Digital Interventions for Self-Management of Type 2 Diabetes Mellitus: A Systematic Literature Review and Meta Analysis

David Kerr, David Ahn, Kayo Waki, Jing Wang, Boris Breznen, David C. Klonoff

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Abstract

Background: The proliferation of digital technology has the potential to transform diabetes management. One of the critical aspects of modern diabetes management remains the achievement of glycemic targets to avoid acute and long-term complications.

Objective: We aimed to describe the landscape of evidence pertaining to the relative effectiveness/efficacy and safety of various digital interventions for the self-management of type 2 diabetes mellitus (T2DM), with a primary focus on reducing glycated hemoglobin A1c (HbA1c) levels.

Methods: A systematic literature review (SLR) was conducted by searching Embase, MEDLINE®, and CENTRAL on April 5, 2022. Study selection, data extraction, and quality assessment were performed by two independent reviewers. The primary meta-analysis was restricted to studies that reported lab measured HbA1c. In secondary analyses, meta-regression was performed with intensity of coaching in the digital intervention as a categorical covariate.

Results: In total 28 studies were included in this analysis. Most studies (82%) used the reduction of HbA1c levels as primary endpoint, either directly or as a part of a multi-component outcome. Twenty-one studies reported statistically significant results with this primary endpoint. When stratified into three intervention categories by the intensity of the intervention supporting the digital health technology, (analyzing all 28 studies) the success rate appeared to be proportional to the coaching intensity (i.e., higher-intensity studies reported higher success rates). When the analysis was restricted to randomized controlled trials (RCTs) using the comparative improvement of HbA1c levels, the effectiveness of the interventions was less clear. Only half of the included RCTs reported statistically significant results. The meta-analyses were broadly aligned with the results of the SLR. The primary analysis estimated greater reduction in HbA1c associated with digital interventions compared to usual care (-0.31%; 0.95% confidence interval [CI]: -0.45, -0.16; P<.0001). Meta-regression estimated reductions of -0.45% (95% CI: -0.81, -0.09; P<.02); -0.29% (95% CI: -0.48, -0.11; P<.003); and -0.28% (95% CI: -0.65, 0.09; P<.2) associated with high, medium, and low intensity interventions, respectively.

Conclusions: These findings suggest that reducing HbA1c levels in individuals with T2DM with the help of digital interventions is feasible, effective, and acceptable. One common feature of effective digital health interventions was the availability of timely and responsive personalized coaching by a dedicated healthcare professional.

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Review

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Results: In total 28 studies were included in this analysis. Most studies (82%) used the reduction of HbA1c levels as the primary endpoint, either directly or as a part of a multi-component outcome. Twenty-one studies reported statistically significant results with this primary endpoint. When stratified into three intervention categories by the intensity of the intervention supporting the digital health technology, (analyzing all 28 studies) the success rate appeared to be proportional to the coaching intensity (i.e., higher-intensity studies reported higher success rates). When the analysis was restricted to RCTs using the comparative improvement of HbA1c levels, the effectiveness of the interventions was less clear. Only half of the included RCTs reported statistically significant results. The meta-analyses were broadly aligned with the results of the SLR. The primary analysis estimated greater reduction in HbA1c associated with digital interventions compared to usual care (-0.31%; 0.95% confidence interval [CI]: -0.45, -0.16; *P*<.0001). Meta-regression estimated reductions of -0.45% (95% CI: -0.81, -0.09; *P*<.02); -0.29% (95% CI: -0.48, -0.11; *P*<.003); and -0.28% (95% CI: -0.65, 0.09; *P*<.2) associated with high, medium, and low intensity interventions, respectively.

Conclusion: These findings suggest that reducing HbA1c levels in individuals with T2DM with the help of digital interventions is feasible, effective, and acceptable. One common feature of effective digital health interventions was the availability of timely and responsive personalized coaching by a dedicated healthcare professional.

Keywords: Coaching, Digital health, eHealth, Meta-analysis, Patient empowerment, Patient engagement, Self-care, Systematic review, Telemedicine, Type 2 diabetes

Introduction

Digital health and telemedicine acceptance is growing rapidly, accelerated by the COVID-19 pandemic restrictions. Although it is difficult to estimate the acceptance of digital health in people with type 2 diabetes mellitus (T2DM) for methodological reasons [1], patients have access to a growing number of digital health technologies to support self-management of their condition. A recent study in Italy found that more than 70% of participants use continuous glucose systems [2]. The concept of self-management as an important part of long-term management of chronic diseases is gaining acceptance and it is now considered essential for achieving long-term improvement in health outcomes and quality of life [3]. Compared to traditional approaches focused on managing a specific disease condition, the new paradigm is based on a patient-provider partnership involving collaborative care and education in chronic disease self-management [3]. Transition to this new paradigm has been increasingly important for patients with T2DM. A recent survey showed that the standard of care in T2DM, although generally acceptable, cannot meet the variety of patients' needs in terms of accessibility and timeliness of psychological, emotional, and behavioral support [4]. This unmet need can be alleviated by a wider use of digital technologies designed to help patients with their lifestyle and health-related decisions through making accessible critical data and on-demand consultations [5]. The technologies for managing T2DM include medical devices such as glucose meters, insulin pumps, continuous glucose monitors, and connected insulin pens; digital interventions including mobile smartphone applications (apps), text messaging, electronic communications, and video conference platforms; and wearable technologies for monitoring health, such as activity trackers, sleep trackers, and smartwatches [6, 7]. Digital health technologies can also support virtual healthcare services, outside of a clinic or office, by using remotely collected data and communication capabilities of mobile devices and the Internet[8]. The specific form of remote care can vary significantly: from occasional automated text messages to real-time teleconferencing with a dedicated healthcare professional. The intensity of the remote care is therefore one of the factors that may impact the success of the interventions.

One of the critical goals of modern diabetes management remains the achievement of an acceptable levels of glycemia to avoid the acute and long-term complications associated with T2DM [9]. Unfortunately, many individuals do not achieve their preferred glycemic targets or experience unwanted glycemic variability [10]. It has been suggested that digital technology has the potential to support people living with T2DM in their efforts towards achieving their glycemic goals [11, 12]. A core need within diabetes self-management is to provide actionable information based on measured glucose levels [13]. This can be accomplished with timely information and possibly additional support from healthcare professionals [8]. The advantages of digital technologies in managing glucose levels from patient's perspective were recently summarized in three essential concepts: competence, autonomy, and connectivity [14]. Competence refers to the understanding of the blood glucose levels with the help of supporting apps, autonomy means that the digital interventions allow for independent and timely decisions, and connectivity means that a healthcare professional is always available thought text messages or e-mail. Digital interventions provide for all three components mentioned here and thus they are empowering the patients in their effort to cope with the disease. However, research suggests that people with T2DM may need more than knowledge about healthy eating,

exercise, and self-monitoring of blood glucose [15]. They also need assistance in building insights into their daily health-related behaviors and routines [16, 17].

The aim of this systematic literature review (SLR) and meta-analysis is to analyze digital health interventions for diabetes stratified by the levels of intensity of the intervention to determine whether 1) digital health interventions for diabetes are associated with improved outcomes and 2) whether the intensity of the intervention affects the degree of improvement. Additional outcomes of interest included user engagement measured by adherence/persistence, retention, and study withdrawal rates.

