Digital Technology Interventions for Risk Factor Modification in Patients with Cardiovascular Disease: A Systematic Literature Review and Meta-Analysis.

Adewale Samuel Akinosun, Rob Polson, Yohanca Diaz - Skeete, Johannes De Kock, Lucia Carragher, Stephen Leslie, Mark Grindle, Trish Gorely

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# Table of Contents

**Original Manuscript** ....................................................................................................................................................................... 5  
**Supplementary Files** ..................................................................................................................................................................... 26  

**Figures** ................................................................................................................................................................................................. 27  
  Figure 16 .............................................................................................................................................................................................. 28  
  Figure 2 .............................................................................................................................................................................................. 29  
  Figure 4 .............................................................................................................................................................................................. 30  
  Figure 3 .............................................................................................................................................................................................. 31  
  Figure 21 ............................................................................................................................................................................................ 32  
  Figure 20 ............................................................................................................................................................................................ 33  
  Figure 19 ............................................................................................................................................................................................ 34  
  Figure 18 ............................................................................................................................................................................................ 35  
  Figure 17 ............................................................................................................................................................................................ 36  
  Figure 15 ............................................................................................................................................................................................ 37  
  Figure 6 ............................................................................................................................................................................................ 38  
  Figure 14 ............................................................................................................................................................................................ 39  
  Figure 13 ............................................................................................................................................................................................ 40  
  Figure 12 ............................................................................................................................................................................................ 41  
  Figure 11 ............................................................................................................................................................................................ 42  
  Figure 10 ............................................................................................................................................................................................ 43  
  Figure 7 ............................................................................................................................................................................................ 44  
  Figure 9 ............................................................................................................................................................................................ 45  
  Figure 8 ............................................................................................................................................................................................ 46  
  Figure 5 ............................................................................................................................................................................................ 47  

**Multimedia Appendixes** ................................................................................................................................................................. 48  
  Multimedia Appendix 1 .................................................................................................................................................................. 49  
  Multimedia Appendix 2 .................................................................................................................................................................. 49
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Abstract

Background: Cardiovascular diseases (CVDs) remain one of the commonest causes of early death and disability worldwide with 17.9 million deaths and 422.7 million cases annually. There are approximately 1.7 million inpatient episodes in the UK per year. Approximately 50% of CVD is attributable to lifestyle risk factors. Despite widespread education, personal knowledge and efficacy, many individuals fail to adequately modify these risk factors, even after a cardiovascular event. Digital technologies have been suggested as a viable equivalent and potential alternative to conventional cardiac rehabilitation centre care. However, little is known about the clinical effectiveness of these technologies in bringing about behaviour change in CVD patients at individual level.

Objective: This systematic review seeks to 1) identify digital technologies and measure effectiveness of their interventions that have been tested in randomized control trials (RCTs) and 2) summarize their behavioural change and clinical outcome applications, and demographic qualities; for risk factor modification among CVD patients.

Methods: Mixed data from studies, extracted from selected research databases and filtered to RCTs only, were analysed using qualitative and quantitative methods.

Results: The use of digital technologies in cardiac patients was associated with improvements in total cholesterol, high density lipoprotein, low density lipoprotein, physical activity, physical inactivity (sedentary), healthy diet and medication adherence (at \( P<0.05 \)). However, there were no differences seen in body mass index, triglycerides, blood pressures (diastolic and systolic), blood sugar, alcohol intake and smoking (at \( P=0.05 \)).

Conclusions: This systematic review concludes that digital technology interventions may have benefit in improving protective behavioural factors (physical activity, healthy diet and medication adherence) and more potent when engaged in multiple behavioural outcome treatment (e.g. medication adherence plus…), but did not appear to reduce risky behavioural factors (smoking, alcohol intake and unhealthy diet) and clinical outcomes (body mass index, diastolic blood pressure, systolic blood pressure and blood sugar, HbA1c).

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Digital Technology Interventions for Risk Factor Modification in Patients with Cardiovascular Disease: A Systematic Review and Meta-Analysis.

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Introduction

Cardiovascular diseases (CVDs) i.e. coronary heart disease, stroke, and peripheral vascular disease remain one of the commonest causes of early death and disability worldwide with 17.9 million deaths and 422.7 million cases each year [1]. In 2017 alone, there were approximately 1.7 million inpatient episodes for CVDs in the UK [2]. This imposes a heavy burden on individuals and society accounting for £19 billion in public expense, 7.4 million disabilities and 167,000 deaths in 2019 [1]. While there are genetic, demographic, and environmental causes of CVDs [3], approximately 50 per cent of CVD risk is attributable to modifiable lifestyle factors such as obesity, diabetes, inactivity, and smoking [4]. However, despite widespread education and personal knowledge, many individuals fail to adequately modify these risk factors, even after a cardiovascular event with cardiac rehabilitation care centre support [4]. Failure to address this challenge (i.e. a change from cognitive insight to action manifest) results in patients remaining at higher risk of future cardiovascular events with associated personal, social, and economic costs.

Several reasons could be responsible for the challenge in personalised management (i.e. modification) of CVD and other chronic diseases risk factors. These include care centre accessibility and out-patient mobility and morbidity, comprehensibility and retainability [5]. These reasons make lifestyle risk factor management (particularly low physical activity and obesity) remain sub-optimally addressed in CVD out-patients [6]. These show that while there is a modest success in rehabilitation care centre interventions, the technical reach of this population-based approach is limited in its ability to bring about a significantly sustainable change in exposed individuals [5].

To achieve a sustainable change, social construct strategies (e.g. self-management, motivation, perceived benefits etc.), embedded in behavioural change interventions, have shown health benefits in chronic disease risk factor management [7]. Their substantial contribution to change in health behaviours suggests a worthy consideration in behavioural health interventions at an individual level. However, as it stands for social constructs’ approach in a population-based health behaviour change in rehabilitation care centres, there are limitations in social constructs’ ability alone to make an individual cope sustainably with its strategies at personal level [6].

