Human support in eHealth lifestyle interventions

Cohen Rodrigues, T.R.

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EFFECTIVENESS OF HUMAN-SUPPORTED AND SELF-HELP EHEALTH LIFESTYLE INTERVENTIONS FOR PATIENTS WITH CARDIOMETABOLIC RISK FACTORS: A META-ANALYSIS

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ABSTRACT

Background: eHealth is a useful tool to deliver lifestyle interventions for patients with cardiometabolic diseases. However, there are inconsistent findings about whether these eHealth interventions should be supported by a human professional, or whether self-help interventions are equally effective.

Methods: Databases were searched between January 1995 and October 2021 for randomized controlled trials on cardiometabolic diseases (cardiovascular disease, chronic kidney disease, type 1 and 2 diabetes mellitus) and eHealth lifestyle interventions. A multilevel meta-analysis was used to pool clinical and behavioral health outcomes. Moderator analyses assessed the effect of intervention type (self-help vs. human-supported), dose of human support (minor vs. major part of intervention), and delivery mode of human support (remote vs. blended). 107 papers fulfilled eligibility criteria and 102 unique (N=20,781) studies were included.

Results: The analysis showed a positive effect of eHealth lifestyle interventions on clinical and behavioral health outcomes (p<.001). However, these effects were not moderated by intervention type (p=.169), dose (p=.698), or delivery mode of human support (p=.557).

Conclusion: This shows that self-help eHealth interventions are equally effective as human-supported ones in improving health outcomes among cardiometabolic disease patients. Future studies could investigate whether higher quality eHealth interventions compensate for a lack of human support.

Keywords: cardiovascular disease; chronic kidney disease; type 1 diabetes mellitus; type 2 diabetes mellitus; eHealth; lifestyle change; human support

INTRODUCTION

Cardiometabolic diseases, i.e. diseases to the heart, are an increasing threat to patients' health and quality of life (Danaei et al., 2014; WHO, 2021). This includes cardiovascular diseases (CVD) and type 1 and 2 diabetes mellitus (T1DM and T2DM), and comprises of conditions such as chronic kidney disease (CKD). These diseases share similar underlying clinical risk factors, such as adiposity, high blood pressure, cholesterol levels, and blood glucose levels (Ryden et al., 2014; Suckling & Gallagher, 2012). Moreover, these four diseases have similar behavioral risk factors, such as smoking, physical inactivity, unhealthy diet, and use of alcohol, which is why a healthy lifestyle is the preferred management strategy for all (Ryden et al., 2014; Suckling & Gallagher, 2012). Participating in lifestyle interventions can, therefore, improve patients' health and quality of life (Piepoli et al., 2016).

Nevertheless, many patients who have participated in cardiac rehabilitation experience difficulties in maintaining a healthy lifestyle in the long-term (Janssen et al., 2013). Research suggests that the use of home-based interventions is more suitable for durable lifestyle change compared to traditional face-to-face interventions (ter Hoeve et al., 2015). For that reason, the implementation of eHealth could be beneficial. eHealth can be defined as the use of information and communication technology, such as the internet, to support or enhance health and health care by means of remote or automated support (Barak et al., 2009). eHealth lifestyle interventions show to be effective in improving cardiometabolic risk factors. For example, eHealth interventions aimed at physical activity or nutrition can improve clinical risk factors such as blood glucose levels (Liang et al., 2011) and blood pressure (Liu et al., 2013), and behavioral risk factors such as fat, fruit and vegetable consumption, and physical activity (Carvalho de Menezes, 2016). Another advantage of eHealth over face-to-face interventions is that the former is easier to implement in a larger and more varied audience. Especially self-help interventions are suitable for widespread implementation, as no human care professional needs to be involved (Barak et al., 2009). Self-help interventions could help reduce the workload for care professionals, and the costs of treatment (Srivastava et al., 2015). Furthermore, studies show that eHealth interventions with low or even no involvement of care professionals are effective in improving clinical and behavioral risk factors among people with CVD (Coorey et al., 2018).

Despite these advantages, previous meta-analyses and reviews showed mixed results regarding the effect of self-help interventions through eHealth. Notably, some studies have found higher effect sizes for digital interventions in which the feedback was provided by a human (Lau et al., 2020). This meant that interventions with fully remote human support (Joiner et al., 2017) or those that additionally incorporated face-to-face human support (otherwise called blended interventions) had more effect (i.e., higher effect sizes) than self-help eHealth interventions without any form of human support. In previous studies, authors have argued that human supported interventions are more effective compared to interventions with only automated feedback because they are tailored to the patient's needs (Lau et al., 2020). Furthermore, human support is found to increase adherence to interventions (Joiner, 2017). In addition, blended interventions would be more effective than fully remote supported interventions because behavior change maintenance is more successful in when they involve face-to-face interactions (Beishuizen et al., 2016). In other studies, however, no differences were found in achieving lifestyle behavior change between human-supported and self-help only lifestyle interventions (Lustria et al., 2013), blended interventions compared to remotely-supported ones (Kloek et al., 2017), and interventions with automated feedback compared to those with human-generated feedback (Webb et al., 2010). These discrepancies in research findings could be explained by the varying 'support dose' (e.g., frequency of contact) within the human-supported interventions. Previous meta-analyses regarding eHealth lifestyle interventions have simply categorized studies into self-help or human-supported, or into blended and remote support. In particular, these meta-analyses made no distinction between the type and channel of human support; This meant that studies in which a clinical psychologist gives daily feedback on assignments, studies in which psychology students give monthly telephone calls based on a script, or studies in which patients have the option to contact a therapist were all treated alike. In contrast, various meta-analyses regarding psychological interventions have looked at these variables in more detail. One of these meta-analyses found that interventions with greater amounts of therapeutic contact encountered lower dropout rates (Pearcy et al., 2016). Other studies found that both administrative support by a layperson and therapeutic support by a professional are equally effective in treating symptoms and preventing dropout (Baumeister et al., 2014; Richards & Richardson, 2012). Similar results have been found in a meta-analysis regarding digital mental health interventions (Leung et al., 2022). Other meta-analyses regarding eHealth interventions revealed that higher intensity of support improves intervention adherence rates (Hoppen et al., 2021; Koelen et al., 2022).

To our knowledge, no other studies have yet focused on the effectiveness of (human-supported and self-help) eHealth lifestyle interventions for multiple cardiometabolic risk factors, or investigated whether the dose of human support in eHealth lifestyle interventions is related to the effectiveness of these interventions. Therefore, the aims of this meta-analysis are: (1) investigating the effectiveness of eHealth lifestyle interventions for people with or at risk of CVD, CKD, T1DM and T2DM on clinical and behavioral health outcomes, (2) investigating whether there is a difference in the effectiveness of human-supported and self-help eHealth lifestyle interventions on clinical and behavioral health outcomes, and (3) investigating whether moderating factors such as dose and delivery mode of human support influence the effectiveness of eHealth lifestyle interventions on clinical and behavioral health outcomes.

METHODS

We preregistered our meta-analysis in the PROSPERO database (PROSPERO 2021 CRD42021269263; Cohen Rodrigues et al., 2021). The meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Page et al., 2021).

Search and Study Selection

A systematic literature search was conducted within multiple databases (see Figure 1). With the help of the university's librarian, a search string was created with key search terms related to (1) eHealth, (2) clinical and behavioral outcomes, (3) cardiometabolic diseases, and (4) randomized controlled trials (see Appendix 1 for the full search string). The search was conducted for studies from 1995 (given the increasing use of Internet from that year onward), and was lastly updated on 6 October 2021. After removal of duplicates, titles and abstracts were screened by two of the three independent researchers to identify studies meeting the inclusion criteria. Inconsistencies were resolved in weekly discussions.

Inclusion and exclusion criteria were established with the help of the PICO statement (population, intervention, comparator, outcome; Schardt et al., 2007). Participants of the included studies were required to be (1) 18 years or older, and (2) either have one or more cardiometabolic risk factors, (as determined and specifically mentioned by the authors of the paper) or be diagnosed with CVD, CKD, T1DM or T2DM. Given the primary focus of our study on cardiometabolic patients we decided to, in case of a population with cardiometabolic risk factors only, exclude studies if cardiometabolic patients were explicitly excluded from participation. Furthermore, studies were included if the intervention (3) aimed at improving one or more lifestyle behaviors (physical activity, nutrition, smoking, alcohol intake, sleep), (4) was delivered via eHealth tools such as through a website or mobile-based application (phone, text-messages: videoconferencing could be used, but not as main mode of communication), (5) provided education or skills training (e.g., using behavior change techniques), and (6) was interactive (involving actions of a user and reactions from the program in response to a user's actions). In addition to this, we only included (7) randomized controlled trials, which used as comparator either a passive control (wait-list or usual care), a non-web- or mobile-based intervention, or a less extensive web- or mobile-based intervention. Finally, studies were included if they (8) reported minimally one self-reported or objectively observed clinical (e.g. blood pressure) or behavioral health outcome (e.g., step count), and (9) the full-text was available in English or Dutch. These inclusion and exclusion criteria were used to check for study eligibility, which was again conducted by two of the three independent researchers. Disagreements were resolved in weekly meetings, and if needed, with the help of a third independent researcher. If two papers reported on the same study, we included the one reporting the outcomes most extensively. After the systematic search, we conducted a forward citation search to find relevant papers that either cited one of our included studies or that were written by one of the authors of our included studies. Finally, we ran a backward citation search to look at articles cited by the authors included in our study. In case original data were not available in the manuscript we contacted the relevant authors in writing to ask for the data. Authors were contacted a maximum of two times over a period of three months.

