Effects of Mobile Health Interventions on Patients with Diabetes:

A Systematic Review

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THESIS

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SUMMARY

A systematic review was carried out to critically appraise and consolidate evidence from multiple randomized controlled trials (RCTs) on the effectiveness of mHealth interventions on glycemic control (HbA1c) in diabetes self-management. Comprehensive searches conducted on four databases to identify relevant studies published between January 1996 and February 2016 yielded 2855 articles. 19 RCTs (2790 patients) that fulfilled inclusion criteria were included in the review. A systematic review with meta-analysis was performed on 18 studies using a random-effects model. Quality of the evidence was determined by the Cochrane Collaboration's tool for assessing ROB. Subgroup analyses were conducted and funnel plots used to examine publication bias.

The mean reduction in HbA1c in participants using an mHealth intervention involving clinical feedback compared with a control was 0.45% (95% CI -0.66, -0.24) with a moderate quality of evidence. Data were heterogeneous (I^2 = 66%). Subgroup analysis indicated that mHealth interventions are more effective for type 2 diabetes than for type 1 diabetes, and studies of type 2 diabetes with shorter follow-up yielded larger effect sizes compared to studies with six months or more of follow-up. Reductions in HbA1c were found to be more pronounced in interventions that used automatic versus manual data entry. Studies with weekly provider feedback were found to have the largest effect on HbA1c but feedback on as needed basis also saw a significant effect. There was insufficient evidence to determine whether mHealth

interventions based on behavioral change theories are more effective. Visual inspection of funnel plots suggested a publication bias.

These findings are consistent with clinically relevant improvements and demonstrate that mHealth interventions may be an effective strategy to help control HbA1c, particularly with respect to type 2 diabetics. While the functionality and use of this technology needs to be standardized, mHealth represents a promising approach to the self-management of diabetes.

I. INTRODUCTION

A. Statement of the Problem

Diabetes mellitus is a chronic medical condition that occurs when the pancreas does not produce insulin or when the body cannot use the insulin it produces resulting in blood glucose levels that are higher than normal (hyperglycemia).[1] Insulin is a hormone produced by the pancreas that helps glucose in the bloodstream enter body cells where it is transformed into energy. [2] Hyperglycemia is a common feature of poorly controlled diabetes and over time leads to significant damage to many of the body's organs, especially the nerves and small blood vessels.[3] This forms the basis of the complications of diabetes including an increased risk of stroke and heart disease, neuropathy (nerve damage), foot ulcers, increased risk of lower extremity amputation, blindness, and kidney failure.[2, 3]

People with type 1 diabetes mellitus, previously known as insulin dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, produce little to no insulin and require insulin injections to control the level of glucose in their blood. [2, 4] Type 1 diabetes mellitus is most frequently diagnosed in children and young adults and accounts for 5% of all diagnosed cases of diabetes.[1, 4] Type 2 diabetes mellitus, once known as non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes, accounts for 90% of all cases of diabetes and is characterized by the body's ineffective use of insulin. [2, 3] This form of the disease, which is largely the result of excess body weight and inactivity, can be diagnosed at any age.[3] Initial management of the condition involves diet and exercise but over time most people will require oral drugs and/or insulin.[2]

According to the World Health Organization (WHO), the number of people with diabetes has quadrupled from 108 million in 1980 to 422 million in 2014; that number is projected to increase to 642 million by 2040.[2, 3] The prevalence in both type 1 and type 2 diabetes has been rising rapidly in middle- to low-income countries and highlights the effects of rapid urbanization, sedentary lifestyles, and increasing obesity.[3, 5] In the U.S., there are more than 29 million people with diabetes with another 89 million living with pre-diabetes, a serious condition that increases a person's risk of developing type 2 diabetes.[1]

The International Diabetes Federation (IDF) estimates that there were five million deaths worldwide due to diabetes in 2015 and WHO projects that diabetes will be the 7th leading cause of death worldwide in 2030.[2, 3] Diabetes is currently the 7th leading cause of death in the U.S.[6] Globally, the direct annual cost of diabetes has reached $825 billion, with China ($170 billion), the U.S. ($105 billion), India ($73 billion), and Japan ($37 billion) having the highest costs.[7, 8] Costs related to diabetes increase over time and with disease severity, indicating that efforts directed towards prevention and effective disease management may be particularly worthwhile.[8]

Primary care physicians are often the main providers of diabetes care, particularly in resource-limited countries, since they are the main source of general medical care.[9] Approximately 90% of the diabetic patients in the U.S. are treated by primary care physicians.[10] Patients treated by endocrinologists are either newly diagnosed type 1 diabetics or type 2 diabetics who are having difficulty controlling their blood glucose or experiencing complications.[11]

Improved blood glucose control as part of a self-management strategy for type 1 and type 2 diabetics has been shown to reduce diabetes-related complications and death.[5] Successful diabetes self-management can be a challenge since patients may have difficulty initiating and sustaining behavioral changes that involve adopting new approaches to diet, physical activity, and medication compliance.[12, 13] Helping patients reconcile these issues can be time-consuming and labor-intensive for healthcare providers; however, mobile health holds the promise of innovative solutions that can improve the management of diabetes. [13, 14]

B. Potential Role of mHealth in the Self-Management of Diabetes

Mobile health, or mHealth, has been defined as the use of mobile computing and communication technologies for health services and information.[15, 16] Mobile technologies include cellphones/smartphones, personal digital assistants (PDAs), handheld tablets, and other wireless devices.[17, 18] These technologies offer new ways to approach remote patient monitoring and delivery of clinical advice, namely through the use of text messages (SMS), mobile phone applications ("apps"), and multiple media (MMS) interventions.[17, 18] It is unlikely that traditional models of diabetes care, such as those consisting of face-to-face clinic appointments and 'diabetes logbooks', can be sustained given the rising prevalence of diabetes and increasingly limited health resources.[19] However, the estimated 5 billion mobile phones worldwide make a powerful platform that can be leveraged to improve diabetes care and reduce costs.[19, 20]

The popularity of mobile phones and advances in consumer mobile technology make mHealth attractive for chronic disease management, particularly for the self-monitoring of

blood glucose (SMBG) in diabetes.[20, 21] Regular SMBG is associated with improved metabolic control and a decrease in glycolated Hb (HbA1c).[21, 22, 23] mHealth can facilitate SMBG by downloading, aggregating, and identifying blood glucose data patterns for the patient's healthcare provider (HCP), who can provide timely clinical feedback based on the transmitted data and intervene in the event of worsening blood glucose control, averting further deterioration in the patient's condition. People carry their mobile phones with them wherever they go which allows for temporal synchronization of the transmission of data with the delivery of clinical feedback such that feedback can be delivered within the relevant context where it can have maximum impact.[17] For example, those with type 1 diabetes can receive timely advice regarding insulin adjustment during an episode of hyperglycemia.

mHealth offers potential economies of scale since it is relatively easy to deliver low-cost interventions to a large population.[17] For example, a diabetes app can be quickly downloaded for free or text messages can be delivered to large numbers of people at low cost.[17] Mobile technology is especially promising for developing countries who can take advantage of the robust mobile market to provide adequate healthcare to underprivileged communities.[24] There is a strong global interest in developing mHealth interventions as evidenced by the 2009 WHO survey that reported 83% of the 112 participating member countries had at least one mHealth intervention in place.[16]

The growing interest in the potential impact of mobile technology-based interventions to improve the management of diabetes has led to an increasing number of published studies investigating their effectiveness. Healthcare policy makers, providers, patients, and researchers interested in the use of mHealth interventions for diabetes management are confronted with

unmanageable amounts of data from numerous clinical trials and observational studies; they need systematic reviews to efficiently integrate existing information and provide data for rational decision making.[25] A current, comprehensive systematic review of mHealth interventions that adheres to available methodological guidelines is lacking and can provide a valuable overview of the existing evidence.[17] Such a review can be used to support evidence-based health policy and ensure that the mHealth interventions used for diabetic patients are based upon the best available empirical data.

C. Objectives of this Review

This systematic review aims to assess the effects of mHealth interventions on HbA1c in diabetes self-management. Secondary objectives include the assessment of medication adherence, compliance with the intervention, patient satisfaction with the intervention, quality of life, and the cost effectiveness of the intervention.

II. REVIEW OF THE LITERATURE

A. Methodological Quality of Prior Systematic Reviews

Systematic reviews (SRs) are an extremely efficient method of summarizing the findings from a body of evidence with minimal bias, providing reliable findings that can inform evidence-based decision making.[18,26] However, available SRs vary in quality and can yield flawed findings as a result of methodological issues and risk of bias, compromising their utility for decision making.[18] A recent overview of SRs[18] identified five SRs [27-31] with an explicit focus on the effectiveness of mHealth interventions for glycemic control in diabetes and all were found to have important methodological limitations according to AMSTAR criteria. None were found to be of high quality (a score of 8 or more on the 11-point AMSTAR scale); two of the five SRs were of moderate quality, scoring between 4 and 7 points.[30, 31] The remaining three SRs were of low quality, scoring less than 4 points.[27-29] As shown in Table I, all of the SRs performed poorly in several domains. None of the five SRs provided evidence of a published *a priori* protocol or provided a list of excluded studies with reasons for exclusion of each study (Q1, Q5). Three of the five reviews did not provide details regarding the number of reviewers involved in data extraction, the selection of studies, or the procedure for resolving disagreements, which raises concerns about the potential subjectivity of decisions at these stages (Q2).[18, 32] The majority (80%) did not search the grey literature (e.g. dissertations or conference proceedings) and restricted their search to only English articles which increases the risk of publication and language bias (Q4). All five SRs failed to assess the sources of support or conflict of interest in their included studies (Q11).