The emergence of digital health technologies (e.g. the internet, phone applications and devices, and wearable sensors for telemedicine, web-browsing, emailing, text messaging, and monitoring) in the healthcare sector [8], designed to manage and monitor chronic disease lifestyle factors, have shown potential in personalized chronic disease lifestyle factors modification [9]. This potential is based on evidence that healthy lifestyle factors are behaviour-specific, measurable, and modifiable [10]. Because of the commercial drive and attributed qualities, many of these technologies and devices
have continually found usage in cardiac rehabilitation care centres and even in place of its care [11,12]. However, despite their popularity and potential, these technologies are lacking secondary prevention evidence summary of clinically relevant outcomes, which results from behaviour change in CVD out-patients especially at a personalized level [12,13].

Objectives
The primary objective of this systematic review is to identify, and measure effectiveness of digital technology (e.g. mobile phones, the internet, software application, wearables etc.) interventions from randomised controlled trials (RCTs), and determine which behaviour change constructs were effective at achieving risk factor modification among CVD patients.

Methods
Study Design
This study is a systematic literature review and meta-analysis of RCTs, designed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement standard [14]. The protocol was registered with PROSPERO - protocol ID CRD42019139801 [15].

Inclusion criteria for considering studies in this review
Types of participants: Adult population (≥ 18 years) with a minimum of 30 participants in the intervention study.
Types of interventions: Digital intervention only VERSUS usual care, or digital intervention plus usual care VERSUS usual care. Studies must be based on well-defined CVD risk factor modification measurement function, intention to modify health behaviour in out-patients diagnosed and/or treated for CVD only or with co-morbidities using a named digital device.
Types of outcome measures: Clinical and behavioural outcomes measured at baseline and endpoint. All outcomes hypothesis testing set at 95% CI and a two-tailed p-value of 0.05 level of statistical significance. Behavioural outcomes included physical activity (exercise), physical inactivity (sedentary), food intake (diet), smoking, alcohol intake and medication adherence. Clinical outcomes included body mass index (BMI); cholesterol levels (total cholesterol, high-density lipoproteins; low-density lipoproteins, and triglycerides); blood pressures (diastolic BP and systolic BP); and blood sugar levels, which are measures of obesity, hypercholesterolemia, hypertension and diabetes.
Exclusion criteria
Studies with non-RCTs, non-digital interventions and journal articles not published in the English language. Also, studies whose population share modifiable risk factors with CVD but not diagnosed with a named CVD; studies with non-clinical or non-behavioural outcomes e.g. studies with genetic outcomes and studies directly measuring hospital/staff service efficiency etc; and healthy population or intensive care studies, were excluded.

No analysis was conducted on data of outcomes from subgroups (endpoint to endpoint) within the population of the included studies.

Search methods for identification of studies
A single study, 6S pyramid systematic literature search strategy was developed (table 6 in appendices). This was run on Ovid Medline and Ovid Embase, Web of Science (Core Collection), Scopus, Cochrane Library, and on the following databases in EbscoHost: CINAHL, Psych Info, Health Source, Open Dissertation, Psych Article, and Business Source Elite. Filters were used to narrow searches to studies using RCTs methodology, written in the English language, and from the year 2000 onwards. The year limit was applied, in line with WHO’s release on digital health strategies [16], being the start of the mass availability and use of digital technologies, making literature pre-2000 less relevant.

Two independent reviewers (AS and RP) were involved in a thorough search strategy build-up and study extraction to identify potentially relevant publications. References and citations were also searched. Where an abstract did not give sufficient precision on selection pre-requisite, it was reserved for full-text review. Relevant abstracts retrieved for full-text review were independently evaluated (AS and MG). The consensus was reached to include or exclude a trial based on study design, method, population demography, intervention mechanism and study outcomes.

Data collection and Analysis
Data Collection
The PRISMA search protocol [14] was followed with all extracted data subsequently managed using Mendeley Desktop reference manager software (Mendeley by Elsevier, London UK). Publication search outcomes were imported in .ris format into Mendeley Desktop and partitioned based on search database source. Imported publications were auto-checked for duplicates by the software and a further manual independent duplicate-check was carried out (AS and YD). Publication papers were
title-read, abstract-read and finally full-text read based on inclusion and exclusion pre-selection criteria. Selected journal papers were read for data synthesis and analysis.

Data Extraction and Management

Data were extracted into a pre-set Excel (Microsoft Corporation, UK) worksheet. The data extraction process was performed independently (AS) using predetermined variables and then validated accordingly (MG). Data extracted included population demographics (population mean age, gender, size, and CVD diagnosed) description of the study (authors, year of publication, country, intervention acronym, digital device, intervention type, trial protocol registration, design, duration) behavioural change context (change technique, risk factors) and clinical study outcomes (outcome measures, outcome units, mean baseline measurements, mean outcome measurements, p values and SDs). Authors of studies with insufficient or required outcome data were contacted for further information.

Data Analysis

All extracted data from selected studies were analysed (Table 1) using Review Manager 5.3 (The Cochrane Collaboration, Oxford UK). An assessment of the risk of bias (Table 2) was carried out by two researchers AS and YD using the modified Cochrane Collaboration AUB KQ1 Risk of Bias Assessment Tool, Review Manager 5.3 (The Cochrane Collaboration, Oxford UK) with assessment result validation by an external independent researcher. Bias quality was assessed as high, low, or unclear for individual elements from six items: selection, performance, attrition, reporting, proportion, outcome, and treatment efficacy. Where the attrition bias risk is High, it is more likely to have high treatment efficacy bias except where the basis of participant dropout is due to the reason of medical, relocation or death. Quality assessment items were evaluated by an external assessor to validate initial scales adjudged by the author. Controversial evaluation differences were discussed, and consensus reached before final documentation. Risk of bias across studies was performed for each analysed outcome for publication bias reporting. Results were generated with meta-analysis data for each outcome and presented in the results section.

Review authors made consideration for variations in outcome measurement across studies by applying appropriate statistical methods (fixed effect and random effect) using the Inverse-Variance and Mantel-Haenszel (DerSimonian and Laird) model to generate meta-analytic estimates of treatment effect using Review Manager 5.3 software. Differences in effects were examined in comparison of digital care vs usual care. The weighted mean difference (WMD) or standardized mean difference (SMD) was calculated for continuous data using inverse variance (IV) statistical
method. Relative risks (RRs) were calculated for dichotomous data using Mantel-Haenszel (The Cochrane Collaboration, Oxford UK) statistical method. Provision for variations among included studies was made by using the random effect meta-analysis model in analysing all included studies. Heterogeneity statistics, $I^2$ was measured to describe the percentage of variation amongst studies. Hypothesis testing was set at a two-tailed 0.05 level of significance and 95% confidence interval (CI). No analysis was conducted on data of outcomes from subgroups within the population of included studies.

