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Multifactorial e- and mHealth interventions for cardiovascular disease primary prevention: Protocol for a systematic review and meta-analysis of randomised controlled trials

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Abstract

Objective: Cardiovascular diseases (CVD) are a leading cause of mortality and disease burden. Preventative interventions to augment the population-level adoption of health lifestyle behaviours that reduce CVD risk are a priority. Face-to-face interventions afford individualisation and are effective for improving health-related behaviours and outcomes, but they are costly and resource intensive. Electronic and mobile health (e- and mHealth) approaches aimed at modifying lifestyle risk factors may be an effective and scalable approach to reach many individuals while preserving individualisation. This systematic review aims to (a) determine the effectiveness of multifactorial e- and mHealth interventions on CVD risk and on lifestyle-related cardiometabolic risk factors and self-management behaviours among adults without CVD; and (b) describe the evidence on adverse events and on the cost-effectiveness of these interventions.

Methods: Methods were detailed prior to the start of the review in order to improve conduct and prevent inconsistent decision making throughout the review. This protocol was prepared following the PRISMA-P 2015 statement. MEDLINE, CINAHL, Embase, PsycINFO, Web of Science, Cochrane Public Health Group Specialised Register and CENTRAL electronic databases will be searched between 1991 and September 2019. Eligibility criteria are: (a) population: community-dwelling adults; (b) intervention/comparison: randomised controlled trials comparing e- or mHealth CVD risk preventative interventions with usual care; and (c) outcomes: modifiable CVD risk factors. Selection of study reports will involve two authors independently screening titles and abstracts, followed by a full-text review of potentially eligible reports. Two authors will independently undertake data extraction and assess risk of bias. Where appropriate, meta-analysis of outcome data will be performed.

Discussion: This protocol describes the pre-specified methods for a systematic review that will provide quantitative and narrative syntheses of current multifactorial e- and mHealth CVD preventative interventions. A systematic review and meta-analysis will be conducted following the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* and reported according to PRISMA guidelines.

Keywords

Digital health, mHealth, eHealth, cardiovascular diseases, risk factors, cholesterol, blood pressure, blood glucose, body weight, primary prevention

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Introduction

Description of the condition

Despite evidence showing preventative measures and early intervention are wise investments in improving health and well-being,[1,2] cardiovascular disease (CVD) is the leading cause of mortality and disease burden globally, accounting for approximately 32% of all deaths in 2017. The total number of deaths is estimated at 17.8 million, with ischaemic heart disease and stroke ranking in the top three causes of disability-adjusted life years.[3,4] Population-level preventative interventions aimed at the adoption of healthier lifestyle behaviours and CVD risk-factor management are a priority, since appropriate self-management of modifiable risk factors can reduce the risk of developing CVD.[5,6] Participation in face-to-face behaviour-change preventative interventions affords individualisation and is modestly effective at decreasing risk factor levels.[7] However, face-to-face approaches are unlikely to be a population-level solution, given the resources needed and the difficulty many individuals have in accessing such services.[8,9]

Description of the intervention

Electronic and mobile health (e- and mHealth, respectively) approaches may be an effective and scalable approach to reach many underserved individuals, while also preserving the individualisation that contributes to the effectiveness of traditional face-to-face interventions.[10–14] Cochrane meta-analytical evidence demonstrates beneficial impacts of e- and mHealth interventions on individual CVD risk factors, such as smoking cessation,[15,16] alcohol intake,[17] weight loss[18] and type 2 diabetes.[19] However, CVD incidence is typically determined by the co-existence of multiple modifiable risk factors.[5] Accordingly, heart and cardiology professional associations highlight the multifactorial nature of CVD in their guidelines, recommending the application of multifactorial CVD risk scores (i.e. risk assessment tools[20–22] such as Framingham[23]) to estimate the likelihood of an individual experiencing a CVD event. Moreover, these guidelines recommend targeting multiple key modifiable risk factors – including abnormal cholesterol, raised blood pressure, diabetes, smoking, unhealthy diet, excessive alcohol, abdominal obesity and insufficient physical activity – for reducing CVD risk.[24–26]