Methods

Eligibility criteria

An SLR was undertaken following the standard methodologies for conducting and reporting systematic reviews as recommended by the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18, 19]. Study eligibility criteria were defined using the PICO framework (Population, Intervention, Comparator, and Outcomes - see **Multimedia Appendix 1**). Briefly, eligibility criteria for the SLR included randomized controlled trials (RCTs) and comparative observational studies evaluating interventions containing both human (e.g., coaching) and digital components (e.g., glucose meter) in adults (>18 years of age) with T2DM.
Two independent reviewers were responsible for reviewing all records, inclusive of conference proceedings and grey literature sources, at the title/abstract stage according to the pre-defined selection criteria. All eligible studies identified during title/abstract screening proceeded to the full-text screening stage, where they were assessed for eligibility by the same reviewers. During each of the title/abstract and full-text screening stages reviewers reconciled differences between their decisions, and in scenarios of unresolved discrepancies a third reviewer intervened to reach consensus.
Studies that matched the PICO criteria following the full-text screening were included for data extraction. A standardized data extraction table was generated to define the study characteristics, including participant characteristics, intervention characteristics, and outcomes from eligible studies. Two independent reviewers extracted all relevant data from the final list of included studies. The reviewers reconciled discrepancies between their data extraction, and in scenarios of unresolved discrepancies a third reviewer intervened to reach consensus.

Information sources

Relevant studies were identified by searching the following databases on April 5, 2022: Embase (**Multimedia Appendix 2**), MEDLINE® (**Multimedia Appendix 3**), and the Cochrane Controlled Register of Trials (CENTRAL) (**Multimedia Appendix 4**). Abstracts from relevant conferences held between 2018-2022 were also searched via Embase or their respective websites. Additionally, selected company websites (Dario, Lark, Livongo, Omada, Onduo, OneDrop, Vida, Virta, and Welldoc) and the United States clinical trials registry (ClinicalTrials.gov) were searched.

Risk of bias

For quality control, two independent reviewers assessed the quality of the included studies

using the Cochrane's Risk of Bias Tool for randomized controlled trials (RCTs) and the Risk of Bias in Non-randomized Studies–Interventions (ROBINS-I) tools. A third investigator intervened to reach consensus if there were any unresolved conflicts. Results were summarized in a narrative form.

Synthesis of results (qualitative)

Following study selection, the results were summarized by grouping the interventions into three broad categories as described below. The two main components present in all interventions were the technological (devices and software) and the human (coaching). The coaching sessions varied markedly in terms of their frequency (how often the healthcare practitioners [HCPs] communicated with the individual with T2DM), duration (both duration of the individual sessions and overall duration of coaching), mode of communication (in-person, video conferencing, phone calls, texting/SMS), and the content (personalized vs. generic). Categories were created by considering the features and intensity of the coaching component, and for categorization, the intervention had to meet most of the following criteria:

1. **High intensity**
    - Participant data is automatically uploaded to the cloud in regular intervals. The coaching includes personalized motivational and goal-setting components based on the most recent data and is delivered by dedicated healthcare professional staff. Communication happens regularly, either in-person or remotely, at least once per week. Education includes specific modules explaining disease, behavioral strategies, and psychological coping.
2. **Medium intensity**
    - Participant data is manually uploaded to the clinic database. Coaching includes personalized advice based on individual data but does not include behavioral advice in terms of motivational and goal-setting components. The communication is ad-hoc and initiated by the HCPs. Education includes general information about disease and technical information about the use of the device(s).
3. **Low intensity**
    - Participant data sharing is limited (e.g., patients brought the glucose meters to the center, or a nurse visited patients), and the feedback is generic often using pre-existing templates. The communication is asynchronous or delayed (e.g., e-mail or follow-up phone call). There is limited or no education.

In addition to separating the studies into the three categories of intervention intensity, three additional features of the coaching were identified as potentially relevant to the success of an intervention:

- **Communication mode**: synchronous vs. asynchronous. Synchronous mode meant that participants were in direct contact in real time with the HCP and/or the coach (e.g., a telephone call or a teleconference) [20]. Asynchronous communications usually involved web-based portals, e-mails, or text messages [21].
- **Frequency of communication**: This varied considerably across the studies and therefore the final binary classification was chosen to be unlimited communications [22] or restricted/scheduled communications [23].
- **Qualification of the coaches**: diabetes specialists (e.g. certified diabetes educators [24] or diabetes nurse educators [25]) vs. general healthcare professionals (HCPs such as general practitioners [26] or study nurses [27]).

Synthesis of results (meta-analysis)

Nine random-effects meta-analyses were conducted on the mean difference in change in HbA1c. The primary analysis comprised all the included RCTs with laboratory measured HbA1c levels and was performed both with and without intervention intensity as a categorical covariate via a meta-regression. Subgroup analyses were conducted for high (number of studies k = 4), medium (k = 12), high and medium (k = 16), and low (k = 4) intensity interventions. Sensitivity analyses were conducted: (a) including studies with non-laboratory measured HbA1c, (b) excluding studies with continuous glucose monitoring (CGM), and (c) excluding studies identified as posing a high risk of bias using the Cochrane risk of bias tool.

All meta-analyses were conducted in R (v4.1.1) using the metafor (v3.0-2) package. The restricted maximum likelihood estimator was used to measure the between-study variance (τ^2) as heterogeneity due to variation in intervention design, follow-up time, and clinical population across the evidence base was anticipated. We also report the estimated heterogeneity using Q and I^2. If more than one usual care arm was present within a single study, then they were pooled into one sample size weighted mean prior to the meta-analysis. In cases where a study reported multiple timepoints, the final timepoint was chosen for analysis.