Sensitivity analyses were proportionately conducted on outcomes to check the cumulative effects of publication year, participant size, efficacy, and category of intervention (risk factors, digital intervention) on statistical significance. For food intake, studies with intervention targeting healthy diet and studies targeting unhealthy diet were analysed separately to give a clearer insight into treatment effects. Studies with treatment for medication adherence were analysed separately for a.) other risk factor treatments plus medication adherence using SMS intervention only, b.) medication adherence treatment only (with no other risk factor) using SMS intervention alone, c.) other risk factor treatment plus medication adherence treatment using non-SMS intervention, d.) medication adherence treatment with SMS intervention only. Results were presented and discussed in the results and discussions sections, respectively.

**Results**

**Search results**

The searches retrieved 1,626 articles with auto-removal of 326 duplicates. Thirty-five articles remained after applying inclusion and exclusion criteria. A further ten papers were excluded because they were systematic literature reviews but not RCTs. A final count of 25 papers was considered for review - 12 from the database searches and 13 from references, citations, and grey literature (see figure 1). The included studies are listed in the table of included studies (table 4 in appendices), and excluded studies are listed in the table of excluded studies (table 5 in appendices) with reasons.
1,626 records identified through database search

1,301 records after duplicates removed from total initial search

287 records were screened for title and abstract relevance

216 records were excluded

46 of full-text articles excluded for the following reasons:
- Pilot and protocol studies: n = 6
- Non behavioural or clinical measure studies: n=11
- On-going studies: n=2
- Systematic literature reviews: n=10
- Updates publications: n=2
- Non RCTs: n=11
- Participants less than 30 or duration less than 1 month: n=4

71 full-text articles were assessed for eligibility

25 studies were included in qualitative and quantitative syntheses (meta-analysis)
**Study characteristics.**

Studies are described in their common characteristics which include population demography, digital technologies and brands, intervention mechanisms and behavioural change constructs, types of CVD and general characteristics. Table 3 (see appendices 1) gives a detailed summary of the studies reviewed.

**Population demography:** Included studies had a total participant count of 36,303 at baseline with a mean age 60.03 (±2.73) years and male proportion of 79%. A geographical analysis of included studies identified evenly distributed locations of studies on a global scale, with countries spanning Europe (five studies), Middle East (two studies), Asia (three studies), Northern America (six studies), Scandinavia (two studies), Australasia (six studies) and the UK (one study).

**Digital technologies and brands:** Cardiovascular digital interventions were delivered using devices such as cell phones, smartphones, personal computers (laptops and desktops) and wearables. Technologies include the internet, software applications and mobile sensors. Intervention device brand names such as Personal Health Assistant, PHA, FIT@Home, HeartLinks, SUPPORT, SMS4Stroke, ProActive Heart, Text4Heart, CHAT, CardioFit, HEART, ActivateYourHeart, MEMS, vCRP, COACH, CHOICE, and TBHC were recorded.

**Intervention mechanisms and behavioural change constructs:** Intervention mechanisms (i.e. the digital strategy plus behavioural construct) were based on online support, telerehabilitation, telemonitoring, and online coaching. The interventions included major behavioural change constructs such as cognition, follow-up, goal setting, record keeping, perceived benefit, persuasion, social engagement (virtual), personalization (or customization), rewards and incentives, support, and self-management.

**CVD types:** Diagnosed CVDs featured as coronary heart diseases (CHD): coronary artery disease (CAD), myocardial infarction (MI) and acute coronary syndrome (ACS), angina, atherosclerosis, and heart failure (HF); transient ischemic attack (TIA) and stroke. Four studies [17,18,19,20] were not specific on CVD diagnosis for the population of the study.

**General characteristics:** Study follow-up ranged from one to four (nine studies), six (12 studies), 12 (three studies), and 24 months (one study); with six months being the most frequent duration of the follow-up period for interventions. No data of outcomes from subgroups within the population of included studies were considered in the analysis.

The main units of outcome measurements were kg/m² (BMI), mg/dL and mmol/L (total cholesterol - TC, high-density lipoprotein - HDL, low-density lipoprotein - LDL, and triglycerides – TG), mmHg (diastolic blood pressure - DBP and systolic blood pressure - SBP), min/week (physical activity - PA.
and physical inactivity - PI), percentage, % (blood sugar - HbA1c, alcohol, smoking, and food intake) and MMAS 8 (Morisky Medication Adherence Scale for Medication Adherence). In the treatment context, all intervention studies were either administered as Digital Intervention vs. Usual Care (15 studies) or Digital Intervention + Usual Care vs. Usual Care (10 studies).

**Synthesis of results.**

The use of digital intervention compared to usual care significantly modified all CVD risk factors except BMI, TG, DBP, SBP, HbA1c, alcohol intake, smoking, and medication adherence. A detailed summary of the findings is presented in table 1 below.

