “text messag*”.tw.
41 multimedia messag*.tw.
42 facebook.tw.
43 email*.tw.
44 (twitter or tweet*).tw.
45 social media*.tw.
46 ((mobile* or cell or smart*) and phone).tw.
47 (ios or android*).tw.
48 (ipad* or iphone* or ipod*).tw.
49 (tablet* and computer*).tw.
50 ((online or web*) and (education* or train*)).tw.
51 personal digital assistant*.tw.
52 (e-health or ehealth or mhealth or m-health or telehealth* or telemedicine*).tw.
53 or/51-52
54 randomized controlled trial.pt
55 controlled clinical trial.pt
56 random*
57 (control* adj2 (trial? or study or studies))
58 ((double or single or triple or treble) adj2 blind*)
59 (quasi-experiment* or quasiexperiment*)
60 Double-blind method/
61 random allocation/
62 single-blind method/
63 ((double or single or triple or treble) adj2 blind*)
64 (quasiexperiment* or quasiexperiment*) OR interrupt* time series
65 or/54-64
66 30 AND 53 AND 65

Appendix B

Table 4. Excluded studies and reasons for exclusion

Study	**Reason for exclusion**
Liddy et al. (2008)	Not meeting definition of multi-morbidity (risk for functional decline or physical deterioration)
Bowles et al. (2009)	Not meeting definition of multi-morbidity (heart failure or diabetes)
Takahashi et al. (2010)	Not meeting definition of multi-morbidity (Mayo Clinic Elder Risk Assessment scores)
Takahashi et al. (2012)	Not meeting definition of multi-morbidity (Elder Risk Assessment Index)
Schweier et al. (2014)	Not meeting definition of multi-morbidity (Coronary Heart Disease or chronic back pain)
Looman et al. (2015)	Not meeting definition of multi-morbidity (children with medical complexity)
Donate-Martinez et al. (2016)	Not meeting definition of multi-morbidity (older adults with chronic conditions at high or moderate risk of hospital admissions)
Foley et al. (2016)	Not meeting definition of multi-morbidity (BMI of 30.0–44.9 kg/m2 and a current diagnosis of hyper- tension, type 2 diabetes, and/or hyperlipidaemia)
Or et al. (2016)	Not meeting definition of multi-morbidity (type 2 diabetes mellitus and/or hypertension)
Bender et al. (2017)	Not meeting definition for multi-morbidity (diabetes type 2 and BMI ≥23)
Lambert et al. (2017)	No RCT (conference abstract)
Bakas et al. (2018)	Not meeting definition of multi-morbidity (healthy older adults included)
Looman et al. (2018)	Not meeting definition of multi-morbidity (children with medical complexity)
Sewick et al. (2018)	Study protocol
Valdivieso et al. (2018)	Not meeting definition of multi-morbidity (high complexity, according to having a probability >98% of using more than 10 non-planned admissions in the following 12 months according to the score of the GeChronic predictive model)
Choudry et al. (2019)	Not meeting definition of multi-morbidity (hyperlipidaemia, hyper- tension, or diabetes)

Appendix C. Summary and risk of bias tables

Yoo et al., 2009	
Methods	Randomized, controlled trial
Participants	The study location was a university hospital in (Korea University) and a community health centre (Guro-Gu Public Health Centre) in Korea. Fifty-seven (n=57) were from the general hospital and sixty-six (n=66) from the Public Health Centre. "62 participants were randomized to the intervention group and 61 participants were randomized to the control group. The inclusion criteria were (i) a diagnosis of both Type 2 diabetes and hypertension at least 1 year previously by a physician; (ii) HbA1C 6.5-10.0%; (iii) blood pressure >130/80 mmHg; and (iv) body mass index (BMI) ≥23.0 kg/m2 (overweight according to Asia-Pacific criteria). The exclusion criteria were (i) severe diabetic complications (e.g. diabetic foot or severe diabetic retinopathy); (ii) liver dysfunction with aspartate aminotransferase or alanine aminotransferase >2.5 times the reference level, or renal dysfunction (serum creatinine > 132 μmol/l); (iii) medical history of congestive heart failure, angina pectoris, myocardial infarction, or stroke based on a physician's diagnosis; (iv) pregnancy or lactation; or (v) other medical problems that could affect study results or trial participation."
Interventions	INTERVENTION: A Ubiquitous Chronic Disease Care System using cellular phones and the internet "Patients in the intervention groups received a cellular phone (LG-SV280; LG Electronics, Seoul, Korea) with a modular blood glucose measuring device (Anycheck; Insung Information Co., Seoul, Korea), strips, and lancets. They also received an automatic blood pressure monitoring device (T5M; Omron, Kyoto, Japan), as well as body weight scales (HD308; Tanita, Tokyo, Japan). The UCDC system sent out an alarm on the cellular phone to remind the participant to measure their blood glucose, blood pressure twice a day (before breakfast and bedtime) and body weight once a day (before breakfast). The Anycheck device attached to their cellular phone conducted the glucose measurements and automatically sent the results to a central study database. As soon as participants transmitted their glucose measurement through their cellular phones, they immediately received messages of encouragement, reminders, and recommendations according to a pre-defined algorithm that was developed by endocrinologists, dieticians and nurses at Korea University based on the American Diabetes Association (ADA) Guidelines and the Korean Staged Diabetes Management Guidelines. Second, the UCDC system automatically recorded participant's exercise time using the short message service (SMS), which was predefined according to each patient's daily schedule. Participants received information via SMS three times a day regarding healthy diet and exercise methods, along with general information about diabetes, hypertension and obesity. Furthermore, using the internet website, physicians could follow participant's trends in blood glucose levels, blood pressure and body weight changes, allowing them to send individualized recommendations to patients when needed (http://kumc.drub.co.kr)." CONTROL: Conventional Healthcare "Patients in the control group visited their clinic according to their routine schedule and received the usual out-patient treatment from their physicians during the study period."
Outcomes	Multiple metabolic parameters were assessed after 12 weeks:

	Body weight, BMI and waist circumference, systolic and diastolic office blood pressure, right/left baPWV, Hba1c, fasting glucose, Homeostasis model assessment insulin resistance, total cholesterol, HDL-cholesterol, LDL-Cholesterol, Triglyceride, levels of adiponectin, hsCRP, IL-6
Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Selective reporting (reporting bias)	High risk	Outcomes were only compared between control and intervention group for those with a statistically significant result.
Other bias	Unclear risk	Insufficient information
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of participants (performance bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of personnel (performance bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Incomplete outcome data (attrition bias) Patient outcome	Low risk of bias	Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).

Wakefield et al., 2011 (1) and 2012 (2)	
Methods	Single-Centre Randomized Controlled Clinical Trial
Participants	The study was conducted at the Iowa City VA Medical Centre (ICVAMC) in the United States. The target population was compromised of patients with type 2 diabetes mellitus and hypertension treated by a veteran affairs (VA) primary care provider. 107 participants were randomized to usual care, 93 participants were randomized to the high-intensity intervention and 102 were randomized to the low-intensity intervention. "The inclusion criteria were coexisting diabetes and hypertension, a landline telephone in the home, receipt of primary care from the VA in the previous 12 months, and anticipation of receiving primary care for the duration of study enrolment. Exclusion criteria were legal blindness, residency in a long-term care facility, and diagnoses indicating dementia or psychosis."
Interventions	"The intervention consisted of a nurse management component and close surveillance via home telehealth. Both Intervention groups received the home-

	telehealth device (Viterion-Bayer Panasonic) uses a standard telephone line to enable data transmission between the patient's home and the study centre. Using the device, intervention patients entered blood pressure and blood glucose measurements and responded to standardized questions based on their group assignment. Patients then received appropriate automated responses depending on how they answered the device prompt. Correct responses were reinforced, and incorrect responses were reviewed and explained. The device automatically downloads data each night, making the patient information available for the nurses to review the next day. The device also allows individualized messages to be transmitted to subjects. Trended data on BP, BG and responses to prompts were viewed via a secure Web site by the nurse. These data enabled the nurse to efficiently provide close surveillance in order to provide earlier intervention when clinical parameters were out of control or the subject indicated through his responses to the device prompts that additional health information or support was needed. Both intervention groups received care management from a study nurse. At enrolment, the subject's primary care physician was contacted for BP and BG parameters that should trigger a call to the physician for changes in the treatment plan. Each weekday, the study nurse reviewed responses from intervention group subjects and determined whether the subject needed follow-up, additional health information, increased monitoring, compliance strategies, problem resolution facilitation, or contact with the subject's physician. " INTERVENTION: High-Intensity Intervention "Subjects were instructed to measure blood pressure daily and blood glucose as directed by their physicians (no change in frequency of home blood pressure monitoring). A branching disease management algorithm was programmed into the device and focused on diet, exercise, smoking cessation, foot care, advice for sick days, medications, weight management, preventive care, behaviour modification and lifestyle adjustments. Subjects received standard prompts each day and a rotation of questions and education content." INTERVENTION: Low-intensity group "Subject were instructed to measure BP daily and BG as directed by their physician. Subjects in this group responded to a small subset of questions from the larger set of questions used with the high-intensity group. Every day subjects in this group were asked "Have you taken all your medication as prescribed?" In addition, subjects were prompted with one additional question each day focused on diet, exercise, foot care, or medication side effects. The questions did not use the branching algorithms used for the high-intensity group, rather they used yes/no or multiple responses." CONTROL: Usual care "Usual care subjects scheduled follow-up appointments with the primary care clinic in the usual manner. They had access to their nurse care manager employed by the medical centre. "
Outcomes	Outcomes were assessed at 6 months (end of the intervention) and 12 months (to determine the maintenance of outcomes following completion of the intervention). The primary outcomes were: Hba1c and SBP. Secondary outcomes were Depressive symptoms measured using the Geriatric Depression Scale (GDS) and patient adherence measured on the self-reported medication taking scale for hypertension and a validated regiment adherence scale for diabetes mellitus. Secondary outcomes (primary outcomes reported in Wakefield et al. 2016). Patient adherence measured on the self-reported medication taking scale for hypertension and a validated regiment adherence scale for diabetes mellitus. Self-efficacy was measured using the Self-Efficacy to Manage Disease in General scale. This scale contains 5 items that rate the patient's confidence in managing a chronic illness using Likert-type scale responses.

Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Allocation concealment (selection bias)	Low risk	"Group assignments were made by the study nurses using sequentially numbered, sealed, opaque envelopes prepared in advance by the project director" (p.255)
Selective reporting (reporting bias)	Unclear	No protocol published before publication of results. In publication of results all outcomes reported.
Other bias	Unclear risk	Insufficient data
Blinding of outcome assessment (detection bias) Patient outcome	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of participants (performance bias) Patient outcome	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of personnel (performance bias) Patient outcome	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Incomplete outcome data (attrition bias) Patient outcome	Low risk	Insufficient information to permit judgement of 'Low risk' or 'High risk'. To account for missing data, primary analyses were performed using a multiple-imputation approach

Rifkin et al., 2013	
Methods	Single-centre Randomized controlled trial (feasibility)
Participants	Patients attending the Chronic Kidney Disease (CKD)/Hypertension clinic at the Veteran Affairs San Diego, California 30 participants were randomized to the intervention, 15 were randomized to the control arm. "Inclusion criteria were stage 3 CKD (estimated glomerular filtration rate of less than 60 ml/min/1.73m2); established hypertension [(systolic blood pressure (SBP) >140 or diastolic blood pressure (DBP) >90 in-clinic or on reported home readings]; and age more than 50 years. Patients had to be community-dwelling and currently self-managing their medications. Exclusion criteria were the presence of a clear secondary cause for HTN (e.g. aldosterone producing tumour), or estimation by clinic physicians that the individual was within 6 months of requiring dialysis or dying from other causes."
Interventions	INTERVENTION "The intervention consisted of two integrated subunits: the A&D Medical UA-767PBT fully automated oscillometric BP unit (A&D Medical, San Jose, California, USA) and the home health hub (HHH). The HHH receives BP and pulse data through Bluetooth from the BP unit, and relays the data through the internet to a secure

	website. The website allowed for viewing of BP data sorted by participant. Patients were asked to measure and record their BP at home according to their physicians' instructions; no study specific instructions were given regarding the frequency of measurement. On a weekly basis the study physicians and pharmacist met to review BP logs of each participant. If a patient had consistently above-goal readings during the prior week, one of the study physicians or pharmacists called to discuss the readings, provide counselling, or adjust medications. Additional in-person follow-up was scheduled at the discretion of the study team. The number of BP readings transmitted by the system for each participant was totalled on a monthly basis, and monthly running averages were created for each participant." CONTROL "Patients were asked to measure and record their BP at home according to their physicians' instructions; no study specific instructions were given regarding the frequency of measurement. They were told that study personnel would be checking in with them at the end of 6 months for an end-of-study visit related to BP."
Outcomes	Outcomes reported were systolic blood pressure (mmHg), diastolic blood pressure (mmHg), Mean arterial pressure (mmHg), creatinine (mg/dl), eGFR (ml/min/1,73m2), total number of medications, number of blood pressure medications, Morisky Medication Adherence Scale.
Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	Unclear risk	Insufficient information
Allocation concealment (selection bias)	Low risk	"Random assignment occurred after the consent and initial enrolment interview, using opaque envelopes containing odd (intervention) or even (control) study numbers." (p.3)
Selective reporting (reporting bias)	High risk	No prespecified outcome parameters; no pre-published protocol or pre-specified outcomes in methods section.
Other bias	High risk	"Limitations of the current study include the small sample size and short duration; we cannot predict whether the intervention would be robustly effective over longer periods of time. Given our small sample, our results do not reach statistical significance for BP between groups, although we believe the magnitude of the difference we found is clinically important."
Blinding of outcome assessment (detection bias) Adherence measure	High risk.	No blinding for outcome assessment.
Blinding of outcome assessment (detection bias) Patient outcome	High risk.	No blinding for outcome assessment.
Blinding of participants (performance bias)	High risk.	No blinding of participants

Adherence measure		
Blinding of participants (performance bias) Patient outcome	High risk.	No blinding of participants
Blinding of personnel (performance bias) Adherence measure	High risk.	No blinding of personnel.
Blinding of personnel (performance bias) Patient outcome	High risk.	No blinding of personnel.
Incomplete outcome data (attrition bias) Adherence measure	Low risk.	Two participants per arm (11% control arm, and 5.5% intervention arm) lost to follow-up. Otherwise complete outcome data.
Incomplete outcome data (attrition bias) Patient outcome	Low risk.	Two participants per arm (11% control arm, and 5.5% intervention arm) lost to follow-up. Otherwise complete outcome data.