TABLE I. METHODOLIGICAL QUALITY OF SYSTEMATC REVIEWS BASED ON AMSTAR CRITERIA

Study ID	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Baron 2012[27]	N	N	CA	N	N	Y	Y	Y	N	N	N	3
Herbert 2013[28]	N	CA	CA	CA	N	Y	N	N	N	N	N	1
Holtz 2012[29]	N	CA	Y	N	N	Y	N	N	N	N	N	2
Liang 2011[30]	N	Y	Y	N	N	Y	Y	Y	Y	Y	N	7
Saffari 2014[31]	N	Y	Y	N	N	Y	Y	N	Y	Y	N	6

Q1: A priori design; Q2: Duplicate study selection and data extraction; Q3: Search comprehensiveness; Q4: Inclusion of grey literature (e.g. non-English articles, and conference proceedings); Q5: Included and excluded studies provided; Q6: Characteristics of the included studies provided; Q7: Scientific quality of the primary studies assessed and documented; Q8: Scientific quality of included studies used appropriately in formulating conclusions; Q9: Appropriateness of methods used to combine studies' findings; Q10: Likelihood of publication bias was assessed; Q11: Conflict of interest-potential sources of support were clearly acknowledged in both the systematic review and the included studies. “Y” (Yes): Criterion met; “N” (No): Criterion not met; CA: Cannot answer; One point was awarded to each item that scored “yes” and summed these to calculate a total score for each review.

B. Health Behavior Theoretical Frameworks

Existing health behavior theories, such as the Health Belief and Self-Efficacy Models described below, have served as the basis for web and computer health interventions and have informed how they can be tailored to an individual’s baseline status.[33] However, mHealth interventions allow individuals to interact with technology over time, generating complex data that has the potential to deliver health behavior interventions not only at baseline but in the context of changing behaviors and environmental contexts.[33,34] While mHealth intervention development stands to benefit from a greater application of health behavior theories, these theories need to evolve to better guide the dynamic process of frequent iterative adjustments made during the course of these interventions.[33, 35] Current theories have been criticized as

being static and linear, rendering them incapable of guiding the dynamic, adaptive interactions that are possible with mobile interventions.[33, 36]

1. Health Belief Model

The Health Belief Model (HBM), one of the first theories of health behavior and one of the most widely applied, was developed in the 1950s to explain the adoption of health behaviors in the US.[37] This model theorizes that people's beliefs about whether they are at risk for a disease or health problem, and their perceptions of the benefits of taking action to avoid it, influence their readiness to take action.[38] The HBM has been applied most often to health concerns that are prevention-related or asymptomatic where beliefs are at least as important as overt symptoms.

The HBM posits that six key constructs impact health behaviors[37, 39]:

1. Perceived susceptibility: A person's opinion regarding their chances of developing a condition.

2. Perceived severity: A person's opinion regarding the seriousness of a specific condition and its consequences.

3. Perceived benefits: The person's belief that a particular course of action would reduce the susceptibility or severity or lead to other positive outcomes.

4. Perceived barriers: The impediments to adopting a health-related behavior.

5. Cues to action: These can be either internal or external, ranging from experiencing symptoms of an illness to exposure to a media campaign or education about a disease, that compel a person to act.

6. Self-efficacy: An individual's judgement of their capabilities to organize and execute courses of action despite considered barriers.

The HBM provides a means to better understand the attitudes, behaviors, and educational needs of populations, making it a practical tool to develop effective interventions.[40] MHealth can utilize this model to effect changes in patients' HBM constructs, leading to improved self-care behavior. Consider an mHealth intervention that acts as an external cue by providing educational information about diabetic foot care which increases the perceived susceptibility of patients to disease-related complications; this information can result in better foot care rendered by the patients themselves.[40]

2. <u>Self-Efficacy Model</u>

Self-efficacy is a person's belief that he or she is capable of performing a particular task successfully; it can be thought of as a kind of self-confidence.[41, 42] One's sense of self efficacy can play a major role in how one approaches goals, tasks, and challenges.[41] For example, we rarely attempt a task if we expect to be unsuccessful.[42]

The self-efficacy model has three dimensions[43] :

1. Magnitude: How difficult a person finds it to adopt a specific behavior.

2. Strength: How certain a person feels about performing a specific task.

3. Generality: The extent to which self-efficacy is generalized; it can be limited to either a specific behavioral situation or it can be generalized across many situations.

Consider a diabetic patient with a low sense of self-efficacy in diabetes management behavior who avoids difficult tasks such as monitoring BG levels which he views as a personal threat. In contrast, another diabetic patient with a high sense of self-efficacy approaches the task of BG monitoring as a challenge to be mastered rather than something to be avoided.[43] A well-designed mHealth intervention can increase a patient's self-efficacy by increasing his or her ability to successfully approach difficult self-care tasks. An app with useful interactive self-management strategies and feedback can result in a more engaged patient, improved BG control, and enhanced patient self-efficacy.[44]

C. Summary

The HBM and self-efficacy model are two health behavior theories that have the potential to inform mHealth development, but in their present form are inadequate since these interventions are becoming increasingly sophisticated.[33] The adoption of more dynamic models is needed, however this does not require discarding the current theories. These theories should evolve to better capture the intra-individual dynamics of mHealth interventions.[33]

III. METHODS

A. Eligibility Criteria for Including Studies in this Review

1. Types of studies

This review includes parallel, cluster, and cross-over randomized controlled trials (RCTs) only. Eligible for inclusion are studies reported as full-text and those published as abstract only.

2. Participants

Participants were patients diagnosed with either type 1 or type 2 diabetes mellitus, regardless of age, sex, ethnicity, or duration of disease.

3. Intervention

MHealth interventions included in this review involved the use of cellular phones, smartphones, personal digital assistants, tablets, and/or other mobile devices that enabled patient monitoring and the delivery of clinical feedback through a wide range of functions and applications (e.g. text messaging, internet, and email) with the aim of improving self-care practices, lifestyle modifications, and adherence to treatment plans.[45]

One-way communication interventions, such as those that involved "push-forward" text messages from the clinician to the patient for either educational or motivational purposes were excluded. Other excluded interventions were those that did not involve transmission of disease-related data via a mobile device from the patient to the clinician and

those that were exclusively focused on peer-to-peer support. Studies that used Skype, interactive voice systems, mixed interventions, home-based monitoring, use of modems or laptops, and provider-to-provider communications were also excluded.

4. Comparison

The comparison group included standard diabetes care as well as other types of non-mobile technology-based interventions.

B. Types of Outcomes Measures

1. Primary Outcome

The primary outcome assessed in this systematic review was the mean difference in hemoglobin A1c (HbA1c, %) between the control and intervention groups pre- and post-intervention.

2. Secondary Outcomes

Secondary outcomes include medication adherence, patient compliance with the intervention, patient satisfaction with the intervention, quality of life, and cost effectiveness of the intervention.

C. Search Methods for Identification of Studies

1. Electronic Searches

Comprehensive searches of MEDLINE, EMBASE, Cochrane Library, and CINAHL for articles published between January 1996 to February 2016 were performed using a

combination of MeSH terms, keywords, and clinical query filters to identify all relevant randomized controlled trials (RCTs). The search strategies used a comprehensive list of MeSH terms including "diabetes mellitus," telemedicine," "cell phones," "monitoring, physiologic," and "randomized controlled trial." Detailed search strategies for each database search can be found in Appendix A.

2. Searching other Sources

Relevant journals, conference proceedings, and abstracts were hand searched for additional references. Reference lists of identified trials were reviewed to identify any relevant studies that were not captured by the original search strategy. Authors of primary studies were contacted to identify additional relevant published or unpublished studies.[46]

D. Selection of Studies

The search strategies were conducted and all retrieved references were imported to a specialized systematic review management software, namely EPPI-Reviewer 4 (http://eppi.ioe.ac.uk/cms/, University of London, UK). Duplicate studies were automatically identified and merged using the EPPI software.

To assess studies for inclusion, a single review author (RK) independently screened the title and abstract of every record retrieved. The full text of all potentially relevant articles was independently assessed by two reviewers. Both reviewers evaluated the inclusion of each paper based on the reported inclusion criteria; reasons for exclusion were recorded. Any disagreements were resolved by discussion.[26]

E. Data Extraction

RK and SK developed and piloted an electronic data extraction form and spreadsheet. Data were extracted by one reviewer (RK) and verified for accuracy by the second reviewer (SK). Study designs were classified as parallel, cluster, or cross-over randomized controlled trials. Extracted data included the study population (Type 1 or Type 2 DM), study setting, sample size, study duration, age range, gender, race, description of the mHealth intervention, frequency of data transmission and feedback, mechanism of feedback delivery, unadjusted HbA1c data and standard deviations.[30] Studies that reported unadjusted HbA1c data were included in the meta-analysis.[30]

F. Risk of Bias Assessment

Two review authors (R.K. and S.K.) independently assessed risk of bias (ROB) in the included studies using the Cochrane Collaboration criteria outlined in Higgins and Green.[26] Disagreements were resolved through discussion.[46] The Cochrane ROB tool uses seven domains to address specific features of each study and recommends the explicit reporting of sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias.[26, 46, 47] Potential sources of bias in each of the seven domains were graded for each study as high, low, or unclear, following the guidelines of the Cochrane risk of bias assessment tool. [26, 46]

G. Quality of Evidence

The quality of evidence in the included studies was determined by the Cochrane Collaboration's tool for assessing risk of bias.[26] Results are reported in a standard Cochrane "Risk of bias graph" and "Risk of bias summary" table.[26]