How the intervention might work

Evidence suggests targeting modifiable risk factors can reduce the global burden of CVD.[27,28] 'Making Every Contact Count'[29] for improving population health is recommended, and evidence demonstrates brief opportunistic behaviour-change counselling interventions have positive effects, such as increasing physical activity,[30] improving dietary behaviours[31] or increasing attempts of smoking cessation.[32] Yet, improvement in cardiometabolic indices and sustaining recommended lifestyle behaviour changes may require additional intervention beyond single practitioner counselling sessions.[33,34] Moreover, time demands impact practitioner's ability to provide recommended preventive services.[35] E- and mHealth approaches capitalise on the processing power and connectivity of digital technologies to mirror strategies used in traditional face-to-face delivery modes and may even offer opportunities to expand these to provide long-term self-management support.

Why it is important to do this review

E- and mHealth lifestyle behaviour change research has mostly produced interventions targeting a single behaviour or risk factor.[36,37] Evidence has demonstrated the beneficial impact of e- and mHealth interventions on single risk factors for CVD, such as smoking cessation,[4,5] alcohol intake,[6] blood pressure,[38] body composition[18] or blood glucose.[7]

Systematic reviews have also examined the effectiveness of e- and mHealth interventions on CVD outcomes and risk factors.[39] This review was broad, included randomised controlled trials (RCTs) and observational cohort studies, populations from both primary and secondary prevention, as well as single and multifactorial interventions. CVD outcomes (e.g. adverse events, including myocardial infarction, stroke or Framingham risk score) were reduced, and positive effects were reported for some (e.g. weight) but not all risk factors (e.g. cholesterol, blood pressure), but heterogeneity was high.[39] Studies included were published until early 2014 and considering the fast pace of change of e- and mHealth interventions, an update is warranted.[40,41] Additionally, differences in risk factor severity in individuals with/without CVD suggests findings from that review may not be applicable to a primary prevention context. Therefore, available evidence does not allow assessment of the effectiveness of multifactorial e- and mHealth interventions for CVD primary prevention. Moreover, data on adverse events and cost-effectiveness of these interventions have not been assessed.

Objectives

This systematic review aims to investigate the effectiveness of multifactorial e- and mHealth interventions for modifying lifestyle-related cardiometabolic risk factors and self-management behaviours among adults

without CVD. Secondary objectives are to describe the evidence on the adverse events and cost-effectiveness of these interventions.

Methods

We detailed our methods prior to the start of the review in order to improve conduct and prevent inconsistent decision making throughout the review processes.[42,43] This manuscript was prepared following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement.[42]

Criteria for considering studies for this review

Search methods for identifying study reports, eligibility criteria and methods for data extraction, assessing risk of bias and statistical analysis were pre-specified in PROSPERO – International Prospective Register of Systematic Reviews[44] (#CRD42019128277).

Types of studies. Eligible studies are RCTs, including individual or cluster randomisation, with parallel-group design and of at least three months duration of intervention (i.e. three months post commencement of intervention or baseline assessment). A minimum post-intervention follow-up period will not be required.

Context. Primary prevention; eHealth and mHealth interventions that target the primary prevention of CVD. Individuals would be recruited from the general population and/or in primary-care settings (e.g. general practice, family practice). Secondary prevention trials that include participants with existent CVD will be excluded.

Types of participants. We will include studies involving free-living, outpatient, community-dwelling adults aged 18 years or older without a previous history of CVD. Study participants can be at increased risk of CVD (i.e. $\geq$1 risk factors and/or prescribed medication to manage $\geq$1 risk factors) but cannot have a prior history of coronary artery disease/angina/myocardial infarction/revascularisation, transient ischaemic attack/stroke, peripheral vascular disease, chronic kidney disease, heart failure or cardiac arrhythmia. Examples of CVD risk factors are dyslipidaemia, high blood pressure, overweight or obesity, smoking, impaired glucose metabolism or diabetes; examples of prescribed medication include drugs for blood pressure and/or cholesterol and/or diabetes.