**Table 1: Summary of meta-analysis results**

<table>
<thead>
<tr>
<th>Outcomes or Subgroups</th>
<th>No. of Studies</th>
<th>Participants</th>
<th>Statistical Methods</th>
<th>Effect Estimates</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body Mass Index</td>
<td>10</td>
<td>2558</td>
<td>MD (IV, Random, 95%) CI</td>
<td>-0.37 [-1.20, 0.46]</td>
<td>.38</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>9</td>
<td>1783</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.29 [-0.44, -0.15]</td>
<td>&lt;.000</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>9</td>
<td>1783</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.09 [-0.19, 0.00]</td>
<td>.05</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>12</td>
<td>3431</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.18 [-0.33, -0.04]</td>
<td>.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>8</td>
<td>1660</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.07 [-0.24, 0.11]</td>
<td>.28</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>11</td>
<td>2460</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.06 [-0.20, 0.08]</td>
<td>.43</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>12</td>
<td>3283</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.03 [-0.18, 0.13]</td>
<td>.74</td>
</tr>
<tr>
<td>Physical Activity</td>
<td>14</td>
<td>3015</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>0.23 [0.11, 0.36]</td>
<td>.0003</td>
</tr>
<tr>
<td>Alcohol Consumption</td>
<td>4</td>
<td>651</td>
<td>SMD (IV, Random, 95%) CI</td>
<td>-0.16 [-1.43, 1.10]</td>
<td>.80</td>
</tr>
<tr>
<td>Blood Sugar, HbA1c</td>
<td>2</td>
<td>380</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>1.04 [0.40, 2.70]</td>
<td>.94</td>
</tr>
<tr>
<td>Physical Activity (Diet)</td>
<td>4</td>
<td>1054</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>0.54 [0.39, 0.75]</td>
<td>.0003</td>
</tr>
<tr>
<td>Food Intake (Diet)</td>
<td>6</td>
<td>716</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>0.79 [0.66, 0.94]</td>
<td>.007</td>
</tr>
<tr>
<td>Health Diet</td>
<td>3</td>
<td>173</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>0.70 [0.55, 0.89]</td>
<td>.004</td>
</tr>
<tr>
<td>Unhealthy Diet</td>
<td>3</td>
<td>185</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>0.90 [0.68, 1.19]</td>
<td>.47</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
<td>2916</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>0.87 [0.67, 1.13]</td>
<td>.30</td>
</tr>
<tr>
<td>Medication Adherence</td>
<td>11</td>
<td>2710</td>
<td>RR (M-H, Random, 95%) CI</td>
<td>1.10 [1.00, 1.22]</td>
<td>.06</td>
</tr>
</tbody>
</table>
Medication Adherence (multiple treatment) | 5 | 758 | RR (M-H, Random, 95% CI) | 1.07 [1.01, 1.14] | .02

Summary of analysed data.

**Summary of results**

Effect estimates (Mean difference, MD; Standard mean difference, SMD; and Risk ratio, RR) were significant in favour of digital interventions for TC, HDL, LDL, PA, PI and food intake.

Clinical outcomes: BMI outcome (figure 2) reported MD effect estimated at -0.37 [-1.20, 0.46], P = .38. TC outcome (figure 3) reported SMD effect estimated at -0.29 [-0.44, -0.15], P < .0001. HDL outcome (figure 4) reported SMD effect estimated at -0.09 [-0.19, 0.00], P = .05. LDL outcome (figure 5) reported SMD effect estimated at -0.18 [-0.33, -0.04], P = .01. TG outcome (figure 6) reported SMD effect estimated at -0.10 [-0.28, 0.08], P = .28. Diastolic and systolic BP outcomes (figure 7 and 8) reported SMD effects estimated at -0.06 [-0.20, 0.08], P = .43 and -0.03 [-0.18, 0.13], P = .74, respectively. HbA1C outcome (figure 9) reported RR effect estimated at 1.04 [0.40, 2.70], P = .94. A summary of clinical outcome findings is presented in figure 2 to figure 9.

Behavioural outcomes: PA outcome (figure 10) reported SMD effect estimated at 0.23 [0.11, 0.36], P = .0003. PI (sedentary) in figure 11 reported RR effect estimated at 0.54 [0.39, 0.75], P = .0003. Alcohol intake outcome (figure 15) reported SMD effect estimated at -0.16 [-1.43, 1.10], P = .80. Diet (food intake) in figure 12 reported RR effect estimated at 0.79 [0.66, 0.94], P = .007. Smoking and medication adherence outcomes (figure 16 and figure 17) reported RR effects estimated at 0.87 [0.67, 1.13], P = .30 and 1.10 [1.00, 1.22], P = .06, respectively. A summary of behavioural outcome findings is presented in figure 10 to 21.

**Risk of bias in included studies**

Table 2 gives a qualitative detail of risk of bias assessment of studies in the review. Proportion bias at baseline was reported in 16% of included studies as High risk. Intervention dropout was recorded in 32% of included studies at less than 10% of participants per study. Dropouts greater than 10% were recorded as High risk for treatment efficacy.

**Table 2: Risk of bias in included studies**

<table>
<thead>
<tr>
<th>N</th>
<th>Authors, Year</th>
<th>Randomisation Sequence</th>
<th>Allocation Concealment</th>
<th>Blinding of Participants</th>
<th>Blinding of Outcome</th>
<th>Incomplete Outcome</th>
<th>Group Balancing</th>
<th>Group Receipt</th>
<th>Selective Reporting</th>
<th>Intent to Treat Analysis</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>Risk Level</th>
<th>Unclear Level</th>
<th>Unclear Low</th>
<th>Low</th>
<th>High</th>
<th>Low</th>
<th>Low</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Akhu-Z et al, 2016</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>2</td>
<td>Chow et al, 2015</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>3</td>
<td>Dale et al, 2015</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>4</td>
<td>Devi et al, 2014</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Uncle</td>
</tr>
<tr>
<td>5</td>
<td>Frederix et al, 2015</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
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Risk of Bias: Review authors' judgements about each risk of bias item for included studies
Risk of bias across studies.

Results of risk of bias across studies for each outcome is presented along with meta-analysis, figure 2 to figure 21. Outcomes are sparsely identified with low and unclear risks for identified risk items.

Additional Analysis

Results of sensitivity analysis were included for considered outcomes in figure 13, figure 14, and figures 18 to 21. Sensitivity analyses proportionately conducted on outcomes to check the cumulative effects of the study population and intervention characteristics (e.g. publication year, participant size, efficacy, and categories of treatment) on subgroup(s) showed significant effects of interest in two outcomes as follow:

Food intake: healthy diet-targeted (figure 13) treatment (P=.004) and unhealthy diet-targeted (figure 14) treatment (P=.47); Medication adherence: medication adherence plus other risk factors (figure 18) treatment (P =.02) and medication adherence treatment alone (P=.11) as shown in figure 19.

