

eHealth for maintenance cardiovascular rehabilitation: a systematic review and meta-analysis

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| Aims | To provide a quantitative analysis of eHealth-supported interventions on health outcomes in cardiovascular rehabilitation (CR) maintenance (phase III) in patients with coronary artery disease (CAD) and to identify effective behavioural change techniques (BCTs). |
|------------------------|---|
| Methods and results | A systematic review was conducted (PubMed, CINAHL, MEDLINE, and Web of Science) to summarize and synthesize the effects of eHealth in phase III maintenance on health outcomes including physical activity (PA) and exercise capacity, quality of life (QoL), mental health, self-efficacy, clinical variables, and events/rehospitalization. A meta-analysis following the Cochrane Collaboration guidelines using Review Manager (RevMan5.4) was performed. Analyses were conducted differentiating between short-term (≤ 6 months) and medium/long-term effects (>6 months). Effective behavioural change techniques were defined based on the described intervention and coded according to the BCT handbook. Fourteen eligible studies (1497 patients) were included. eHealth significantly promoted PA (SMD = 0.35; 95%CI 0.02–0.70; $P = 0.04$) and exercise capacity after 6 months (SMD = 0.29; 95%CI 0.05–0.52; $P = 0.02$) compared with usual care. Quality of life was higher with eHealth compared with care as usual (SMD = 0.17; 95%CI 0.02–0.32; $P = 0.02$). Systolic blood pressure decreased after 6 months with eHealth compared with care as usual (SMD = -0.20 ; 95%CI $-0.40-0.00$; $P = 0.046$). There was substantial heterogeneity in the adapted BCTs and type of intervention. Mapping of BCTs revealed that self-monitoring of behaviour and/or goal setting as well as feedback on behaviour were most frequently included. |
| Conclusion | eHealth in phase III CR is effective in stimulating PA and improving exercise capacity in patients with CAD while increasing QoL and decreasing systolic blood pressure. Currently, data of eHealth effects on morbidity, mortality, and clinical outcomes are scarce and should be investigated in future studies. |
| Registration | PROSPERO: CRD42020203578. |
| Lay summary | • This paper reviews the impact of eHealth-supported interventions on health outcomes during cardiovascular rehabilita- tion maintenance phase III for patients with coronary artery disease, with a meta-analysis performed to differentiate be- tween short-term (≤6 months) and medium/long-term effects (>6 months). |

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Key findings

- eHealth interventions in cardiovascular rehabilitation maintenance may be used to increase physical activity and exercise capacity as well as quality of life while reducing systolic blood pressure.
 - Effective behavioural change techniques used in eHealth interventions may include self-monitoring of behaviour, goal setting, and feedback on behaviour; thus, future studies are needed to define effective eHealth components based on behavioural change theories and associated behavioural change techniques to assist patients with coronary artery disease.

Keywords Coronary artery disease • Rehabilitation • eHealth • mHealth • Telemedicine • Maintenance

Introduction

Cardiac rehabilitation (CR) is the most effective way to decrease the morbidity and mortality risk among patients with coronary artery disease (CAD).^{1,2} The European Society of Cardiology (ESC) defines CR as multifactorial intervention with core components in patient assessment, physical activity counselling, diet/nutritional counselling, risk factor control, patient education, psychosocial management, vocational advice, and lifestyle behaviour change including patients' adherence and self-management.³ Cardiac rehabilitation is not uniformly implemented and differs on the local and national level comprising inpatient, outpatient, or home-based programs.

Cardiac rehabilitation may be classified in three stages.⁴ Phase I takes place in the acute clinic, typically after a coronary intervention or surgery. In this phase, patients discuss their health situation and cardiovascular risk factors with the treating physician and/or a CR nurse. This phase lasts only a few days and aims at early mobilization and patients' ability for mild activity.⁵ Phase II is the reconditioning phase provided at inpatient or outpatient CR centres or in the home environment with different levels of support.⁶ Phase II typically consists of a multidisciplinary program involving education on risk factors, supervised exercise training, and psychological support,⁷ aiming at increasing patients' exercise capacity, functional mobility, and self-management.⁸ A successful phase II CR not only reduces patients' risk but also restores workability and participation in social life. The length of phase II differs among countries and depends on the setting. The duration (1-6 months) and frequency (1-5 sessions per week) of home-based CR, outpatient and inpatient CR vary.⁹ Of note, different studies provide evidence that inpatient and outpatient/home-based CR can be equally effective.^{10,11} Achievements of phase II should be consolidated in phase III CR also referred to as maintenance phase,⁵ performed in a community or homebased setting. Phase III maintenance is the longest and least-structured phase of care. It aims at lifelong self-care with continuous risk-factor management and regular physical activity.⁵ It has been discussed that active transition from phase II CR to phase III maintenance is of central importance⁴ and 'after-care' programs, offered already during centrebased CR, can be defined as a bridge between phase II and the life-long maintenance phase.

Despite the solid evidence of the effectiveness of structured phase II CR,¹² it is known that the cardiovascular risk profile worsens significantly over time after this period.¹³ However, adherence to a healthy lifestyle including regular physical activity (PA) and risk factor management during phase III maintenance is challenging and often poorly supported.¹⁴ Main reasons include unsustainable costs for life-long patients support in addition to usual care by general practitioners or cardiologists.^{15,16} In addition, patient-and healthcare provider barriers such as time and travel burden may add to lower adherence and uptake of maintenance programs. Electronic communication and health information technology in health care practice (eHealth) has already been discussed as an effective alternative to phase II CR.^{17–19} Also, mobile device-based healthcare (mHealth) delivery through smartphones may be as effective as traditional centre-based CR, showing significant improvements in health-related quality of life (QoL). These novel interventions may support the patient to maintain long-term health

behaviours after specialized CR programs. This is also reflected in the recent ESC Guidelines on cardiovascular disease (CVD) prevention.²⁰ Rawstorn et al.¹⁹ included 11 trials (1189 participants) in their meta-analysis and suggested that telehealth-based phase II CR may be even more effective than centre-based phase II CR for enhancing PA levels but not for improving maximal aerobic exercise capacity. The authors concluded that telehealth phase II CR may be an effective option for patients who cannot attend centre-based CR at least for improving PA as one dimension of functioning. Cost-efficiency has been suggested by a systematic review and meta-analysis (2429 patients) investigating the use of commercial activity trackers, which were found to significantly increase the daily step count and aerobic capacity in CR patients.²¹ In the general population, interventions including health professional consultations combined with wearable activity trackers such as accelerometers, fitness trackers, and pedometers have been shown to improve PA significantly.²² Of note, Chaudhry *et al.*²³ (16 355 healthy adults analysed) provided evidence that already simple step-counters lead to short and long-term increase in daily activity (i.e. steps), without the need for smartphone applications, or additional counselling/incentives. In terms of cost efficiency, Frederix et $al.^{24}$ investigated the long-term health benefits of a 6-month internet-based telerehabilitation program including an exercise training program with telemonitoring support, webservice, and text messages. They reported significantly improved exercise capacity, increased adherence to healthy lifestyle behaviour, and higher QoL induced by the eHealth support. It was estimated that the program was cost-efficient up to 2 years after the end of the intervention in that the total average cost per patient in the intervention group (IG) was lower (3262 ± 339) , compared with usual care (4140 \pm 513 \in). These findings are in line with two recent systematic reviews suggesting cost-effectiveness of cardiac telerehabilitation in general.^{25,26} Besides limitations for phase III CR implementation and participation such as program funding and socio-economic barriers, the COVID-19 pandemic has highlighted the urgency of implementing telerehabilitation including eHealth solutions in different fields including cardiology in general and CAD in particular.

However, current eHealth-based maintenance programs are heterogeneous in type of intervention and behavioural change techniques (BCTs) applied, and programs target different aspects of secondary prevention including stimulation of physical activity, self-empowerment, and (clinical) risk factor control. Today, the efficacy of eHealth-based phase III maintenance programs in patients with CAD is a matter of ongoing research, and the effects on health outcomes including PA and exercise capacity, QoL, mental health, self-efficacy, clinical variables, and events/rehospitalization have not been analysed systematically.

Objective

This systematic review and meta-analysis aims (i) to provide a structured summary of the existing maintenance studies on eHealth interventions for patients with CAD and (ii) to determine the effects of eHealth interventions in phase III CR maintenance on short and medium/long-term health outcomes using meta-analysis. Further, we investigated which BCTs may be effective as a basis to support future eHealth interventions in phase III CR.

| Phase II CR | Phase III CF | R Maintenance |
|-------------|---|---|
| | Baseline data | Follow-Up data |
| | Quantitative analysis by comparisons betwee | en intervention and control group at end of trial ↑ |

Figure 1 Methodical approach. Only studies with coronary artery disease patients who had completed a structured centre-based inpatient or outpatient phase II cardiac rehabilitation previous to the intervention were included. All included studies had to provide baseline data at the end of phase II cardiac rehabilitation as the starting point of the controlled trial. The actual eHealth interventions had to be initiated subsequent to phase II cardiac rehabilitation, covering direct aftercare/transition and maintenance phase. The Cochrane Collaboration guidelines for meta-analysis based on comparisons between intervention and control group at a specified time point, in this case, the end of the maintenance phase of included studies were followed. CR, cardiac rehabilitation.

Methods

Study design and eligibility criteria

We performed a systematic review (PROSPERO, CRD42020203578) in accordance with the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) guidelines (see Supplementary material online, *Document S1*).^{27,28} Any original article reporting on intervention supported by eHealth in phase III CR was considered for the analysis. Articles available as full-text (after an attempt to contact the corresponding author) reporting on patients with CAD that underwent a structured centre-based inpatient or outpatient phase II CR were included. eHealth interventions had to be initiated subsequent to phase II CR, covering direct aftercare/transition and maintenance phase. To study the isolated effects of eHealth-supported phase III after a structured phase II CR, studies had to provide baseline data at the end of phase II CR as the starting point of the controlled trial (Figure 1). Studies were only included if they realized a randomized controlled trial (RCT) or a quasi-experimental design (i.e. having a having a control or comparison arm) at the beginning of phase III. Articles were not eligible if they (i) reported on eHealth use in patient cohorts other than patients with CAD and (ii) were not original research [a review or book (chapter)]. Publications were excluded if they (i) focused on eHealth in phase II CR, (ii) were not written in English (full text), (iii) were grey literature or website articles, and (iv) did not clearly report on included participants, interventions, outcome measures, and statistical analysis.