Pharmacological therapies commonly prescribed to people with diabetes are associated with reduced risk of CVD events[45,46] and may therefore reduce the impact of concurrent lifestyle interventions. However, the effects of multifactorial diabetes lifestyle interventions on modifiable CVD risk factors can reduce the need for pharmacological therapy while also having a comparable effect on CVD event risk.[47] While outcomes in controlled trials of diabetes lifestyle interventions will be affected by medication use in each treatment group, impaired glucose metabolism remains a key CVD risk factor, and lifestyle interventions can play an important role in CVD risk management. Therefore, trials targeting diabetes cohorts will not be excluded from this review if they satisfy remaining eligibility criteria.

Studies that focus on secondary prevention have been reviewed previously[48] and will be excluded. Studies that recruited children and adolescents (i.e. $<$18 years old) and patient populations with prevalent CVD as defined above will be excluded. Studies that recruited individuals with and without prevalent CVD will be included only if results are reported separately for primary prevention participants.

Types of interventions. Eligible interventions will be those that use e- and mHealth to target the modification of multiple lifestyle behaviours to improve quantitative CVD risk score and/or modifiable risk factor profile (i.e. primary objective was the primary prevention of CVD). eHealth interventions are defined as those that use information and communications technologies—mainly the Internet—to improve health and health care. mHealth interventions are defined as those that use mobile devices—such as mobile phones, patient monitoring devices, personal digital assistants and other wireless devices—to support medical/public-health practice.

Eligible lifestyle behaviours and CVD risk factors will include smoking, diet, alcohol, physical activity, sedentary behaviour, sleep, stress management, cholesterol and glucose/HbA_{1c} concentrations, blood pressure and body composition/anthropometry.

The e/mHealth intervention can be supplemented with other forms of delivery, but e/mHealth needs to be the predominant mode of delivery/main component. Similar criteria has been applied in previous reviews due to difficulty in assessing impact of e/mHealth on health outcomes when used as an adjunct to other interventions.[37] Studies that deliver interventions via desktop or laptop computers but do not require an Internet connection will be excluded.

We will exclude studies where interventions target a single risk factor/self-care behaviour, those which include a drug as the primary intervention (i.e. pharmacological intervention is the main component) and those where the sample includes individuals younger than 18 years old.

Permitted comparison groups are inactive controls/comparators, such as usual care, placebo, no

intervention or waiting list. 'Usual care' CVD preventative treatment is defined as no systematic provision of e/mHealth CVD preventative treatment (i.e. primary preventive treatments that are not received via e/mHealth delivery models). Active control comparators including any e/mHealth component, a different variant of e/mHealth, such as a different version of a website/app, or a 'less intensive' intervention including e/mHealth components will be excluded.

In summary, the following will be reasons to exclude studies: non-random allocation, no multifactorial risk factor intervention, no e/mHealth intervention, no relevant CVD risk-factor changes measured and/or reported, control group receiving substantial intervention, no comparable control group identified, report included participants younger than 18 years old, report included CVD diagnosed participants, baseline or post-intervention data not provided or post-intervention data to at least three months was not reported.

Types of outcome measures. Outcomes of interest will include CVD risk scores and CVD risk factors as either a primary or secondary outcome.

Primary outcomes. The primary outcome measure will be multivariable CVD summary scores of risk (e.g. Framingham, QRISK), assessed at baseline and post intervention. Regarding timing of effect measures, both short-term (i.e. measured immediately post intervention) and long-term outcomes (i.e. measured at longer-term follow-up) will be considered. Congruency of measures and timing with protocols (registries and/or published) will be checked.