Discussion

This systematic literature review of digital technology interventions addressing clinical and behavioural risk factors modification in people with CVDs demonstrates that not all CVD lifestyle risk factor modification are favoured by the use of digital interventions. Digital technology intervention in cardiac patients was associated with improvements in total cholesterol, high-density lipoprotein, low-density lipoprotein, physical activity, physical inactivity, healthy diet, and medication adherence (all at P≤.05). However, there were no differences in intervention effects for BMI, triglycerides, BP (diastolic and systolic), blood sugar, alcohol intake and smoking (all at P>.05).

Behavioural change constructs and digital intervention strategies

The mechanism of risk factors’ modification in included studies are based on behavioural change constructs [21,22] which include self-management, feedback mechanism, progress recording and tracking (monitoring), one-on-one/social support, persuasion, personalization (customization), reiteration, self-efficacy, and motivation. For this review, these constructs are commonly used in study trials than other constructs in literature such as perceived risk and perceived benefits, incentives, and reimbursement (rewards), which were rarely used in study trials.

The use of behavioural change constructs in combination with digital technologies in study trials reveals their successful application in individual behavioural risk factor modification [7]. The overall
desired effect has been found in digital interventions alone (15 studies) when compared to digital plus usual care interventions (10 studies) hence giving support to out-of-clinic risk factor modification at personalized level [9].

From our results, the use of behavioural change constructs and digital intervention strategies, largely rely on patient’s self-dependency (low to moderate risk CVD patients) - interventions that favour digital technologies were reported for all CVD populations but barely for study trials on stroke and rarely for study trials on angina out-patients. An exception to this reliance is found in studies on medication adherence, which has been successfully self-managed with digital intervention (SMS) - this informs advice-based instead of activity-based option for moderate risk CVD out-patients in risk factor modification prescriptions. Effect of mobile sensor technology using wearable devices was inconclusive as there is only one study that engaged this digital intervention in its trial (see appendices: table 4).

**Clinical outcomes**

There was no clinical benefit with the use of digital interventions for BMI, TG, SBP, DBP and HbA1c compared to usual care intervention in study trials. This finding suggests a form of association between clinical factors and unhealthy behaviour modification using digital technologies; noting that these clinical factors are main indicators for unhealthy behaviour conditions such as obesity, hypercholesterolemia, hypertension, and diabetes.

However, an exception to these similarities is the significant effect of digital technologies intervention on clinical factors such as TC, HDL, and LDL, which could only be inferred by their shared physiological response to regulations in and by healthy behavioural factors such as healthy diet and medication adherence, from a lifestyle perspective [23]. This response is less prompting on TG, which are stored lipids in fatty cells and though considered bad cholesterol like LDL, are less regulated by medication (e.g. statin) as compared to diet [23]. Our findings suggest that this exception is not necessarily based on the application of behavioural change techniques or other change-effective variables. This view is validated in that BMI (an indicator for obesity) and HbA1c (an indicator for excess sugar) in association with unhealthy food intake, which are precursors for obesity and diabetes as CVD risk factors, appears not modifiable by digital technology interventions. Furthermore, we consider that the modification of LDL (bad cholesterol) by digital intervention might have been due to the positive inverse effect derived from the modification benefits of TC and HDL (good cholesterols) within each study population.

TC, HDL, and LDL modification is associated with the use of cell phone devices in study trials. Behaviour change techniques in TC, HDL and LDL population include progress self-reporting and

[unpublished, peer-reviewed preprint]
self-recording, one-on-one support and persuasion. TC, HDL, and LDL study population share common diagnosed CVDs and digital intervention strategies.

**Behavioural outcomes**

PA trials are characterized by smartphone and cell phone devices in ratio 1:1. In order of preference, usage of intervention strategies is first, telerehabilitation and online education; followed by online feedback (tele-support) and telemonitoring; lastly and least, SMS support by active coaching (20% of trials). PI (sedentary) trials revealed a higher population mean age, which suggests a close association with co-morbidity and immobility amongst out-patients [24] hence the need to tailor digital interventions treatment to patient’s level of engagement.

PA and PI have gained modification preference and digital intervention effectiveness due to active participant engagement in eleven smartphone studies using tele-intervention (audio-visual) strategy, two cell phone studies engaging active coaching (audio) strategy and six cell phone studies using automated SMS support (text) strategy (in 19 studies) overall. This finding suggests greater effectiveness of smartphones in audio-visual based interventions compared to cell phones; noting that cell phones might have only gained usage than smartphones (in medication adherence study trials) due to their affordability and ease of use [22,25]. However, both audio-visual support and audio/text support appear to be efficient digital interventions for risk factor modification for PA but audio/text support only appears sufficient for PI modification.

Generally, PA (a healthy behavioural factor) had been viewed as a null to PI - sedentary (an unhealthy behavioural factor) effects in maintaining a healthy lifestyle. This view has been disproved in literature [26]. However, this disapproval has only been validated in a healthy population prospective study. More evidence is needed to validate this in a CVD population to elucidate the effectiveness of digital technology interventions for PI risk factor modification. We, therefore, consider that the modification of PI, just as in LDL, might have been due to the positive inverse effect of PA modification in the CVD populations reviewed.

Studies reporting effects on diet, alcohol consumption and smoking share similar characteristics in behavioural change techniques which include mostly social support and group discussion; followed by self-management, goal setting, follow-up, progress self-reporting and self-recording, and auto-reminders. Social support and group discussion, which are related to online support and online discussion have been identified as activity-based behavioural change techniques in mental health management for diet, alcohol consumption and smoking behaviour modification [27]. Interactivity (as a result of social support and group discussion) can therefore be affirmed as an effective potential in these (diet, alcohol consumption and smoking) risk factors’ behaviour change technique on a
digital platform. However, digital interventions for alcohol consumption and smoking behaviour change show a weak effect in their modification when compared to conventional CVDs usual care interventions. Several reasons could be responsible for this – one of them being that social support and group discussions/interaction are less effectively accomplished compared to cell phone device interventions, which have no ‘smart’ facial contact technology feature but have gained wider usage in reviewed study trials due to their affordability and availability to participants in both risk factors studies. The second being that digital technology interventions, from the trend of this review, appear to be effective in healthy behaviour modification but less effective in attending to unhealthy behaviour modification when compared to usual care: healthy dieting is physiologically linked to lipid regulation in the body [28] – a strong basis for clinical factors (TC, HDL, and LDL) modification.