Data Extraction

A predefined coding form was used to extract the data. We extracted (1) study characteristics, (2) population characteristics at baseline, (3) characteristics of each condition (control and intervention), and (4) self-reported or objectively observed clinical or behavioral outcome data. For the population characteristics, we coded the diagnosis of the participants (CVD, T1DM, T2DM, CKD, at-risk population (without diagnosis, but with cardiometabolic risk factors), or mixed patient population), mean age of the participants per group, percentage of female participants per group, and educational level of the participants per group. For the condition characteristics, we coded the type of control condition (passive or active), intervention length (duration of the intervention in weeks irrespective of pre-post design or longer term follow-ups), the type of intervention (self-help or human-supported), dose of human support (minor or major part of intervention), and delivery mode of human support (remote or blended). Type of intervention was coded as 'self-help" 'if the study investigated an intervention without any involvement from another human coach and could be followed completely independently, and as 'human-supported' if a human coach (healthcare professional or layperson) was involved to support the participant in following the intervention. Dose of human support was coded as 'minor"' if the study investigated an intervention that was delivered through an eHealth tool, which the patient could practice independently or with some additional involvement of a human coach. It was coded as "major'' if the study investigated an intervention which was delivered by a human coach, in which eHealth served as an additional tool that supported the human guidance. Delivery mode was coded as "remote'' if human support was solely delivered via mediated forms of communication (e.g. text messages), and as "blended'' if the human support was delivered both via digital communication tools and in face-to-face settings. For the outcome data, all self-reported or objectively observed clinical (blood pressure, glucose, cholesterol, weight, CVD composite score, physical activity capacity) and behavioral (physical activity behavior, smoking, nutrition, alcohol, sleep and relaxation) outcome data were extracted. We decided to treat physical activity capacity, such as distance walked in a specific amount of time or oxygen uptake during physical effort (VO2max), as a clinical variable and physical activity behavior, such as steps or minutes of physical activity per day, as a behavioral variable. For each outcome variable baseline and follow-up measures, mean differences (pre-post measure within one group), or change scores (difference between control and experimental group) were extracted. In case of multiple intervention conditions, all conditions were extracted, and in case of multiple control conditions, only the least extensive condition was extracted. To assess the methodological quality, we used the latest Cochrane Risk of Bias tool (RoB 2.0) to extract and assess potential risks at study level regarding the randomization process, deviations from intended interventions (effect of assignment), missing outcome data, measurement of the outcome, and selection of the reported result (Sterne et al., 2019). Studies were assessed as "low", "some concerns", or "high" risk of bias in the above mentioned domains. For each study, two of the three independent researchers conducted both the data extraction and risk of bias assessment, and compared their outcomes (interrater reliability of 78%). Possible differences were all resolved in regular meetings, and if needed, with the help of a third independent researcher. Corresponding authors were contacted in case of missing information on key variables.

Statistical Analyses

An important feature differentiating this study from existing meta-analyses on the effectiveness of eHealth lifestyle interventions for cardiometabolic diseases is our use of a multilevel approach. Rather than conducting a meta-analysis for each outcome separately, a three-level model allowed us to combine different outcome variables from the same study as it can deal with interdepency of effect sizes (Assink & Wibbelink, 2016). The analyses were performed with the Metafor package in RStudio (version 1.4.1103). We estimated pooled effects for all clinical and behavioral outcome variables, using a random effects multilevel model (Assink & Wibbelink, 2016). We used a three-level model to take into account that multiple effect sizes can be nested within a sample. This model allows for effect size variance (level 1), nested in effect sizes (level 2), nested in study samples (level 3). Thus, all outcomes of each study were included in the analysis, and coded with the same study ID. For continuous variables, standardized mean differences (Hedges' G) with 95% confidence intervals were calculated (Hedges & Olkin, 1985). For categorical variables, we calculated odds ratios with 95% confidence intervals, and transformed those to standardized mean differences (Polanin & Snilstveit, 2016). Variances were calculated based on the provided standard deviations or confidence intervals (Higgins et al., 2019). In case outcomes were measured at multiple time points, we included the outcome directly measured after the end of the intervention as defined by the studies. The intention was to prevent a large variety in long-term measurements.

We assessed publication bias by inspecting funnel plots and performed an Egger's test (Egger et al., 1997) with the Metafor package in RStudio. Publication bias results from studies reporting statistically or clinical significant results more often than non-significant results (Egger et al., 1997). Hence, the effect sizes of studies included in the meta-analysis can differ from the general effect size if all (including non-significant) studies would be considered. We determined statistical heterogeneity using log-likelihood-ratio tests for both within-study variance (level 2) and between-study variance (level 3) (Assink & Wibbelink, 2016). Additionally, we conducted moderator analyses to assess the effectiveness of self-help and human-supported eHealth lifestyle interventions, and the effect of dose and delivery mode of human support on the effectiveness of eHealth lifestyle interventions on clinical and behavioral health outcomes. For this, the three-level random effects model was extended to a three-level mixed effects model (Assink & Wibbelink, 2016) with the following moderators: type of intervention (self-help vs. human-supported), dose of human support (minor vs. major part of intervention), and delivery mode of human support (remote vs. blended). Furthermore, we conducted a moderator analysis with the risk of bias-scores (low risk of bias, some concerns, and high risk of bias) and study, intervention and population characteristics (control condition type, intervention length, patient age and diagnosis).

RESULTS

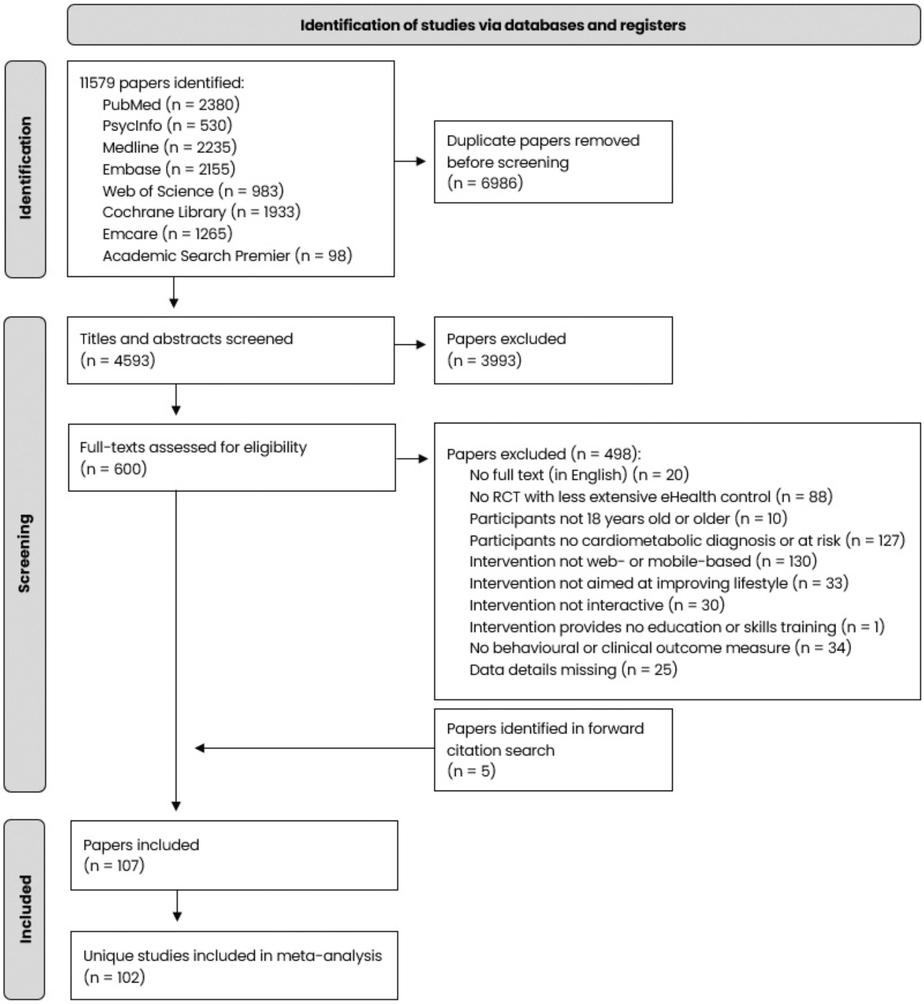
Study Selection

The search resulted in 4593 papers without duplicates. After abstract screening, a total of 600 full-texts were screened for eligibility. 498 papers did not meet the eligibility criteria and were, therefore, excluded. Five more papers were identified during the forward search, which resulted in a total of 107 papers fulfilling eligibility criteria, corresponding with 102 unique studies. The study selection process is summarized in Figure 1 (Pages et al., 2021).

Study Characteristics

The 102 studies produced 809 effect sizes, which all reflected the association between the use of an eHealth lifestyle intervention and either a clinical or behavioral outcome. A total of N = 20,781 patients were included in the studies, of which were N = 3428 CVD patients (26 studies), N = 72 T1DM patients (1 study), N = 7.143 T2DM patients (38 studies), N = 365 CKD patients (3 studies), N = 3,648 people at-risk (19 studies), and N = 6,125 patients from a sample with a combination of two or more of the before-mentioned diseases (15 studies).

Figure 1. Prisma flowchart of literature search and screening.



Sample sizes ranged from 20 to 2724. The mean age of the patients ranged from 35.2 to 75.9 years old. All studies included a combination of female and male patients. The duration of the interventions ranged from 1.5 to 24 months. The majority of the studies investigated the effect of interventions aimed either at physical activity (25), or a combination of multiple lifestyle behaviors (70). 30 investigated interventions (29%) were self-help, while 85 interventions (83%) offered some form of human support. See Appendix 2 for an overview of all studies included in the meta-analysis.

Risk of Bias Assessment & Publication Bias

The methodological quality of the included studies varied, but was overall sufficient. Almost all studies scored 'some concerns' on one of the domains in the Risk of Bias assessment, resulting in a 'some concerns' overall score for the majority of the studies (see Appendix 3). We found that the risk of bias-score did not moderate the association between eHealth lifestyle interventions and clinical and behavioral health outcomes ($F(2, 829) = .637$, $p = .529$). This indicates that there were no significant differences in mean effect size between studies with a low risk of bias-, some concerns-, or high risk of bias-score.

Possible publication bias was initially examined by visual inspection of a funnel plot. The funnel plot showed some asymmetry (indicating possible publication bias). Next, we tested funnel plot asymmetry by regressing the standard normal deviation against the estimate's precision (Egger et al., 1997). The analysis confirmed the visual inspection of the funnel plot, and showed that the intercept significantly deviated from zero, $t(808) = 3.12$, $p <.001$. This means that there are reasons to believe there is a publication bias for studies on eHealth lifestyle interventions.

Effectiveness of eHealth lifestyle interventions

The overall mean effect size of eHealth lifestyle interventions on clinical and behavioral health outcomes is 0.10 (expressed in Hedges' g; $p < .001$). A standardized mean difference of 0.10 is considered as small (Cohen, 1988). This indicates that patients with cardiometabolic diseases who follow an eHealth lifestyle intervention show more improvement in clinical and behavioral health outcomes compared to patients in control conditions. The overall mean effect size of eHealth lifestyle interventions on clinical outcomes only, as well as behavioral outcomes only, were 0.09 ($p < .001$) and 0.13 ($p < .001$), (see Table 1). We did not find a significant difference between the mean effect sizes of eHealth lifestyle interventions on clinical versus behavioral health outcomes ($p = 0.051$).

We conducted additional analyses for each outcome category separately. For the clinical outcome measures, we found significant mean effect sizes of eHealth lifestyle interventions on glucose outcomes (0.16, $p = .022$), weight outcomes (0.12, $p = .015$), and physical activity capacity outcomes (0.14, $p < .001$), but not for eHealth lifestyle interventions on blood pressure outcomes, cholesterol outcomes, and composite score outcomes. For the behavioral outcome measures, we found significant mean effect sizes of eHealth lifestyle interventions and physical activity outcomes (0.17, $p < .001$), and nutrition outcomes (0.13, $p = .007$), but not for eHealth lifestyle interventions on smoking outcomes, alcohol outcomes, and sleep and relaxation outcomes. See Table 1 for all mean effect sizes of eHealth lifestyle interventions on each outcome category.