Secondary outcomes. Secondary outcomes will include:

- CVD risk factors:
  - Cholesterol concentrations (e.g. total, low-density lipoprotein, high-density lipoprotein, triglycerides);
  - Blood pressure (systolic and diastolic);
  - Body composition (e.g. body mass index (BMI), body fat percentage, waist and hip circumference);
  - Insulin resistance (e.g. fasting blood glucose, HbA_{1c}); and
  - Cardiorespiratory fitness (e.g. VO_2max).
- Health-related quality of life and/or health status (e.g. physical function domain);
- Mental health–related outcomes (e.g. depression);
- Health-related behaviours:
  - dietary intake;
  - smoking;
  - alcohol;
  - physical activity;
  - sedentary behaviour; and
  - medication adherence.
- Adverse events, as defined by trial investigators, such as physical or psychosocial events (e.g. anxiety) and informed by the PRISMA harms checklist[49]; and
- Cost-effectiveness and economic data.

Search methods for identification of studies

Electronic searches. The following electronic databases will be searched between 6 August 1991 (World Wide Web live/onset) and September 2019:

- Cochrane Central Register of Controlled Trials (CENTRAL);
- Cochrane Public Health Group Specialised Register;
- PsycINFO (Ovid);
- MEDLINE (Ovid);
- EMBASE;
- CINAHL; and
- Web of Science.

The Cochrane sensitivity-maximising RCT filter for MEDLINE will be applied. Following advice from a medical librarian, a search strategy was developed for MEDLINE and was adapted for other databases (see Supplemental Material). Search terms will include medical subject headings (MeSH) and keywords and are based on previous Cochrane reviews.[7,50] Searches will be limited to human studies published in English.

Searching other resources. Electronic database searches will be supplemented by hand searching reference lists of included studies and relevant review articles identified by the search. Only original research articles will be included. Non peer-reviewed search results (e.g. reports, notes, abstracts, editorials, evaluations) will be excluded. Conference abstracts and dissertations are ineligible, but authors will be contacted to request full-text peer-reviewed manuscripts.

We will further search the Interdisciplinary Database: mHealth Evidence (https://www.mhealthevidence.org/) using combinations of the terms 'cardiovascular disease' and 'primary prevention'.

Data collection and analysis

Selection of studies. Two researchers (shared between A. D., J.M. and R.D.) will independently assess eligibility by screening the titles and abstracts of all records retrieved. Potentially eligible studies will undergo full

text screening. We will record reasons for exclusion of the ineligible studies. Duplicate reports will be identified and excluded. We will collate multiple reports of the same study so that each study is the unit of analysis. Covidence software (Melbourne, Australia) will be used to assist with the screening and distribute the review workload amongst the three researchers.[51] Discrepancies will be discussed until reaching a consensus or by involving the third researcher. If required, study authors will be contacted up to twice for additional information to confirm eligibility.

Data extraction and management

Two researchers (shared between A.D., J.R. and R.D.) will independently extract data from included study reports into a data-extraction form designed for this review. Cross-checks will be conducted computationally for all quantitative data. Cross-checks for free-text data will be conducted on 10% of included studies to verify accuracy. Discrepancies will be resolved by discussion or, when necessary, by involving the third researcher. Study authors will be contacted via email up to twice for additional outcome data or trial details when necessary (e.g. any missing required data or to confirm data). Should standard deviations for outcomes not be available, these will be imputed from within study data according to methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.1.3 of Higgins[52]).

Data to be extracted from each included study report will include:

- Eligibility (inclusion and exclusion criteria);
- Study design (e.g. number of arms, relevant arms, level of randomisation – individual, cluster, block);
- Country, year, trial registration number;
- Participant characteristics (*N*, age mean, age standard deviation (*SD*), age range, % male/female, education, % white/ethnicity, BMI, baseline CVD risk – described by group or altogether, as provided);
- Intervention characteristics (e.g. duration, dose/schedule, setting, type of technology/device – mobile phone, smartphone, PDA –; media – application software, MP3 audio, SMS, MMS, voice, MP4 video –; comprehensiveness, individualisation, *N* randomised, *N* completed, withdrawals);
- Comparator characteristics;
- Outcome characteristics (e.g. primary or secondary, outcome variables, continuous/dichotomous, data format – mean and *SD* or *SE* or 95% confidence interval (CI), mean difference (MD) and *p*-value or 95% CI, odds ratio (OR) or risk ratio (RR) and 95% CI –, end point or change from baseline, time points, units);
- Methodological quality (risk of bias domains); and
- Sources of funding.