Definitions

eHealth was defined as any intervention (alone or in combination with other actions) applying digital technologies with the potential to (self-)monitor or mediate health-promoting behaviour. Phone calls or emails alone were not considered as eHealth. Phase II CR was considered as any structured multidisciplinary program for CAD patients involving components such as education on disease, risk factors, and diet, supervised exercise training, and/or psychological support. Maintenance phase was accepted as defined by authors and included aftercare/ transition programs from phase II CR. Health outcomes were defined as changes in PA and exercise capacity (fitness), QoL, mental health, self-efficacy, clinical variables relevant to cardiovascular risk (i.e. BMI, blood pressure, lipids, etc.), and events/rehospitalization. Participation outcomes were not part of the studies and could therefore not be included into analysis. The BCTs were accepted as indicated by authors (if available) or were defined based on the described intervention characteristics and coded according to the handbook of BCTs.²⁹ Individuals were classified as having CAD based on the authors' descriptions. If interventions included cohorts described as CVD patients, proportion of patients with CAD had to exceed 80%. In case of imprecise, uncommon, unclear/conflicting, or missing descriptions of phase II CR, country-specific CR implementations were reviewed (MHe and BS) for additional information such as type and duration of prior phase II CR. The overall effect estimate was outcome-oriented following the Cochrane handbook for meta-analyses and divided into subgroups. After determining the length of the interventions reported in identified studies, the effects were subdivided into short-term (≤6 months) and medium to long-term outcomes (>6 months). This was done based on the assumption that behavioural change will occur within the first 6 months,³⁰ while consolidation will need assessment over longer periods (i.e.

>6 months).³¹ If multiple data were reported at multiple time points, the most recent value (i.e. the value after the longest intervention period) was included in the analysis. If different questionnaires were used to measure a single construct (e.g. QoL and mental health), then data were combined to evaluate the outcome of interest.

Search strategy, data sources, and study selection

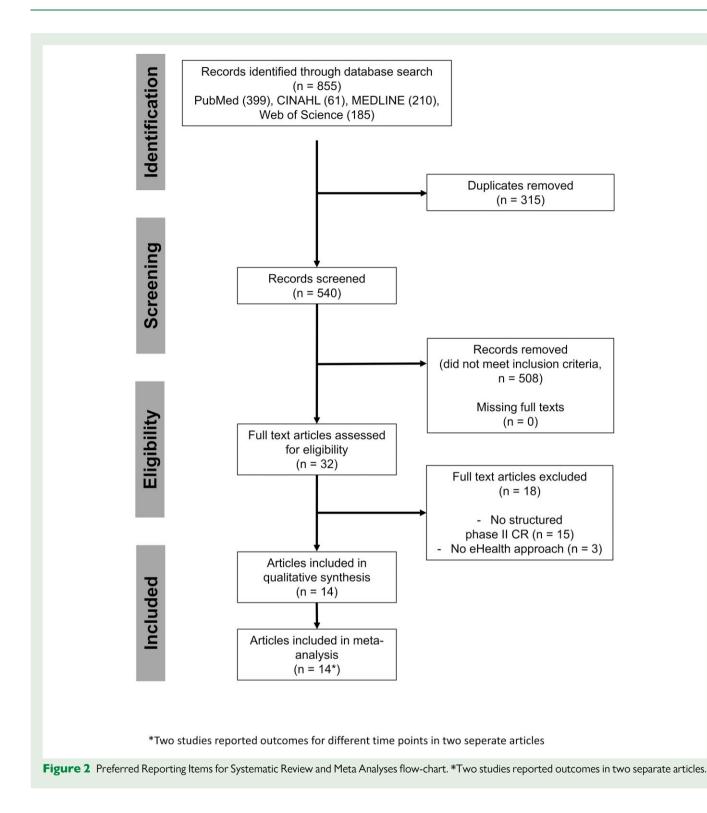
A systematic search of the literature was conducted (M.He., M.T., and B.S.) using PubMed, CINAHL, Medline, and Web of Science for records published until May 2022. Databases were searched using variations and combinations of the following keywords: cardiac rehabilitation/methods*/instrumentation*; telemedicine/methods*; telerehabilitation/instrumentation*; heart disease; cardiovascular disease; coronary artery disease/rehabilitation*; coronary disease; myocardial infarction; wearable electronic device; information sciences; internet. The detailed search syntax used for the individual databases is provided in Supplementary material online, *Table S1*. Additional filters were used if applicable. Manual searches were also performed using reference lists from identified articles and available reviews. The individual steps of report identification, screening, and processing are documented in the PRISMA flow chart (*Figure 2*).³² Search results and fulfilment of eligibility criteria were discussed if unclear (M.He. and B.S.) until consensus was reached and in case of disagreement, a third person was consulted to determine inclusion.

Data extraction

Data were extracted by two reviewers (M.He. and M.T.) and tables were created including information on first author, year of publication, sample, country, outcome variables and main results, type of CR (inpatient or outpatient), type of control group (usual care), detailed information about the intervention including technical components (fitness tracker/accelerometer, smartphones, website, text messaging, apps, platforms), applied BCTs (if available), related BCTs identified based on intervention description (i.e. self-monitoring of behaviour, goal setting, feedback on behaviour, prompts/hints, action planning, problem solving, instructions on how to perform behaviour, increasing self-efficacy, biofeedback, social support, and prevention strategies), frequency of coach-to-patient contact (if any), and duration of the maintenance phase. Data were extracted at the end of the intervention phase. If follow-up assessment were performed, data were extracted after the longest reported period. Data on outcomes used for meta-analysis were checked by two independent reviewers (H.S., Sa.S.). Variables were reported as mean \pm SD. Heterogeneity was reported as l^2 . If no body mass index (BMI) was reported, body weight was used for the calculation.

Statistical analysis

The Cochrane Collaboration guidelines for meta-analysis were followed, and effect sizes are based on comparisons between intervention and control group at a specified time-point.³³ The effect of eHealth in CR maintenance was analysed by using the inverse variance in a random-effect model for continuous, and the Mantel–Haenszel method in a fixed-model for dichotomous data. Effects were estimated by standard mean difference (SMD) for continuous and risk ratios for dichotomous data, including their 95% confidence intervals (CI). The direction of effect was calculated based



on the intended effect, e.g. in Hospital Anxiety and Depression Scale (HADS)– Type D scale, a lower value was coded favourable, while in the Short-form (SF-36) questionnaire, a higher value was coded favourable. In case multiple indicators were provided at one time point, the most meaningful indicator was selected to avoid statistical dependencies among indicators. For example, duration of exercise per week was preferred over the number of exercises per week. In case of unplausible values, the corresponding author was contacted for correction. If mean and standard difference (SD) were not reported by the original studies, the median was used with SD estimated based on the given information, e.g. quartiles, range, and the number of participants as described by Wan et *al.*³⁴ In one case, ³⁵ the mean was inferred using the graphical information provided in a supplemental figure (boxplot). All statistical analyses were performed using Review Manager (RevMan) version 5.4.³⁶ The contribution of each effect of the included studies to the overall estimator depended especially on the precision of the individual effect as accounted for by RevMan5.4.^{33,37} Results are presented by forest plots with 95% Cl for overall effects and for short-term (≤ 6 months) and medium to long-term (> 6 months) subgroups.

| Author | Number of participants [#] | Disease | Disease Country Type of cardiac rehabili | Type of cardiac rehabilitation | | Control/ usual care | Behavioural change theory applied | Related behavioural change techniques | Maintenance phase duration | Outcome variables assessed | Main results ^b |
|----------------------------------|--|------------------|--|--|--|--|---|---|----------------------------------|--|--|
| Antypas (2014) | IG: 29 CG: 40 | CVD ^c | Norway | inpatient CR (4 weeks) | Website ^e text messages as the mean of planned activity and at the end of activity | undefined/ according to guideline | 'I change' and Health Action Process Approach | self-monitoring, goal setting, prompts/ cues, problem solving, feedback, action clanning | 12 weeks | depression/mental health, self-efficacy, physical activity | depression/mental increased physical health, activity self-efficacy, physical activity |
| Avila (2018) | Avila (2018) IG: 30 CG: 30 | CAD | Belgium | outpatient CR (undefined) | 3 supervised training sessions Optional heart rate monitor with exerci app (Garmin Forerunner progra 210) feedback on outpat performed exercise via clinic o nbone/email | Optional exercise program at outpatient clinic or | none reported | goal setting (behaviour), 12 weeks feedback on behaviour, problem solving, self-monitoring of behaviour |), 12 weeks | exercise capacity) BMI, BP, lipids, depression/ mental health, quality of life, nhvsiral activity | increased (submaximal) exercise capacity |
| Avila (2020) ^a | Avila (2020) ^a IG: 28 CG: 26 | CAD | Belgium | outpatient CR (undefined) | vention | usual care | none reported | n.a. | 52 weeks | exercise capacity, BMI, BP | exercise capacity, no significant changes BMI, BP |
| Claes (2020) Duscha (2018) | Claes (2020) IG: 60 CG: 60 Duscha IG and CG: 32 (2018) | C C D * C C D | Belgium and Ireland USA | (undefined) outpatient CR (~4 weeks) | exercise platform for training undefined/ sessions text messages/ according th emails to support guideline adherence and progress toward achieving goal(s), no frequency reported accelerometer, not further specified (actigraph GT9X) step count via activity tracker standard care weekly phone calls with as ordered health coaches text by physician messages, frequency and content were individual, used to remind patient to practice healthy habits, provide motivation to exercise, set-up coaching session calls physical | undefined/ according to guideline standard care as ordered by physician | none reported | goal setting, self-monitoring goal setting, prompts/ cues, self-monitoring of behaviour, feedback on behaviour, problem solving, action planning, instructions on how to perform behaviour | 24 weeks 12 weeks | exercise capacity, BMI, BP, lipids, depression/ mental health, self-efficacy, quality of life, physical activity, events exercise capacity, physical activity | increased physical activity increased exercise capacity, increased moderate-to-high physical activity |