In addition to this, digital intervention effectiveness in TC, HDL and LDL as earlier stated might also be largely linked to the positive pharmacological effect of medication adherence in study trials. Out of the six studies on food intake (diet), unhealthy food intake (figure 14) modification is not favoured by digital intervention at P=.47 but healthy diet (figure 13) shows significant modification effect in favour of digital intervention at P=.004 when compared with usual care. This partition reveals significant alignment and potency of digital intervention towards healthy behavioural factors than unhealthy behavioural factors. The same being confirmed in PA, a healthy behavioural factor. Healthy behavioural factors (e.g. PA, healthy diet and medication adherence) modification using digital technology is supported by findings from Chow et al. [29].

Medication adherence outcome from trials in this review was achieved only by the use of cell phones with SMS support strategy in line with finding by Palmer et al. [30]. However, smartphones’ effectiveness is inconclusive as only one trial is available in this review – this could be responsible for its limitation in maximizing change technique features e.g. telerehabilitation in medication adherence trials. On the other hand, cell phones remain the most affordable and available [25] digital device in medication adherence-targeted interventions compared to other behavioural factor interventions as they cut across all CVD types and engage behavioural change techniques based on cognition such as auto-support, auto-reminders, persuasion (iteration); goal-setting, self-management and customization (personalization).

Trials (figure 19) that have strictly targeted medication adherence outcome only, using SMS strategy with cell phone device did not show significant effect (P=.11) when collectively analysed for digital intervention effectiveness. However, trials (figure 18) with similar strategy and device as the former but having multiple clinical and behavioural outcomes treatment (analysed with or without the...
previous trials) were significantly effective (P=.02) with the use of digital intervention compared to usual care. Non-SMS-administered medication adherence trials (figure 20) did not favour digital intervention. In summary, these findings suggest the effectiveness of multiple clinical and behavioural outcomes treatment when designing digital technology (SMS) interventions.

Few meta-analysed results e.g. in smoking, LDL, BMI, and SBP were limited by high heterogeneity not fully explained (or not explained at all e.g. in alcohol consumption and sedentary with low included study counts) by study population or intervention characteristics. However, minor adjustment (exclusion of Chow et al., Widmer et al., and Redfern et al.) in the number of included studies towards increased homogeneity does not show a significant change from initial treatment effect by either digital intervention or usual care.

The main intervention strategies in this review are first, automated SMS support (auto-reminder based on cognition which is largely accessible using cell phones in study trials), a feature supported by Kassavou et al. [22]; and secondly, online education and coaching; followed by telerehabilitation and telemonitoring, which were barely represented in analyses that favoured digital intervention – representation might be due to limited access to smartphones based on participants’ affordability or level of technological advancement/inclination as at the time of trial. A desirable device of choice is the smartphone because it combines all operability features needed to attain desirable intervention outcomes engaging identified behavioural change-specific strategies. However, a major limitation to the use of smartphones by the population age group in the review could be due to their level of comprehensibility [5].

Limitations
While this collection of studies is evenly distributed on a global scale, no RCT study was identified in Africa, where only cost-effective digital health programs have presently gained widespread use [25]. A high proportion of male to female gender would be considered a major participant inclusion limitation in studies. However, this trend appears to be in resonance with quantitative analyses of CVD gender prevalence in the literature [32] and therefore may reflect disease prevalence rather than study design.

This review further reveals gaps in the application of emerging technologies (immersive media e.g. 3-D animations and games – an ongoing trial by Gallagher et al. [31], big data technologies e.g. artificial intelligence, AI applications and user experience, UX) in CVD risk factor modification using evidence-based RCT intervention studies on a digital device platform. This review, therefore, suggests the initiation of cutting-edge research in the field of emerging digital technologies.
Conclusions
This review showed that the use of digital technology interventions did not improve all CVD lifestyle risk factors compared with usual care interventions. Effective digital technology interventions appear to improve healthy behavioural factors (PA, healthy diet) and associated clinical outcomes (TC, HDL and LDL); and more potent in multiple outcome treatment (medication adherence plus…) but are weak in abating unhealthy behavioural factors (smoking, alcohol intake and unhealthy food intake) and their outcomes (BMI, BP and HbA1c).
Cell phones are considered efficient digital device with the use of cognitive intervention strategy and have been most widely studied but, smartphones may have advantages due to additional interactivity features. This review was not able to analyse cutting edge technology (such as immersive media technologies) as the data does not exist or is not reported. Newer immersive media technologies, therefore, warrant more studies. Further RCT research is deemed necessary to consolidate the use of digital technology interventions, especially in CVD risk factors (e.g. diabetes) with fewer RCT studies.

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Acknowledgements
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Declarations of interest
The authors declare that there is no conflict of interest.
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Supplementary Files
Figures
Smoking.
Body mass index.
High-density lipoprotein.
Total cholesterol.

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Total (95% CI): 982
Heterogeneity: Tau² = 0.02, CH² = 14.60, df = 8 (P = 0.07), I² = 45%
Test for overall effect: Z = 4.03 (P < 0.0001)

Footnotes:
1. Vale et al, 2002: SD derived using p value on Cochrane SD calculator
2. Southard et al, 2003: Baseline outcome SD used in trial result
3. Redfern et al, 2009: SD derived from SEM using Cochrane SD calculator
4. Lear et al, 2014: SD derived using p value on Cochrane SD calculator
5. Chow et al, 2015: SD derived using p value on Cochrane SD calculator

Favours Digital Care | Favours Usual Care
--- | ---
-0.5 | 0.5

Risk of Bias Legend:
A. Random sequence generation (selection bias)
B. Allocation concealment (selection bias)
C. Blinding of participants and personnel (performance bias)
D. Blinding of outcome assessment (detection bias)
E. Incomplete outcome data (attrition bias)
F. Selective reporting (reporting bias)
G. Intention to treat analysis (treatment efficacy)

[unpublished, peer-reviewed preprint]
Medication adherence treatment for all sms intervention.
Medication adherence for treatment with non-sms intervention.