H. Data Analysis and Synthesis

The changes in HbA1c at follow-up were compared between intervention and control groups using a mean difference (MD). Missing data was investigated by contacting the study authors. If there was no response, imputation of the missing SDs was performed using the Within Groups formula from the Cochrane Handbook[26] or the study was not included in the meta-analysis. A meta-analysis of the MDs was conducted using Review Manager (RevMan) software, version 5.3 (http://community.cochrane.org/tools/review-production-tools/revman-5/revman-5-download). The effect sizes of each study with 95% confidence intervals are represented graphically by RevMan forest plots.[26, 48] This review assumed a random-effects model based on the assumption that there is a degree of clinical heterogeneity between studies.[49] Statistical heterogeneity between studies was examined with the I^2 statistic.[26, 49]

IV. RESULTS

A. Description of the Included Studies

The literature search yielded 2855 citations after removal of duplicates (Figure 1). After completion of the screening process, 19 RCTs were identified as eligible for inclusion.[50-68] (Table II). All studies employed mobile phone-based interventions with exception of a single study[56] that used tablet computers. Most of the studies (n=13) were published in 2011 and after, with 5 published in 2014 alone. The duration of the interventions ranged from one to 12 months. The majority of RCTs (n=12) focused on type 2 diabetes and 5 RCTs targeted type 1 diabetes. The remaining RCTs (n=2) included studies of both type 1 and type 2 diabetes. The majority (63%) of studies were conducted in primary settings, 16% were conducted in diabetes clinics, and 11% were conducted in tertiary hospitals. Four of the five studies which focused on type 1 diabetes were undertaken in Europe[51-53, 64] and one in the USA.[57] Of the 12 studies which focused on type 2 diabetics, five were conducted in Europe[54, 58, 60, 61, 65] and five in the U.S.A.[55, 56, 62, 63, 67] Of the remaining two studies, one was conducted in Africa[66] and the other in Japan.[68]

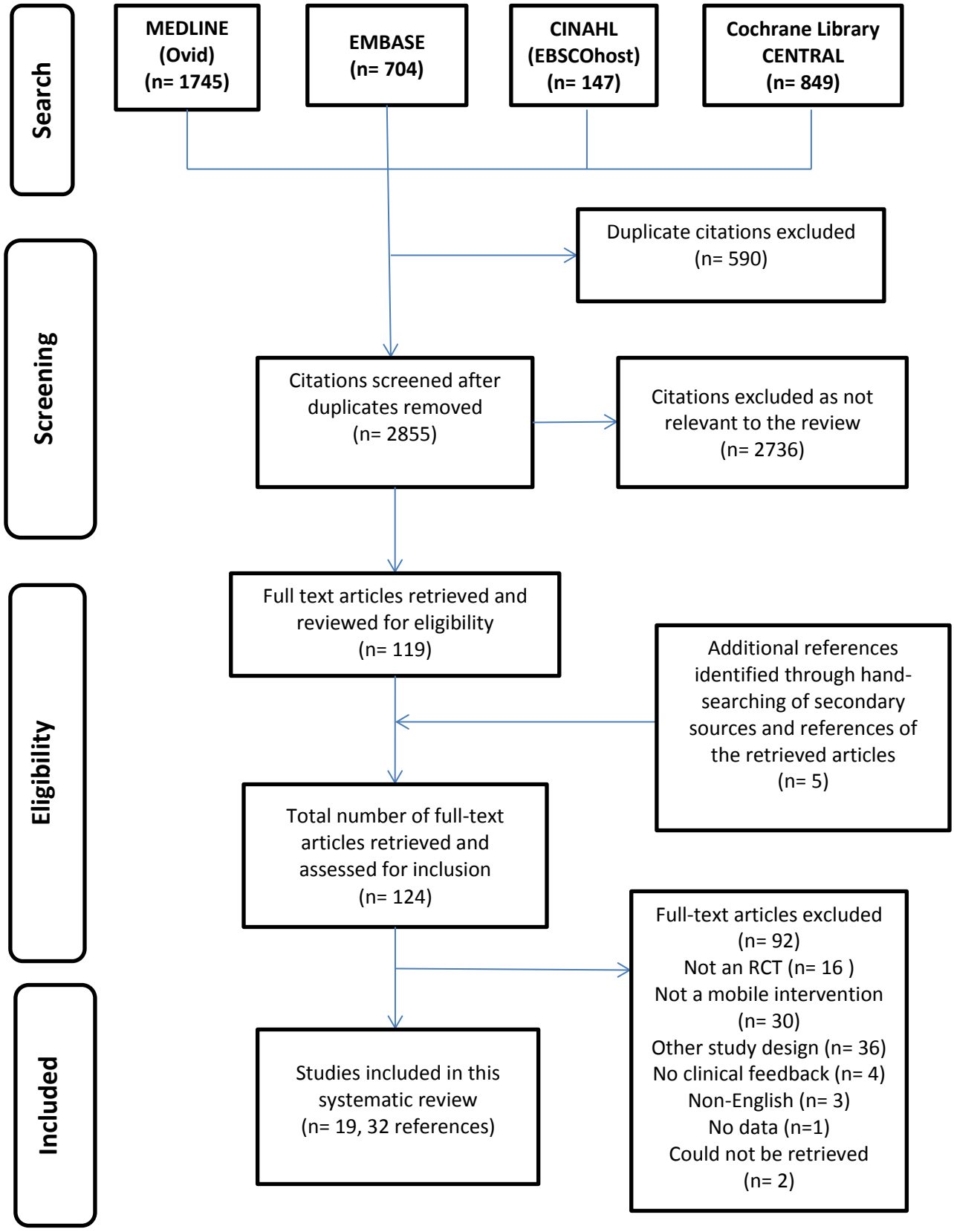


Figure 1. Screen and selection process

TABLE II. CHARACTERISTICS OF INCLUDED STUDIES

Study	Duration (months)	Sample (n)	Type	Study Design	Study Setting	Technology	Intervention
Baron *et al.* 2016 (50)	12	81	Type 1 and type 2 DM	RCT	Outpatient clinic (U.K.)	Mobile phone, Bluetooth, and Internet	Managing out-of-range blood glucose readings, patient education, medication adjustment
Berndt *et al.* 2014 (51)	1	68	Type 1 DM	RCT	Outpatient clinic (Germany)	Mobile phone or tablet, Internet	BG, optimization of medication
Bowes *et al.* 2009 (52)	6	13	Type 1 DM	RCT	Outpatient clinic (UK)	Mobile phone, Internet	BG, diet & medication adjustments
Charpentier *et al.* 2011 (53)	6	180	Type 1 DM	RCT	Outpatient clinic (France)	Mobile phone, Internet	BG, diet & medication adjustments
Dafoulas *et al.* 2015 (54)	12	823	Type 2 DM	RCT	Outpatient clinic (Italy, Greece, Germany)	Mobile phone	BG, medication & lifestyle adjustments
Garcia *et al.* 2014 (55)	3	71	Type 2 DM	RCT	Federally qualified health center (USA)	Mobile phone	BG, medication reminders, educational messages
Greenwood *et al.* 2015 (56)	6	90	Type 2 DM	RCT	Large health care system (USA)	Tablet computer, Internet	BG, medication adjustment, motivational interviewing
Hanauer *et al.* 2009 (57)	3	40	Type 1 DM	RCT	Joslin Diabetes Center (USA)	Mobile phone, Internet	BG
Holmen *et al.* 2014 (58)	12	151	Type 2 DM	RCT	Outpatient clinics (Europe)	Mobile phone, Internet	BG, diet, physical activity
Istepanian *et*	9	137	Type 2	RCT	Outpatient clinic	Mobile phone,	BG, treatment

al. 2009 (59)			DM		(UK)	Bluetooth, Internet	modifications
Nagrebetsky *et al.* 2013 (60)	6	14	Type 2 DM	RCT	Outpatient clinic (UK)	Mobile phone, internet	BG, medication adjustments
Orsama *et al.* 2013 (61)	10	56	Type 2 DM	RCT	Community Health Center (Finland)	Mobile phone, Internet	BG, educational & behavioral skills
Quinn *et al.* 2008 (62)	3	30	Type 2 DM	RCT	Community physician practices (USA)	Mobile phone, Bluetooth, Internet	BG, educational messages
Quinn 2011 *et al.* 2011 (63)	12	163	Type 2 DM	Cluster RCT	Community physician practices (USA)	Mobile phone, Internet	BG, medication adjustment, educational & motivational messages
Rami *et al.* 2006 (64)	6	36	Type 1 DM	Cross-over RCT	Outpatient clinic (Europe)	Mobile phone, Internet	BG, medication adjustment
Rodriguez-Idigoras *et al.* 2009 (65)	12	328	Type 2 DM	RCT	Community family practices (Spain)	Mobile phone, Internet	BG, therapeutic advice
Takenga *et al.* 2014 (66)	2	40	Type 2 DM	RCT	African health care system	Mobile phone, Internet	BG, medication & diet adjustment
Tang *et al.* 2013 (67)	12	415	Type 2 DM	RCT	Outpatient clinic (USA)	Mobile phone, Bluetooth, Internet	BG, medication & diet recommendations
Waki *et al.* 2014 (68)	3	54	Type 2 DM	RCT	Outpatient clinic (Japan)	Mobile phone, Internet	BG, medication adjustment, diet evaluation

Abbreviations: BG, blood glucose; DM, diabetes mellitus; RCT, randomized controlled trial

B. Population

There is a total of 2790 patients from the 19 RCTs included in this review. Five RCTs[51-53, 57, 64] involved 337 patients with type 1 diabetes and 12 RCTs[54-56, 58, 60-63, 65-68] involved 2235 patients with type 2 diabetes. Two studies[50, 59] involved both type 1 and type 2 diabetics (218 patients) but neither study specified the type of diabetes of the participants.