Mira et al., 2014	
Methods	Single-blind randomized controlled trial
Participants	Patients were recruited from health centres in the health districts of Alicante and Bilbao, Spain. 102 patients were randomized, 51 in the control group and 51 in the experimental group. "Inclusion criteria were multimorbid patients taking multiple medications, older than 65 years, with a Bartel score of more than 60, living in their own home, and able to manage the administration of their medication at home. Exclusion criteria were refusing to participate in the study or more than 90 years old."
Interventions	INTERVENTION "The intervention group was composed of people who used this tool for 3 months. A tablet-based medication self-management application (ALICE) was designed to help patients to remember to take all their medications at the correct doses, distinguish between drugs to avoid confusions, avoid known potential interactions and common errors in use of the medications, and know how to properly store the medications. The application was also designed to remember doctors' recommendations for healthy habits, such as physical exercise and diet. The tablet used was a BQ Verne Plus 3G 7-inch with an easy-to-use touch screen with a tactile screen and an iPad 2 were used. The ALICE app was designed to work with

	personalized prescriptions and recommendations given to patients. A second function established a customized system of alerts and reminders to remind patients when to take their medications and to put into practice healthy habits (e.g. intake with meals). A third function was to enable monitoring of the level of adherence to the prescriptions and medical advice, the tablet connecting via a wireless or 3 G network with the study monitoring system. When it's time to take a medication, an alarm sounds and the patient accesses the main menu of the application. The app reports the medications the patient must take in a day and reports medicines that the patient has forgotten to take that day." CONTROL "The control group was composed of participants who did not use the application."
Outcomes	The primary outcomes was adherence to treatment measured by the 4-item Morisky Medication Adherence Scale (MMAS-4). Further outcomes were the number of missed doses and of medication errors, the self-perceived health status, the level of glycated haemoglobin (mmol/mol), the cholesterol level and blood pressure (Systolic and diastolic).
Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk': „Patients were randomly assigned to the control or experimental group"
Allocation concealment (selection bias)	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Selective reporting (reporting bias)	Low risk	In protocol primary outcome measure was adherence (MMAS-4) and the secondary outcome measure was "safety medication use". In published results there are also self-perceived health status, glycated haemoglobin, cholesterol and blood pressure reported.
Other bias	High risk	"The small number of participants and the number of months using ALICE affected our ability to detect differences between the group using the ALICE application and the control group (e.g., in relation to biomarkers) as well as our ability to generalize the results." There is some evidence that the MMAS-4 overestimates the adherence, yielding higher rates than those obtained from pill counts." (p.11)
Blinding of outcome assessment (detection bias) Adherence measure	Low risk	"To maintain the blinding and be able to link the pre and post measurements, patients were assigned codes based on their date of birth and initials." (p. 4)
Blinding of outcome assessment (detection bias) Patient outcome	Low risk	"To maintain the blinding and be able to link the pre and post measurements, patients were assigned codes based on their date of birth and initials." (p. 4)
Blinding of participants (performance bias)	High risk	Not blinded

Adherence measure		
Blinding of participants (performance bias) Patient outcome	High risk	Not blinded
Blinding of personnel (performance bias) Adherence measure	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Blinding of personnel (performance bias) Patient outcome	Unclear	Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Incomplete outcome data (attrition bias) Adherence measure	Low risk.	No loss to follow-up, no exclusion from analysis.
Incomplete outcome data (attrition bias) Patient outcome	Low risk.	No loss to follow-up, no exclusion from analysis.

Donesky et al., 2017	
Methods	Controlled, nonrandomized trial
Participants	Patients were recruited at pulmonary rehabilitation programs in the San Francisco Bay Area and from previous research studies of COPD and heart failure. Seven (n=7) patients were assigned to the tele-yoga intervention and 8 (n=8) to the control intervention. "Inclusion criteria were (i) provider diagnosed COPD, (ii) provider permission for participation, (iii) speak English, (iv) be older than the age of 40 years, (v) have NYHA class I-III systolic or diastolic heart failure, (vi) have access to television and a broadband internet connection, (vii) have space to practice yoga at their home and (viii) be willing to have a research assistant connect videoconferencing equipment to their home television. Exclusion criteria were (i) hospitalization within the three months before enrolment, (ii) cognitive impairment as determined by a score of <3 on the Mini-Cog or (iii) oxygen saturation <85% on 6 liters of nasal oxygen."
Interventions	INTERVENTION "Those assigned to the TeleYoga group were provided a yoga mat, automatic blood pressure cuff, oximeter, and scale. Videoconferencing equipment was installed in the homes of the intervention group participants during the baseline home visit. They were taking their own blood pressure, weight, heart rate, and oxygen saturation levels before and after each class and reported them to the TeleYoga nurse.