Table 1. Mean effect sizes (expressed in Hedges' G) for each outcome category.

Outcome category	Nr. of studies	Nr. of ES	Mean ES (SE)	95% CI	*t*-Value	*p*-Value	Within-study variance	Between-study variance
All outcomes	102	809	.100 (.018)	0.065; 0.135	5.635	<.001***	.056***	.014***
Clinical outcomes	92	597	.086 (.019)	0.050; 0.123	4.672	<.001***	.066***	.010**
Blood pressure	49	99	.067 (.042)	-0.016; 0.150	1.597	.101	.034***	.047***
Glucose	55	84	.161 (.069)	0.024; 0.298	2.343	.022*	.000	.220***
Cholesterol	44	157	-.007 (.026)	-0.057; 0.044	-0.270	.788	.003	.016***
Weight	60	138	.117 (.048)	0.023; 0.211	2.463	.015*	.026***	.098***
CVD composite score	9	11	.025 (.031)	-0.044; 0.095	0.814	.435	.000	.000
PA capacity	24	61	.138 (.036)	0.065; 0.211	3.794	<.001***	.022*	.000
Behavioral outcomes	60	212	.131 (.031)	0.069; 0.193	4.165	<.001***	.020***	.031***
PA behavior	49	119	.170 (.038)	0.094; 0.246	4.453	<.001***	.000	.045***
Smoking	11	12	-.086 (.056)	-0.209; 0.037	-1.533	.154	.000	.013
Nutrition	24	74	.133 (.048)	0.037; 0.229	2.756	.007**	.040***	.020*
Alcohol	3	3	-.085 (.085)	-0.449; 0.279	-1.004	.279	.000	.000
Sleep & relaxation	3	4	.081 (.126)	-0.320; 0.482	0.641	.567	.000	.018

Note. ES = effect size (Hedges' G); SE = standard error; CI = confidence interval; PA = physical activity; * $p < .05$; ** $p < .01$; *** $p < .001$

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Heterogeneity

Given the three-level model, we assessed both between-study heterogeneity (variance between studies) and within-study heterogeneity (variance between effect sizes from the same study). For all outcomes, we found significant between-study heterogeneity ($\sigma^2 = .014$, χ^2 (1) = 29.53, $p < .001$), as well as within-study heterogeneity ($\sigma^2 = .055$, χ^2 (1) = 499.77, $p < .001$). For clinical outcomes, the between-study heterogeneity ($\sigma^2 = .010$, χ^2 (1) = 8.92, $p = .003$) and within-study heterogeneity ($\sigma^2 = .064$, χ^2 (1) = 440.83, $p < .001$) were also significant. Also, for behavioral outcomes we found a significant between-study heterogeneity ($\sigma^2 = .034$, χ^2 (1) = 22.83, $p < .001$) and within-study heterogeneity ($\sigma^2 = .021$, χ^2 (1) = 26.07, $p < .001$). Given these significant heterogeneity values, we conducted moderator analyses for all outcomes combined, for clinical outcomes, and for behavioral outcomes separately (see Table 1).

Moderator Analyses

Intervention Type, Delivery Mode, and Dose of Support

To test the effect of intervention type (self-help vs. human-supported), dose of human support (minor vs. major), and delivery mode of human support (remote vs. blended) on the relationship between eHealth lifestyle interventions and clinical and behavioral health outcomes, we conducted moderator analyses. We found that intervention type did not moderate the mean effect size of eHealth lifestyle interventions on all health outcomes (clinical and behavioral health outcomes combined; $p = .169$) (see Table 2). Moreover, both dose ($p = .698$) and delivery mode of human support ($p = .557$) did not moderate the mean effect size eHealth lifestyle interventions on all health outcomes (clinical and behavioral health outcomes combined). We performed the same moderator analyses on the mean effect size of eHealth lifestyle interventions, and on both clinical and behavioral outcomes separately (see Table 2). For clinical outcomes, we again found no significant moderator effect of intervention type ($p = .374$), dose of human support ($p = .439$), or delivery mode ($p = .308$). For behavioral outcomes, we also found no significant moderator effect of intervention type ($p = .080$), dose of human support ($p = .272$), or delivery mode ($p = .144$).

Study, Intervention and Population Characteristics

We conducted several additional moderator analyses to explore whether study, intervention or population characteristics could explain this heterogeneity (see Table 3). Control condition type (passive vs. active; $p = 0.344$), intervention length ($p = .588$), mean sample age ($p = .053$), or diagnosis (CVD, T1DM, T2DM, CKD, at-risk, or mixed; $p = .197$) did not significantly moderate the mean effect size of eHealth lifestyle interventions on all health outcomes, or on either clinical or behavioral health outcomes separately (see Table 3).

Table 2. Results for the moderator analyses of intervention type, dose of human support, and delivery mode of human support on the association between eHealth interventions and clinical and behavioral health outcomes.

Moderator	Nr. of studies	Nr. of ES	Overall test	*p*-Value of overall test	Mean ES (SE)	95% CI	*t*-Value	*p*-Value of ES
All outcomes								
Intervention type	102	809	$F(1, 807) = 1.900$	.169				
Self-help interventions					.137 (.032)	0.074; 0.201	4.241	<.001***
Human-supported interventions					.086 (.020)	0.047; 0.125	4.292	<.001***
Dose of human support	76	590	$F(1, 588) = .150$	.698				
Minor level					.105 (.036)	0.034; 0.176	2.907	.004**
Major level					.087 (.031)	0.027; 0.147	2.839	.005**
Delivery mode of human support	75	586	$F(1, 584) = .346$	.557				
Remote					.102 (.026)	0.052; 0.152	3.988	<.001***
Blended					.080 (.036)	0.010; 0.150	2.250	.025*
Clinical outcomes								
Intervention type	92	597	$F(1, 595) = .792$	.374				
Self-help interventions					.113 (.035)	0.044; 0.182	3.204	.001**
Human-supported interventions					.077 (.021)	0.035; 0.118	3.610	<.001***

Table 2. *Continued*

Moderator	Nr. of studies	Nr. of ES	Overall test	*p*-Value of overall test	Mean ES (SE)	95% CI	*t*-Value	*p*-Value of ES
Dose of human support	69	440	F(1, 438) = .599	.439				
Minor level					.111 (.041)	0.030; 0.191	2.696	.007**
Major level					.068 (.037)	-0.005; 0.142	1.834	.067^{+}
Delivery mode of human support	68	436	F(1, 434) = 1.041	.308				
Remote					.099 (.029)	0.042; 0.157	3.386	<.001***
Blended					.063 (.038)	-0.012; 0.137	1.653	.099^{+}
Behavioral outcomes								
Intervention type	60	212	F(1, 210) = 3.100	.080^{+}				
Self-help interventions					.207 (.053)	0.102; 0.312	3.886	<.001***
Human-supported interventions					.101 (.034)	0.034; 0.167	2.993	.003**
Dose of human support	44	150	F(1, 148) = 1.215	.272				
Minor level					.038 (.058)	-0.076; 0.153	0.662	.509
Major level					.117 (.042)	0.034; 0.201	2.790	.006**
Delivery mode of human support	44	150	F(1, 148) = 2.159	.144				
Remote					.062 (.038)	-0.014; 0.138	1.614	.109
Blended					.167 (.062)	0.044; 0.290	2.679	.008**

Note. ES = effect size (Hedges' G); SE = standard error; CI = confidence interval; $^{+}$ < .10; * *p* < .05; ** *p* < .01; *** *p* < .001

Table 3. Results for the moderator analyses of study, intervention and population characteristics on the association between eHealth interventions and clinical and behavioral health outcomes.

Moderator	Nr. of studies	Nr. of ES	Overall test	*p*-Value of overall test	Mean ES (SE)[a]	95% CI	*t*-Value	*p*-Value of ES
All outcomes								
Outcome type	102	809	F(1, 807) = 3.810	.051⁺				
Clinical outcomes					.086 (.019)	0.049; 0.124	4.500	<.001***
Behavioral outcomes					.142 (.028)	0.087; 0.196	5.109	<.001***
Control condition type	102	809	F(1, 807) = .897	.344				
Passive					.110 (.021)	0.070; 0.151	5.320	<.001***
Active					.071 (.036)	-0.000; 0.142	1.959	.050⁺
Intervention length	101	805	F(1, 803) = .294	.588	.117 (.031)	0.056; 0.177	3.792	<.001***
Mean sample age	91	750	F(1, 748) = 3.758	.053⁺	.198 (.053)	0.095; 0.301	3.760	<.001***
Diagnosis	102	809	F(5, 803) = 1.470	.197				
CVD					.146 (.037)	0.075; 0.218	4.000	<.001***
T1DM					.034 (.212)	-0.382; 0.450	.161	.872
T2DM					.104 (.030)	0.046; 0.162	3.497	<.001***
CKD					.024 (.098)	-0.168; 0.215	.242	.809
At-risk					.126 (.038)	0.051; 0.202	3.286	.001**
Mixed patient group					.002 (.046)	-0.089; 0.092	.040	.968
Clinical outcomes								
Control condition type	92	597	F(1, 595) = .653	.420				

Table 3. *Continued*

Moderator	**Nr. of studies**	**Nr. of ES**	**Overall test**	***p*-Value of overall test**	**Mean ES (SE)[a]**	**95% CI**	***t*-Value**	***p*-Value of ES**
Passive					.095 (.021)	0.053; 0.137	4.451	<.001***
Active					.059 (.039)	-0.016; 0.135	1.538	.125
Intervention length	91	596	F(1, 594) = .025	.873	.094 (.033)	0.029; 0.158	2.864	.004**
Mean sample age	83	551	F(1, 549) = 2.750	.098	.179 (.058)	0.065; 0.292	3.095	.002**
Diagnosis	92	597	F(5, 591) = 1.244	.287				
CVD					.135 (.039)	0.059; 0.211	3.490	<.001***
T1DM					.183 (.378)	-0.560; 0.926	.483	.629
T2DM					.095 (.031)	0.034; 0.156	3.062	.002**
CKD					.028 (.096)	-0.161; 0.218	.295	.768
At-risk					.095 (.040)	0.017; 0.173	2.390	.017*
Mixed patient group					-.015 (.050)	-0.114; 0.083	-.015	.762
Behavioral outcomes								
Control condition type	60	212	F(1, 210) = .211	.646				
Passive					.141 (.038)	0.066; 0.217	3.692	<.001***
Active					.109 (.058)	-0.004; 0.223	1.900	.059[+]
Intervention length	59	209	F(1, 207) = 1.242	.266	.188 (.057)	0.076;0.301	3.298	<.001**
Mean sample age	55	199	F(1, 197) = 2.441	.120	.243 (.082)	0.081; 0.405	2.960	.003**