### Table

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**Footnotes**

(1) Zheng et al, 2019: Result (%) considered for Aspirin+Statin adherence only

### Risk of Bias Legend

- A: Random sequence generation (selection bias)
- B: Allocation concealment (selection bias)
- C: Blinding of participants and personnel (performance bias)
- D: Blinding of outcome assessment (detection bias)
- E: Incomplete outcome data (attrition bias)
- F: Groups balanced at baseline (proportion bias)
- G: Groups received same intervention (outcome bias)
- H: Selective reporting (reporting bias)
- I: Intention to treat analysis (treatment efficacy)
Medication Adherence for target treatment only with sms intervention.
Medication adherence for multiple treatment with SMS.

Footnotes
(1) Zheng et al, 2019: Result (%) considered for Aspirin+Statin adherence only
Medication adherence for all trials.
Alcohol consumption.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkes et al 2012</td>
<td>111</td>
<td>4.95</td>
<td>150</td>
<td>106</td>
<td>4.95</td>
<td>183</td>
<td>25.3%</td>
<td>1.01 [0.77, 1.24]</td>
<td>2012</td>
</tr>
<tr>
<td>Dale et al 2015</td>
<td>53</td>
<td>1.41</td>
<td>61</td>
<td>56</td>
<td>1.41</td>
<td>62</td>
<td>24.8%</td>
<td>-2.11 [-2.56, -1.67]</td>
<td>2015</td>
</tr>
<tr>
<td>Wan et al 2016</td>
<td>3.85</td>
<td>0.36</td>
<td>40</td>
<td>3.88</td>
<td>0.33</td>
<td>40</td>
<td>24.8%</td>
<td>-0.09 [-0.52, 0.35]</td>
<td>2016</td>
</tr>
<tr>
<td>Tiede et al 2017</td>
<td>11.4</td>
<td>22.47</td>
<td>87</td>
<td>0</td>
<td>22.47</td>
<td>48</td>
<td>25.1%</td>
<td>0.50 [0.15, 0.86]</td>
<td>2017</td>
</tr>
</tbody>
</table>

Total (95% CI) 338 313 100.0%

Heterogeneity: Tau² = 1.62; Chi² = 152.54, df = 3 (p = 0.00001), I² = 98%

Test for overall effect Z = 0.25 (p = 0.80)

Footnotes:
(1) Tiede et al: SD derived using p value on Cochrane SD calculator

Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Groups balanced at baseline (imputation bias)
(G) Groups received same intervention (outcome bias)
(H) Selective reporting (reporting bias)
(I) Intention to treat analysis (treatment efficacy)
Triglycerides.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Digital Intervention Mean</th>
<th>SD</th>
<th>Total</th>
<th>Usual Care Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vale et al 2002 (1)</td>
<td>1.6</td>
<td>1.53</td>
<td>107</td>
<td>1.65</td>
<td>1.53</td>
<td>112</td>
<td>-0.03 (-0.30, 0.23)</td>
<td>2002</td>
<td></td>
</tr>
<tr>
<td>Southard et al 2003 (2)</td>
<td>176.1</td>
<td>122.6</td>
<td>49</td>
<td>152</td>
<td>105.3</td>
<td>51</td>
<td>0.21 (0.18, 0.60)</td>
<td>2003</td>
<td></td>
</tr>
<tr>
<td>Redfern et al 2009 (3)</td>
<td>1.5</td>
<td>0.87</td>
<td>67</td>
<td>1.8</td>
<td>0.87</td>
<td>69</td>
<td>-0.34 (-0.88, -0.00)</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Vermeul et al 2012</td>
<td>1.6</td>
<td>1.3</td>
<td>155</td>
<td>1.4</td>
<td>0.7</td>
<td>159</td>
<td>-0.20 (-0.82, 0.43)</td>
<td>2012</td>
<td></td>
</tr>
<tr>
<td>Lear et al 2014 (4)</td>
<td>1.37</td>
<td>0.8</td>
<td>34</td>
<td>1.3</td>
<td>0.8</td>
<td>37</td>
<td>-0.09 (-0.38, 0.55)</td>
<td>2014</td>
<td></td>
</tr>
<tr>
<td>Chow et al 2015 (5)</td>
<td>140</td>
<td>80.64</td>
<td>352</td>
<td>160</td>
<td>80.64</td>
<td>358</td>
<td>0.25 (-0.45, -0.10)</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Frederik et al 2016</td>
<td>105.35</td>
<td>36.93</td>
<td>32</td>
<td>118.23</td>
<td>59.92</td>
<td>34</td>
<td>-0.25 (-0.74, 0.23)</td>
<td>2015</td>
<td></td>
</tr>
<tr>
<td>Widmer et al 2017</td>
<td>115</td>
<td>61.9</td>
<td>25</td>
<td>133.7</td>
<td>128.8</td>
<td>19</td>
<td>-0.19 (-0.78, 0.41)</td>
<td>2017</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 821

Heterogeneity: $I^2 = 0.03; C^2 = 16.73, df = 7 (P = 0.03); I^2 = 56%$

Test for overall effect: $Z = 0.76 (P = 0.45)$

Footnotes:
1. Vale et al, 2002: SD derived using p value on Cochrane SD calculator
2. Southard et al, 2003: Baseline outcome SD used in trial result
3. Redfern et al, 2009: SD derived from SEM using Cochrane SD calculator
4. Lear et al, 2014: SD derived using p value on Cochrane SD calculator
5. Chow et al, 2015: SD derived using p value on Cochrane SD calculator

Risk of bias legend:
A: Random sequence generation (selection bias)
B: Allocation concealment (selection bias)
C: Blinding of participants and personnel (performance bias)
D: Blinding of outcome assessment (detection bias)
E: Incomplete outcome data (attrition bias)
F: Other bias (bias)
G: Intention-to-treat analysis (treatment efficacy)
Unhealthy food intake.
Healthy diet.
Food intake.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Digital Intervention</th>
<th>Usual Care</th>
<th>Risk Ratio</th>
<th>Year</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouchard et al 2003</td>
<td>26 70 28 70</td>
<td>70 17.6% 0.93 [0.61, 1.41]</td>
<td>2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lear et al 2014</td>
<td>39 100 46 100</td>
<td>29.3% 0.85 [0.61, 1.17]</td>
<td>2014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dale et al 2015</td>
<td>32 61 47 62</td>
<td>40.0% 0.69 [0.52, 0.91]</td>
<td>2015</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akho-Z et al 2016</td>
<td>2 12 2 11</td>
<td>1.0% 0.92 [0.15, 5.44]</td>
<td>2016</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trued et al 2017</td>
<td>19 100 27 100</td>
<td>11.5% 0.70 [0.42, 1.18]</td>
<td>2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilder et al 2017</td>
<td>4 15 1 15</td>
<td>0.7% 4.00 [0.50, 31.74]</td>
<td>2017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 358 358 100.0% 0.79 [0.66, 0.94]

Risk of bias legend:
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Groups balanced at baseline (proportion bias)
(G) Groups received same intervention (outcome bias)
(H) Selective reporting (reporting bias)
(I) Intention to treat analysis (treatment efficacy)
Physical inactivity.