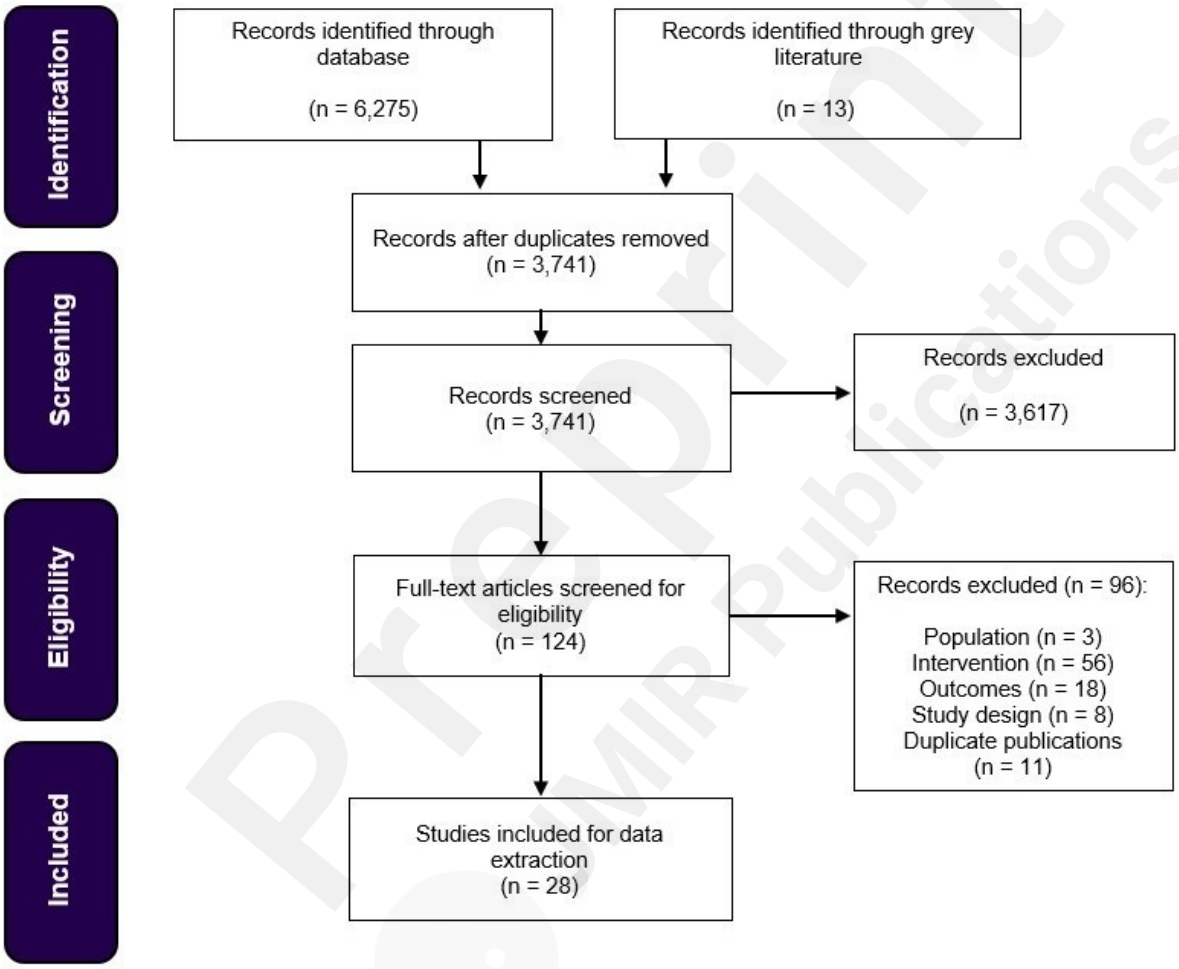
Results

Systematic literature review

Study selection and study characteristics

In total, 6,288 articles were identified from the SLR including 6,275 via Embase, MEDLINE, and CENTRAL, and 13 additional articles through conference proceedings and company websites. After title and abstract screening and full-text screening a total of 28 studies [20-47] were included in the SLR (**Figure 1**).

Figure 1: PRISMA diagram.



Of the 28 included studies, 23 were RCTs [20-30, 32-34, 36-43, 45], two were non-randomized comparative [31, 46], and the remaining three were cross-sectional [44], prospective cohort [47], and retrospective cohort [35] studies. There were nine countries where the studies were conducted: USA (12 studies), South Korea (6), United Kingdom (3), China (2), and one each in Belgium, Canada, France, India, and Malaysia. The studies were published between 2003 and 2021. Study population ranged from a minimum of 17 [42] to 772 [35] with an average population size of 202 and a median of 143 participants.

Follow-up durations ranged from 1 month [26] to 24 months [31] with an average follow up duration of 7.9 months and median of 6 months (one abstract did not include information on the follow-up duration [44]).

Participant characteristics

All studies enrolled T2DM populations, but some studies targeted sub-populations of T2DM individuals that met specific criteria. Four studies enrolled only participants taking glucose-lowering prescription medications [24, 37, 39, 42]. Individuals with sub-optimally controlled diabetes were investigated by five studies [27, 29, 35, 41, 44]. The definition of "sub-optimally controlled" varied. In some cases, the criterion was set by quantitative thresholds: two consecutive HbA1c recordings greater than 8.0% in the previous 12 months [29, 41], or HbA1c ≥7.5% to ≤13% [27]. However, in two studies, the definition was only descriptive with no quantitative data [35, 44]. Four studies targeted low income/low socioeconomic status populations [20, 22, 32, 38]. Two studies enrolled only individuals that were overweight (BMI≥25) [31] or obese (BMI≥41) [46] respectively. Two studies selected participants from a pool of insured patients [30, 45]. One study enrolled only women with T2DM [36], and one study enrolled self-described physically inactive individuals [34]. Mean age of the participants ranged from 47.3 years of age [40] to 64 years [24], with an overall mean of 55.7 years and median of 54.3 years with 51% (range: 29% - 100%) being female. Ethnicities and races in the studies included Black, Chinese, Korean, and White. Eleven studies reported the baseline average disease duration from 2.6 years [42] to 14 years [23], with overall mean of 7.9 years and median of 8 years.

All included studies reported the average (or median) level of HbA1c at baseline, and all studies tested disparities between intervention groups. None of them reported significant differences in baseline HbA1c levels. The overall average baseline HbA1c levels varied from the 6.8% [40] to 10.9% [39] with overall mean of 8.6% and median of 8.5%. The distribution of the mean baseline HbA1c across the studies was as follows (see **Multimedia Appendix 5**): ≤7% (2 studies), >7% and ≤8% (7 studies), >8% and ≤9% (10 studies), and >9% (9 studies).

Intervention characteristics

The technology component of the interventions included a technology for measuring glucose: either CGM (5 studies) [26, 35, 36, 43, 47], self-monitoring of blood glucose (SMBG) (21 studies) [20-24, 27-33, 37-42, 44-46], or both [25]. An exception was a study measuring blood glucose in a clinic setting [34]. In addition to glucose-monitoring devices, several studies used connected scales [31, 46] for weight monitoring or accelerometers to monitor physical activity [21, 25, 30, 34, 36, 41]. The glucose data were usually uploaded to a central server and then used by HCPs to adjust the treatment regimen and to coach and/or advise the participants on appropriate actions. The information about the measured glucose levels was generally available to participants either directly through the device display, or in some cases through a visualization software app or a dedicated website. Additional details on the digital interventions, the usual care groups, and coaching components of the included studies are summarized in **Multimedia Appendix 6**.

Outcome characteristics

Most studies reported improvement of the glycemic control in T2DM patients using HbA1c levels as the primary endpoint either directly or as a part of a multi-component outcome. A few studies used feasibility, acceptability and/or self-efficacy of the intervention as their endpoint [36, 43, 47], and one study used a physical activity endpoint [34]. The breakdown of study endpoints and respective number of significant results is summarized in **Table 1**.

Table *1*: Study endpoints and reported results.

Primary endpoint	Number of studies	Number of studies with significant results [a]
Change in HbA1c	19	14
Multi-component outcomes including HbA1c [b]	4	4
HOMA2-IR	1	1
Feasibility, acceptance, self-efficacy	3	2
Physical activity	1	0
Total	**28**	**21**

[a] *Number of studies achieving statistically significant results in primary endpoint.*

[b]*Multiple primary endpoints: HbA1c, glycemic control (HOMA2-IR, glycemic variability, fasting blood glucose, postprandial two-hour blood glucose), medication use, BMI, weight control, retention rate. HOMA2-IR: Homeostatic Model Assessment of Insulin Resistance.*

The classification of the studies into the three categories of interventions as outlined in the methods section yielded the following stratification:

- Seven studies in the high intensity category [20, 22, 26, 35, 41, 45, 46] (out of which five were RCTs) [20, 22, 26, 41, 45].
- Sixteen studies in the medium intensity category [21, 23, 25, 27, 29-33, 37-40, 42-44] (out of which fourteen were RCTs) [21, 23, 25, 27, 29, 30, 32, 33, 37-40, 42, 43].
- Five studies in the low intensity category [24, 28, 34, 36, 47] (out of which four were RCTs) [24, 28, 34, 36].