Table 3. *Continued*

Moderator	Nr. of studies	Nr. of ES	Overall test	*p*-Value of overall test	Mean ES (SE)[a]	95% CI	*t*-Value	*p*-Value of ES
Diagnosis	60	212	F(5, 206) = .508	.770				
CVD					.122 (.062)	-0.001; 0.245	1.955	.052⁺
T1DM					-.016 (.253)	-0.514; 0.482	-.063	.950
T2DM					.155 (.060)	0.037; 0.273	2.595	.010*
CKD					-.003 (.212)	-0.420; 0.415	-.013	.990
At-risk					.196 (.070)	0.058; 0.334	2.803	.006**
Mixed patient group					.064 (.076)	-0.086; 0.215	.843	.400

Note. ES = effect size (Hedges' G); SE = standard error; CI = confidence interval; ⁺ < .10; * $p < .05$; ** $p < .01$; *** $p < .001$
[a] For continuous predictors: represents the ES size of a participant with an average value on the corresponding predictor

4

DISCUSSION

Our multilevel meta-analysis demonstrated that eHealth interventions are effective in improving cardiometabolic health outcomes. Yet, overall effect size, both on clinical and behavioral health outcomes, was small. The small effect sizes are comparable to other meta-analyses investigating eHealth lifestyle interventions (e.g. 0.139 in Lustria et al. (2013); 0.16 in Webb et al. (2010)). More specifically, eHealth lifestyle interventions positively influenced the clinical health outcomes glucose, weight and physical activity capacity (but not blood pressure, cholesterol and CVD composite score), and the following behavioral health outcomes: physical activity behavior, and nutrition (but not smoking, alcohol and sleep or relaxation).. Furthermore, we found that study, intervention or sample characteristics did not impact the positive effect of eHealth lifestyle interventions on health outcomes. Finally, control group type, intervention length, mean sample age, and diagnosis did not influence the effect of eHealth lifestyle interventions on clinical and behavioral health outcomes.

Contrary to our expectations, our meta-analysis did not show the expected difference between human-supported and self-help eHealth interventions. Both human-supported and self-help eHealth interventions were effective in improving clinical and behavioral health outcomes. Our results contrast other meta-analyses (Beishuizen et al., 2016; Joiner et al., 2017; Lau et al., 2020) which did find a stronger effect of human support in eHealth interventions on improving cardiometabolic risk factors, or a more pronounced effect of blended interventions compared to remotely supported ones. Instead, our results are more in line with studies that indicated that there is no difference in the improvement of cardiometabolic risk factors between human-supported and self-help eHealth interventions (Lustria et al., 2013; Webb et al., 2010), or blended and remotely supported eHealth interventions (Kloek et al., 2017). Although one of the aims of this meta-analysis was to find an explanation for the inconsistent results of human support in eHealth interventions in these different meta-analyses, our results with regard to dose and delivery mode of the support did not provide this explanation. However, these inconsistencies could be due to population-, outcome- or intervention-related factors.

Regarding the first factor that could provide an explanation to inconsistent results of human support, the study population, meta-analyses focusing on the general population did not find a difference between human-supported and self-help eHealth interventions (Lustria et al., 2013; Webb et al., 2010). However, contrary to our results, those studies that focused on a patient or at-risk population did encounter differences between human-supported and self-help eHealth interventions (Beishuizen et al., 2016; Joiner et al., 2017; Lau et al., 2020). Our meta-analysis with patients and an at-risk population did not find these differences, and also no differences between conditions. We did however find that age had a borderline significant effect. Possibly, patients are generally older, and therefore, more in need of human support when using eHealth compared to the general population (Crouch & Gordon, 2019).

With regard to outcome-related factors, our study showed no difference between human-supported and self-help eHealth interventions in the outcome measure we used: effectiveness. Possibly, we would have found a difference if we used intervention adherence as an outcome measure. Multiple studies have shown that self-help eHealth interventions suffer from low levels of intervention adherence, which refers to the extent to which the individual uses the intervention as intended (Kelders et al., 2012; Kelders et al., 2011; Murray et al., 2013; Wangberg et al., 2008). However, meta-analyses on multiple studies investigating intervention adherence to eHealth interventions are difficult to conduct because only a small proportion of the studies report eHealth intervention adherence (Sieverink et al., 2017). As intervention adherence is related to intervention effectiveness (Donkin et al., 2011), the level of intervention adherence could possibly be the missing explanation for the inconsistent results found in previous meta-analyses regarding the possible added contribution of human support to self-help eHealth interventions.

Finally, the effectiveness of human support in eHealth interventions could depend on the characteristics of the specific interventions. In our study, the inclusion criteria was that the tested intervention was delivered via a website or mobile-based application, provided education or skills training, and was interactive. This narrowed down the type of interventions included in our analyses, which may have positively influenced the quality of both human-supported and self-help interventions, and consequently reduced the difference in effectiveness between the two. Some meta-analyses did find a lower effectiveness of self-help eHealth interventions, possibly because they included a broader variety of interventions, including interventions lacking important behavior change techniques or lower quality of interactive components. For example, Beishuizen and colleagues (2016) included interventions without education or skills training, Lau and colleagues (2020) included interventions that were not interactive, and Joiner and colleagues (2017) included any intervention that used some form of digital communication (including social media, DVDs, or videoconferencing). We know that interventions that are more elaborate, for example because they incorporate multiple behavior change techniques, are more effective in improving health behavior (Webb et al., 2010). It is therefore not surprising that automated support is frequently combined with behavior change techniques and persuasive system design principles (Asbjørnsen et al., 2019). Furthermore, an advantage of self-help interventions is that users can customize what behavior change technique features are used in their eHealth intervention, which users appreciate (Coorey, 2018). This means that cardiometabolic patients themselves can decide whether their eHealth lifestyle intervention shows motivational messages (e.g. through push messages on their smartphone) or not, in what frequency they want to track their behaviors (e.g. filling in a food diary daily or weekly) or whether they want to watch all the educational videos or whether they already have enough knowledge on the topic. So the more thorough implementation of behavior change techniques and interactive components as well as the freedom for the user to choose, could positively affect the quality of self-help eHealth interventions.

Finally, it is important to note that our hypotheses with regard to the dose and delivery mode of support were based on findings in mental health interventions. Based on meta-analyses focusing on both eHealth and regular interventions or eHealth interventions only, aimed at patients with obsessive-compulsive disorder (Pearcy et al., 2016), depression and anxiety (Etzelmueller et al., 2020; Karyotaki et al., 2018; Richards & Richardson, 2012) or mental disorders in general (Baumeister et al., 2014) found that human-supported interventions are more effective, and that higher levels of support lead to higher effect sizes. Our meta-analysis however, focused on lifestyle interventions showed contradictory results. Possibly, mental health issues require more complex interventions that might require more human support than self-help interventions. Future studies could investigate whether interventions aimed at mental health improvement necessitate (more extensive) human support compared to interventions aimed at lifestyle behavior change.

Strengths, Limitations and Future Research

A strength of our study is that we used a precise definition of eHealth as a study eligibility criteria. As noted previously, many other meta-analyses on eHealth included a larger variety of digital tools (e.g. DVDs and videoconferencing) or less elaborate types of eHealth interventions (e.g., without interactive or educational components). Our definition created more homogeneity in the inclusion of eHealth studies. Another strength would be the inclusion of four different types of cardiometabolic diseases. Not only is there a high comorbidity between CVD, CKD, T1DM and T2DM, but they also share similar underlying risk factors and have a similar management strategy (i.e. lifestyle modifications; Ryden et al., 2014; Suckling, 2012). Finally, another advantage of our study was our multi-level approach for the meta-analysis. Other studies concerning eHealth lifestyle interventions for people with cardiometabolic diseases used a more traditional univariate approach, and conducted a meta-analysis for each outcome separately. We contributed to these studies by applying a three-level model approach (Assink & Wibbelink, 2016), which does not only deal with interdependency of effect sizes, but also presents an overall picture of the effect of eHealth lifestyle interventions on clinical and behavioral health outcomes.

A number of limitations need to be considered. Firstly, our sensitivity analyses revealed that there was some publication bias. This may have caused the mean effect sizes in our study to be different from the true effect sizes for the effect of eHealth interventions on clinical and behavioral cardiometabolic health outcomes. The results should, therefore, be interpreted with caution. Another limitation of the study was the methodological quality of the included studies. The Risk of Bias assessment resulted in a generally good evaluations of the studies, and we found that Risk of Bias assessment had no moderating effect on the relation between eHealth intervention and clinical and behavioral health outcomes. Since self-management interventions cannot be blinded, almost all studies lacked double blinding, leading to a possible risk of bias due to deviations from the intended interventions and in measurement of the outcome (e.g. health professionals measuring participants blood pressure or weight). Furthermore, only a minority of the studies preregistered their study and analyses, which may cause a risk of bias in selection of the reported results. As another limitation, we should mention that the included studies were substantially heterogeneous on several levels. With regard to the control group, some of the studies had a passive control group (waitlist or care as usual), while in other studies patients in the control group received another intervention. Furthermore, there was a large variety in intervention duration, which ranged from 1.5 to 24 months. There were also big differences in mean age of the study samples, which varied from 35.2 to 75.9 years. In spite of this, our analyses revealed that control group type, intervention length, and mean sample age had no moderating effect on the relation between eHealth intervention and clinical and behavioral health outcomes.

Our study has raised new questions regarding eHealth interventions and human support that would be interesting to address in future research. Adherence to interventions is still poorly defined and underreported. Therefore, we suggest that future randomized controlled trials evaluating eHealth lifestyle interventions implement better intervention adherence measures. This would also enable the investigation of the relationship between human-supported and self-help eHealth interventions on intervention adherence. In contrast to previous meta-analyses, our study did not find a difference between these human-supported and self-help eHealth interventions. As stated before, this inconsistency could be due to the quality of eHealth interventions, as we had strict inclusion and exclusion criteria with regard to the way eHealth interventions were designed and executed. Future meta-analyses could investigate what components make self-help eHealth interventions as effective as human-supported eHealth interventions, and whether lower-quality eHealth interventions benefit more from applying human support. Another suggestion for future research would be to further investigate the need for human support for specific subgroups of patients. For example it is important to specifically examine implementation, intervention adherence and effects of eHealth interventions for patients of lower socioeconomic status including those with less digital literacy or resources (van der Vaart et al., 2019). These variables were reported inconsistently among the included studies and require more attention in future studies.