Continued

| Author | | | | | | | | | | | |
|---------------------------------|--|-----|--|---|--|---|--|--|----------------------------------|---|--|
| | Number of participants [#] | | Disease Country Type of cardiac rehabili | tation | Intervention | Control/ usual care | Behavioural change theory applied | Related behavioural change techniques | Maintenance phase duration | Outcome variables assessed | Main results ^b |
| Frederix (2015) | IG: 70 CG: 70 | CAD | Belgium | outpatient CR (12 weeks) | activity tracker and app (Fitbit charge) exercise training program with telemonitoring support accelerometer (data uploaded to online platform) webservice (not spectified) text messages, 1x/week, with tailored dietary and smoking cessation recommendations | undefined/ according to guideline | none reported | instructions on how to perform behaviour, self-efficacy enhancement, goal setting, feedback on behaviour | 18 weeks | exercise capacity, BMI, BP, lipids, physical activity, events | increased exercise capacity, increased HRQL |
| Frederix ^a (2017) | lG: 62 CG: 64 | CAD | Belgium | outpatient CR (12 weeks) | no further support | usual care | none reported | n.a. | 104 weeks | lipids, physical activity, cost effectiveness | increased cost-effectiveness |
| Johnston (2016) | IG: 91 CG: 83 | CAD | Sweden | 2 post-hospital discharge visits | App ^d SMS reminders and educational text messages | undefined/ according to guideline | none reported | self-monitoring of behaviour, feedback on behaviour, biofeedback, prompts/cues | 24 weeks | BMI, BP, lipids, quality of life | increased drug adherence, increased satisfaction |
| Lunde (202 | Lunde (2020) IG: 57 CG: 56 | CAD | Norway | outpatient or inpatient CR (1, 4 or 12 weeks) | App ^f individualized feedback via app or email | undefined/ according to guideline | none reported | goal setting, prompts/ cues, self-monitoring of behaviour, feedback on behaviour, action planning, social support (unspecified) | 52 weeks | Exercise capacity, BMI, BP, lipids, quality of life, physical activity/ exercise training | Exercise capacity, increased exercise BMI, BP, lipids, capacity, increased quality of life, exercise habits, physical improved activity/ self-perceived goal exercise achievement training |
| Moore (2006) | IG and CG: 273 | CAD | USA | outpatient CR (undefined) | wristwatch heart rate monitor combined with exercise diaries mailed to the study team (no app) (Polar Vantage NV) | undefined/ according to guideline | social problem-solving self-efficacy model, self-efficacy enhancer theory, problem expectancy-value preventic theory, relapse strategies prevention theory support, | self-efficacy enhancement, problem solving, prevention strategies, social support, goal setting | 52 weeks | self-efficacy, physical activity/ exercise training | decreased likeliness to stop exercising |
| | IG: 61 CG: 62 | CAD | | | text messages educating | usual care | social cognitive theory goal setting, prompts/ | goal setting, prompts/ | 24 weeks | BMI, BP, lipids, | increased adherence to Continued |

| Table 1 | Continued | | | | | | | | | | |
|--|---|---|--|---|--|---|--|---|---|---|---|
| Author | Number of participants [#] | Disease | Disease Country Type of cardiac rehabili | tation | Intervention | Control/ usual care | Behavioural change theory applied | Related behavioural change techniques | Maintenance phase duration | Outcome variables assessed | Main results ^b |
| Pfaeffli Dale (2015) | | | New Zealand | inpatient CR (undefined) | patients about their cardiovascular risk factors and supporting them to make relevant lifestyle changes website ⁸ step counter documented via text messages to study nerconnel | | | ues, prompts/cues, self-monitoring of behaviour, feedback on behaviour, biofeedback | | depression/ mental health, self-efficacy, events | healthy lifestyle (at 3 months not at 6 months), increased medication adherence |
| Тоті (2018) | Torri (2018) IG: 26 CG: 27 | CAD | Italy | inpatient CR (3 weeks) | Website ^b online documentation of daily physical activity | undefined/ according to guideline | none reported | goal setting, self-monitoring of behaviour, feedback on behaviour | 24 weeks | exercise capacity, BMI, BP, lipids, depression/ mental health, | improved cardiovascular risk |
| Vieria (2018) | Vieria (2018) IG: 15 CG: 15 | CAD | Portugal | previous CR (undefined) | virtual reality training (Kinect, undefined/ Xbox Microsoft) accordir onidelin | , undefined/ according to anideline | none reported | self-monitoring of behaviour, hiofeedhark | 24 weeks | BMI, lipids | Improved selective attention and conflict resolution shility |
| Wienbergen (2019) | Wienbergen IG: 155 CG: 155 (2019) | CAD | Germany | outpatient CR (3 weeks) | group education sessions phone calls step counter with online documentation or activity tracker | sectific disease management program not further defined | serctific disease none reported management program not further defined | feedback on risk factors 48 weeks based on behaviour, self-monitoring of behaviour, feedback on behaviour | s 48 weeks | BMI, BP, lipids, depression/ mental health, quality of life, physical activity, events | Improved physical activity (steps), reduced smoking, improved low-density lipoprotein cholesterol, systolic blood pressure, quality of life |
| IG, interventic applicable: ap) ^a Follow-up st ^b Significant ch ^b Significant ch ^b Contained 4 low-density lig ^e Provided gen ^f Jncluded gen ^h ¹ Included gen intervention d | IG intervention group; CG, control group; CVD, cardiovascular disease; C applicable; app, application. "Number of included participants at baseline." Prollow-up study, discontinued eHealth intervention. ¹⁵ Significant change as reported by authors. ¹⁶ Significant change as reported by authors. ¹⁶ Including mainly CAD patients. ¹⁶ Contained 4 main modules: extended drug adherence e-diary, exercise, w ¹⁶ Contained 4 main modules: extended drug adherence e-diary, exercise, w ¹⁶ Significant change as reported by authors. ¹⁶ Contained 4 main modules: extended drug adherence of tasks, weekly ¹⁶ Forovided general information about CAD and self-management, includin ⁶ Coal setting with tasks, automatic reminders, evaluations of tasks, weekly ¹⁶ Included a blog for questions, social support, and a graph to monitor phy ¹⁰ Included general information and educational materials on the important intervention description according to the handbook of BCTs. | ol group; C ber of incl, lealth inter authors. ut CAD ar ut CAD ar ut CAD ar ial support education? to the har | VD, cardiovas uded participa vention. d glucose leve d glucose leve e valuations c , e and a graph' il materials or dbook of BC ⁻ | IG, intervention group; CG, control group; CVD, cardiovascular disease; CAD, coronar, applicable; app, application. [#] Number of included participants at baseline. [#] Follow-up study, discontinued eHealth intervention. ^{b5} ginificant change as reported by authors. ¹⁰ Including mainly CAD patients. ¹⁰ Including mainly CAD patients. ¹⁰ Contained 4 main modules: extended drug adherence e-diary, exercise, weight, and sm ¹⁰ Contained 4 main modules: extended drug adherence e-diary, exercise, weight, and sm ¹⁰ Contained 4 main modules: extended drug adherence e-diary, exercise, weight, and sm ¹⁰ Contained 4 main modules: extended drug adherence and set ¹⁰ Fovided general information about CAD and self-management, including information ¹⁰ Coal setting with tasks, automatic reminders, evaluations of tasks, weekly goal achieve ⁸ Included a blog for questions, social support, and a graph to monitor physical activity. ¹⁰ Included general information and educational materials on the importance of exercise intervention description according to the handbook of BCTs. | IG intervention group; CG, control group; CVD, cardiovascular disease; CAD, coronary artery disease; BMI, body mass index; CR, cardiac rehabilitation; BP, blood pressure; VT, ventilatory threshold; HRQL, heart-related quality of life; n.a., not applicable; app, application. [#] Number of included participants at baseline. ¹⁵ Follow-up study, discontinued effeath intervention. ¹⁵ Significant change as reported by authors. ¹⁶ Significant change as reported by authors. ¹⁶ Contained A main modules extended drug adherence e-diary, exercise, weight, and smoking module. Patents were encouraged to actively register information in these 4 modules. Patients could also register data regarding their blood pressure. ¹⁰ Contained A main modules extended drug adherence e-diary, exercise, weight, and smoking module. Patents were encouraged to actively register information in these 4 modules. Patients could also register data regarding their blood pressure. ¹⁰ Contained A main modules extended drug adherence e-diary, exercise, weight, and smoking module. Patents were encouraged to actively register information in these 4 modules. Patients could also register data regarding their blood pressure. ¹⁰ Contained A main modules extended drug adherence e-diary, exercise, weekly goal achievement. Patients replied with a red or green emoji. depending on whether they had completed the planned task or not. ⁴ Included general information and educational materials on the importance of exercise training, detary regimen, and medication adherence for green emoji. depending on whether they had completed the planned task or not. ⁴ Included general information according to the handbook of BCTs. | ody mass index; were encourage ation. Personaliz ivity, smoking, r goal achievemen en, and medicat | CR, cardiac rehabilitati d to actively register inf ied feedback messages nedication, access to ar it. Patients replied with ion adherence for pati | on; BP, blood pressure; V formation in these 4 mod with feedback and inform n online discussion forum i a red or green emoji, de ents and their caregiver. | T, ventilatory thresho ules. Patients could als nation messages. t. epending on whether gending on whether | ld; HRQL, heart-rel so register data rega they had complete thange techniques v | ated quality of life; n.a., not rding their blood pressure, d the planned task or not. vere assigned according to |

Quality assessment

The methodological quality of the studies was assessed using the 11-item PEDro scale for risk of bias assessment based on the Delphi list developed by Verhagen et $al.^{38}$ The Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment.³⁹ was used to evaluate the quality of the evidence for all key outcomes according to the Cochrane Handbook. The overall quality of the evidence was assessed for each key outcome irrespective of study duration. Studies and key outcomes were rated by two reviewers (M.H. and B.S.), and disagreements were discussed until consensus was reached. The researchers were not blinded to study authors, results, or publication journal.