Table 2 shows reported outcomes across the three categories as measured by the number of significant primary endpoints (all studies and RCTs only).

Table *2*: Success rate in achieving its predetermined primary endpoint across the three intervention categories.

Intervention category	No. of studies	No. of significant endpoints[a]	% significant	No. of RCTs	No. of significant endpoints*	% significant
1. High intensity	7	6	86%	5	4	80%
2. Medium intensity	16	12	75%	14	10	71%
3. Low intensity	5	3	60%	4	3	75%

[a] *Number of studies achieving statistically significant results in primary endpoint.*

Table 3 summarizes the reported successes in comparative reduction of HbA1c across the three intervention categories within the included RCTs. The data show the number of studies reporting a statistically significant difference in HbA1c reduction between the intervention arm and the comparator arm.

Table *3*: Success rate of RCTs in achieving a reduction of HbA1c across the three intervention categories.

Intervention category	Number of RCTs	Number of significant results[a]	% Significant
1. High intensity	5	2	40%
2. Medium intensity	14	8	57%
3. Low intensity	4	2	50%

[a] *Number of studies achieving statistically significant results in comparative reduction of HbA1c.*

Table 4 shows the summary of the successes in comparative reduction of HbA1c separated into the categories outlined above. Only results from RCTs are included.

Table 4: Significant comparative reduction of HbA1c by intervention features.

Intervention feature		Number RCTs	Number of significant results[a]	% Significant
Communication mode	Synchronous	12	4	33%
	Asynchronous	11	8	73%
Frequency of communications	Unlimited	7	4	57%
	Restricted	16	8	50%
Qualification of coaches	Diabetes specialists	11	6	55%
	General HCPs	12	6	50%

[a] *Number of studies achieving statistically significant results in comparative reduction of HbA1c.*

Participant engagement and satisfaction was investigated in three studies based on their involvement in the counselling and educational sessions [36], reported measurement of the burden [47], or using validated questionnaires targeting self-care and self-efficacy [43]. The tools by which the studies measured some aspect of participant satisfaction consisted of standardized questionnaires and exit interviews. In the studies investigating user engagement, significant differences between the intervention and usual care groups in terms of changes in self-care behaviors were observed. Overall, digital interventions were well received with high completion rates (most of the studies had drop-out rates below 20%) and acceptable additional burden to the patients. In the studies investigating satisfaction using the Diabetes Treatment Satisfaction Questionnaire (DTSQ), two out of three studies reported significant improvement in DTSQ scores in the digital intervention groups, compared to usual care. One study reported DTSQ improvement from 31.9 ± 10.1 points to 42.0 ± 3.8 points (P=.001) in the intervention group, and from 34.3 ± 8.5 points to 36.4 ± 8.9 points in the control group (P=.1). This difference between the two groups was significant (P=.01) [39]. In the second study DTSQs showed a significant rise only in the intervention group, resulting in a 2.21-point increase in the intervention group compared with the control group at 3 months (P=.01) [33].

Another aspect of user engagement can be inferred from drop-out rates. Twenty-five studies reported drop-out rates (defined as the number of participants enrolling into the program but not finishing for any reason). Most studies reported ≤20% drop-out, with rates of >30% reported in only three studies [20, 27, 45].

Eleven of the 28 included studies reported on adverse events. Seven of these studies reported no intervention-related adverse events [22, 25, 27, 37, 38, 45, 46]. Four studies reported the occurrence of adverse events without commenting on their relationship to the digital interventions [30, 31, 33, 42]. The most common adverse event reported in these four studies was hypoglycemia, followed by cardiovascular events, cancer, and metabolic disruptions. Adverse events were reported in both the intervention groups and the usual care groups. The authors of these studies were agnostic about the causal relationship between digital interventions and adverse events.

Study quality assessment and risk of bias

The Cochrane risk of bias tool [48] was used to assess the 23 RCTs (**Multimedia Appendix 7**). One study had a low risk of bias, seventeen studies had some concerns regarding the overall

risk of bias, and five studies had a high risk of bias overall: (three studies did not blind investigators, participants, or interventionists to group assignment [20, 23, 36], one study used an inappropriate method of measuring HbA1c [self-reported via a questionnaire] [26], while another did not report how outcome data was collected) [37]. The ROBINS-I assessment tool [49] was used to evaluate the five non-randomized interventional studies (**Multimedia Appendix 8**). Overall, three studies had a low risk of bias, and two studies were considered to contain insufficient information on which to base a judgement about the risk of bias, mainly because of missing information in one or more key domains [35, 44].