Moreover, meta-analyses on interventions for psychological outcomes instead of lifestyle outcomes indicate that human support is particularly important for cognitive-behavioral interventions focusing on psychological distress and related outcomes (Baumeister et al., 2014; Etzelmueller et al., 2020; Karyotaki et al., 2018; Pearcy et al., 2016; Richards & Richardson, 2012). Therefore, it would be interesting to investigate whether mental health also influences the need for support in eHealth lifestyle interventions. Finally, the studies included in our analyses were heterogenous in regard to patient groups and outcomes. Most studies focused on CVD and T2DM patients, and to a lesser degree on patients with T1DM and CKD. Despite alcohol use and sleep and relaxation being important risk factors to be address in cardiometabolic disease management, only very few studies targeted these health outcomes. It would, therefore, be important for eHealth researchers to also focus on these less represented patients groups and behavioral risk factors in future studies.

CONCLUSION

Our meta-analysis demonstrated that eHealth lifestyle interventions are effective in improving clinical and behavioral health outcomes among people with cardiometabolic diseases. However, there was no difference between self-help and human-supported eHealth interventions' effectiveness. Neither dose nor delivery mode of support affected human-supported intervention effectiveness. Several population-, outcome-, and intervention-related factors were ruled out as possible moderators of these relationships. These findings add substantially to our understanding of the role of human support in lifestyle eHealth interventions, which is important to make lifestyle interventions accessible for a larger and more varied audience. Although further research is required to unravel the possible added contribution of human support for specific eHealth interventions in subgroups of patients, our results seem promising for the broad application of self-help eHealth interventions in cardiometabolic diseases.

REFERENCES CHAPTER 4

Asbjørnsen, R. A., Smedsrød, M. L., Nes, L. S., Wentzel, J., Varsi, C., Hjelmesæth, J., & van Gemert-Pijnen, J. E. (2019). Persuasive system design principles and behavior change techniques to stimulate motivation and adherence in electronic health interventions to support weight loss maintenance: scoping review. *Journal of medical Internet research, 21*(6), e14265. https://10.2196/14265

Assink, M., & Wibbelink, C. J. (2016). Fitting three-level meta-analytic models in R: A step-by-step tutorial. *The Quantitative Methods for Psychology, 12*(3), 154-174. https://10.20982/tqmp.12.3.p154

Barak, A., Klein, B., & Proudfoot, J. G. (2009). Defining internet-supported therapeutic interventions. *Annals of behavioral medicine, 38*(1), 4-17. https://10.1007/s12160-009-9130-7

Baumeister, H., Reichler, L., Munzinger, M., & Lin, J. (2014). The impact of guidance on Internet-based mental health interventions: A systematic review. *Internet interventions*, *1*(4), 205-215. https://10.1016/j.invent.2014.08.003

Beishuizen, C. R., Stephan, B. C., van Gool, W. A., Brayne, C., Peters, R. J., Andrieu, S., ... & Richard, E. (2016). Web-based interventions targeting cardiovascular risk factors in middle-aged and older people: a systematic review and meta-analysis. *Journal of medical Internet research, 18*(3), e5218. https://10.2196/jmir.5218

Carvalho de Menezes, M. (2016). Interventions directed at eating habits and physical activity using the TRANSTHEORETICAL model: A systematic review. *Nutrición Hospitalaria, 33*(5). https://10.20960/nh.586

Cohen, J. (1992). A power primer. *Psychological bulletin*, *112*(1), 155-159. https:// 10.1037/0033-2909.112.1.155

Cohen Rodrigues, T. R., Breeman, L. D., Reijnders, T., Kinik, A., Janssen, V. R., Kraaijenhagen, R. A., Atsma, D. E., Evers, A. W. M. Effectiveness of eHealth lifestyle support interventions for patients with cardiometabolic diseases and the role of human support: A meta-analysis. PROSPERO 2021 CRD42021269263 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021269263

Coorey, G. M., Neubeck, L., Mulley, J., & Redfern, J. (2018). Effectiveness, acceptability and usefulness of mobile applications for cardiovascular disease self-management: Systematic review with meta-synthesis of quantitative and qualitative data. European journal of preventive cardiology, 25(5), 505-521. https://10.1177/2047487317750913

Crouch E, Gordon NP. Prevalence and Factors Influencing Use of Internet and Electronic Health Resources by Middle-Aged and Older Adults in a US Health Plan Population: Cross-Sectional Survey Study. JMIR Aging 2019;2(1):e11451. https:// 10.2196/11451

Danaei, G., Lu, Y., Singh, G. M., Carnahan, E., Stevens, G. A., Cowan, M. J., ... & Kobayashi, J. (2014). Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. *Lancet Diabetes & Endocrinology, 2*(8), 634-647.

Donkin, L., Christensen, H., Naismith, S. L., Neal, B., Hickie, I. B., & Glozier, N. (2011). A systematic review of the impact of adherence on the effectiveness of e-therapies. *Journal of medical Internet research, 13*(3), e52. https://10.2196/jmir.1772

Egger, M., Smith, G. D., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal, 315*, 629–634. https://10.1136/bmj.315.7109.629

Etzelmueller, A., Vis, C., Karyotaki, E., Baumeister, H., Titov, N., Berking, M., ... & Ebert, D. D. (2020). Effects of internet-based cognitive behavioral therapy in routine care for adults in treatment for depression and anxiety: Systematic review and meta-analysis. *Journal of medical Internet research, 22*(8), e18100. https://10.2196/18100

Hedges, L. V., & Olkin, I. (1985). *Statistical methods for meta-analysis.* Orlando: Academic Press.

Higgins, J. P., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., & Welch, V. A. (Eds.). (2019). *Cochrane handbook for systematic reviews of interventions*. John Wiley & Sons.

Ter Hoeve, N., Huisstede, B. M., Stam, H. J., van Domburg, R. T., Sunamura, M., & van den Berg-Emons, R. J. (2015). Does cardiac rehabilitation after an acute cardiac syndrome lead to changes in physical activity habits? Systematic review. *Physical Therapy*, *95*(2), 167-179. https://10.2522/ptj.20130509

Hoppen, L. M., Kuck, N., Bürkner, P. C., Karin, E., Wootton, B. M., & Buhlmann, U. (2021). Low intensity technology-delivered cognitive behavioral therapy for obsessive-compulsive disorder: a meta-analysis. *BMC psychiatry, 21*(1), 1-17. https://10.1186/s12888-021-03272-5

Janssen, V., De Gucht, V., van Exel, H., & Maes, S. (2013). Beyond resolutions? A randomized controlled trial of a self-regulation lifestyle programme for post-cardiac rehabilitation patients. *European journal of preventive cardiology, 20*(3), 431-441. https://10.1177/2047487312441728

Joiner, K. L., Nam, S., & Whittemore, R. (2017). Lifestyle interventions based on the diabetes prevention program delivered via eHealth: *A systematic review and meta-analysis. Preventive medicine, 100*, 194-207. https://10.1016/j.ypmed.2017.04.033

Karyotaki, E., Ebert, D. D., Donkin, L., Riper, H., Twisk, J., Burger, S., ... & Cuijpers, P. (2018). Do guided internet-based interventions result in clinically relevant changes for patients with depression? An individual participant data meta-analysis. *Clinical psychology review, 63*, 80-92. https://10.1016/j.cpr.2018.06.007

Kelders, S. M., Kok, R. N., Ossebaard, H. C., & Van Gemert-Pijnen, J. E. (2012). Persuasive system design does matter: a systematic review of adherence to web-based interventions. *Journal of medical Internet research, 14*(6), e152. https://10.2196/jmir.2104

Kelders, S. M., Van Gemert-Pijnen, J. E., Werkman, A., Nijland, N., & Seydel, E. R. (2011). Effectiveness of a Web-based intervention aimed at healthy dietary and physical activity behavior: a randomized controlled trial about users and usage. *Journal of medical Internet research, 13*(2), e32. https://10.2196/jmir.1624

Kloek, C., Bossen, D., De Bakker, D. H., Veenhof, C., & Dekker, J. (2017). Blended interventions to change behavior in patients with chronic somatic disorders: systematic review. *Journal of medical Internet research*, *19*(12), e418. https://10.2196/jmir.8108

Koelen, J. A., Vonk, A., Klein, A., de Koning, L., Vonk, P., de Vet, S., & Wiers, R. (2022). Man vs. machine: A meta-analysis on the added value of human support in text-based internet treatments ("e-therapy") for mental disorders. *Clinical Psychology Review, 102179*. https://10.1016/j.cpr.2022.102179

Lau, Y., Chee, D. G. H., Chow, X. P., Cheng, L. J., & Wong, S. N. (2020). Personalised eHealth interventions in adults with overweight and obesity: A systematic review and meta-analysis of randomised controlled trials. *Preventive medicine, 132*, 106001. https://10.1016/j.ypmed.2020.106001

Leung, C., Pei, J., Hudec, K., Shams, F., Munthali, R., & Vigo, D. (2022). The Effects of Nonclinician Guidance on Effectiveness and Process Outcomes in Digital Mental Health Interventions: Systematic Review and Meta-analysis. *Journal of Medical Internet Research, 24*(6), e36004. https://10.2196/36004

Liang, X., Wang, Q., Yang, X., Cao, J., Chen, J., Mo, X., ... & Gu, D. (2011). Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. *Diabetic medicine, 28*(4), 455-463. https://10.1111/j.1464-5491.2010.03180.x

Liu, S., Dunford, S. D., Leung, Y. W., Brooks, D., Thomas, S. G., Eysenbach, G., & Nolan, R. P. (2013). Reducing blood pressure with Internet-based interventions: a meta-analysis. *Canadian Journal of Cardiology, 29*(5), 613-621. https://10.1016/j.cjca.2013.02.007

Lustria, M. L., Noar, S. M., Cortese, J., Van Stee, S. K., Glueckauf, R. L., & Lee, J. (2013). A meta-analysis of web-delivered tailored health behavior change interventions. *Journal of Health Communication, 18*, 1039-1069. https://10.1080/10810730.2013.768727

Murray, E., White, I. R., Varagunam, M., Godfrey, C., Khadjesari, Z., & McCambridge, J. (2013). Attrition revisited: adherence and retention in a web-based alcohol trial. Journal of medical Internet research, 15(8), e162. https://10.2196/jmir.2336

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj, 372*(71). https://doi.org/10.1136/bmj.n71

Pearcy, C. P., Anderson, R. A., Egan, S. J., & Rees, C. S. (2016). A systematic review and meta-analysis of self-help therapeutic interventions for obsessive–compulsive disorder: Is therapeutic contact key to overall improvement?. *Journal of behavior therapy and experimental psychiatry*, *51*, 74-83. https://10.1016/j.jbtep.2015.12.007