Results

Study characteristics

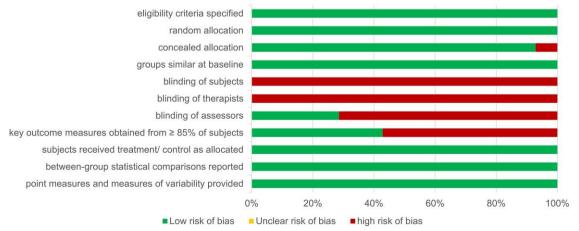
A total of 14 articles met the eligibility criteria, involving 1497 participants at baseline. At least one outcome was reported for a total of 1296 patients at follow-up. Studies evaluated the effects of eHealth on different outcomes, change in PA and exercise capacity, clinical risk factors, QoL, and events/rehospitalization. *Table 1* summarizes the characteristics of included studies. The follow-up periods ranged from 12 weeks^{40–42} to 104 weeks.²⁴ Included trials were published between 2006 and 2020. Mean age of participants was 56.5–65 years in the IGs and 56.5–67 years in the control groups (CGs). Overall, the study populations comprised mostly men, with the proportion of women varying from zero⁴³ to 38%.⁴⁴ The type of phase II rehabilitation comprised mostly outpatient CR (10 studies).

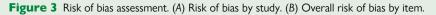
Study quality

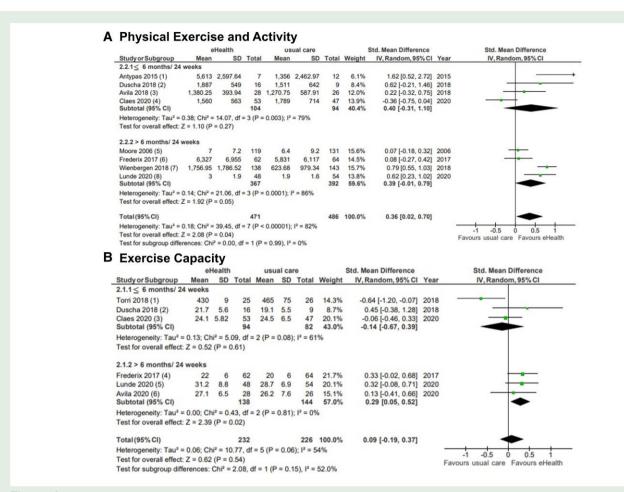
Risk of bias assessment is presented in Figure 3. Overall, studies showed a medium to high risk of bias (Figure 3B). Of note, a large number of studies (n = 6) did not report key outcome measures for more than 85% of

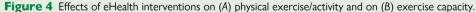
| Study | PEDro final score | Eligibility criteria specified | Random allocation | Concealed allocation | Similar groups at baseline | Blinding of therapists | Blinding of assessors | Blinding of subjects | Measure one key outcome from 85% subjects | Intention-to-treat analysis | Between group statistical analysis for at least one outcome | Variability and point measurements for at least one outcome |
|----------------------|-------------------|-----------------------------------|-------------------|----------------------|-------------------------------|------------------------|-----------------------|----------------------|---|--------------------------------|---|---|
| Antypas (2015) | 7/10 | Yes | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes |
| Avila (2018) | 7/10 | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |
| Avila (2020) | 7/10 | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |
| Claes (2020) | 7/10 | Yes | Yes | Yes | Yes | No | Yes | No | No | Yes | Yes | Yes |
| Duscha (2017) | 8/10 | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Yes |
| Frederix (2015) | 6/10 | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Yes |
| Frederix (2017) | 8/10 | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Yes |
| Johnston (2016) | 7/10 | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |
| Lunde (2020) | 8/10 | Yes | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Yes |
| Moore (2006) | 7/10 | Yes | Yes | Yes | Yes | No | Yes | No | No | Yes | Yes | Yes |
| Pfaeffli Dale (2015) | 7/10 | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |
| Torri (2018) | 6/10 | Yes | No | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |
| Varnfield (2014) | 6/10 | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Yes |
| Vieira (2016) | 6/10 | Yes | Yes | Yes | Yes | No | No | No | No | Yes | Yes | Yes |
| Wienbergen (2018) | 7/10 | Yes | Yes | Yes | Yes | No | No | No | Yes | Yes | Yes | Yes |











participants due to dropout.^{40,42–46} There was no blinding of therapists, assessors, and participants in most of the studies, as blinding is limited by this type of intervention. A general inconsistency was observed in terms of reporting on BMI since some studies reported on weight and height instead.^{40,47} The studies differed in length and type of the preceding phase II CR, confirming that CR is not uniformly implemented with differences at the local and national level. Even though a previous CR phase II was reported in all studies, five studies did not define the length of phase II intervention.^{42–45,48} Based on l^2 and Cl, large heterogeneity was seen between studies (*Figures 4–8*), which may be based on the differences in the type of intervention, technology applied, and related BCTs.

According to GRADE, the level of certainty for the evidence regarding the different outcomes included was mainly evaluated as 'low' (nine outcomes), while the evidence for exercise capacity, QoL, and systolic blood pressure was rated as 'moderate'. The results of the assessments are described in detail in Supplementary material online, *Table S2*.

Intervention characteristics

In the reviewed studies, eHealth-based CR maintenance differed largely in terms of duration, type of intervention, applied technology, and related BCT.

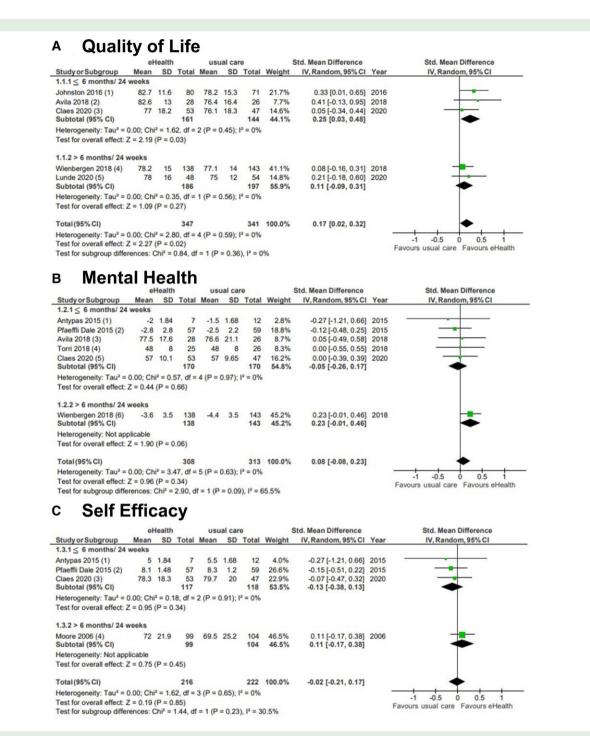
Applied eHealth technology

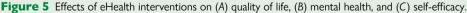
The used eHealth technologies involved different combinations of at least two features including access to disease-related information on

websites comprising general information about CAD and selfmanagement, diet, PA, smoking, medication, and access to an online discussion forum; a blog for questions, social support, and a graph to monitor physical activity: general information and educational materials on the importance of exercise training, dietary regimen, and medication adherence for patients and their caregiver (n = 3 studies);^{40,47,48} individualized text messages aiming to remind patients of their planned activity, as a support for adherence and progress towards achieving goals, to provide motivation to exercise, to remind to practice healthy habits, to educate on diet and smoking cessation, and to educate patients about their cardiovascular risk factors, and supporting them to make relevant lifestyle changes such as stopping smoking, limiting alcohol consumption, eating five servings of fruit and vegetables per day while decreasing salt and saturated fat content, and starting and/or maintaining regular PA (n = 6 studies);^{40,42,45–47,49} emails on individualized feedback, to support adherence and progress toward achieving goal(s) and feedback on performed exercise (n = 3 studies);^{41,45,50} commercial wristwatch heart rate monitors (and respective apps) (n = 3 studies);^{41,42,44} exercise platform for training sessions (one study);⁴⁵ activity trackers/accelerometers with online data documentation (four studies);^{35,42,45,46} mobile phone applications including extended drug adherence e-diary, exercise, weight, and smoking modules, the possibility to actively register information in these four modules and register data regarding blood pressure, low-density lipoprotein cholesterol, and blood glucose levels, personalized feedback messages with feedback and information messages; goal setting with tasks, automatic reminders, evaluations of tasks,

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weekly goal achievement, rating of weekly goal achievement, including option to reply with a red or green emoji, depending on whether patients had completed the planned task or not (two studies studies);^{49,50} step counters with online documentation (four studies);^{35,42,47} and virtual reality exercise programs (one study)⁴³ and online documentation and feedback on PA.⁴⁸ Three studies used phone calls as feedback support in addition to the applied eHealth technology.^{35,41,42} Overall, details about the content of the intervention (text messages, mails, and phone calls) were often missing.