![Risk of bias diagram and table]

Physical activity.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Digital Intervention Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>Usual Care Mean</th>
<th>SD</th>
<th>Total Mean</th>
<th>Std. Mean Difference</th>
<th>IV, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Southard et al 2003 (1)</td>
<td>208.4</td>
<td>118.1</td>
<td>49</td>
<td>165</td>
<td>127.96</td>
<td>51</td>
<td>0.15</td>
<td>0.05</td>
<td>0.74</td>
</tr>
<tr>
<td>Redfern et al 2009 (2)</td>
<td>1,369</td>
<td>1,154.17</td>
<td>67</td>
<td>715</td>
<td>1,154.17</td>
<td>69</td>
<td>0.15</td>
<td>0.02</td>
<td>0.91</td>
</tr>
<tr>
<td>Reid et al 2011</td>
<td>201</td>
<td>153.2</td>
<td>115</td>
<td>163.4</td>
<td>151.3</td>
<td>108</td>
<td>0.15</td>
<td>0.02</td>
<td>0.51</td>
</tr>
<tr>
<td>Hawker et al 2012</td>
<td>208.7</td>
<td>207.9</td>
<td>156</td>
<td>200.8</td>
<td>212.8</td>
<td>170</td>
<td>0.15</td>
<td>0.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Cim et al 2014</td>
<td>1,946.4</td>
<td>351.79</td>
<td>35</td>
<td>1,822</td>
<td>306.47</td>
<td>40</td>
<td>0.15</td>
<td>0.07</td>
<td>0.53</td>
</tr>
<tr>
<td>Lear et al 2014</td>
<td>1,956</td>
<td>114.7</td>
<td>34</td>
<td>1,920</td>
<td>114.7</td>
<td>37</td>
<td>0.15</td>
<td>0.31</td>
<td>0.78</td>
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<tr>
<td>Israil et al 2014</td>
<td>26</td>
<td>5.9</td>
<td>25</td>
<td>26.1</td>
<td>7.6</td>
<td>25</td>
<td>0.15</td>
<td>-0.01</td>
<td>0.57</td>
</tr>
<tr>
<td>Maddison et al 2014 (3)</td>
<td>1,555</td>
<td>1,268.81</td>
<td>85</td>
<td>1,321</td>
<td>1,268.81</td>
<td>86</td>
<td>0.15</td>
<td>0.18</td>
<td>0.48</td>
</tr>
<tr>
<td>Chow et al 2015</td>
<td>932.1</td>
<td>1,019.56</td>
<td>352</td>
<td>587</td>
<td>1,019.56</td>
<td>350</td>
<td>0.15</td>
<td>0.34</td>
<td>0.48</td>
</tr>
<tr>
<td>Frederix et al 2015</td>
<td>2,360</td>
<td>475</td>
<td>32</td>
<td>1,791</td>
<td>503</td>
<td>34</td>
<td>0.15</td>
<td>1.15</td>
<td>0.63</td>
</tr>
<tr>
<td>Dale et al 2015 (4)</td>
<td>19</td>
<td>1.44</td>
<td>61</td>
<td>1.44</td>
<td>62</td>
<td>Not estimatable</td>
<td>0.15</td>
<td>0.18</td>
<td>0.48</td>
</tr>
<tr>
<td>Johnston et al 2016</td>
<td>180.2</td>
<td>208.8</td>
<td>80</td>
<td>201.1</td>
<td>198.8</td>
<td>71</td>
<td>0.15</td>
<td>-0.10</td>
<td>0.42</td>
</tr>
<tr>
<td>Wang et al 2016</td>
<td>2.21</td>
<td>0.74</td>
<td>40</td>
<td>2.23</td>
<td>0.72</td>
<td>40</td>
<td>0.15</td>
<td>-0.03</td>
<td>0.47</td>
</tr>
<tr>
<td>Wilm et al 2017</td>
<td>148.1</td>
<td>78.5</td>
<td>21</td>
<td>117.3</td>
<td>61.6</td>
<td>13</td>
<td>0.15</td>
<td>0.41</td>
<td>0.29</td>
</tr>
<tr>
<td>Zheng et al 2019 (5)</td>
<td>2,079</td>
<td>3,020.59</td>
<td>411</td>
<td>1,680</td>
<td>3,020.59</td>
<td>411</td>
<td>0.15</td>
<td>0.13</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**Footnotes**

1. Southard et al, 2003: Baseline outcome SD used in trial result
2. Redfern et al, 2009: SD derived from SEM using Cochrane SD calculator
3. Maddison et al, 2014: SD derived from CI from Cochrane SD calculator
4. Dale et al, 2015: SD derived from CI from Cochrane SD calculator
5. Zheng et al, 2019: SD derived using p value on Cochrane SD calculator

**Risk of bias legend**

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Intention to treat analysis (treatment efficacy)
Diastolic blood pressure.
Blood sugar HbA1c.
Systolic blood pressure.
Low-density lipoprotein.
Multimedia Appendixes
Study characteristics.
URL: https://asset.jmir.pub/assets/399ea04a51b4a0401c6b276f9ba432c7.doc

Protocol registration link and tables and abbreviations and definition of terms.
URL: https://asset.jmir.pub/assets/50f8ba9559eeb1429ab0a9bd9b8e8e2.doc