	Participants were visually monitored for safety during each session by the TeleYoga nurse via the multipoint videoconferencing system interface. The nurse called each participant on the telephone before and after each TeleYoga session to assess symptoms of HF and COPD. TeleYoga classes were offered twice weekly for 8 weeks to participants in their homes using videoconferencing. The yoga intervention was provided by the same certified yoga instructor/physical therapy assistant. The yoga protocol was based on the previously tested yoga programs for COPD and HF, originally developed by a certified Iyengar yoga instructor with experience working with individuals with chronic disease. Classes began with 10 minutes of relaxation followed by ca. 35 minutes of poses and concluded with 15 minutes of meditation and relaxation. All participants could see the yoga teacher (and vice versa) and received personalized instruction but could not see each other. If participants had questions they could talk with the teacher." CONTROL "Participants assigned to the attention control group received educational materials in the mail once per week for 8 weeks. The intervention nurse called each week for 15-30 minutes to discuss the educational information so as to provide and equal number of phone or mail contacts as in the intervention group. The educational materials covered the following topics: evaluating health information, problems sleeping, elder abuse, flu vaccinations, accessing information about therapy, accessing information about medications online, depression and a low sodium diet."
Outcomes	Outcomes measured were physical function, Quality of Life, and symptoms. Physical function was defined as muscle strength and endurance. Strength was tested via upper body (biceps) and lower body (quadriceps) testing using the total number of arm curls using two-pound hand weights and chair stands completed in 30 seconds. Endurance was measured with the home-adapted 6-min walk test that measured number of feet walked within 6 minutes. Validated QOL questionnaires included the St. George's respiratory questionnaire that is used for patients with COPD and the Kansas City Cardiomyopathy Questionnaire (KCCQ) used for measurement in heart failure patients. Symptoms of depression, dyspnoea, and insomnia were evaluated at baseline and after study completion. Depression was evaluated using the validated Personal Health Questionnaire. Dyspnoea was measured using the Dyspnea-12 questionnaire and dyspnoea and distress related to dyspnoea were measured using the modified Borg scale at the end of the 6-min walk. Sleep was measured using the General Sleep Disturbance Scale.
Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	High risk	"The first seven patients were enrolled in the intervention group and the following eight in the control group" (p. 2).
Allocation concealment (selection bias)	High risk	"The first seven patients were enrolled in the intervention group and the following eight in the control group" (p. 2)
Selective reporting (reporting bias)	Low risk	All outcomes from the methods section were also reported in the results section.
Other bias	High risk	"The characteristics of the four participants who declined enrolment in the study could not be compared with the study participants. Reports of vital signs before and after TeleYoga sessions were not observed, and there is a possibility that they were fabricated to please investigators, although this is thought

		highly unlikely. The time allotment ("dose") of the intervention and control intervention was not equal."
Blinding of outcome assessment (detection bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of participants (performance bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Blinding of personnel (performance bias) Patient outcome	Unclear risk	Insufficient information to permit judgement of 'Low risk' or 'High risk';
Incomplete outcome data (attrition bias) Patient outcome	Low risk.	One person lost to follow-up in intervention and in control arm. Otherwise no loss to follow-up.

Bernocchi et al., 2017	
Methods	Randomized open controlled multicentre trial
Participants	Patients were recruited consecutively from the Cardiology and Pulmonary Departments of three rehabilitation hospitals in Italy (Salvatore Maugeri Foundation IRCCS Institutes of Lumezzane and Montescano; and San Raffaele Pisana IRCCS, Rome). Fifty-six participants were included in the intervention group and fifty-six participants were recruited in the control group. "Inclusion criteria were (i) Age over 18 years, (ii) Chronic obstructive pulmonary disease (COPD) GOLD classification (classes B, C, and D) (iii) Systolic and/or diastolic heart failure (HF) New York Heart Association (NYHA) classes II, II, and IV (iv) At least one hospitalization or visit due to HF or COPD exacerbation in the previous 12 months (v) Signed informed consent Exclusion criteria were (i) Physical activity limitations due to noncardiac and/or pulmonary conditions (ii) Limited life expectancy (iii)Severe cognitive impairments"
Interventions	INTERVENTION "Patients in the intervention group received an educational intervention from a nurse tutor (NT) and a physiotherapist tutor (PT) and were followed by both during the Telereab-HBP, which lasted 4 months. The NT made a weekly structured phone call to each participant collecting information about the disease status and symptoms, offering advice regarding diet, lifestyle and medications, previously defined with the cardiologist and pulmonologist supervising the programme. Patients were provided with a pulse oximeter (GIMA, Milan, Italy), and a portable one-lead electrocardiograph (Card Guard Scientific Survival Ltd., Rehovot, Israel) for real time monitoring of vital signs. The PT designed a personalized exercise programme for each patient who were provided with mini-ergometer, pedometer and diary. The