Effects of eHealth maintenance on physical activity and capacity

Figure 4 displays detailed results on the effects of eHealth vs. care as usual on PA and related measures. Eight studies reported on change in PA as study outcome assessed as frequency, intensity, and duration of physical exercise and as daily PA in terms of step count.^{24,35,40–42,44,45,50} Physical activity was measured either automatically by wearable devices (wristwatches, accelerometers, or

A Total Cholesterol

| | eł | lealth | | USL | al car | 9 | 1 | Std. Mean Difference | | Std. Mean Difference |
|-----------------------------------|----------|--------------------|---------|----------|----------|-------------------|--------|----------------------|------|---|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.4.1≤ 6 months/ 24 | weeks | | | | | | | | | |
| Plaeffli Dale 2015 (1) | 3.6 | 0.7 | 61 | 3.8 | 1.1 | 62 | 15.1% | -0.22 [-0.57, 0.14] | 2015 | |
| /ieira 2016 (2) | 141.6 | 26.5 | 8 | 168.9 | 22.8 | 8 | 3.4% | -1.04 [-2.11, 0.02] | 2016 | • • • |
| Forri 2018 (3) | 152 | 27 | 25 | 163 | 33 | 26 | 9.3% | -0.36 [-0.91, 0.20] | 2018 | |
| vila 2020 (4) | 3.75 | 0.7 | 28 | 3.46 | 0.5 | 26 | 9.5% | 0.47 [-0.07, 1.01] | 2020 | |
| Claes 2020 (5) | 3.81 | 1.01 | 53 | 3.84 | 1.08 | 47 | 13.7% | -0.03 [-0.42, 0.36] | 2020 | |
| Subtotal (95% CI) | | | 175 | | | 169 | 51.0% | -0.13 [-0.46, 0.21] | | - |
| leterogeneity: Tau ² = | 0.07; Ch | 2 = 8.5 | 9, df = | 4 (P = (| 0.07); 1 | 2 = 539 | 6 | | | |
| fest for overall effect: | Z = 0.74 | (P = 0. | .46) | | | | | | | |
| 3.4.2 > 6 months/ 24 | weeks | | | | | | | | | |
| rederix 2017 (6) | 149 | 31 | 62 | 152 | 43 | 64 | 15.3% | -0.08 [-0.43, 0.27] | 2017 | |
| Vienbergen 2018 (7) | 143.2 | 26 | 138 | 153.3 | 34 | 143 | 19.9% | -0.33 [-0.57, -0.10] | 2018 | |
| unde 2020 (8) | 4.1 | 1 | 48 | 3.9 | 1 | 54 | 13.8% | 0.20 [-0.19, 0.59] | 2020 | |
| ubtotal (95% CI) | | | 248 | | | 261 | 49.0% | -0.10 [-0.41, 0.21] | | - |
| leterogeneity: Tau ² = | 0.05; Ch | 2 = 5.5 | 0, df = | 2 (P = (| 0.06); 1 | 2 = 649 | 6 | | | |
| lest for overall effect: | Z = 0.65 | (P = 0. | .52) | | | | | | | |
| Total (95% CI) | | | 423 | | | 430 | 100.0% | -0.11 [-0.32, 0.10] | | • |
| leterogeneity: Tau ² = | 0.04; Ch | ² = 14. | 24, df | = 7 (P = | 0.05); | ² = 51 | 1% | | | |
| est for overall effect: | | | | | | | | | | -1 -0.5 0 0.5 1 Favours eHealth Favours usual ca |
| | | | | | | | | | | |

в Triglyceride

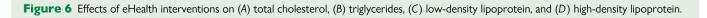
| | el | Health | | usu | al car | re | : | Std. Mean Difference | | Std. Mean Difference |
|-------------------------------------|----------|----------------------|-----------|-----------|--------|------------|----------------|--|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.7.1≤ 6 months/ 24 | weeks | | | | | | | | | |
| Vieira 2016 (1) | 104.1 | 38.2 | 8 | 100.6 | 14 | 8 | 3.6% | 0.12 [-0.87, 1.10] | 2016 | |
| Torri 2018 (2) | 118 | 55 | 25 | 98 | 46 | 26 | 11.2% | 0.39 [-0.17, 0.94] | 2018 | |
| Avila 2020 (3) | 1.04 | 0.4 | 28 | 0.94 | 0.3 | 26 | 12.0% | 0.28 [-0.26, 0.81] | 2020 | |
| Claes 2020 (4) Subtotal (95% CI) | 1.25 | 0.65 | 53 114 | 1.2 | 0.56 | 47 107 | 22.4% 49.2% | 0.08 [-0.31, 0.47] 0.20 [-0.06, 0.47] | 2020 | |
| Heterogeneity: Tau ² = | 0.00; Cł | ni ² = 0. | 90, df = | = 3 (P = | 0.82); | 12 = 0% | 6 | | | 10 Autor |
| Test for overall effect: | Z = 1.49 | (P=0 | 0.14) | | | | | | | |
| 3.7.2 > 6 months/ 24 | weeks | | | | | | | | | |
| rederix 2017 (5) | 136 | 72 | 62 | 139 | 92 | 64 | 28.3% | -0.04 [-0.39, 0.31] | 2017 | |
| Lunde 2020 (6) Subtotal (95% CI) | 1.6 | 1.6 | 48 110 | 1.2 | 0.7 | 54 118 | 22.5% 50.8% | 0.33 [-0.06, 0.72] 0.13 [-0.22, 0.49] | 2020 | |
| Heterogeneity: Tau ² = | 0.03; Cł | 1 ² = 1. | 85, df = | = 1 (P = | 0.17); | $l^2 = 46$ | % | | | |
| Test for overall effect: | Z = 0.74 | (P=(| 0.46) | | | | | | | |
| Total (95% CI) | | | 224 | | | 225 | 100.0% | 0.16 [-0.02, 0.35] | | • |
| Heterogeneity: Tau ² = | 0.00; CH | ni² = 2. | 92, df = | = 5 (P = | 0.71); | 12 = 0% | 6 | | | |
| Test for overall effect: | | | | | | | | | | -1 -0.5 0 0.5 1 Favours eHealth Favours usual car |
| Test for subgroup diffe | | | | df = 1 (P | = 0.7 | 7), 12 = | 0% | | | Payours enealin Fayours usual car |

c Low-Density Lipoprotein

| | e | Health | | us | ual care | • | | Std. Mean Difference | | Std. Mean Difference |
|---|------------------------|---------|-----------|----------|------------------------|---------|--------|----------------------|------|---------------------------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.5.1≤ 6 months/ 24 | weeks | | | | | | | | | |
| Pfaeffli Dale 2015 (1) | 1.7 | 0.6 | 61 | 1.9 | 0.8 | 62 | 13.0% | -0.28 [-0.64, 0.07] | 2015 | |
| Johnston 2016 (2) | 3.8298 | 0.672 | 34 | 3.267 | 0.666 | 30 | 10.2% | 0.83 [0.32, 1.34] | 2016 | |
| Vieira 2016 (3) | 71.4 | 28.2 | 8 | 97.7 | 21.5 | 8 | 4.4% | -0.99 [-2.05, 0.07] | 2016 | · · · · · · · · · · · · · · · · · · · |
| Torri 2018 (4) | 97 | 20 | 25 | 96 | 30 | 26 | 9.6% | 0.04 [-0.51, 0.59] | 2018 | |
| Avila 2020 (5) | 1.89 | 0.6 | 28 | 1.73 | 0.3 | 26 | 9.8% | 0.33 [-0.21, 0.87] | 2020 | |
| Claes 2020 (6) | 1.95 | 0.8 | 53 | 2.01 | 0.87 | 47 | 12.3% | -0.07 [-0.46, 0.32] | 2020 | |
| Subtotal (95% CI) | | | 209 | | | 199 | 59.4% | 0.05 [-0.34, 0.44] | | - |
| Heterogeneity: Tau ² = (| 0.16; Chi ² | = 17.33 | 3, df = 5 | 5(P = 0. | .004); l ² | = 71% | | | | |
| Test for overall effect: | Z = 0.24 (| P = 0.8 | 1) | | | | | | | |
| 3.5.2 > 6 months/ 24 | weeks | | | | | | | | | |
| Frederix 2017 (7) | 79 | 28 | 62 | 80 | 39 | 64 | 13.1% | -0.03 [-0.38, 0.32] | 2017 | |
| Wienbergen 2018 (8) | 67.6 | 21 | 138 | 78.4 | 29 | 143 | 15.1% | -0.42 [-0.66, -0.19] | 2018 | |
| Lunde 2020 (9) | 2.2 | 1 | 48 | 2.3 | 0.9 | 54 | 12.4% | -0.10 [-0.49, 0.28] | 2020 | |
| Subtotal (95% CI) | | | 248 | | | 261 | 40.6% | -0.22 [-0.48, 0.05] | | - |
| Heterogeneity: Tau ² = Test for overall effect: 2 | | | | (P = 0.1 | 3); l ² = : | 52% | | | | |
| Total (95% CI) | | | 457 | | | 460 | 100.0% | -0.05 [-0.30, 0.21] | | + |
| Heterogeneity: Tau ² = | 0.10; Chi ² | = 26.25 | 5. df = 8 | B(P = 0) | 0010); | 2 = 709 | 6 | | | |
| Test for overall effect: | | | | | | | | | | -1 -0.5 0 0.5 1 |
| | | | | | 0.27), l ² | | | | | Favours eHealth Favours usual |