The mean age across all studies was 48.43 years. The mean age of the type 1 patients in the five RCTs was 24.02 years and the mean age of the type 2 diabetics in the 12 RCTs was 57.04 years. The mean age of patients in the two studies involving both type 1 and type 2 diabetics was 57.75 years.

C. Comparison Groups

17 of the 19 included studies compared an mHealth intervention to usual care. The remaining two studies[52, 57] which focused on type 1 diabetes used a different type of non-mHealth comparator group.

1. Usual Care

Participants randomized to usual care attended in-person clinic appointments for routine diabetes treatment. Holmen (58) reported that patients in this group received diabetes care per national guidelines. Three studies[53, 62, 64] reported that participants in the usual care groups recorded their BG values in paper logbooks which were brought to clinic appointments for review. Baron (50) was a mixed study that included both type 1 and type 2 diabetics; the participants in the usual care group had one to two semi-annual appointments with a diabetes

educator to promote self-management education and support. Greenwood (56) stated that the participants in usual care received diabetes educational booklets and formal diabetic education. Participants in usual care groups also received annual check-ups and preventive guideline-based laboratory tests and screenings.[61, 67]

2. Other Comparison Groups

Bowes (52) used patients randomized to BERTIE, a structured educational program for type 1 diabetics, as the comparison group to the mHealth intervention Diabetes Interactive Diary, a software program installed on a patient's mobile phone. BERTIE is a comprehensive educational program that consists of four six-hour group sessions that focus on carbohydrate counting and insulin dose adjustment. A second study[57] used email reminders as the comparison group to a cell phone text messaging intervention. Email reminders or cell phone text messages were sent from the Computerized Automated Reminder Diabetes System (CARDS) at preset times telling participants to check their blood glucose. Once a BG value was received, CARDS sent positive feedback to the user regardless of the result.

D. Types of mHealth Interventions Included in this Review

Nineteen diabetes apps were identified and examined in this review, with five domains of functionality (Table III).

TABLE III. CHARACTERISTICS OF THE MOBILE APPS USED IN THE INCLUDED STUDIES

Type 1 Diabetes

Study	**App**	**Self-monitoring tasks**	**Data entry method**	**CHO/insulin bolus calculator**	**Medication adjustment support**	**Graphical feedback**	**Automated feedback**	**Frequency of HCP feedback**	**Other functionalities**
Berndt *et al.* 2014 (51)	Mobil Diab	BG, nutrition, insulin dosages, activity	Data were manually entered	X	X	+	X	As needed	Risk monitoring
Bowes *et al.* 2009 (52)	Diabetes Interactive Diary	BG, carbohydrate and calorie counts	Data were manually entered	+	X	X	X	Not specified	N/A
Charpentier *et al.* 2011 (53)	Diabeo	BG, carbohydrate count, physical activity	Data were manually entered	+	+	X	+	weekly	Glycemic target setting
Hanauer *et al.* 2009 (57)	CARDS	BG	Data were manually entered	X	X	+	+	As needed	BG reminders
Rami *et al.* 2006 (64)	VIE-DIAB	BG, insulin dosages, carbohydrate intake, activity	Data were manually entered	X	X	+	+	weekly	N/A

Type 2 Diabetes

Study	App	Self-monitoring tasks	Data entry method	CHO/insulin bolus calculator	Medication adjustment support	Graphical feedback	Automated feedback	Frequency of HCP feedback	Other functionalities
Dafoulas *et al.* 2015 (54)	Not specified	BG	Not specified	X	X	X	X	As needed	N/A
Garcia *et al.* 2014 (55)	Dulce Digital	BG	Not specified	X	X	X	X	As needed	N/A
Greenwood *et al.* 2015 (56)	Care Innovations Guide	BG	BG data automatically transferred to app	X	X	+	+	weekly	Virtual health sessions
Holmen *et al.* 2014 (58)	Few Touch	BG	BG automatically transferred to app, food intake and physical activity entered manually	X	X	+	+	monthly	Personal goal setting system
Nagrebetsky *et al.* 2013 (60)	t+Diabetes	BG	BG data were automatically transferred to app	X	+	+	X	monthly	N/A
Orsama *et al.* 2013 (61)	Monica	BG, BP, weight, physical activity	All data were input manually	X	X	+	+	As needed	DSS linked to EHR
Rodriguez-Idigoras *et al.* 2009 (65)	DIABECOM	BG	Not specified	X	X	X	X	As needed	Alarm for abnormal BG readings

Study	App	Self-monitoring tasks	Data entry method	CHO/insulin bolus calculator	Medication adjustment support	Graphical feedback	Automated feedback	Frequency of HCP feedback	Other functionalities
Takenga *et al.* 2014 (66)	Mobil Diab	BG, BP, weight, body size, physical activity	BG data were automatically transferred to app, other data were manually entered	X	X	+	X	As needed	The app is embedded on the telemedical platform
Tang *et al.* 2013 (67)	Not specified	BG, dietary intake, physical activity, BP, insulin doses, weight	BG data were automatically transferred to app, other data were manually entered	X	X	X	X	As needed	BG data uploaded to PHR
Quinn *et al.* 2011 (63)	Diabetes Manager	BG, carbohydrate intake, medications	BG data were automatically transferred to app, other data manually entered	X	X	X	+	Weekly to two-three months	Adverse event reporting
Quinn *et al.* 2008 (62)	Diabetes Manager	BG, carbohydrate intake, medication dosages	BG data were automatically transferred to app, other data manually entered	X	+	X	+	As needed	Guided compliance tool
Waki *et al.* 2014 (68)	DialBetics	BG, BP, weight, pedometer counts	BG, BP, pedometer automatically transmitted to app, meals and exercise were input by voice/text messages and photos	X	X	+	+	As needed	Dr. Call alert for abnormal BG readings

Type 1 and 2 Diabetes

Study	App	Self-monitoring tasks	Data entry method	CHO/insulin bolus calculator	Medication adjustment support	Graphical feedback	Automated feedback	Frequency of HCP feedback	Other functionalities
Baron *et al.* 2016 (52)	MTH	BG, BP, weight, time since last meal, physical activity, insulin dose	BG automatically transferred to app, other data were manually entered	X	X	+	X	From 24 hours to as needed	N/A
Istepanian *et al.* 2009 (61)	Not specifed	BG	BG automatically transferred to app	X	X	X	X	As needed	BG reminders

Table adapted from Hou et al. 2016 (69)

1. Type 1 Diabetes Apps

Five apps were used by participants with type 1 diabetes. Two apps[52, 53] used by participants with type 1 diabetes aimed to help patients calculate the most appropriate insulin dose based on blood glucose levels. Three apps[52, 53, 64] helped patients track their carbohydrate intake, e.g., one app[52] featured a photographic database of foods in different portion sizes with corresponding carbohydrate counts. Three of the apps[51, 53, 64] allowed participants to track their physical activity. Special functionalities included an app[51] with risk monitoring that featured automated alarm messages in the event of abnormal BG readings and another[53] that offered patients specific plasma glucose targets. Data for all apps was manually entered. The frequency of healthcare provider feedback ranged from as needed to weekly.

2. Type 2 Diabetes Apps

Twelve apps were used by participants with type 2 diabetes. In eight of the apps, BG data was automatically transferred. Six apps featured personalized feedback on other self-monitoring data such as blood pressure, weight, carbohydrate intake, and physical activity, with these data being manually entered. One exception was the DialBetics app which automatically transferred blood pressure, weight, and pedometer counts in addition to blood glucose.[68] Two apps[65, 68] featured alarms for abnormal BG readings. Graphical feedback was provided by six apps[56, 58, 60, 61, 66, 68] to promote self-management through awareness of BG trends. The Care Innovations Guide app[56] provided virtual health sessions for patient education in the style of a PowerPoint slide or short video clip. The Few Touch Application intervention[58] offered food habit, physical activity, and personal goals registration systems in which the user entered

information manually. Eight apps provided feedback as long as blood glucose data was abnormal; the frequency of feedback in the other apps ranged from weekly to once every two to three months.

3. Type 1 and 2 Diabetes Apps

There were two apps used by participants with either type 1 or type 2 diabetes. One app provided personalized feedback on health data in addition to blood glucose,[50] the other app provided reminders when a blood glucose measurement was due.[59]

E. Risk of Bias Assessment of the Included Studies

The results of the risk of bias assessment are presented in a summary table and graph (Figure 2, Table IV).