	number/intensity of training sessions according to patients' progress were adjusted during 4 months or in the case of problems. The "basic level" of programme consisted of 15-25 min of exercise with mini-ergometer without load and 30 minutes of callisthenic exercises, performed three times/week and free walking twice a week. The "high level" consisted of 30-45 minutes of mini-ergometer with incremental load (from 0 to 60 W), 30-40 minutes of muscle reinforcement exercises using 0.5 kg weights and pedometer-based walking, performed from 3 to 7 days/week." CONTROL "On discharge from in-hospital rehabilitation, patients in the control group received the standard care program including medications and oxygen prescription, visits from the general practitioner, and in-hospital check-ups on demand. Patients were free to conduct physical activity without any monitoring or reinforcement provided by the hospital. At study enrolment, patients were instructed in an educational session about the desirability of maintaining a healthy lifestyle and were invited to practice daily physical activity as preferred."
Outcomes	The primary outcome was exercise tolerance improvement measured by difference in the meters walked in the 6MWT. The secondary outcomes were: (1) reduction of hospitalizations for cardiovascular and/or respiratory diseases, (2) reduction of hospitalizations for all causes, (3) improvement of QoL in the MLHFQ and the CAT, (4) reduction in impairment/disability evaluated by the Barthel Index, (5) reduction in dyspnoea evaluated by the MRC scale, (6) reduction in dyspnoea and fatigue at rest evaluated by the Borg scale, (7) improvement of physical activity profile evaluated by the PASE questionnaire and daily steps reported by patients, and (8) improvement of oxygenation (PaO2/FiO2). In the intervention group only, it was also evaluated: (1) adherence to at least 70 % of the prescribed rehabilitation sessions, (2) qualitative evaluation of patients' compliance to the rehabilitation program, (3) use of health services, calculated as total and per-person number of PT and NT scheduled and unscheduled calls, total and per-person number of PT home visits, total and per- person number of educational sessions, and total and per-person time spent by the PT and NT in the study.
Notes	

Risk of Bias		
Bias	**Authors' Judgement**	**Support for Judgement**
Random Sequence Generation (Selection Bias)	Low risk	A computer-generated table to allocate patients in fixed blocks of 4.
Allocation concealment (selection bias)	Low risk	In order to prevent selection bias, the allocation sequence was concealed from the investigators enrolling and assessing patients, in sequentially numbered, opaque, sealed envelopes. (Study Protocol, p. 2)
Selective reporting (reporting bias)	Low risk	All outcomes from the protocol were reported in the final article
Other bias	Low risk	-
Blinding of outcome assessment (detection bias) **Adherence measure**	Low risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)
Blinding of outcome assessment (detection bias) **Patient outcome**	Low risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)

Blinding of participants (performance bias) Adherence measure	High risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)
Blinding of participants (performance bias) Patient outcome	High risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)
Blinding of personnel (performance bias) Adherence measure	High risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)
Blinding of personnel (performance bias) Patient outcome	High risk	Due to the nature of the intervention, neither the patients nor the physicians were blinded to patients' group allocation; however, outcome assessors and data analysts will be blinded. (Study Protocol p.3)
Incomplete outcome data (attrition bias) Adherence measure	High risk	"Overall, 11 (20%) patients in the intervention group were lost to follow-up, and 21 (37.5%) in the control group (p=0.0365)" (p. 3)
Incomplete outcome data (attrition bias) Patient outcome	High risk	"Overall, 11 (20%) patients in the intervention group were lost to follow-up, and 21 (37.5%) in the control group (p=0.0365)" (p. 3)

Supplement A – Secondary outcomes

a. Secondary outcomes for studies with links to usual care

Two studies (Yoo et al., Rifkin et al.) with links to usual care reported clinical outcomes (Table 1A). There was a large and significant effect size (SES = 0.94) for Adiponectin (Yoo et al.) and small, non-significant effect sizes for Creatinine (SES = 0.12) and estimated glomerular filtration rate (SES = 0.22) (Rifkin et al.).