D High-Density Lipoprotein

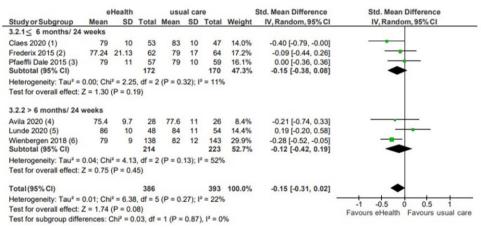
| | | Health | | | al car | | | Std. Mean Difference | | Std. Mean Difference |
|-----------------------------------|----------|-------------|---------|----------|---|-------------|--------|----------------------|------|------------------------------------|
| | | | | | | - | | | | |
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.6.1 ≤ 6 months/ 24 | weeks | | | | | | | | | |
| Pfaeffli Dale 2015 (1) | 1.1 | 0.3 | 61 | 1.2 | 0.4 | 62 | 21.5% | -0.28 [-0.64, 0.07] | 2015 | |
| Vieira 2016 (2) | 45.3 | 6.4 | 8 | 48.6 | 10.1 | 8 | 2.8% | -0.37 [-1.36, 0.62] | 2016 | |
| Torri 2018 (3) | 41 | 9 | 25 | 47 | 13 | 26 | 8.7% | -0.53 [-1.09, 0.03] | 2018 | |
| Avila 2020 (4) | 1.39 | 0.3 | 28 | 1.31 | 0.3 | 26 | 9.4% | 0.26 [-0.27, 0.80] | 2020 | |
| Claes 2020 (5) | 1.28 | 0.33 | 53 | 1.34 | 0.47 | 47 | 17.6% | -0.15 [-0.54, 0.25] | 2020 | |
| Subtotal (95% CI) | | | 175 | | | 169 | 60.0% | -0.19 [-0.43, 0.04] | | - |
| Heterogeneity: Tau ² = | 0.01 Ch | 2 = 4 4 | 55 df = | 4 (P =) | 34) | 2 = 129 | 6 | | | 10000 |
| Test for overall effect: | | | | . 1. | | | | | | |
| restroi oreitai eneot. | | 1. 0 | | | | | | | | |
| 3.6.2 > 6 months/ 24 | weeks | | | | | | | | | |
| Frederix 2017 (6) | 45 | 11 | 62 | 47 | 11 | 64 | 22.2% | -0.18 [-0.53, 0.17] | 2017 | |
| Lunde 2020 (7) | 1.3 | 0.4 | 48 | 1.4 | 0.5 | 54 | 17.9% | -0.22 [-0.61, 0.17] | 2020 | |
| Subtotal (95% CI) | | | 110 | | | 118 | 40.0% | -0.20 [-0.46, 0.06] | | • |
| Heterogeneity: Tau ² = | 0.00: Ch | $i^2 = 0.0$ |)2 df = | 1 (P = (| (98.0 | $ ^2 = 0\%$ | | | | |
| Test for overall effect: | | | | | ,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,, | | | | | |
| Test for overall enour. | 1.40 | 1 0 | | | | | | | | |
| Total (95% CI) | | | 285 | | | 287 | 100.0% | -0.20 [-0.36, -0.03] | | • |
| Heterogeneity: Tau ² = | 0.00 Ch | $i^2 = 4.5$ | 57 df = | 6 (P = (| 0.60) | $1^2 = 0\%$ | | | | |
| Test for overall effect: | | | | -1. | | | | | | -1 -0.5 0 0.5 1 |
| Test for subgroup diffe | | | | - 1 /D | - 0.00 | 12 - 0 | 0/ | | | Favours usual care Favours eHealth |
| rest for subgroup diffe | rences. | OIII. = | 0.00, d | (P | - 0.98 | , · · · · | 70 | | | |



A Systolic Blood Pressure

| | 0 | Health | | usu | al care | | : | Std. Mean Difference | | Std. Mean Difference |
|-------------------------------------|-----------|---------------------|-----------|------------|-----------------------|-----------|----------------|---|------|--|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.1.1≤ 6 months/ 24 | weeks | | | | | | | | | |
| Pfaeffli Dale 2015 (1) | 136 | 20 | 57 | 135 | 16 | 59 | 15.1% | 0.05 [-0.31, 0.42] | 2015 | |
| Johnston 2016 (2) | 130.3 | 14.56 | 80 | 123.82 | 17.83 | 72 | 16.7% | 0.40 [0.08, 0.72] | 2016 | |
| Torri 2018 (3) | 125 | 15 | 25 | 129 | 18 | 26 | 9.6% | -0.24 [-0.79, 0.31] | 2018 | |
| Claes 2020 (4) Subtotal (95% CI) | 127 | 16 | 53 215 | 131 | 20 | 47 204 | 14.0% 55.5% | -0.22 [-0.61, 0.17] 0.03 [-0.28, 0.34] | 2020 | |
| Heterogeneity: Tau ² = | 0.06; Chi | 2 = 7.29 |), df = 3 | (P = 0.0 | 6); l ² = | 59% | | | | |
| Test for overall effect: | | | | | | | | | | |
| 3.1.2 > 6 months/ 24 | weeks | | | | | | | | | ~ |
| Wienbergen 2018 (5) | 130 | 15 | 138 | 135 | 18 | 143 | 20.3% | -0.30 [-0.54, -0.07] | 2018 | |
| Avila 2020 (6) | 125.3 | 15 | 28 | 123.8 | 17 | 26 | 10.0% | 0.09 [-0.44, 0.63] | 2020 | |
| Lunde 2020 (7) Subtotal (95% CI) | 143 | 19 | 48 214 | 145 | 20 | 54 223 | 14.2% 44.5% | -0.10 [-0.49, 0.29] -0.20 [-0.40, -0.00] | 2020 | • |
| Heterogeneity: Tau ² = | 0.00; Chi | ² = 2.10 |), df = 2 | (P = 0.3) | 5); l ² = | 5% | | | | 1000 |
| Test for overall effect: | | | | | | | | | | |
| Total (95% CI) | | | 429 | | | 427 | 100.0% | -0.05 [-0.26, 0.17] | | + |
| Heterogeneity: Tau ² = | 0.04; Chi | 2 = 13.5 | 8, df = | 6 (P = 0. | 03); l ² = | = 56% | | | | |
| Test for overall effect: | Z = 0.41 | (P = 0.6) | (8) | | | | | | | -1 -0.5 0 0.5 1 Favours eHealth Favours usual car |
| Test for subgroup diffe | | | | = 1 (P = (| 0.21), l ² | = 35.7 | % | | | Favours enearth Favours usual car |

B Diastolic Blood Pressure



c Body Mass Index

| | el | lealth | | usu | al car | e | 1 | Std. Mean Difference | | Std. Mean Difference |
|-----------------------------------|----------|---------|---------|----------|--------|-----------------------|--------|----------------------|------|----------------------------------|
| Study or Subgroup | Mean | SD | Total | Mean | SD | Total | Weight | IV, Random, 95% CI | Year | IV, Random, 95% CI |
| 3.3.1 ≤ 6 months/ 24 | weeks | | | | | | | | | |
| Frederix 2015 (1) | 28 | 5 | 62 | 27 | 5 | 64 | 13.0% | 0.20 [-0.15, 0.55] | 2015 | |
| Pfaeffli Dale 2015 (2) | 30.3 | 5.4 | 57 | 28.1 | 4.4 | 59 | 12.4% | 0.44 [0.08, 0.81] | 2015 | |
| Vieira 2016 (3) | 27.4 | 4.2 | 10 | 28.1 | 3.5 | 10 | 4.2% | -0.17 [-1.05, 0.71] | 2016 | |
| Johnston 2016 (4) | 28.3 | 3.6 | 80 | 27.9 | 2.7 | 72 | 13.9% | 0.12 [-0.19, 0.44] | 2016 | |
| Torri 2018 (5) | 26.6 | 4 | 25 | 25 | 2 | 26 | 8.1% | 0.50 [-0.06, 1.06] | 2018 | |
| Claes 2020 (6) | 27.5 | 3.6 | 53 | 29.2 | 4.3 | 47 | 11.6% | -0.43 [-0.83, -0.03] | 2020 | |
| Subtotal (95% CI) | | | 287 | | | 278 | 63.2% | 0.13 [-0.15, 0.41] | | - |
| Heterogeneity: Tau ² = | 0.07; Ch | 2 = 12 | .67, df | = 5 (P = | 0.03) | : I ² = 61 | % | | | |
| Test for overall effect: | Z = 0.90 | (P = 0 | .37) | | | | | | | |
| 3.3.2 > 6 months/ 24 | weeks | | | | | | | | | |
| Wienbergen 2018 (7) | 28 | 4 | 138 | 28.3 | 4.2 | 143 | 16.6% | -0.07 [-0.31, 0.16] | 2018 | |
| Avila 2020 (8) | 26.9 | 2.6 | 28 | 28.2 | 2.9 | 26 | 8.4% | -0.47 [-1.01, 0.08] | 2020 | |
| Lunde 2020 (9) | 90.4 | 16.6 | 48 | 88.6 | 17.6 | 54 | 11.9% | 0.10 [-0.28, 0.49] | 2020 | |
| Subtotal (95% CI) | | | 214 | | | 223 | 36.8% | -0.09 [-0.33, 0.16] | | - |
| Heterogeneity: Tau ² = | 0.01; Ch | 2 = 2.8 | 2, df = | 2(P = 0) | 0.24); | l ² = 299 | 6 | | | |
| Test for overall effect: | Z = 0.71 | (P = 0 | .48) | | | | | | | |
| Total (95% CI) | | | 501 | | | 501 | 100.0% | 0.04 [-0.16, 0.24] | | • |
| Heterogeneity: Tau ² = | 0.05; Ch | 2 = 18 | 21, df | = 8 (P = | 0.02) | : I ² = 56 | % | | | |
| | | | | 1000 | | | | | | -1 -0.5 0 0.5 1 |
| Test for overall effect: | | | | | | | | | | Favours eHealth Favours usual ca |

Figure 7 Effects of eHealth interventions on (A) systolic blood pressure, (B) diastolic blood pressure, and (C) body mass index.

Rehospitalization / Adverse Events

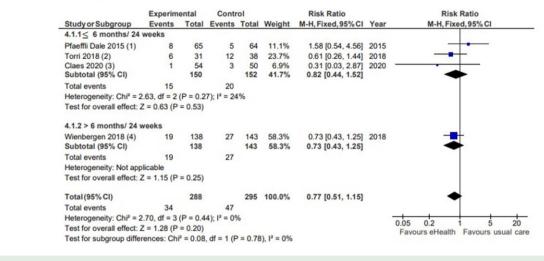


Figure 8 Effects of eHealth interventions rehospitalization/adverse events.

pedometers) in combination with apps or (online) diaries. Overall, eHealth interventions induced a significantly higher level of PA including exercise and daily activity (steps) in the IG compared with control (SMD = 0.35; 95% CI 0.02 to 0.70; P = 0.04; $I^2 = 82.3\%$; n = 957; Figure 4A). Further analysis did not reveal a clear indication for higher levels of PA with shorter intervention times (<6 months) or for a temporal stability (>6 months). Six studies investigated the effect on exercise capacity and physical fitness using cardiopulmonary exercise tests with respiratory gas analysis. The overall effect was not significant (SMD = 0.09; 95% CI -0.19 to 0.37; P = 0.54; $l^2 = 54.0\%$; n = 458; Figure 4B).^{24,42,45,48,50,51} However, the subgroup analysis indicated a significantly higher level of exercise capacity in the IG compared with CG in studies with longer follow-up (>6 months) (three studies; SMD = 0.29; 95% CI 0.05 to 0.52; P =0.02; $l^2 = 0.0\%$; n = 282),^{24,50,51} which was not detected in studies with shorter intervention periods (three studies; SMD = -0.14; 95% CI -0.67 to 0.39; P = 0.61; $I^2 = 61\%$; n = 176).^{42,45,48} This observation is in line with the assumption that significant changes in physical fitness may only be achieved after a longer period of regular PA.