Piepoli, M. F., Hoes, A. W., Agewall, S., Albus, C., Brotons, C., Catapano, A. L., ... & Binno, S. (2016). 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The sixth joint task force on the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice. *European Heart Journal, 37*(29), 2315-81. https://10.1093/eurheartj/ehw106

Polanin, J. R., & Snilstveit, B. (2016). Converting between effect sizes. *Campbell Systematic Reviews, 12*(1), 1-13. https://10.4073/cmpn.2016.3

Richards, D., & Richardson, T. (2012). Computer-based psychological treatments for depression: a systematic review and meta-analysis. *Clinical psychology review, 32*(4), 329-342. https://10.1016/j.cpr.2012.02.004

Ryden, L., Grant, P. J., Anker, S. D., Berne, C., Cosentino, F., Danchin, N., ... & Neyses, L. (2014). ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD-summary. *Diabetes & vascular disease research*, *11*(3), 133-73. https://10.1177/1479164114525548

Schardt, C., Adams, M. B., Owens, T., Keitz, S., & Fontelo, P. (2007). Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC medical informatics and decision making, 7*(1), 1-6. https://10.1186/1472-6947-7-16

Sieverink, F., Kelders, S. M., & van Gemert-Pijnen, J. E. (2017). Clarifying the concept of adherence to eHealth technology: systematic review on when usage becomes adherence. *Journal of medical Internet research, 19*(12), e8578. https://10.2196/jmir.8578

Srivastava, S., Pant, M., Abraham, A., & Agrawal, N. (2015). The Technological Growth in eHealth Services. *Computational and Mathematical Methods in Medicine, 894171*, 1-18. https://10.1155/2015/894171

Sterne, J. A., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., ... & Higgins, J. P. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *bmj, 366*. https://10.1136/bmj.l4898

Suckling, R., & Gallagher, H. (2012). Chronic kidney disease, diabetes mellitus and cardiovascular disease: risks and commonalities. *Journal of renal care*, *38*, 4-11. https://10.1111/j.1755-6686.2012.00274.x

Wangberg, S. C., Bergmo, T. S., & Johnsen, J. A. K. (2008). Adherence in Internet-based interventions. *Patient preference and adherence, 2*, 57-65.

Van der Vaart R, van Driel D, Pronk K, Paulussen S, te Boekhorst S, Rosmalen JGM, Evers AWM. The Role of Age, Education, and Digital Health Literacy in the Usability of Internet-Based Cognitive Behavioral Therapy for Chronic Pain: Mixed Methods Study. JMIR Form Res 2019;3(4):e12883. https:// 10.2196/12883

Webb, T., Joseph, J., Yardley, L., & Michie, S. (2010). Using the internet to promote health behavior change: a systematic review and meta-analysis of the impact of theoretical basis, use of behavior change techniques, and mode of delivery on efficacy. *Journal of medical Internet research*, *12*(1), e1376. https://10.2196/jmir.1376

World Health Organization. (2017). Cardiovascular diseases (CVDs). Retrieved February 7, 2019, from https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

CHAPTER 4 | APPENDIX 1

Search string.

Randomized controlled trials about eHealth lifestyle interventions to promote lifestyle modification in cardiometabolic disease patients.

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CHAPTER 4 | APPENDIX 2

Table 4. Characteristics of the included studies.

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Agarwal 2019(a)	50 T2DM and hypertension patients	64.1	44.5	2-arm; Canada	4-month mobile-based intervention aimed at physical activity, nutrition, and sleep	Human-supported, blended, major, layperson	Usual care	Glucose, physical activity behavior
Agarwal 2019(b)	223 T2DM patients	51.8	47.5	2-arm; Canada	3-month mobile-based intervention, aimed at physical activity and nutrition	Self-help	Waitlist	Glucose
Akinci 2019	66 T2DM patients	52.5	72.3	3-arm*; Finland	2-month web-based intervention aimed at physical activity	Human-supported, remote only, minor, layperson	Usual care	Glucose, cholesterol, weight, physical activity capacity, physical activity behavior
Appel 2011	415 CVD patients	54.0	63.6	3-arm; USA	24-month web-based interventions aimed at physical activity and nutrition	(1) Human-supported, remote, minor, professional (2) Human-supported, blended, major, professional	Usual care	Weight
Baer 2020	840 T2DM patients	59.3	60.0	3-arm; USA	12-month web-based interventions aimed at physical activity and nutrition	(1) Self-help (2) Human-supported, remote, minor, professional	Usual care	Weight
Bailey 2020	20 T2DM patients	56.0	45.0	2-arm; UK	2-month mobile-based intervention aimed at physical activity	Self-help	Usual care	Blood pressure, glucose, weight, physical activity capacity, physical activity behavior
Bennett 2010	101 CVD patients	54.4	47.5	2-arm; USA	3-month web-based intervention aimed at physical activity and nutrition	Human-supported, blended, minor, professional	Usual care	Blood pressure, weight

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Bennett 2018	351 hypertension, diabetes, hyperlipidemia, and obesity patients	50.7	68.0	2-arm; USA	12-month mobile-based intervention aimed at nutrition	Human-supported, blended, minor, professional	Usual care	Blood pressure, glucose, cholesterol, weight
Bond2007	62 T1DM and T2DM patients	67.2	45.0	2-arm; USA	6-month web-based intervention aimed at nutrition and physical activity	Human-supported, remote, major, professional	Usual care	Blood pressure, glucose, cholesterol, weight
Bozorgi 2021	120 patients with hypertension	51.8	41.0	2-arm; Iran	2-month mobile-based intervention aimed at nutrition and smoking	Self-help	Usual care	Blood pressure, weight, physical activity capacity, physical activity behavior, nutrition
Cai 2021	100 CVD patients	57.0	35.0	2-arm; China	3-month mobile-based intervention aimed at physical activity	Human-supported, remote, minor, professional	Usual care	Physical activity capacity, physical activity behavior
Chao2019	121 T2DM patients	N.A.	39.0	2-arm; Taiwan	18-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, minor, professional	Usual care	Blood pressure, glucose, weight
Choi2019	100 CVD patients	56.9	38.9	2-arm; USA	3-month mobile-based intervention aimed at nutrition	Human-supported, blended, major, professional	Usual care	Blood pressure, glucose, cholesterol, weight
Chow2021	41 at-risk population	N.A	49.4	2-arm; USA	4-month mobile-based intervention aimed at smoking, physical activity and nutrition	Human-supported, remote, major, professional	Other eHealth intervention	Physical activity behavior, nutrition

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Connely2017	31 T2DM patients	66.7	41.7	3-arm; UK	6-month web-based intervention aimed at physical activity	(1) Self-help (2) Human-supported, blended, minor, professional	Non eHealth intervention	Weight, glucose, physical activity behavior
Dorje2019	312 CVD patients	60.5	18.5	2-arm; China	6-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, minor, professional	Usual care	Blood pressure , cholesterol, weight
Dorsch2020	50 CVD patients	57.4	59.5	2-arm; USA	2-month mobile-based intervention aimed at nutrition	Self-help	Usual care	Blood pressure, nutrition
Duan2018	114 CVD patients	48.7	53.2	2-arm; USA	2-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, minor, professional	Waitlist	Physical activity behavior, nutrition
Duscha2018	32 CVD patients	63.2	52.1	2-arm; China	3-month web-based intervention aimed at physical activity	Human-supported, remote, major, professional	Usual care	Physical activity capacity, physical activity behavior
Engelen2020	208 CVD patients	63.5	31.5	2-arm; The Netherlands	12-month Web-based intervention aimed at smoking, alcohol, and physical activity	Self-help	Usual care	Blood pressure, cholesterol, weight, physical activity behavior, nutrition, alcohol
Fukuoka2015	61 at-risk population	55.3	77.1	2-arm; USA	5-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, blended, major, layperson	Usual care	Blood pressure, glucose, cholesterol, weight
Glasgow2012	463 T2DM patients	58.7	77.4	3-arm; USA	4-month web-based intervention aimed at physical activity and nutrition	(1) Self-help (2) Human supported, remote, major, professional	Other eHealth intervention	Blood pressure, glucose, cholesterol, weight, cardiovascular compost score, physical activity behavior, nutrition

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Gong2020	187 T2DM patients	56.9	41.8	2-arm; Australia	12-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, minor, layperson	Waitlist	Glucose, weight
Grau-Pellicer 2020	41 CVD patients	65.8	49.4	2-arm; Spain	3-month mobile-based intervention aimed at physical activity	Human-supported, blended, major, professional	Usual care	Physical activity behavior
Gunawardena 2019	67 T1DM and T2DM patients	52.5	40.0	2-arm; Sri Lanka	6-month mobile-based intervention aimed at nutrition and physical activity	Self-help	Usual care	Glucose
Hansel2017	120 T2DM patients	56.6	66.7	2-arm; France	4-month web-based intervention aimed at nutrition and physical activity	Self-help	Usual care	Glucose, cholesterol, weight, nutrition
Haste2017	61 T2DM patients	N.A.	N.A.	2-arm; UK	12-month web-based intervention aimed at nutrition and physical activity	Human-supported, remote, minor, professional	Usual care	Weight
Hilmarsdóttir 2021	37 T2DM patients	51.2	63.4	2-arm; Iceland	6-month mobile-based intervention aimed at nutrition, stress and physical activity	Human-supported, remote, minor, layperson	Waitlist	Blood pressure, glucose, cholesterol, weight
Höchsmann 2019	36 T2DM patients	N.A.	52.8	2-arm; Switzerland	6-month mobile-based intervention aimed at physical activity	Self-help	Non eHealth intervention	Blood pressure, glucose, cholesterol, weight, physical activity behavior
Holmen2014	151 T2DM patients	57.3	36.5	3-arm; Norway	12-month mobile-based intervention aimed at nutrition and physical activity	Self-help	Usual care	Glucose, weight

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Houchen-Wolloff2018	60 CVD patients	61.5	10.0	2-arm; UK	2-month web-based intervention aimed at physical activity, nutrition, stress and smoking	Human-supported, remote, minor, professional	Usual care	Physical activity capacity
Humalda2020	99 CKD patients	56.7	16.0	2-arm; The Netherlands	9-month web-based intervention aimed at nutrition	Human-supported, blended, major, professional	Usual care	Blood pressure, nutrition
Imanaka2014	193 at-risk population	50.2	14.0	2-arm; Japan	3-month web-based intervention aimed at nutrition	Human-supported, remote, major,	Non eHealth intervention	Weight
Jahangiry2017	160 at-risk population	44.0	27.0	2-arm; Iran	3-month web-based intervention aimed at physical activity and nutrition	Self-help	Usual care	Blood pressure, glucose, cholesterol, weight
Javaheri2020	34 CVD patients	71.6	25.7	2-arm; USA	1.5-month web-based intervention aimed at sleep	Self-help	Waitlist	Blood pressure, sleep and relaxation
Johnston2016	174 CVD patients	57.6	19.3	2-arm; Sweden	6-month mobile-based intervention aimed at weight management, smoking and physical activity	Self-help	Other eHealth intervention	Cholesterol, weight, smoking
Keyserling2014	385 CVD patients	62.0	48.0	2-arm; USA	4-month mobile-based intervention aimed at physical activity, nutrition, and smoking	Human-supported, remote, major, professional	Usual care	Blood pressure, cholesterol, weight, cardiovascular composite score, physical activity behavior, smoking , nutrition