Table 1A. Clinical outcomes in studies with links to usual care (2)

Study	**Multimorbidity**	**Outcomes**	**Intervention**	**Control**	**Results**
Yoo et al.	DM Type 2 and hypertension	Adiponectin µg/ml (3 months)	7.5 (SD 4.3)	3.5 (SD 4.2)	Absolut diff 4.0, Relative % diff 214.0% p<0.001 SES = 0.94
Rifkin et al.	CKD and heart failure	Creatinine mg/dL (6 months)	2.2 (SD 0.8)	2.3 (SD 0.84)	Absolut diff 0.15 Relative % diff 6.5 p=0.12 SES = 0.12
		Estimated glomerular filtration rate ml/min (6 months)	37.9 (SD 16.7)	34.5 (SD 13.2)	Absolut diff 3.4 Relative % diff 9.0 p=0.14 SES = 0.22

SES = Standardized Effect Size, SD = Standard Deviation.

Three studies with links to usual care reported medication adherence outcomes (Mira et al., Wakefield et al. (2), Rifkin et al.) (Table 2A). The reported outcomes were the Morisky medication adherence scale (Mira et al., Rifkin et al.), the number of medication errors (Mira et al.), medication adherence for diabetes mellitus (Edward's) scale (Wakefield et al.), medication taking adherence for blood pressure (Wakefield et al.) and the total number of medication (Rifkin et al.). There were only two significant results (Mira et al.). Medication adherence (Morisky scale) was significantly improved, albeit with a

small effect size (SES = 0.12). Furthermore, with a moderate effect size of 0.47 the reduction of medication errors (Mira et al.) was reported.

Table 2A. Adherence outcome in studies with links to usual care

Study	**Multimorbidity**	**Outcomes**	**Intervention**	**Control**	**Results**
Mira et al.	DM type 2 and several comorbidities	Morisky Medication Adherence Scale-4 points (mean) (3 months)	7.4 (SD 0.9)	7.3 (SD 0.7)	Absolut diff 0.1 Relative % diff 1.4 p<0.001 SES = 0.12
		Medication errors (number)	Several subscales/timepoints		p=0.02 SES = 0.47
Wakefield et al. (2)	DM Type 2 and hypertension	Medication adherence for diabetes mellitus score on Edward's scale (6 months)	Low - 3.4 (SD 0.4) High - 3.2 (SD 0.5)	3.3 (SD 0.5)	Absolut diff (+0.1; -0.1) Relative % diff (3.1; -3.1) High intensity p=0.21 SES = 0.18 Low intensity p=0.21 SES. = 0.17
		Medication adherence for diabetes mellitus – score on Edward's scale (12 months)	Low - 3.4 (SD 0.6) High - 3.2 (SD 0.5)	3.3 (SD 0.5)	Absolut diff (+0.2; -0.1) Relative % diff (+3.1; -3.1) High intensity p=0.21 SES = 0.18 Low intensity p = 0.21 SES = 0.17
		Medication taking adherence % - blood pressure (12 months)	Low - 99.8 (SD 1.4) High - 99.6 (SD 2.0)	99.6 (SD 2.2)	Absolut diff (+0.2;0) Relative % diff (0.2;0) High intensity p = 0.79 SES = 0.04 Low intensity p = 0.79

					SES = 0.04
		Medication taking adherence % - blood pressure (12 months)	Low - 99.7 (SD 1.4) High - 100 (SD 0)	98.9 (SD 6.0)	Absolut diff (+0.8; 1.1) Relative % diff (+0.8; +1.1) High intensity p=0.20 SES = 0.18 Low intensity p = 0.2 SES = 0.18
Rifkin et al.	CKD and heart failure	Morisky Medication Adherence Scale points (6 months)	7 (SD 1.2)	7.2 (SD 1.4)	Absolut diff 0.2 Relative % diff 2.9 p=0.17 SES = 0.16
		Total number of medications (6 months)	12 (SD 4.6)	12.8 (SD 5.1)	Absolut diff 0.8 Relative % diff 6.2 p=0.33 SES = 0.17
		Number of blood pressure medication (6 months)	4 (SD 1.2)	3.9 (SD 1.3)	Absolut diff 0.1 Relative % diff 2.5 p=0.91 SES = 0.08

SES = Standardized Effect Size, SD = Standard Deviation.

Self-efficacy outcomes were reported by one study in this category (Wakefield et al. (2)). The results were non-significant (Table 3A).

Table 3A. Self-efficacy outcome in studies with links to usual care

Study	**Multimorbidity**	**Outcomes**	**Intervention**	**Control**	**Results**
Wakefield et al. (2)	DM Type 2 and hypertension	Self-efficacy score points (6 months)	Low - 8.1 (SD 1.9) High - 7.7 (SD 2.0)	8.1 (SD 1.8)	Absolut diff (0;0.4) Relative % diff (0;5.2) High intensity p=0.19 SES = 0.19 Low intensity p = 0.19 SES = 0.18

		Self-efficacy scores (12 months)	Low - 8.3 (SD 2.0) High- 7.8 (SD 1.9)	8.3 (SD 1.9)	Absolut diff (0;0.5) Relative % diff (0;6.4) High intensity p = 0.53 SES = 0.09 Low intensity p = 0.53 SES = 0.09

SES = Standardized Effect Size, SD = Standard Deviation.

a. Secondary outcomes for studies without links to usual care

Both studies (Bernocchi et al., Donesky et al.) reported physical functioning outcomes (Table 4A). The outcomes were endurance at the 6-minute walk (6 MW) in feet (both studies), the Barthel score, the COPD assessment test, the medical research council dyspnoea scale, the physical activity scale for the elderly, arm curls in 30 seconds, chair stands in 30 seconds, shortness of breath after 6MWT and dyspnoea after the 6MWT.