Effects of eHealth maintenance on quality of life, mental health, and self-efficacy

Five studies assessed the effects of phase III eHealth maintenance on QoL. Studies applied the European Quality of Life–5 Dimensions Visual Analogue Scale, Short-form (SF)-36 questionnaire, perceived health questionnaire, and Warwick–Edinburgh mental well-being scale. Overall, a small but significant effect was detected (SMD = 0.17; 95% CI 0.02 to 0.32; P = 0.02; $I^2 = 0.0\%$; n = 688; *Figure 5A*) indicating higher QoL with eHealth. The subgroup analysis suggested a positive short-term effect (≤ 6 months) (three studies; SMD = 0.25; 95% CI 0.03 to 0.48; P = 0.03; $I^2 = 0.0\%$; n = 305), while no long-term effect was detected (two studies; SMD = 0.11; 95% CI -0.09 to 0.31; P = 0.27; $I^2 = 0.0\%$; n = 383). In the domains mental health measured by the HADS and SF-36 (six studies; SMD = 0.08; 95% CI -0.08 to 0.23; P = 0.34; $I^2 = 0.0\%$; n = 621; *Figure 5B*) and self-efficacy measured using the perceived competence for regular Physical Exercise scale, the Self-efficacy for Managing Chronic Disease 6-item scale, the SCI

Exercise Self-Efficacy Scale, and the differences in outcomes between the IG and CG groups at 6 months (four studies; SMD = -0.02; 95% CI -0.21 to 0.17; P = 0.85; $I^2 = 0.0\%$; n = 438; *Figure 5C*), no significant effects were detected in the overall or the subgroup analyses.

Effects of eHealth maintenance on clinical parameters

Clinical parameters investigated involved lipid levels, blood pressure, and BMI (Figures 6 and 7). Nine studies analysed serum lipid levels after the intervention [high density lipoprotein (HDL), n = 572; low density lipoprotein (LDL), n = 917; total cholesterol, n = 853; triglyceride, n =449]. In this domain, a significant overall effect was found for reduced HDL cholesterol levels (seven studies; SMD = -0.20; 95% Cl -0.36to -0.03; P = 0.02; $l^2 = 0.0\%$; n = 572; Figure 6D).^{24,43,45,47,48,50,51} Further analysis did not indicate any effect in the longer or shorter IGs. For total cholesterol levels (eight studies; SMD = -0.11; 95% CI -0.32 to 0.10; P = 0.30; $l^2 = 51.0\%$; n = 853; Figure 6A),^{35,43,45-48,50,51} LDL (nine studies; SMD = -0.05; 95% CI -0.30 to 0.21; P = 0.71; $l^2 = 70.0\%$, n = 917; Figure 6C)^{35,43,45-51} and triglycerides (six studies; SMD = 0.16; 95% CI -0.02 to 0.35; P = 0.09; $I^2 = 0.0\%$; n = 449; Figure 6B),^{43,45,46,48,50,51} no significant effect was detected overall or in the respective subgroup analyses. Three studies reported decreased systolic blood pressure after 6 months (three studies; SMD = -0.20; 95%CI -0.40-0.00; P = 0.046, Figure 7A). 35,50,51 With respect to systolic blood pressure <6 months (four studies; SMD = -0.05; 95% CI -0.26 to 0.17; P = 0.68; $l^2 = 56.0\%$; n = 856; Figure 7A)^{35,45,47-51} and diastolic blood pressure (six studies; SMD = -0.15; 95% CI -0.31 to 0.02; P = 0.08; $l^2 = 22.0\%$; n = 779; Figure 7B), 35,45-47,50,51 no effect was detected. Findings on BMI/body weight were also not different in the IG compared with CG after the interventions (nine studies; SMD = 0.04; 95% CI -0.16 to 0.24; P = 0.68; $l^2 = 56.0\%$; n = 1002; Figure 7C).^{35,43,45–51}

Re-hospitalization and adverse events

Four studies (n = 583 patients) reported on rehospitalizations defined as hospital admissions and unplanned medical visits, serious adverse

events, all-cause mortality, (unplanned) hospitalization for CVD, serious atrial or ventricular arrhythmia, reinfarctions, or unplanned revascularizations among included participants (*Figure 8*).^{35,45,47,48} No significant difference was detected in the overall analysis or for the subgroups, which may be explained by the rather short follow-up period of the included studies.

Behavioural change techniques

Only three studies reported on specific behavioural change theories used to design the CR program (*Table 1*). This involved the Health Action Process Approach (HAPA) and I-Change Model,⁴⁰ social cognitive theory⁴⁷ and social problem-solving model, as well as self-efficacy theory, expectancy-value theory, and relapse prevention theory.⁴⁴ All other studies did not report use of a specific behavioural change theory. Based on the described interventions, mapping of BCTs revealed that the majority of studies used self-monitoring of behaviour (10 studies),^{35,40–43,45,47–50} and/or goal setting (nine studies),^{40–42,44–48,50} as well as feedback on behaviour (nine studies).^{35,40–42,45–50} Studies also used prompts/cues (five studies),^{40,42,47,49,50} action planning (three studies),^{40,42,50} problem solving (three studies),^{40,42,44} instructions on how to perform behaviour (two studies),^{42,46} self-efficacy enhancement (two studies),^{44,450} and prevention strategies (one study).⁴⁴

Discussion

The aim of this systematic review was to provide a structured overview of existing phase III CR eHealth-based maintenance studies in CAD and provide a meta-analysis of the effects of eHealth on health-related outcomes. An additional focus was set on characterizing the applied BCTs delivered by the respective eHealth solutions. In brief, our findings suggest that eHealth in phase III CR may be used to induce significant effects on regular PA, systolic blood pressure, and QoL of patients with CAD. Furthermore, our findings indicate that eHealth may be applied to cause significant improvements in exercise capacity, at least >6months post-intervention. No significant differences were found in rehospitalization and adverse events between the intervention and control groups. This lack of significant difference could be due to the small sample sizes of the individual studies, variability in the definition and measurement of adverse events, as well as differences in patient populations. Additionally, the duration and intensity of the intervention may not have been sufficient to produce significant changes in adverse events.

Our findings are partly in line with a recent systematic review analysing structured or centre-based maintenance CR programs, which resulted in increased or maintained functional capacity, QoL, and PA levels, when compared with control.⁵² Moreover, a number of analyses have already identified eHealth as an effective alternative to phase II CR.^{53–56} Our findings are further consistent with another recent systematic review and meta-analysis focusing on the use of wearable PA monitoring devices (WPAM) for patients with CVD in general in the maintenance phase of CR. $^{\rm 57}$ The report suggested that the use of WPAMs may be effective for higher cardiorespiratory fitness (CRF) in the maintenance phase of CR. Since recent WPAMs are provided with multifunctional apps including different effective BCTs such as goal setting, self-monitoring, etc., it is difficult to deduce which components of WPAM used in CR maintenance add the observed effect on CRF. In this regard, earlier systematic-reviews and meta-analyses reported that simple step counters can stimulate regular PA in different populations,^{21–23} suggesting that already self-monitoring may induce effects on PA. This is also supported by studies in which patients are initially blinded from data recorded by devices and PA subsequently increases once participants can view the data.⁵⁸ Since participants

may respond differently to the set of BCTs provided by WPAMs and associated apps, identification of specific effects of isolated components is a complex task. The studies included in our analysis also used different eHealth components, which positively affected regular PA and CRF, and it can only be speculated that common BCT components such as goal setting, action planning, feedback on behaviour, or self-monitoring contributed to these outcomes. Moreover, large differences between the included studies in terms of devices used, type and delivery of exercise instructions, as well as documentation of daily PA, exist. Physical activity and CRF are negatively correlated with cardiovascular morbidity and mortality⁵⁹ and physical inactivity has been identified as an independent risk factor for CAD.⁶⁰ Vice versa, exercise-based CR is known to reduce cardiovascular mortality.⁶¹ As the results of this meta-analysis showed an increase in PA and exercise capacity, eHealth interventions may contribute to a reduction in mortality rates.

Besides effects on CRF, CR includes different aspects of risk reduction, adherence to a healthy lifestyle, and improvement of QoL, which were directly or indirectly addressed by the included studies. Patients experiencing a better QoL may have higher motivation to participate in a program for a longer duration compared with patients with a worse OoL. Our analysis revealed that eHealth interventions had a significant impact on QoL, which may increase the long-term acceptance or an eHealth-based program.⁶² We did not find effects on self-efficacy and mental health, since self-efficacy is not related to individual skills, but rather to the estimation of what one can attain with the given skills.⁶³ Therefore, autonomous motivation for exercise, in particular participation in motivational counselling sessions, has been found to increase self-efficacy in IGs⁶⁴ and could therefore be added to future interventions. To increase self-efficacy, volitional strategies could be included in further interventions. Even though a healthy lifestyle is related to selfrated mental health in general,⁶⁵ no improvement in mental health was detected. This observation may be based on the fact that the included studies mainly focused on increasing PA, but not on mental health improving strategies such as relaxation techniques and stress management.⁶⁶ It may also be argued that the majority of patients is likely mentally stable 3 months post-cardiac event, with less room for further improvement. Of note, the included studies provided extensive detail on the use of eHealth in general but often failed to describe details of the intervention itself including applied BCTs. For instance, in most cases, no information from the original publication was available on the purpose and content of phone calls, emails and messages, the level of individualization, or on which BCTs those components were based.