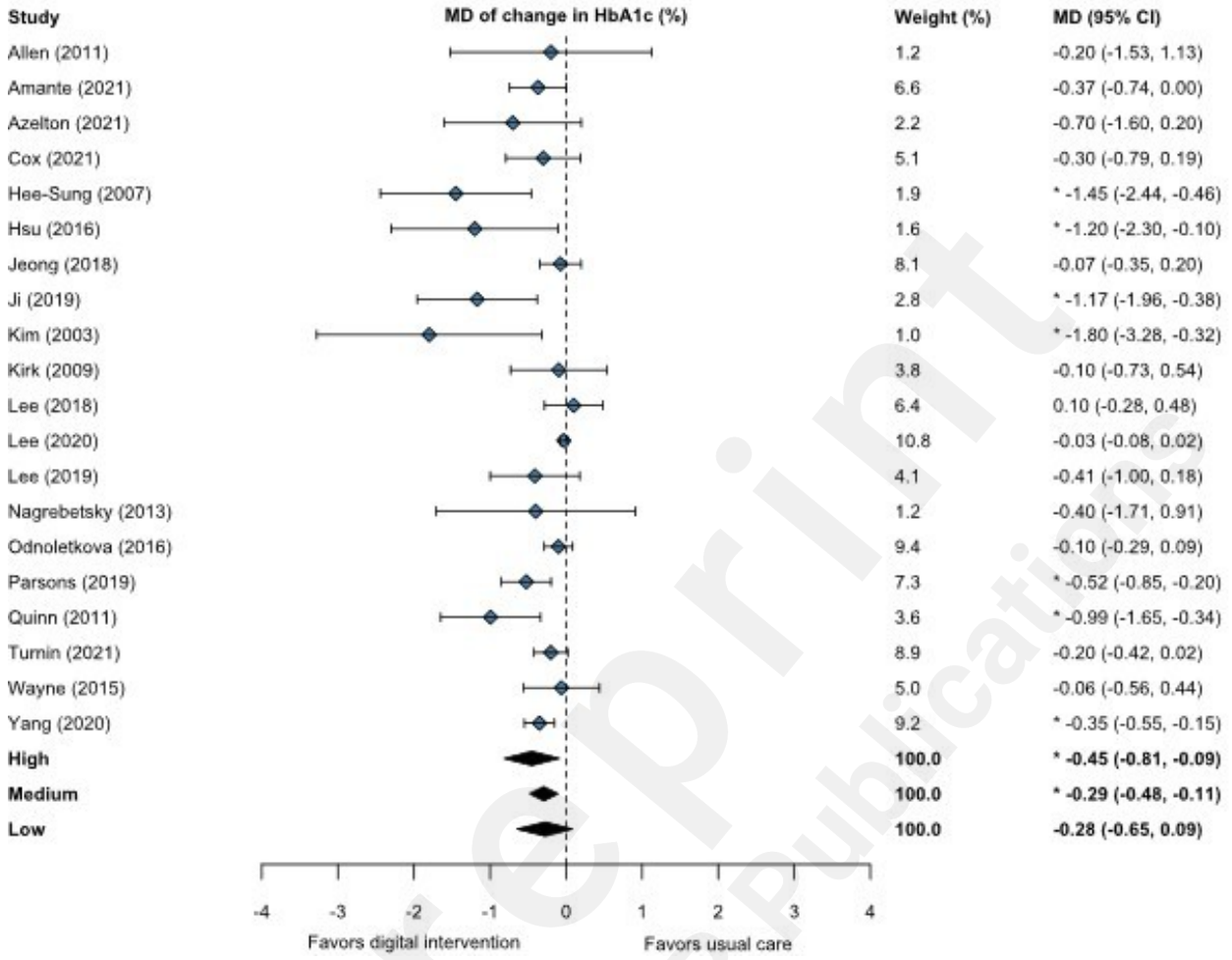
Meta-analysis

Primary analyses

In the primary analysis, the random-effects meta-analysis (20 studies) [20-25, 27, 28, 30, 33, 34, 36-43, 45] comparing change in HbA1c for intervention (number of patients across all studies [*N*] = 1637) vs. usual care (*N* = 1389) estimated an MD of -0.31% (0.95% CI: -0.45, -0.16;
P<. 0001. Heterogeneity was statistically significant (*Q* = 57.64, df = 19, *P*<.0001), with an estimated τ of 0.21 (95% CI: 0.12, 0.61) and I^2 of 67.54% (95% CI: 41.19, 94.48).
In the meta-regression of studies which measured HbA1c in a lab with intervention intensity as a categorical covariate (**Figure 2**), random-effects meta-analysis (20 studies) [20-25, 27, 28, 30, 33, 34, 36-43, 45] of change in HbA1c on intensity for intervention (*N* = 1637) vs. usual care (*N* = 1389) estimated an equation of

$$\widehat{MD} = -0.45 + 0.17(\text{intensity=low}) + 0.16(\text{intensity=medium}),$$

Figure 2: Forest plot of the mean difference (MD) and confidence interval (CI) of change in HbA1c with meta-regression on intervention intensity. Asterisks indicate statistical significance.



where $\widehat{MD}$ is the predicted MD, “intensity=low” is 1 if the intervention is low intensity and 0 otherwise; and “intensity=medium” is 1 if the intervention is medium intensity and 0 otherwise. This predicts an MD of -0.45% (95% CI: -0.81, -0.09; *P*<.02) for high intensity interventions,
-0.29% (95% CI: -0.48, -0.11; *P*<.003) for medium intensity interventions, and -0.28% (95% CI: -0.65, 0.09; *P*<.2) for low intensity interventions. The low (*P*=.51) and medium (*P*=.45) intensity coefficients were not statistically significant. Heterogeneity was statistically significant
(Q = 50.84, df = 17, *P*<.001), with an estimated τ of 0.23 (95% CI: 0.13, 0.68) and I^2 of 67.74% (95% CI: 40.87, 94.72).

Subgroup analyses

For the high intensity interventions, the random-effects meta-analysis (4 studies) [20, 22, 41, 45] of change in HbA1c for intervention (N = 253) vs. control (N = 201) estimated an MD of -0.46% (95% CI: -0.84, -0.07; *P*<.02). Heterogeneity was statistically significant (Q = 5.35, df = 3, *P*<.2), with an estimated τ of 0.27 (95% CI: 0.00, 1.47) and I^2 of 46.77% (95% CI: 0.00, 96.43).
For the medium intensity interventions, the random-effects meta-analysis (12 studies) [21, 23,

25, 27, 30, 33, 37-40, 42, 43] of change in HbA1c for intervention (N = 989) vs. control (N = 847) estimated an MD of -0.28% (0.95% CI: -0.45, -0.11; P<.002). Heterogeneity was statistically significant (Q = 38.76, df = 11, P<.0001), with an estimated τ of 0.20 (95% CI: 0.11, 0.87) and I^2 of 68.18% (95% CI: 39.74, 97.57).

For the combined high and medium intensity interventions, the random-effects meta-analysis (16 studies) [20-23, 25, 27, 30, 33, 36-43, 45] of change in HbA1c for intervention (N = 1242) vs. usual care (N = 1048) estimated an MD of -0.32% (0.95% CI: -0.47, -0.16; P<.0001). Heterogeneity was statistically significant (Q = 50.34, df = 15, P<.0001), with an estimated τ of 0.21 (95% CI: 0.12, 0.68) and I^2 of 67.49% (95% CI: 38.55, 95.46).

For the low intensity interventions, random-effects meta-analysis (4 studies) [24, 28, 34, 36] of change in HbA1c for intervention (N = 395) vs. usual care (N = 341) estimated an MD of -0.34% (0.95% CI: -0.83, 0.16; P<.2). Heterogeneity was not statistically significant (Q = 6.73, df = 3, P<.09), with an estimated τ of 0.38 (95% CI: 0.00, 1.90) and I^2 of 60.64% (95% CI: 0.00, 97.50).

Sensitivity analyses

Three sensitivity analyses were performed using (1) inclusion of studies using non-lab based HbA1c measurement, (2) exclusion of studies which employed CGM, and (3) exclusion of studies identified as high risk of bias according to the Cochrane Risk of Bias assessment. The results of all three analyses were in line with the primary analysis yielding significant MD effect in favor of the digital intervention as compared to usual care (**Table 5**).

Table 5: Summary results of all conducted analyses.

Analysis Set	*Studies*	Pooled Mean Difference Estimate (%)	Significant Heterogeneity
Primary			
Studies with lab measured HbA1c	20	-0.31 (95% CI: -0.45, -0.16)	Yes
Studies with lab measured HbA1c, Meta-regression	20	**High**: -0.45% (95% CI: -0.81, -0.09)	Yes
		Medium: -0.29% (95% CI: -0.48, -0.11)	
		Low: -0.28% (95% CI: -0.65, 0.09)	
Subgroups			
High intensity interventions	4	-0.43 (95% CI: -0.78, -0.09)	No
Medium intensity interventions	12	-0.28 (95 CI: -0.45%, -0.11)	Yes
High and medium intensity interventions	16	-0.32 (95% CI: -0.47, -0.16)	Yes
Low intensity interventions	4	-0.34 (95% CI: -0.83, 0.16)	No
Sensitivity			
Including non-lab measured HbA1c studies	23	-0.40 (95% CI: -0.56, -0.24)	Yes
Excluding continuous glucose monitoring studies	18	-0.31 (95% CI: -0.47, -0.15)	Yes
Excluding high-risk studies	16	-0.31 (95% CI: -0.46, -0.15)	Yes

Cells shaded in green indicate statistical significance, while those in yellow indicate non-significance.