Significant results with small to large effect sizes were reported for endurance at the 6 MW test (SES 0.87), shortness of breath after 6MWT (SES = 0.47) and dyspnoea after 6MWT (SES = 0.88) (Donesky et al.), the Barthel score (SES = 0.34), the CAT test (SES = 0.97), the MRC dyspnoea scale (SES = 0.31) and the physical activity scale for the elderly (SES = 0.91) (Bernocchi et al.).

Table 4A. Physical functioning outcomes in studies without links to usual care

Study	**Multimorbidity**	**Outcomes**	**Intervention**	**Control**	**Results**
Bernocchi et al.	COPD and heart failure	6MWT, feet (8 weeks)	389 (SD 141.1)	293 (SD 65.5)	Absolut diff 96 Relative % diff 24.7 p=0.004 SES = 0.87
		6MWT, feet (12 weeks)	336 (SD 69.5)	265 (SD 77.1)	Absolut diff 71 Relative % diff 21.2 p=0.004 SES = 0.97
		Barthel score (8 weeks)	95.3 (SD 6.7)	93.2 (SD 5.6)	Absolut diff 2.1 Relative % diff 2.2 P=0.0006 SES = 0.34

		Barthel score (12 weeks)	91.2 (SD 4.9)	91.3 (SD 3.4)	Absolut diff 0.1 Relative % diff 0.1 p=0.002 SES = 0.03
		COPD assessment test (CAT) score (8 weeks)	10.4 (SD 6.3)	17 (SD 7.3)	Absolut diff 6.6 Relative % diff 63.5 p=0.0001 SES = 0.97
		CAT score (12 weeks)	15.8 (SD 5.0)	16.2 (SD 7.3)	Absolut diff 0.4 Relative % diff 2.5 p=0.5525 SES = 0.06
		Medical research council (MRC) dyspnoea scale (8 weeks)	2.6 (SD 0.6)	2.8 (SD 0.7)	Absolut diff 0.14 Relative % diff 5.3 p=0.05 SES = 0.31
		MRC dyspnoea scale (12 weeks)	2.8 (SD 0.4)	2.7 (SD 0.9)	Absolut diff 0.05 Relative % diff 2 p=0.686 SES = 0.14
		Physical activity scale for the elderly score (8 weeks)	113.9 (SD 70.0)	56.9 (SD 53.6)	Absolut diff 57 Relative % diff 100 p=0.002 SES = 0.91
		Physical activity scale for the elderly score (12 weeks)	83.3 (68.9)	68.3 (SD 41.4)	Absolut diff 15 Relative % diff 18 p=0.8228 SES = 0.26
Donesky et al.	COPD and heart failure	6-minute walk (6 MW) endurance distance, feet (8 weeks)	751 (SD 324.9)	663 (SD 337.3)	Absolut diff 88 Relative % diff 13.3 p=0.75 SES = 0.27
		Arm curls in 30 seconds, number (8 weeks)	16.9 (SD 7.6)	19.2 (SD 7.8)	Absolut diff 2.3 Relative % diff 13.6 P=0.47 SES = 0.3
		Chair stands in 30 seconds,	13.3 (SD 6.1)	12.1 (SD 6.3)	Absolut diff 1.2 Relative % diff 9

		number (8 weeks)			P=0.82 SES = 0.19
		Shortness of breath after 6 MW score (8 weeks)	INT 2.8 (SD 3.0)	CON 4.3 (SD 3.3)	Absolut diff 1.5 Relative % diff 53.6 p=0.02 SES = 0.47
		Dyspnoea after 6 MW score (8 weeks)	0.5 (SD 1.5)	2.4 (SD 2.6)	Absolut diff 1.9 Relative % diff 79.1 p=0.03 SES = 0.88
		St. George's respiratory questionnaire score (8 weeks)	55.1 (SD 22.3)	44.3 (SD 22.4)	Absolut diff 10.8 Relative % diff 19.7 p=0.74 SES = 0.48
		Dyspnea-12 score (8 weeks)	10.7 (SD 8.1)	10.8 (SD 7.8)	Absolut diff 0.1 Relative % diff 1 p=0.79 SES = 0.01

SES = Standardized Effect Size, SD = Standard Deviation.