Our analysis revealed no effects on clinical parameters such as total cholesterol, triglycerides, LDL, and BMI. In terms of lipid management, this may be due to the fact that guideline-based medication was delivered over the trial in both groups and the trials did not aim to optimize medication, even though increased medication adherence was targeted by one trial.⁴⁹ Studies used websites and other components to deliver information on disease management and risk factors, but, to the best of our knowledge, did not address individual risks and respective actions (i.e. clinical visits). It can thus be concluded that potentially induced lifestyle changes did not exceed the impact of medication, leaving lipid levels unchanged. However, it needs to be noted that interpretation of reported mean and SD LDL levels indicates that a larger number of patients did not reach guideline-recommended levels. It is thus recommended to include tools for medication adherence and continuous monitoring of risk factors to improve eHealth effects also on clinical parameters. In addition, while RCTs are generally considered to be the gold standard for evaluating the effectiveness of interventions, they are not immune to limitations or bias and RCTs fail to detect differences in medication adherence or associated outcomes, even if such differences exist in the real world.

It is important to note that use of technology alone may not be sufficient for targeted interventions and to induce desired effects. Instead, critical appraisal of behavioural theories and associated BCTs is likely

necessary to achieve long-term habitual change and related health benefits. In the studies included in this review, the most common BCTs were action control strategies, which represent an important tool to sustained behaviour change.⁶⁷ The combination of action planning and coping planning strategies (problem solving) was applied in a fewer number of studies although post-intentional factors, such as action planning and coping planning, are important in translating intentions into actions to overcome the intention-behaviour gap.⁶⁸ There is evidence that the volitional construct of action planning, action control, and coping planning is effective in changing behaviour as well as increasing PA.⁶⁸ Action planning is considered to be more influential early in the rehabilitation process, whereas coping planning is hypothesized to facilitate behaviour change maintenance, as participants with higher levels of coping planning after discharge were more likely to report higher levels of exercise.⁶⁹ Self-regulation strategies have also been shown as effective behaviour change technique. However, the combination of goal setting and problem-solving strategies may be more effective to reach long-term effects and teaching mental contrasting with implementation intentions as a self-regulation strategy has been shown to enhance long-term PA in stroke patients⁷⁰ and to increase smoking cessation.71

eHealth applications may be helpful to support and sustain lifestylechanges and could be assisted further by blended care as an option for psychological treatment or volitional strategies for temporal stability. For example, according to the HAPA,⁷² health behaviour maintenance requires a specific input, including (i) action planning, to specify situation parameters ('when' and 'where') and a sequence of action ('how') to implement intended behaviour, (ii) action control, to help sustaining the behavioural change, and (iii) coping planning as a self-regulatory strategy or alternative behaviour to overcome barriers.⁷² Overall, only three studies mentioned specific BCTs and connected theories as a basis of their intervention.^{40,44,47} Antypas et al.⁴⁰ applied the HAPA model in their study in a tailored intervention based on sociocognitive determinants, leading to a significantly higher PA than the control group after 3 months. Pfaeffli Dale et $al.^{47}$ based their intervention on social cognitive⁷³ and self-efficacy theory,⁶³ to maintain patients' motivation by self-regulating their behaviour by setting goals, creating incentives, and enlisting social support from others. The adherence to a healthy lifestyle behaviour (defined as smoking cessation, healthy diet, and regular PA) was increased at 3 months, but not at 6 months. The authors interpreted this observation as an effect of frequency of text messaging decreased, and that relapse prevention and coping content should be delivered to re-engage those who drop off. Relapse prevention theory⁷⁴ was applied in the study by Moore et al.⁴⁴ to address patients' exercise maintenance problems. The intervention decreased patients' likeliness to stop exercising in the year following a cardiac event. All other studies reported no concerted approach and combined different technical features likely based on experience, availability, and simplicity. Our analysis identified that self-empowerment has been applied in most studies as an indirect BCT. Self-empowerment by information, education, and communication is considered as a key component of effective health care.⁷⁵

Overall, examining which BCTs, and combinations of BCTs, are most effective in specific contexts presents a major challenge and a valid method of determining the degree of confidence of BCT effectiveness has not been established.⁷⁶ A greater number of BCTs may seem more likely to improve health behaviours, but increasing the number of identified BCTs is not necessarily associated with better outcomes.⁷⁷ Furthermore, studies investigating behavioural support for smoking cessation and increase in PA have shown that the implementation of BCTs is often poor, as fewer than 50% of planned BCTs were later reported in the published article.^{78,79}

About 43% of the present studies reported a drop-out rate of \geq 15%, in line with expected rates for eHealth intervention^{80,81} and also non-technology-based behaviour maintenance interventions in

general.⁸² One reason for this observation might be that participants subjectively achieved a satisfactory PA level, expecting no further improvement. However, patients who do not achieve their behavioural goals are more likely to drop out of an intervention as they do not expect any further value in participating. Lack of individual adaptations of training programs for further improvement, lack of variability and missing options in case of non-response may have also added to this observation. With time, motivation might ease, especially if participants are unable to move forward in their stages of change.^{30,83,84} Future studies in the field should report the actual time point and individual reason for drop out to allow adaptations of eHealth concepts. In addition, codesign with end-users of eHealth concepts in particular is of utmost importance to achieve high user acceptance and lower the barriers for use.

With respect to study duration, a number of studies evaluated maintenance effects after more than 6 months, while some studies had shorter follow-up periods, which may not be sufficient to capture intervention effects aiming at behavioural change. However, studies with shorter follow-up periods may still provide valuable information about the immediate effects of these interventions and can inform the development of future studies with longer follow-up periods. It is also worth noting that excluding studies with shorter follow-up periods may limit the generalizability of the findings, as the effects of eHealth interventions may differ depending on the duration of follow-up.

Our analysis revealed small effect sizes comparable with a recent systematic review and meta-analysis on eHealth in phase II CR when compared with no interventions, waiting lists, etc.⁸⁵ However, eHealth approaches may be used for larger populations since the costeffectiveness of eHealth CR is high compared with centre-based CR.²⁴ Frederix et al.²⁴ estimated that their intervention remained costefficient for up to 2 years after the intervention ended. Outcomes such as cost-effectiveness may show only small effects if the number of participants is limited. However, the overall potential may be significant if larger populations can be addressed in the health sector and eHealth interventions should thus be implemented in standard CR maintenance. To this respect, a recent systematic review acknowledged that the outcomes of telehealth in real-world settings may vary due to factors such as economies of scale and patient adherence to technology over uncertain durations, while the cost-effectiveness may be affected by the type and severity of the patient's disease as well as the cost of the technology and the rehabilitation program.²⁵

With the growing use and popularity of home-based eHealth interventions, there are concerns about the potential risks associated with practicing exercise-based CR without direct supervision.⁸⁶ Even if latest evidence suggests that home-based eHealth interventions for CR can be safe and effective when appropriately designed and implemented, it is important to note that studies typically involve carefully selected stable patient populations and may not be generalizable to all patients with CVD.⁹ The safety of home-based eHealth interventions can be ensured by developing guidelines for patient selection, risk assessment, and monitoring, and by training clinicians and patients to recognize and report symptoms and adequately respond to potential adverse events.²⁰

Limitations

Some limitations regarding the presented analysis may exist. Reporting and publication bias may have affected the present review since some data/studies may have remained unreported or were not published because of unexpected/contradictory, negative, or not significant outcome. Further, selection bias may have affected the individual studies, as participants are often male, relatively young, highly educated, and have low residual risk, which may limit the generalizability of the findings and the external validity of the results. Strategies such as targeted recruitment efforts and stratified analyses can help address this issue and improve the external validity of the study results. Furthermore, the record search was limited to studies published in English, and inclusion of data reported in other languages may have altered the results preliminary in subgroups with smaller sample sizes. Grey literature was not included as results of grey literature may be affected by different aspects of missing quality control.

Conclusion and perspective

This study shows that eHealth in phase III maintenance may be used to increase PA, exercise capacity, and QoL and to decrease systolic blood pressure of patients with CAD 6 months after phase II CR with low- to moderate-guality evidence. Since the number of available studies in phase III CR is currently rather limited, this topic requires more and comprehensive investigations to examine how eHealth tools in cardiovascular maintenance programs work with respect to behavioural change. Future studies are needed to carefully select eHealth components based on behavioural change theories and associated BCTs. Future eHealth-based interventions will likely implement state-of-the-art devices for disease monitoring but should carefully investigate user acceptance and needs already during program design. Since available studies predominantly included male participants, examinations on needs and expectations of female patients with CAD are needed. As only five of the included studies examined maintenance of behavioural outcomes longer than 6 months after the end of the intervention, further studies on long-term effects are needed. Further, there is a need for more detailed intervention description in eHealth studies. A useful tool might be the checklist Consolidated Standards of Reporting Trials of Electronic and Mobile HEalth Applications and onLine TeleHealth,⁸⁷ which provides guidance for authors of eHealth and mHealth interventions.

Supplementary material

Supplementary material is available at European Journal of Preventive Cardiology online.

Author contributions

Melina Heimer, Boris Schmitz, and Frank C. Mooren designed the study. Melina Heimer and Boris Schmitz performed the systematic literature search. M.He., B.S., H.S., and M.T. screened records and extracted data. Sandra Schmitz and Thorsten Meyer transformed data and performed the meta-analysis. Melina Heimer, Frank C. Mooren, Boris Schmitz, Emma R. Douma, Willem J. Kop, and Mirela Habibovic interpreted results. Melina Heimer and Boris Schmitz wrote the manuscript. All authors contributed to the revision of the manuscript and approved the final version of the manuscript.

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Conflict of interest: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

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