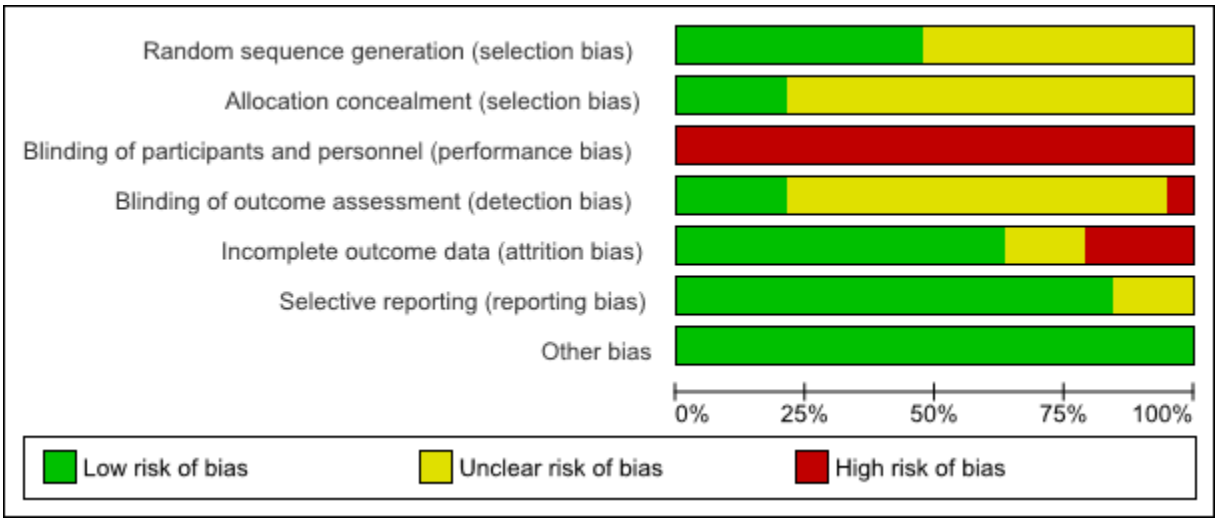
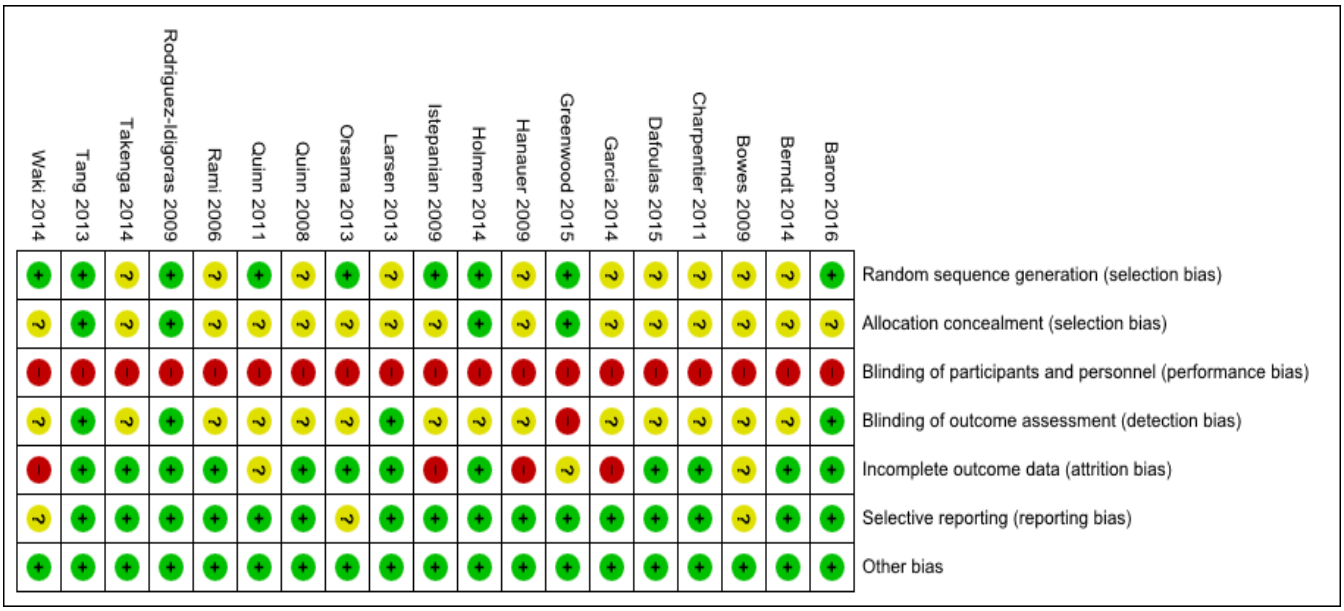


Figure 2. Risk of bias graph: Review authors' judgements about each risk of bias item presented as percentages across all included studies.

TABLE IV. RISK OF BIAS SUMMARY: REVIEW AUTHORS' JUDGEMENTS ABOUT EACH RISK OF BIAS ITEM FOR EACH INCLUDED STUDY



Nine studies[50, 56, 58, 59, 61, 63, 65, 67, 68] used adequate sequence generation methods (e.g., computer generated random numbers or a random numbers table), the other ten studies did not specify the method of randomization. Only four of the 19 studies demonstrated adequate allocation concealment.[56, 58, 65, 67] Three studies explicitly addressed the lack of blinding of participants and study personnel.[56, 58, 65] Though not stated, it was assumed that blinding did not take place in the other studies due to the nature of the intervention. Two studies explicitly addressed the blinding of outcome assessors.[65, 67] One study reported the use of the same outcome assessors in both study groups with potential for bias in the intervention effects.[56] Hanauer (57) stated that only 15% of the study participants remained at the conclusion of the study. In three studies all those who were randomized completed the study.[60, 64, 66] Study

protocols were available for only two studies to make fully informed inferences on selective reporting.[50, 58] There were no other potential sources of bias identified.

F. Analysis of Effect Size

The effect size of the analysis was calculated as the mean difference in the change of HbA1c from baseline to post-intervention, between the intervention and comparison group. Eighteen studies provided enough data about glycemic control to use HbA1c in a meta-analysis. Pooled results from these studies (1734 patients) showed a statistically significant reduction in HbA1c of -0.45% (95% CI -0.66, -0.24; P < 0.0001) (Figure 3). This was associated with substantial heterogeneity (I^2 = 66%) indicating variability in the intervention effect due to differences in both magnitude and direction of effect.

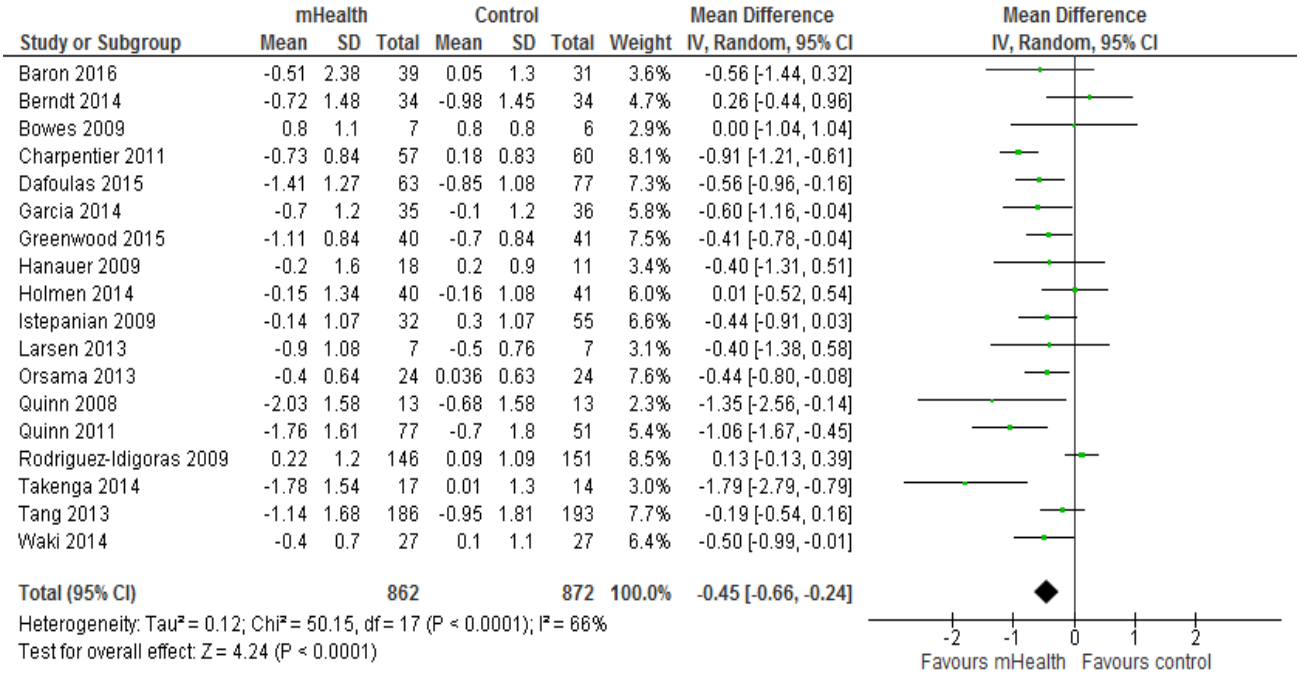


Figure 3. Impact of mHealth interventions on HbA1c for patients with type 1 or type 2 diabetes

Subgroup analysis demonstrated a statistically insignificant reduction in HbA1c of 0.33% in patients with type 1 diabetes (95% CI -0.96, 0.29; I^2 = 74%; studies = 4: participants = 227) and a statistically significant reduction in HbA1c of -0.46% in patients with type 2 diabetes (95% CI -0.71, -0.22; I^2 = 67%; studies = 12; participants = 1350) (Figures 4 and 5).