A.D. will transfer data extracted into Review Manager v5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Assessment of risk of bias in included studies. Risk of bias of each study will be assessed by two independent researchers (shared between A.D., J.R. and J.M.) using the Cochrane Collaboration tool.[53] Sources of bias assessed will be sequence generation, allocation concealment, blinding of personnel and outcome assessors (blinding of participants is impractical for e/mHealth interventions), incomplete outcome data, selective reporting and other potential threats to validity (e.g. baseline imbalance in cluster-randomised trials). Risk of bias of cluster RCTs will consider recruitment, baseline imbalances, loss of cluster or incorrect analyses. Discrepancies will be resolved by discussion or by involving the third researcher if necessary. Treatment effects will be considered according to risk of bias of each study that contributes to a pooled outcome.

The GRADE framework will be used to assess the quality of evidence for each outcome.[54] Based on the critical appraisal of risk of bias, evidence directness, precision of effect estimates, heterogeneity and risk of publication bias, evidence quality will be rated as high, moderate, low or very low.

Measures of treatment effect. We anticipate effects of e- and mHealth interventions will be analysed using a series of random-effects model meta-analyses for each modifiable CVD risk factor and behaviour. For continuous outcomes (e.g. blood pressure, blood cholesterol) measured on the same scale/instrument, we will use MDs with 95% CIs to compare net differences (i.e. intervention group minus comparison group). Standardised MDs (SMDs) will be compared for outcomes measured using different scales/instruments. Outcome data extraction will source post-intervention/end-point values where possible (i.e. instead of change from baseline). We will not combine post intervention/end point with change outcomes in meta-analysis of SMDs, but we may consider combining studies reporting post intervention/end point with studies reporting change from baseline when using MDs (*Cochrane Handbook for Systematic Reviews of Interventions*, section 9.4.5 of Deeks[55]). If necessary, where meta-analysis will be inappropriate, studies reporting outcome data as change from baseline will be reported narratively. For dichotomous outcomes

(e.g. smoking, clinical events), we will use OR or RR with 95% CI.

Outcome data extraction will be sourced at both the immediate post-intervention time point (i.e. short term; outcome measured at the closest time to end of intervention) and at the longest duration of follow up time point that was reported in the primary study publication. For studies reporting both short- and long-term outcomes, we plan to include the short-term outcome data in the meta-analyses. We will consider pooling the longest duration of follow-up reported in primary reports, but the number of included studies reporting long-term outcomes may be insufficient to consider meta-analyses. We do not plan to use follow-up data published in subsequent reports, as it is conceivable that such long-term findings may reflect effects of co-interventions, such as medication use.[7]

Where meta-analysis is not feasible (e.g. heterogeneity, insufficient studies to pool), a narrative synthesis will be presented. We will summarise data narratively and in tabular form.

Unit of analysis issues. This review may include RCTs with parallel and cluster designs. We will extract data on whether study investigators account for clustering in their statistical analyses, such as a multilevel model or generalised estimating equations. If analyses of included studies are adjusted for clustering, then we plan to meta-analyse individual RCTs with cluster RCTs. Should cluster randomised trials not adjust for the clustering effect in study reports, we will follow the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (section 16.3 of Higgins[52]).