Discussion

In this SLR and meta-analysis, the currently available evidence suggests that the use of digital health interventions, compared with usual care, is associated with clinically significant improvement in HbA1c levels for individuals with T2DM. Furthermore, the intensity of support provided by healthcare professionals also appears to impact the HbA1c levels. Here, intensity included the types and frequency of interactions between professionals and people with T2DM as well as the qualifications of the professional.

Although most of the RCTs reported their primary endpoints as defined by the study protocol, achieving significant comparative reduction of HbA1c between the digital health intervention and usual care appears to be challenging. Only half of the RCTs reported that the digital health interventions, compared to usual care, were successful in achieving a statistically significant difference in HbA1c reduction. In addition, there was variability in the performance of different digital interventions. Based on this analysis, two essential components of each intervention, technology, and coaching, seem to independently influence the outcomes. Information about the self-measured glucose levels was available to participants in all included studies. With one exception, the intervention arm included either SMBG or CGM devices. The devices provided on-demand glucose data to the person using the device as well as to the supervising healthcare team. Therefore, the availability of raw glucose data does not account for the observed outcome differences between the studies since the glucose data was available to both the intervention group and the control group in all studies. Even the presence or absence of additional devices (such as connected weight scales [46] or accelerometers [25, 34]) did not appear to make a difference. Consequently, easy access to self-measured data alone did not seem to be a sufficient condition for improved glycemic control.

In addition to the data provided by the devices, the other aspect of the intervention was coaching. Coaching can be stratified into two components: education and counseling. All studies provided educational sessions to the participants, albeit the extent and quality of the education varied. Some studies provided only basic forms of education usually based on pre-existing materials published by outside sources (such as the American Diabetes Association guidelines [37, 45] or Diabetes UK [34]). The educational content was restricted to general diabetes information and to the technical aspects of blood glucose monitoring [24, 27, 30, 38]. The educational sessions were led by nurses and the participants were mostly receiving pre-printed materials and watching pre-recorded videos. In higher-tier interventions (as defined in the Methods section), the educational materials were usually produced in-house by the institution conducting the study [20, 29, 35, 36] and tailored to the needs of the target population. The educational sessions were led by specialists (such as diabetes educators [20, 36], dietitians [29, 31], or pharmacists [38]) and often in small groups or in one-on-one settings. The sessions were interactive, with active participation of both the healthcare staff and the participants.

The coaching element was the most distinctive feature which differentiated the more intensive interventions from the lower-tier interventions (see **Table 2**). The top-tier interventions provided regular, individualized coaching sessions with trained diabetes educators, using graphical visualization tools to go over an individual's data with them and advise on the best course of action. Sessions were in person [36], or remote via videoconferencing [35, 41, 45], voice-call [26], texting [46], or a mixture of these. The content of the coaching sessions was tailored to the specific goals of the digital intervention. Three examples of such coaching are problem-solving [36], where participants were asked to discuss their specific barriers in implementing the intervention; development of an individualized plan to improve problem-

solving skills, self-care [41], implemented within the diabetes program and targeting seven self-care behaviors, and motivational interviewing, goal-setting, and confidence-building [20].
Across the high-intensity studies (of which three examples are listed above) coaching was frequent, available on-demand, and tailored for the individual. The medium for communication did not appear to be important.
Further, additional features of the interventions such as mode of communication, frequency of the communications, and qualification of the coaches were also important. The most pronounced difference was between studies using synchronous compared to asynchronous communication, with the advantage favoring use of an asynchronous mode of communication. This finding appears counterintuitive, as direct human-to-human contact is the most common way of coaching (health or otherwise). One possible explanation may come from the fact that the unlimited frequency of communication also seems to have a slight advantage over restricted/scheduled communications. The availability of the coaches for direct contact is constrained by the patient-to-coach ratios and the limited amount of time that each coach will be available in real time. On the other hand, asynchronous communications modalities such as text messages and e-mails allow for near-real time communication without the logistic constraints of direct interactions.
This finding is novel and not yet supported by other studies. A systematic review of longitudinal management of chronic conditions by telehealth interventions [8] reported no difference between asynchronous and in-person (synchronous) review of patient data. However, the asynchronous mode was represented by a dedicated webpage rather than text messaging, so the comparison may not be quite relevant. In an umbrella review of technology-enabled diabetes self-management [50] a new taxonomy for digital interventions was proposed. This taxonomy includes a distinction between synchronous and asynchronous feedback modes, but the authors noted poor reporting on this issue in the reviewed studies. Here, the qualifications of the coaches were the least significant factor in this analysis. However, all included RCTs were driven by a protocol outlining the important details of the intervention. All staff participating in those interventions were therefore instructed before the beginning of the trial in the proper method of coaching and patient interactions. Even the non-diabetes specialists were given specialized instructions on how to approach the patients which may have contributed to blurring the distinction between diabetes specialists and general HCPs.
When analyzing the comparative reduction of HbA1c within the context of RCTs, the meta-analysis confirmed the findings from the SLR. A statistically significant reduction in HbA1c relative to usual care was observed globally for high and medium intensity interventions, but not for low intensity interventions. Meta-regression coefficients were not statistically significant, and hence no support was found for a difference in efficacy according to intervention intensity; but this finding was limited by the relatively small number of high and low intensity interventions. The relatively modest, although statistically significant, effect size observed in the comparative reduction of HbA1c levels may be explained by several factors present in all included RCTs. First, the participants in the comparator arms of the studies were receiving usual diabetes care and the results show that this level of care also reduced their HbA1c. In this context, digital interventions can be viewed as adjunct therapy. Second, the improved efficacy relative to the usual care might not be the only advantage of digital interventions. Lastly, the effect size observed in this meta-analysis is similar to the one reported elsewhere investigating mobile health efficacy in diabetes treatment and management across developing and developed countries [51]. In addition, digital intervention can induce behavior change via coaching session that included problem solving, identifying barriers, etc., so effects of HbA1c improvement caused by this behavior change could be sustainable compared to usual care.

The sensitivity analysis including studies with non-lab measured HbA1c levels resulted in a more favorable result for digital interventions. This suggests that the decision to exclude those studies led to a more conservative result. The other two sensitivity analyses did not change the result, and so we conclude that the inclusion of CGM and high risk of bias studies was not a determining factor in the results. One caveat to the observation that the inclusion of CGM did not change the results was the fact that the number of studies with CGM was two. In this analysis the evidence base had studies spanning a broad range of years including early years when CGM was less prevalent.

In the studies from this review investigating engagement, the results showed that the digital intervention led to a significant difference between the intervention and usual care groups in terms of changes in self-care behaviors; and that digital interventions are well received with high completion rates and no additional burden. In the three studies investigating patient satisfaction using DTSQ questionnaires, all reported significant improvement in DTSQ scores in the digital intervention groups, suggesting a high satisfaction with the treatment. A challenge facing the reports on engagement is the lack of clear differentiation between patient participant adherence and engagement. Those two concepts are often used interchangeably, however they refer to different aspects of patient's an individual's behavior [52]. The usual definition of patient adherence is includes willingness to follow the study protocol in all aspects. Engagement includes an individual's initiative to actively seek improvement in their disease management. This distinction is important for differentiating between passive following of instructions and self-initiated activities.