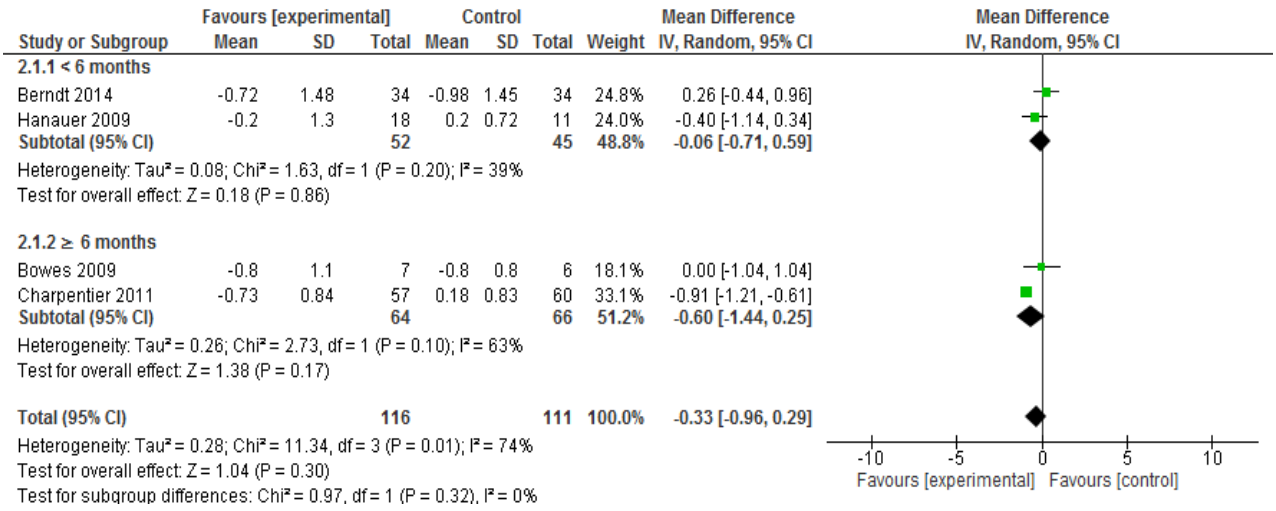


Figure 4. Impact of mHealth interventions on HbA1c for patients with type 1 diabetes (Subgroup analysis: Follow-up period <6 months vs. ≥ 6months)

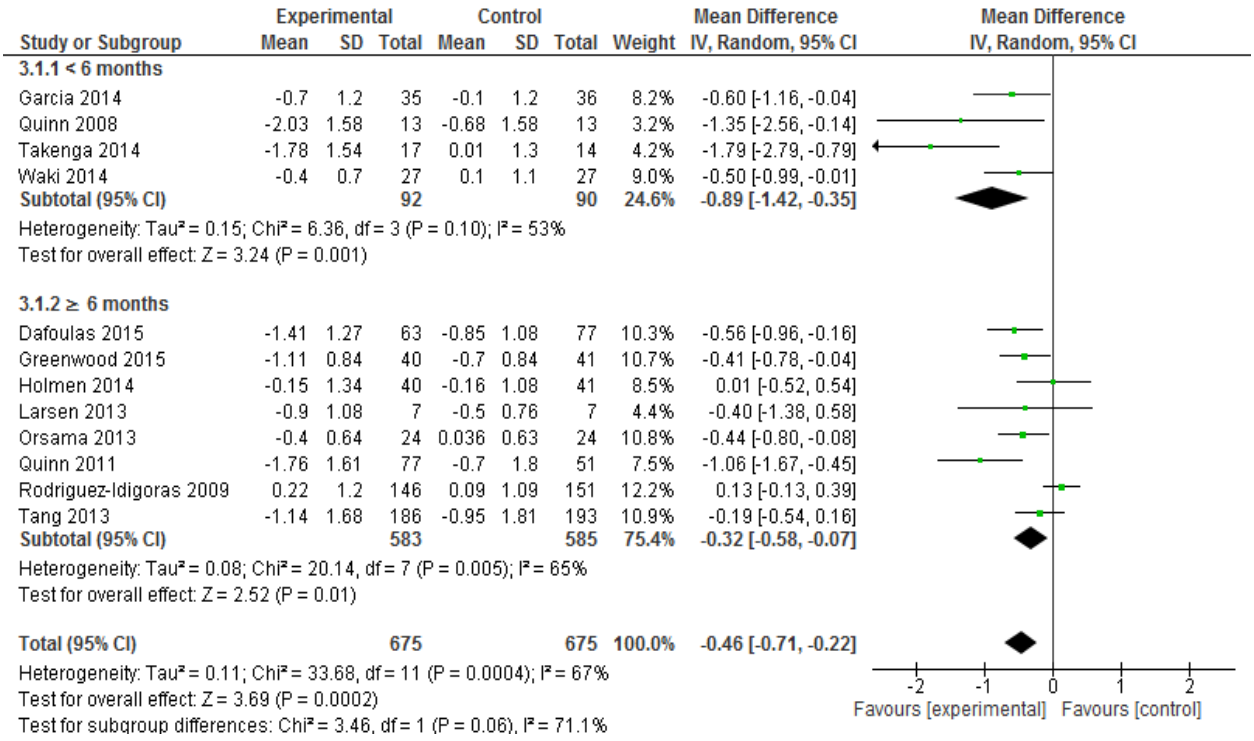


Figure 5. Impact of mHealth interventions on HbA1c for patients with type 2 diabetes (Subgroup analysis: Follow-up period <6 months vs. ≥ 6months)

Two studies involving both type 1 and type 2 diabetes patients showed a statistically significant reduction in HbA1c of 0.47% (CI -0.88, -0.05; P = 0.81; I^2 = 0%) (Figure 6).

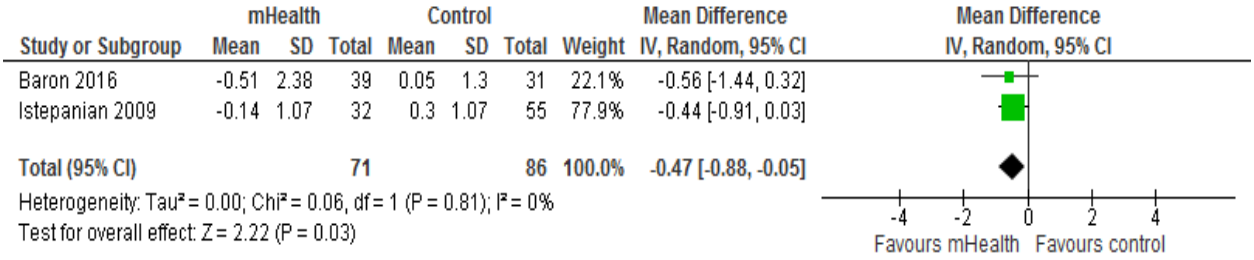


Figure 6. Impact of mHealth interventions on HbA1c in studies involving both type 1 and type 2 diabetes

Subgroup analysis by follow-up duration for type 1 diabetes showed that studies with a longer duration (≥ 6 months) displayed a larger but insignificant reduction in HbA1c than studies with a shorter duration (< 6 months) (-0.60%, 95% CI -1.44 to 0.25; -0.06%, 95% CI -0.71 to 0.59, respectively) (Figure 4, Table V). Studies of type 2 diabetes with a follow-up duration of less than six months reported a larger, statistically significant reduction in HbA1c compared to studies with a follow-up duration of six months or more (-0.89%, 95% CI -1.42 to -0.35; -0.32%, 95% CI -0.58 to -0.07, respectively) (Figure 5, Table IV).

TABLE V. HbA1c DATA COLLECTION FREQUENCY TABLE

Study ID	**T1, T2, or both**	**1 month**	**2 months**	**3 months**	**4 months**	**6 months**	**9 months**	**10 months**	**12 months**
Baron *et al.* 2016 (50)	both			X			X		
Berndt *et al.* 2014 (51)	T1	X							
Bowes *et al.* 2009 (52)	T1					X			
Charpentier *et al.* 2011(53)	T1					X			
Dafoulas *et al.* 2015 (54)	T2								X
Garcia *et al.* 2014 (55)	T2			X					
Greenwood *et al.* 2015 (56)	T2			X		X			
Hanauer *et al.* 2009 (57)	T1			X					
Holmen *et al.* 2014 (58)	T2				X				X
Istepanian *et al.* 2009 (59)	both						X		
Nagrebetsky et al. 2013 (60)	T2					X			
Orsama *et al* 2013 (61)	T2							X	
Quinn *et al.* 2008 (62)	T2			X					

Study ID	T1, T2, or both	1 month	2 months	3 months	4 months	6 months	9 months	10 months	12 months
Quinn *et al.* 2011 (63)	T2			X		X	X		X
Rami *et al.* 2006 (64)	T1			X	X				
Rodriguez-Idigoras *et al.* 2009 (65)	T2					X			X
Takenga *et al.* 2014 (66)	T2		X						
Tang *et al.* 2013 (67)	T2					X			X
Waki *et al.* 2014 (68)	T2			X					

Subgroup analysis by BG data entry method showed that the five interventions that used manual entry had a statistically insignificant reduction in HbA1c of -0.39% (95% CI -0.81, 0.03) and those interventions that supported automatic data entry had a statistically significant reduction in HbA1c of -0.52% (95% CI -0.79, -0.26) (Figure 7).