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Khanji2019	402 CVD patients	65.5	37.0	2-arm; The Netherlands	6-month mobile-based intervention aimed at alcohol consumption, smoking, physical activity, weight, nutrition, stress management	Human-supported, remote only, minor, professional	Usual care	Blood pressure, glucose, cholesterol, weight
Kim2006	73 T2DM patients	N.A.	N.A.	3-arm*; South Korea	3-month mobile-based intervention aimed at physical activity	Human-supported, blended, minor, professional	Usual care	Glucose, physical activity behavior, alcohol
Kim2016	160 patients with hypertension, diabetes, or cardiac arrhythmia	57.6	68.0	2-arm; South Korea	6-month mobile-based intervention aimed at alcohol consumption, smoking and physical activity	Human-supported, remote, minor, professional	Usual care	Blood pressure, physical activity behavior, smoking, alcohol
Kim2019	151 T2DM patients	N.A.	52.0	2-arm; South Korea	2-month mobile-based intervention aimed at nutrition management, physical activity.	Human-supported, blended, major, professional	Non eHealth intervention	Glucose
Kirwan2013	72 T1DM patients	35.2	61.1	2-arm; Australia	4-month mobile-based intervention aimed at diet and physical activity.	Human-supported, remote, major, professional	Usual care	Glucose, nutrition
Kooiman2018	72 T2DM patients	56.3	N.A.	2-arm; The Netherlands	3-month mobile-based intervention aimed at physical activity	Human-supported, remote, minor, professional	Usual care	Glucose, weight
Kouwenhoven-Pasmooij2018	491 at risk-population	51.0	19.3	2-arm; The Netherlands	6-month web-based intervention, aimed depending on patient's profile	Human-supported, blended, major, professional	Other eHealth intervention	Weight, physical activity behavior

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Ku2020	40 T2DM patients	50.0	65.0	2-arm; South Korea	3-month web-based intervention aimed at nutrition and physical activity	Human-supported, remote, major, professional	Non eHealth intervention	Glucose, physical activity behavior, nutrition
Kulick2013	61 at-risk population	52.2	75.3	2-arm; USA	3-month web-based intervention aimed at nutrition	Self-help	Waitlist	Cholesterol, weight, cardiovascular composite score, nutrition
Kumar2020	300 T2DM patient	64.65	60.0	2-arm; India	6-month mobile-based intervention aimed at nutrition	Self-help	Usual care	Glucose
Lear2014	78 CVD patients	60.0	15.0	2-arm; Canada	4-month web-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Usual care	Blood pressure, glucose, cholesterol, weight, physical activity capacity, physical activity behavior, smoking
Lee2018	148 T2DM patients	52.0	36.5	2-arm; South-Korea	6-month mobile and web-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Usual care	Blood pressure cholesterol, physical activity behavior, smoking, nutrition
Lee2020	72 T2DM patients	51.6	29.3	2-arm; South-Korea	6-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Usual care	Glucose, cholesterol, weight, smoking, nutrition
Li2019	462 at-risk population	61.5	62.8	2-arm; China	6-month mobile-based intervention aimed at nutrition, physical activity, smoking, alcohol intake.	Human-supported, remote, major, layperson	Usual care	Blood pressure, glucose
Li2020	60 CKD patients	51.3	26.5	2-arm; Taiwan	3-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Usual care	Cholesterol, weight

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Liebreich2009	49 T2DM patients	54.1	N.A.	2-arm; Canada	3-month web-based intervention aimed at physical activity	Human-supported, remote, major, professional	Other eHealth intervention	Physical activity behavior
Lim2021	204 T2DM patients	51.2	35.2	2-arm; Singapore	6-month mobile-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, layperson	Non eHealth intervention	Blood pressure, glucose, cholesterol, weight, nutrition
Lindberg2017	166 T2DM patients	66.6	29.5	2-arm; Sweden	19-month web-based intervention aimed at. nutrition, physical activity, smoking and alcohol consumption	Human-supported, blended, major, professional	Usual care	Blood pressure, glucose, cholesterol
Lisón2020	105 at-risk population	53.2	N.A.	2-arm; Spain	3-month web-based intervention aimed at nutrition and physical activity	Human-supported, blended, minor, layperson	Usual care	Blood pressure, glucose, weight, physical activity capacity, physical activity behavior
Little2017	826 at-risk population	53.7	63.6	3-arm; UK	6-month web-based intervention aimed at nutrition and physical activity	(1) Human-supported, blended, minor, professional (2) Human-supported, remote, minor, professional	Other eHealth intervention	Glucose, cholesterol, weight, physical activity behavior, nutrition
Lorig2006	958 CVD patients	57.5	71.4	2-arm; USA	1,5-month web-based intervention aimed at physical activity an stress management	Human-supported, remote, major, layperson	Usual care	Physical activity behavior, sleep
Lorig2010	761 T2DM patient	54.3	72.7	3-arm; USA	1,5-month web-based intervention aimed at nutrition and physical activity	(1) Human-supported, remote, major, layperson (2) Human-supported, remote, major, layperson	Usual care	Glucose, physical activity behavior

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Lunde2020	113 CVD patients	59.0	22.2	2-arm; Norway	12-month mobile-based intervention aimed at target behavior set by patient	Human-supported, remote, major, professional	Usual care	Blood pressure, glucose cholesterol, weight, physical activity capacity, physical activity behavior
Maddison2015	171 CVD patients	60.2	19.0	2-arm; New Zealand	6-month Physical activity mobile based and web-based intervention aimed at physical activity	Human-supported, remote, minor, layperson	Usual care	Physical activity capacity, physical activity behavior
Maddison2019	162 CVD patients	61.3	14.2	2-arm; New Zealand	3-month Physical activity mobile based and web-based intervention aimed at physical activity	Human-supported, remote, major, professional	Usual care	Blood pressure, glucose cholesterol, weight, physical activity capacity physical activity behavior
McDermott2018	200 CVD patients	70.3	52.5	2-arm; USA	6-month web-based intervention aimed at physical activity	Human-supported, blended, major, professional	Usual care	Physical activity capacity, physical activity behavior
McKay2001	78 T2DM patients	N.A.	N.A.	2-arm; USA, Canada	2-month Physical activity web-based intervention aimed at physical activity	Human-supported, remote, major, professional	Non eHealth intervention	Glucose cholesterol, nutrition
McKay2002	160 T2DM patients	59.5	53.2	4-arm; USA	2-month web-based intervention aimed at nutrition and others	(1) Self-help (2) Human supported, remote, major, professional (3) Human supported, remote, major, professional (4) Human supported, remote, major, professional	Non eHealth intervention	Glucose cholesterol, nutrition

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
McLeod2020	429 T2DM and pre-diabetes patients	62.1	50.9	2-arm; New Zealand	13-month web-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Usual care	blood pressure, glucose, weight, physical activity behavior, nutrition
McMahon2012	152 T2DM patients	61.0	7.0	3-arm*; USA	12-month web-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, professional	Non eHealth intervention	Glucose, cholesterol, weight
Mensorio2019	106 at-risk population	N.A.	N.A.	2-arm; Spain	3-month web-based intervention aimed at physical activity and nutrition	Self-help	Usual care	Weight, physical activity behavior
Murray2018	374 T2DM patients	64.8	71.0	2-arm; UK	12-month web-based interventions aimed at physical activity, nutrition, smoking, alcohol intake.	Self-help	Other eHealth intervention	Blood pressure, glucose
Nolan2018	264 at-risk population	57.6	58.5	2-arm; Canada	3-month Web-based intervention aimed at nutrition, smoking and physical activity	Self-help	Other eHealth intervention	Blood pressure, cholesterol, cardiovascular composite score
Orsama2013	56 T2DM patients	61.9	46.0	2-arm; Finland	10-month Web-based and mobile-based intervention aimed at nutrition and physical activity	Human-supported, remote, minor, professional	Usual care	Blood pressure glucose, weight,
Paldán2021	47 CVD patients	65.1	46.0	2-arm; Germany	6-month mobile-based intervention aimed at physical activity	Self-help	Usual care	Physical activity capacity, physical activity behavior

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Park2021	60 CVD patients	66.8	21.5	2-arm; USA	2-month mobile-based intervention aimed at physical activity	Human-supported, remote, major, layperson	Non eHealth intervention	Physical activity capacity, physical activity behavior
Peacock2020	204 at-risk population	63.5	36.0	2-arm; UK	3-month Web-based intervention aimed at physical activity	Human-supported, blended, major, professional	Non eHealth intervention	Blood pressure, glucose, cholesterol, weight, physical activity behavior
Plotnikoff2017	84 T2DM and at-risk patients	44.7	70.2	2-arm; Australia	5-month web-based intervention aimed at physical activity	Human-supported, blended, major, professional	Waitlist	Blood pressure, weight, physical activity capacity, physical activity behavior
Quinn2011	213 T2DM patients	52.6	50.0	4-arm*; USA	12-month web-based and mobile-based intervention aimed at physical activity and nutrition	Self-help	Usual care	Blood pressure, glucose, cholesterol
Riangkam2021	129 T1DM patients	51.5	39.6	3-arm; Thailand	3-month mobile-based intervention aimed at	Human-supported, blended, major, layperson	Usual care	Glucose
Richard2019	2724 CVD, diabetes or at-risk patients	69.0	47.7	2-arm; The Netherlands, Finland, France	18-month web-based intervention aimed at nutrition, smoking and physical activity	Human-supported, remote, minor, professional	Other eHealth intervention	Cholesterol, cardiovascular composite score, physical activity capacity, physical activity behavior, smoking, nutrition
Siebmanns2021	48 CVK patients	72.5	35.5	2-arm; Sweden	2-month web-based intervention aimed at sleep	Human-supported, remote, major, professional	Other eHealth intervention	Sleep