Eleven of the 28 included studies reported on adverse events. Seven of these studies reported no intervention-related adverse events and four studies did report the occurrence of adverse events without stating whether those were related to the intervention or not. Given the nature of these events and the fact that the participants remained on their previously prescribed medication regimen, the link between the digital interventions and the adverse events is difficult to establish. Overall, the reporting on adverse events in the included studies was poor and this constitutes an unmet need in the domain of digital interventions.

Limitations to the Review/Meta Analysis

There are multiple limitations to our review and meta-analysis. First, the apparent relationships and conclusions regarding the intensity of the digital intervention must be tested in a prospective manner to see whether they prove to be valid. Next, the heterogeneous nature of the featured interventions makes it difficult to generalize the findings. This has been a consistent theme and conclusion in other systematic reviews with or without meta-analyses in digital health. The heterogeneity can be seen in a variety of study settings across multiple countries with different cultures that may influence the acceptance of the intervention. This aspect was not addressed in the individual studies. Our approach in this study was to stratify the interventions based on the intensity of the coaching as the most distinctive pattern among the interventions. However, because of a wide variety of coaching strategies, clear boundaries between the categories were not easy to draw. This was also true for selecting the three additional features of the interventions (communication mode, frequency of communications, and qualification of the coaches), used to further investigate the factors contributing to efficacy.

The meta-regression and subgroup analyses were limited by the small number of high and low intensity interventions, which resulted in low power to detect differences in HbA1c reduction according to intervention intensity. The effect of time of follow-up was also not investigated.

As well, only RCTs were included in the meta-analysis. Although this reduced the introduction of bias associated with non-randomized studies, it does limit the generalizability of the findings into the real world [53]. The risk-of-bias analysis revealed that all RCTs in the evidence base

contained some degree of bias. Although no difference in the degree of bias between one intervention and another was found, the presence of bias confounds the results of the meta-analysis.

With respect to scalability of the interventions into the real world, the need for dedicated staff of healthcare professionals for supporting the higher-intensity studies adds additional economic and logistic burden. Some of the solutions may require a dedicated database, communication infrastructure, customized user software, and trained, professional staff. After adding the necessary maintenance expenditures, the overall cost of these solutions may be out of the reach of certain clinics. Finally, some digital interventions are intended to deliver behavior change, but there was a paucity of clear evidence that behavior changed because the behavior change aspects of the intervention were not measured appropriately.

Recommendations for Future Research

Based on the findings, recommendations for future research in digital health include:

- An agreed definition of engagement in digital health as an endpoint may help with improved targeting of interventions.
- Reporting should standardize digital health data into meaningful outcomes by therapeutic area (and then beyond), such as sensor data, patient-reported outcome measures, etc. so that future systematic reviews and meta-analyses can be less heterogeneous.
- Studies in digital interventions should strive for a clear reporting of adverse events, especially in terms of the relationship between the digital health product and the adverse events.
- Digital health studies that include coaching should systematically record multiple dimensions of the intervention, including frequency, duration, asynchronous vs synchronous, coaching and/or behavioral change techniques deployed, human coach qualification (if relevant), guidance and introduction to patients, etc. For methodological purposes, a newly developed scoring system for classification of the intensity of coaching would help future analyses of virtual interventions.
- Consider different designs and methodologies to study digital health interventions, especially in those that are intended to deliver behavior change, so that meaningful patient engagement in the digital solution and outcome measures aligned with intended use can be assessed. To eliminate bias, perhaps cluster randomization (or some other method for eliminating bias) should be used in future digital health interventions.

Conclusions

Reducing HbA1c levels in patients with T2DM with the use of digital interventions, in addition to usual care, is feasible and acceptable to people with T2DM, as consistently demonstrated by a large number of studies of various populations, goals and methods of interventions. When analyzing the comparative efficacy of digital interventions within the context of RCTs, the advantage of digital interventions becomes less pronounced. Some forms of intervention perform better than others, but it is difficult to identify the exact reasons for this difference given the variety of methodologies featured in the studies. However, a broadly defined intensity of coaching seems to play an important role. A common feature of successful studies was the availability of timely and responsive personalized coaching. Therefore, the relevance and the content of the coaching is more important than the communication medium used to deliver the

messages. Scaling up the personalized, on-demand coaching featured in some of the studies may lead to logistical and economic roadblocks. Overcoming these roadblocks will largely determine the success of digital interventions in real-world clinical practice. In conclusion, digital health interventions for diabetes appear to be a useful tool for improving outcomes.

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Conflicts of Interest

David Kerr is a consultant to Sanofi and Better Therapeutics.

David Ahn has received speaker's fees from Abbott, Ascensia, Eli Lilly, Mannkind, Novo Nordisk, and Xeris Pharmaceuticals. He has received consulting/advisory fees from Eli Lilly, Ascensia, and Mannkind.

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Abbreviations

CENTRAL = Cochrane Central Register of Controlled Trials
CGM = Continuous Glucose Monitoring
CI = Confidence Interval
HbA1c = Glycated hemoglobin A1c
HCP = healthcare practitioners
MD = Mean Difference
PICO = Population, Intervention, Comparator, and Outcomes
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT = Randomized controlled trials
ROBINS-I = Risk of Bias in Non-randomized Studies–Interventions
SLR = Systematic Literature Review
SMBG = Self-Measured Blood Glucose
T2DM = Type 2 Diabetes Mellitus