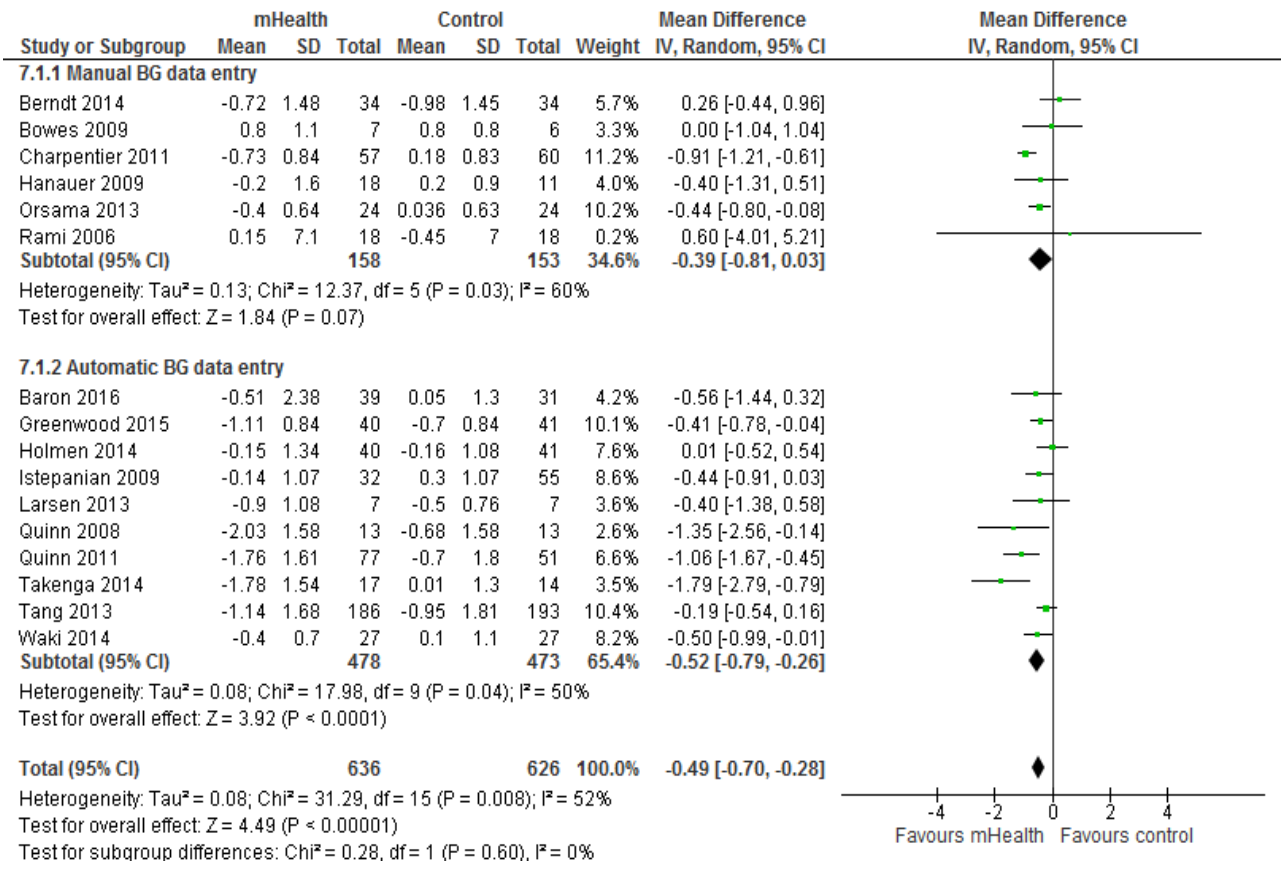


Figure 7. Impact of mHealth interventions on HbA1c (Subgroup analysis: Manual BG data entry vs. Automatic BG data entry)

Subgroup analysis of frequency of feedback showed that three studies with weekly feedback showed a statistically significant reduction of HbA1c of -0.76% (95% CI -1.15, -0.38) versus daily feedback (- 0.56%, 95% CI -1.44, 0.32) (Figure 8). Feedback on an as needed basis also showed a statistically significant reduction in HbA1c but not as great as weekly feedback (-0.41%, 95% CI -0.66, -0.15). Monthly feedback showed a statistically insignificant reduction in HbA1c of -0.08% (95% CI -0.55, 0.38).

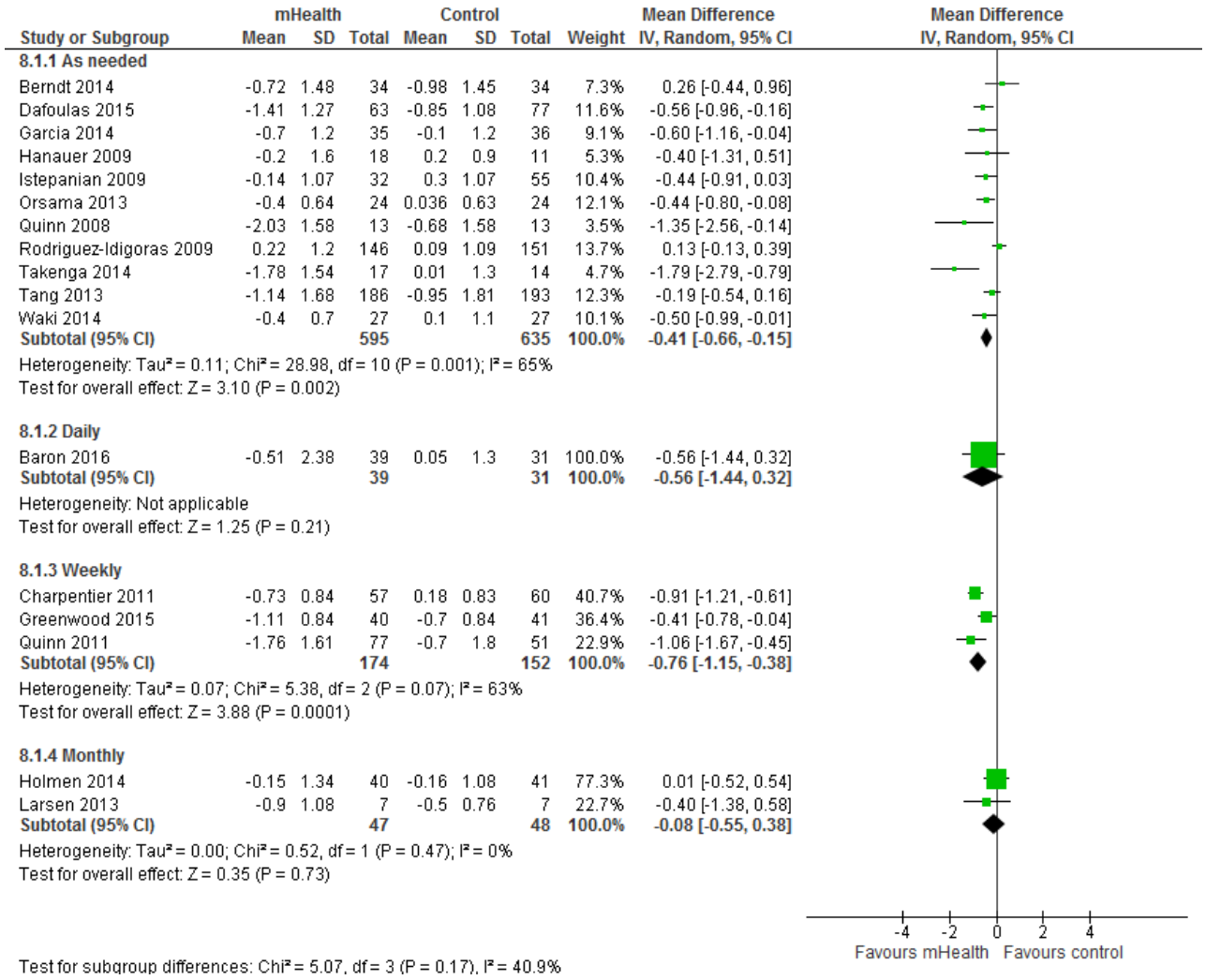


Figure 8. Impact of mHealth interventions on HbA1c (Subgroup analysis: Frequency of feedback)

Four studies reported incorporating a behavioral change theory into the design of the intervention (Table VI).

TABLE VI. STUDIES USING A BEHAVIORAL THEORY

Baron *et al.* 2016 (50)	Bandura's Social Cognitive Theory, Leventhal's model of illness beliefs, Davis's Technology Acceptance Model
Holmen *et al.* 2014 (58)	Motivational interviewing
Orsama *et al.* 2013 (61)	Information-Motivation-Behavioral Skills Model
Tang *et al.* 2013 (67)	Universal models of behavioral change

Subgroup analysis by use of a behavioral change theory showed a greater reduction in HbA1c in those studies that did not use a behavioral theory (-0.52%, 95% CI -0.78, -0.25) compared to those studies that did (-0.27%, 95% CI -0.49, -0.05) (Figure 9).