If a study has multiple intervention groups, we will select the most relevant pair of arms and exclude the others in order to avoid including a group of participants twice in the same meta-analysis. Pooling intervention arms of interest into one group to obtain a single pair comparison will be considered where appropriate (i.e. considering intervention arms' characteristics) according to the methods outlined in section 16.5 of Higgins.[52]

Dealing with missing data. We will follow the methods outlined in section 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* to calculate and impute missing statistics of interest, such as outcome standard deviations (or change outcomes if this is the outcome of interest and only baseline and post-intervention/endpoint values are reported).[52,55] We will investigate attrition rates and losses to follow-up, and appraise methods used by study investigators to address missing data (e.g. imputation methods).

Assessment of heterogeneity. Heterogeneity will be tested using the I^2 and chi-square statistic for each outcome. We may undertake fixed-effects model meta-analyses where heterogeneity of effects is not substantial (i.e. defined as I^2 statistic $<50\%$).[55] We will investigate potential reasons for heterogeneity by considering individual study and subgroup characteristics.

Subgroup analysis. Depending on viability (e.g. number of included studies[55]), we will undertake moderator/subgroup analyses to assess potential effect modifiers. Selection of subgroup characteristics will be informed by effect modifiers previously identified in the literature or motivated by clinically relevant hypotheses. Subgroup analyses will be conducted as a means to investigate heterogeneity and compare the magnitudes of effect (rather than statistical significance).[55] Pre-specified potential subgroup analyses are:

- Intervention comprehensiveness (i.e. defined as number of targeted risk factors). Based on evidence indicating CVD, incidence is determined by the co-existence of multiple modifiable risk factors and importance of targeting the multifactorial risk profile.[20–22,36,56]
- Mode of delivery. Studies of eHealth (e.g. web-based) versus mHealth (e.g. SMS or smartphone app or wearable sensors) versus combination of e- and mHealth. Based on observational data suggesting effects may differ according to mode of delivery (e.g. web-based, telemedicine, SMS, email).[39]
- Co-intervention. Studies where the e/mHealth intervention was stand-alone versus studies where interventions combine e/mHealth and non-digital components (e.g. face-to-face sessions, behavioural counselling). Based on evidence suggesting that e/mHealth can be effective when delivered as stand-alone interventions or combined with a non-digital adjunct.[57–62]
- Intervention length. Studies where intervention was up to three months versus longer than three months, as the impact of intervention duration is unknown. Alternatively, the median intervention duration will be computed based on the included studies and used as the cut-off value for subgroup analyses.

The following prognostic factors will also be considered for potential subgroup analyses:

- Co-morbidity. Studies among general populations versus high-risk populations (i.e. diabetes or hypertension or dyslipidaemia or obesity) versus high-risk co-morbidity population (i.e. diabetes or hypertension or dyslipidaemia or obesity and one co-morbidity). Based on evidence indicating effects

are beneficial in high-risk populations but negligible in the general population.[7]
- Pharmacological intervention. Studies without pharmacological treatment part of the intervention versus including pharmacological treatment (e.g. anti-hypertensives or cholesterol-lowering drugs or smoking cessation medication). Based on evidence suggesting a pharmacological intervention is a possible source of heterogeneity[39] and on differential effectiveness depending of outcome (e.g. coronary heart disease mortality, stroke mortality, cholesterol, blood pressure).[7,63]

Sensitivity analysis. Robustness of pooled estimates from random-effects models will be considered with sensitivity analyses. The 'leave one out method' will be used to investigate the influence of individual studies on pooled outcomes with considerable heterogeneity (i.e. defined as I^2 >50%). We will exclude studies judged to have a high risk of bias from the meta-analysis of primary and secondary outcomes.

Assessment of reporting biases. We will use funnel plots to investigate publication bias for each outcome including at least 10 studies.[64]

Discussion

This protocol describes the pre-specified methods for a systematic review that will provide quantitative and narrative syntheses of current evidence for the benefits, risks and costs of multifactorial e- and mHealth CVD preventative interventions. Deviations from this protocol and the future published review manuscript will be reported in a section titled 'Differences between protocol and review'. Findings from this review may highlight opportunities for future development of CVD primary prevention interventions and potentially support evidence-based decision making by health practitioners and other decision makers working to target CVD.

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