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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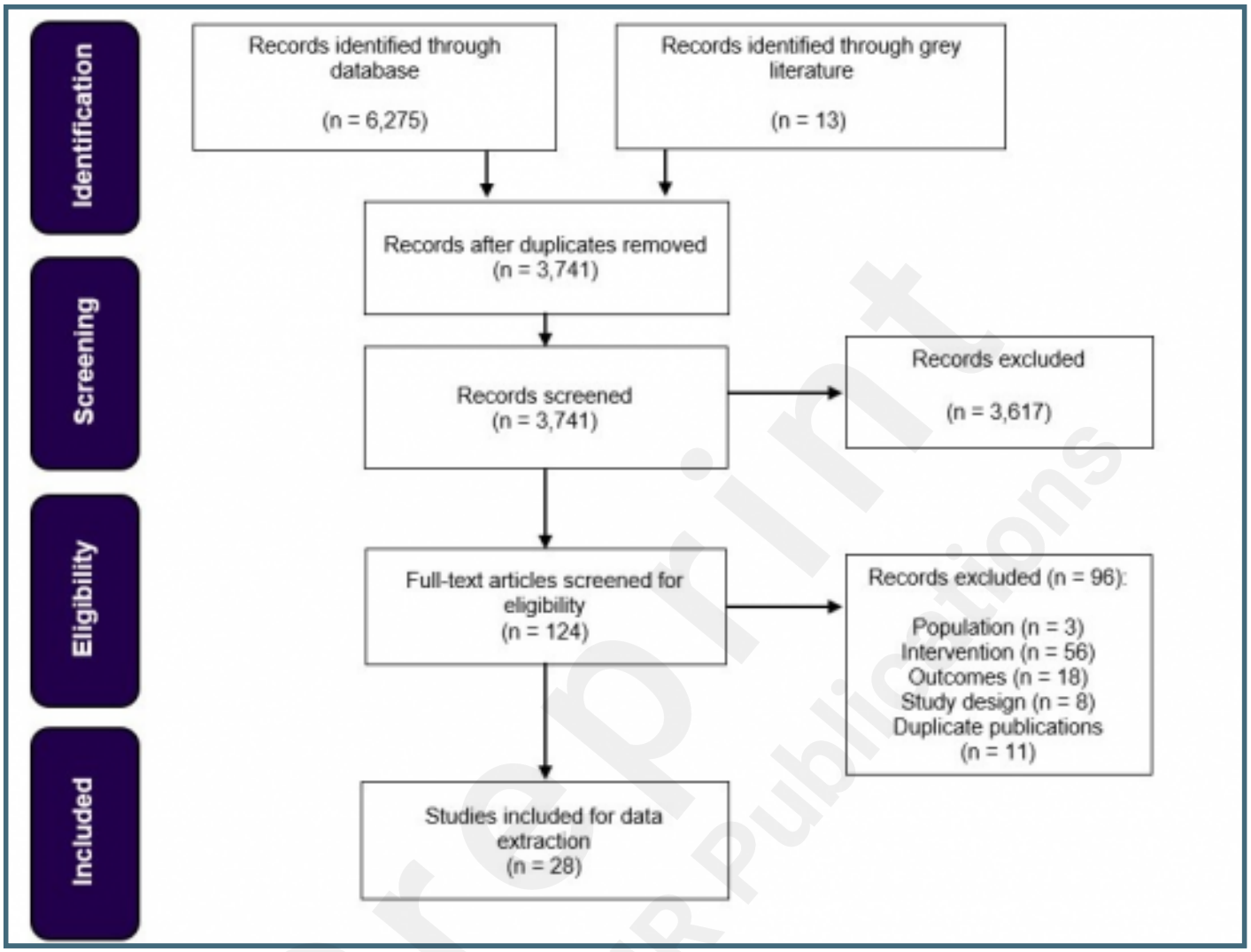
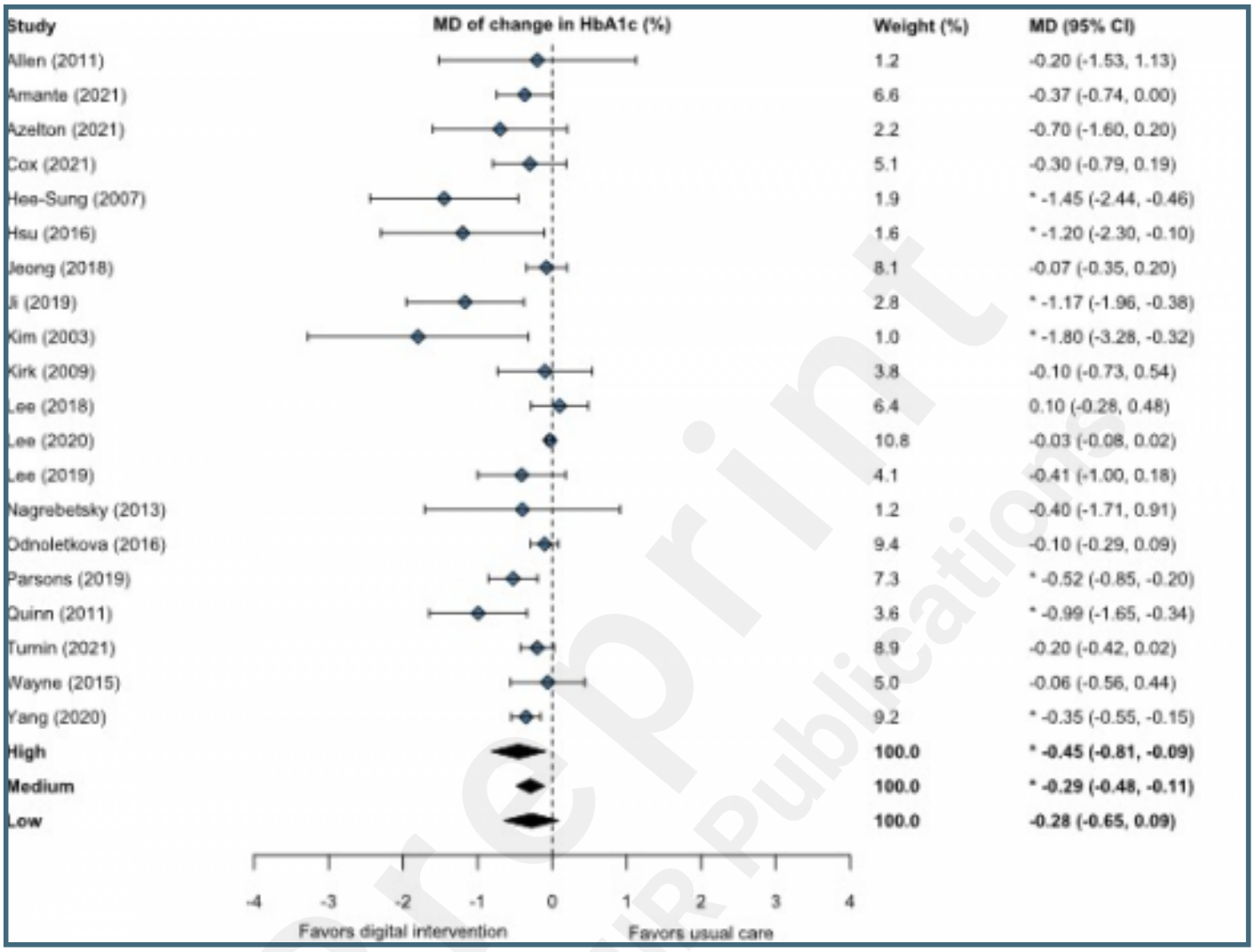
Supplementary Files

Figures

PRISMA diagram.



Forest plot of the mean difference (MD) and confidence interval (CI) of change in HbA1c with meta-regression on intervention intensity. Asterisks indicate statistical significance.



Multimedia Appendixes

PICO criteria used for study selection.
URL: http://asset.jmir.pub/assets/a662a4a7225cb8c746cebdabf73de630.docx

Search strategy for Embase via OvidSP.
URL: http://asset.jmir.pub/assets/fc1627537761e23ad397c24f32e15aeb.docx

Search strategy for MEDLINE® via OvidSP.
URL: http://asset.jmir.pub/assets/fc00d7f2a2fd8c10e11f3204c580f7d4.docx

Search strategy for CENTRAL via OvidSP.
URL: http://asset.jmir.pub/assets/22d46ec59a31cf177c57deae7e6e607b.docx

Distribution of the mean baseline HbA1c levels across included studies reporting.
URL: http://asset.jmir.pub/assets/41a27652ad87e6285b34c6934eb1b52e.png

Categorization of the studies into the intervention categories.
URL: http://asset.jmir.pub/assets/807e2f4d4b814edbe73abf7421c675d4.docx

Risk of bias as percentage across RCTs (intention-to-treat).
URL: http://asset.jmir.pub/assets/0675f7255845444c9628c4895bc87ce7.png

Risk of bias in non-randomized studies.
URL: http://asset.jmir.pub/assets/a75a058bc18fe312c76de8d6ea3d6840.png

CONSORT (or other) checklists

PRISMA checklist.
URL: http://asset.jmir.pub/assets/3f4c19c568b4d560869946af44f10a52.pdf