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Skobel2017	118 CVD patients	59.0	11.0	2-arm; Spain, Germany, UK	6-month web and mobile-based intervention aimed at physical activity	Human-supported, remote, minor, professional	Usual care	Cholesterol, physical activity capacity
Smith2009	41 at-risk population	43.5	N.A.	2-arm; USA	4-month web-based intervention aimed at physical activity	Human-supported, remote, minor, layperson	Waitlist	Blood pressure, glucose, insulin, cholesterol, weight, cardiovascular composite score, physical activity capacity, physical activity behavior
Spring2017	96 at-risk population	40.2	86.0	3-arm; USA	6-month mobile-based intervention aimed at nutrition and physical activity	Human-supported, blended, major, professional	Non eHealth intervention	Weight
Su2021	146 CVD patients	55.8	32.9	2-arm; China	3-month mobile-based intervention aimed at nutrition, stress, smoking	Human-supported, remote, minor, professional	Usual care	Blood pressure, glucose, weight, physical activity behavior
Tanaka2018	112 at-risk population	46.7	0.7	2-arm; Japan	2-month mobile-based intervention aimed at nutrition	Human-supported, remote, major, professional	Waitlist	Blood pressure, cholesterol, weight, nutrition
Tang2013	415 T2DM patients	53.8	40.1	2-arm; USA	12-month Web-based intervention aimed at physical activity and nutrition	Human-supported, remote, major, layperson	Usual care	Blood pressure, glucose, cholesterol, weight, cardiovascular composite score
Thomas2015	154 at-risk population	53.2	79.9	2-arm; USA	3-month web-based intervention aimed at physical activity	Human-supported, blended, minor, professional	Other eHealth intervention	Blood pressure, glucose, weight
Tjam2006	57 T1DM and T2DM patients	N.A.	53.2	2-arm; USA	12-month Web-based intervention aimed at	Human-supported, major, remote, professional	Usual care	Glucose, Cholesterol

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Tomita2009	40 CVD patients	75.9	68.8	2-arm; USA	12-month web-based intervention aimed at	Human-supported, minor, professional	Usual care	Blood pressure, sleep
Turnin2021	282 T2DM patients	59.6	36.9	2-arm; France	12-month web-based and mobile-based intervention aimed at physical activity and nutrition	Self-help	Usual care	Glucose
Van der Weegen2013	199 T1DM and T2DM patients	58.4	53.4	3-arm; The Netherlands	6-month web-based and mobile-based intervention	Human-supported, major, blended, professional	Usual care	Physical activity behavior
Vluggen2021	478 T2DM patients	60.2	32.5	2-arm; The Netherlands	6-month mobile-based intervention aimed at physical activity and nutrition	Self-help	Waitlist	Physical activity behavior
Vogel2017	36 CVD patients	62.8	0	2-arm; Austria	1.5-month mobile-based intervention aimed at physical activity	Self-help	Usual care	Physical activity capacity
Watson2015	65 at-risk population	52.2	55.5	2-arm; UK	12-month web-based intervention aimed at nutrition and physical activity	Self-help	Usual care	Blood pressure, cholesterol, weight, nutrition
Wayne2015	131 T2DM patients	53.2	72.5	2-arm; Canada	6-month mobile-based intervention aimed at nutrition and physical activity	Human-supported, blended, major, professional	Non eHealth intervention	Glucose, weight
Widmer2017	80 CVD patients	63.1	18.5	2-arm; USA	3-month mobile- and web-based intervention aimed at physical activity, nutrition, and smoking	Self-help	Usual care	Blood pressure, glucose, cholesterol, weight, physical activity behavior, nutrition

Table 4. *Continued*

Study	Participants	Age (mean)	Gender (% female)	RCT setting	Intervention group(s)	Support type	Control group	Outcomes types
Widyanata2019	65 T2DM patients	N.A.	56.7	2-arm; Indonesia	3-month mobile-based intervention aimed at nutrition and physical activity	Self-help	Waitlist	Glucose, insulin cholesterol,
Wong2020	438 CVD patients	52.4	34.5	2-arm; China	6-month web-based intervention aimed at physical activity	Self-help	Usual care	Blood pressure, cholesterol physical activity behavior
Wong2021	77 at-risk population	59.0	55.8	2-arm; China	3-month mobile-based intervention aimed at physical activity, stress and nutrition	Self-help	Non eHealth intervention	Blood pressure, glucose, cholesterol, weight, physical activity behavior
Wongrochan-anan 2015	126 T2DM patients	52.5	46.8	2-arm; Thailand	3-month web-based intervention aimed at physical activity, and nutrition.	Self-help	Usual care	Blood pressure, glucose, cholesterol, weight, nutrition
Yu2019	92 T2DM patients	52.3	29.7	2-arm; China	6-month mobile-based intervention aimed at nutrition and physical activity	Human-supported, remote, major, professional	Usual care	Blood pressure, glucose, weight
Yudi2021	206 CKD patients	56.5	31.2	2-arm; USA	2-month mobile-based intervention aimed at physical activity	Human-supported, remote, minor, professional	Usual care	Glucose, cholesterol, weight, physical activity behavior, smoking
Zhang2019	156 T1DM and T2DM patients	53.5	39.1	2-arm; China	6-month mobile-based intervention aimed at nutrition and physical activity	Human-supported, remote, major, professional	Usual care	Glucose, cholesterol, weight

*multiple control conditions, only the least extensive condition was extracted
CVD = cardiovascular disease; CKD = chronic kidney disease; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus

CHAPTER 4 | APPENDIX 3

Table 5. Risk of bias assessment of the included studies.

Study	D1	D2	D3	D4	D5	Overall
Agarwal2019(a)	!	!	+	+	+	!
Agarwal2019(b)	!	!	+	+	+	!
Akinci2019	+	+	+	+	+	+
Appel2011	!	–	–	!	+	–
Baer2020	+	+	!	+	+	!
Bailey2020	!	!	+	+	+	!
Bennett2010	+	+	+	+	!	!
Bennett2018	+	+	+	+	!	!
Bond2007	!	!	+	+	!	!
Bozorgi2021	+	!	+	!	!	!
Cai2021	!	!	+	+	!	!
Chao2019	!	!	+	–	!	–
Choi2019	!	+	+	+	+	!
Chow2020	!	!	+	+	!	!
Connely2017	+	!	+	+	+	!
Dorje2019	+	+	+	+	+	+
Dorsch2020	!	!	+	!	+	!
Duan2018	!	!	+	!	!	!
Duscha2018	!	+	+	+	!	!
Engelen2020	+	+	–	!	!	–
Fukuoka2015	+	!	+	!	!	!
Glasgow2012	+	+	+	!	!	!
Gong2020	+	+	+	+	!	!
Grau-Pellicer2020	!	!	+	!	!	!
Gunawardena2019	+	+	!	+	!	!
Hanswel2017	!	+	+	+	!	!
Haste2017	+	!	!	+	!	!
Hilmarsdóttir2021	+	+	+	+	!	!
Höchsmann2019	+	+	+	+	+	+

Table 5. *Continued*

Study	D1	D2	D3	D4	D5	Overall
Holmen2014	+	+	+	+	+	+
Houchen-Wolloff2018	+	!	!	+	!	!
Humalda2020	+	+	+	+	!	!
Imanaka2014	!	+	+	+	!	!
Jahangiry2015	!	+	-	+	!	-
Javaheri2020	!	!	+	+	+	!
Johnston2016	!	!	+	+	+	!
Keyserling2014	-	!	+	!	!	-
Khanji2019	+	+	+	+	+	+
Kim2006	!	!	+	+	+	!
Kim2016	+	!	+	!	+	!
Kim2019	+	!	!	+	!	!
Kirwan2013	!	!	+	+	!	!
Kooiman2018	!	+	+	+	!	!
Kouwenhoven-Pasmooij2018	+	+	+	!	-	-
Ku2020	!	!	+	+	!	!
Kulick2013	+	!	+	!	!	!
Kumar2020	+	!	+	+	!	!
Lear2014	+	+	+	+	!	!
Lee2018	+	!	+	!	!	!
Lee2020	+	!	+	!	!	!
Li2019	-	!	+	+	+	-
Li2020	!	!	+	+	!	!
Liebreich2009	!	+	+	!	!	!
Lim2021	+	+	+	+	+	+
Lindberg2017	+	+	-	+	-	-
Lisón2020	+	+	!	+	!	!
Little2017	+	+	+	+	!	!
Lorig2006	!	!	+	!	!	!
Lorig2010	!	+	+	!	!	!
Lunde2020	+	!	+	+	!	!

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Table 5. *Continued*

Study	D1	D2	D3	D4	D5	Overall
Maddison2015	+	+	!	!	+	!
Maddison2019	+	+	+	+	+	+
McDermott2018	!	+	+	+	+	!
McKay2001	!	!	+	!	!	!
McKay2002	!	!	+	!	!	!
McLeod2020	+	+	+	+	+	+
McMahon2012	+	+	+	+	!	!
Mensorio2019	+	+	–	+	+	–
Murray2018	!	+	+	+	!	!
Nolan2018	+	+	!	+	!	!
Orsama2013	!	!	!	+	!	!
Paldán2021	!	!	+	+	+	!
Park2021	!	!	!	+	!	!
Peacock2020	+	+	+	+	+	+
Plotnikoff2017	+	+	!	+	+	!
Quinn2011	!	+	–	+	+	–
Riangkam2021	+	+	+	+	!	!
Richard2019	!	+	+	+	+	!
Siebmanns2021	!	+	!	!	!	!
Skobel2017	!	!	–	+	!	–
Smith2009	!	+	+	+	!	!
Spring2017	+	+	–	+	!	–
Su2021	+	!	+	+	+	!
Tanaka2018	!	+	+	+	!	!
Tang2013	!	+	+	+	!	!
Thomas2015	+	+	+	!	!	!
Tjam2006	!	!	!	+	!	!
Tomita2009	!	+	+	!	!	!
Turnin2021	!	+	+	+	!	!
Van der Weegen2013	+	+	!	+	+	!
Vluggen2021	+	+	+	!	+	!

Table 5. *Continued*

Study	D1	D2	D3	D4	D5	Overall
Vogel2017	+	+	+	+	!	!
Watson2015	+	+	+	+	!	!
Wayne2015	+	+	+	+	!	!
Widmer2017	!	!	!	+	!	!
Widyanata2019	!	!	-	+	!	-
Wong2020	!	+	+	+	!	!
Wong2021	+	+	+	+	!	!
Wongrochananan2015	!	+	!	!	!	!
Yu2019	+	+	+	+	!	!
Yudi2021	+	+	+	+	+	+
Zhang2019	+	+	+	+	!	!

Domain 1: Risk of bias arising from the randomization process
Domain 2: Risk of bias due to deviations from the intended interventions
Domain 3: Risk of bias due to missing outcome data
Domain 4: Risk of bias in measurement of the outcome
Domain 5: Risk of bias in selection of the reported result

+	Low risk
!	Some concerns
-	High risk

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