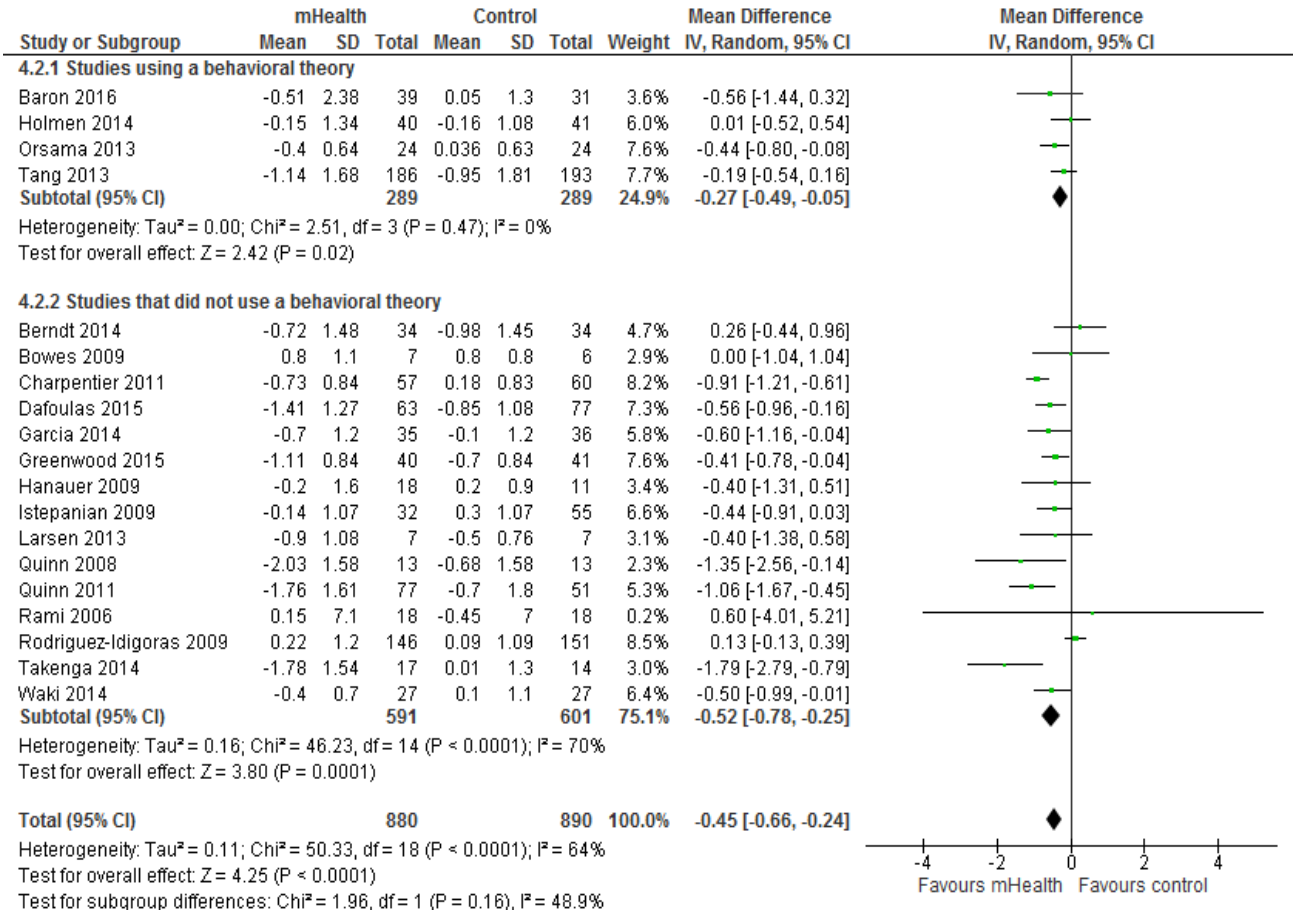


Figure 9. Impact of mHealth interventions on HbA1c (Subgroup analysis: Studies using a behavioral theory vs. studies that did not report using a behavioral theory)

The funnel plot analysis showed an asymmetrical distribution of studies suggesting publication bias (Figures 10 and 11). Publication bias could not be properly assessed with funnel plots for type 1 diabetes due to the small number of studies.

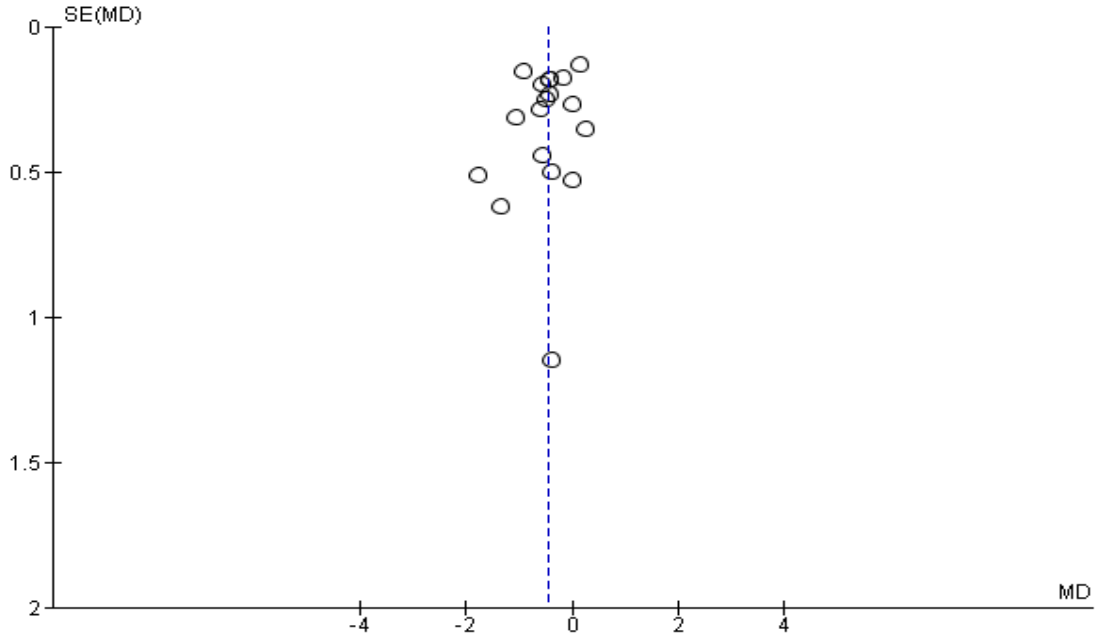


Figure 10. Funnel plot of mHealth studies involving patients with type 1 or type 2 diabetes

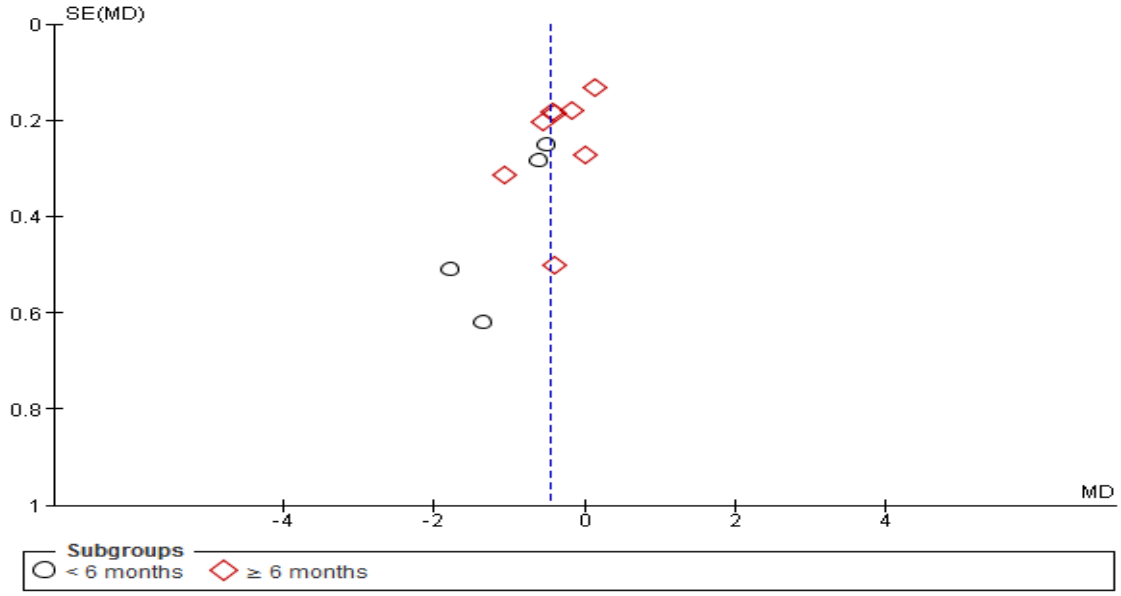


Figure 11. Funnel plot of mHealth studies involving patients with type 2 diabetes

G. Secondary Outcomes

Thirteen of the 19 studies reported at least one secondary outcome (Table VII). Patient satisfaction with the intervention was assessed in 62% of studies, of which 78% reported that patients were satisfied with this type of intervention. Quality of life was reported as an outcome in 26% of studies, with improvements reported in three studies. Patient compliance with the intervention was good in both studies that reported this as an outcome. A single study reported medication adherence as an outcome and also saw improvement. None of the studies examined the cost effectiveness of the interventions.

TABLE VII. OUTCOMES FREQUENCY TABLE

Study ID	**HbA1c**	**Medication adherence**	**Patient compliance with the intervention**	**Patient satisfaction with the intervention**	**Quality of life**	**Cost effectiveness of the intervention**
Baron *et al.* 2016 (50)	X				X	
Berndt *et al.* 2014 (51)	X				X	
Bowes *et al.* 2009 (52)	X	X				
Charpentier *et al.* 2011 (53)	X			X	X	
Dafoulas *et al.* 2015 (54)	X				X	
Garcia *et al.* 2014 (55)	X					
Greenwood *et al.* 2015 (56)	X					
Hanauer *et al.* 2009 (57)	X			X		
Holmen *et al.* 2014 (58)	X				X	

Study ID	HbA1c	Medication adherence	Patient compliance with the intervention	Patient satisfaction with the intervention	Quality of life	Cost effectiveness of the intervention
Istepanian *et al.* 2009 (59)	X					
Nagrebetsky *et al.* 2013 (60)	X					
Orsama *et al.* 2013 (61)	X			X		
Quinn *et al.* 2008 (62)	X		X	X		
Quinn *et al.* 2011 (63)	X			X†		X†
Rami *et al.* 2006 (64)	X			X		
Rodriguez-Idigoras *et al.* 2009 (65)	X					
Takenga *et al.* 2014 (66)	X			X		
Tang *et al.* 2013 (67)	X			X		
Waki *et al.* 2014 (68)	X		X	X		

(† outcome stated in protocol, not reported in study)

V. DISCUSSION

A. Summary of Main Results

This review demonstrates that mHealth interventions involving clinical feedback improve HbA1c compared to usual care or other non-mHealth approaches by an average of 0.45% (95% CI -0.66, -0.24), but it appears that they are more effective for patients with type 2 diabetes. The estimated 0.45% reduction is modest but evidence suggests that this difference is clinically relevant and large enough to reduce the risk of development and progression of diabetic microvascular complications.[70] The improvement in glycemic control found in this study is similar to the effect seen in previous reviews analyzing the effect of mHealth technologies on glycemic control in diabetes self-management.[30, 69]

Studies of type 2 diabetes with shorter follow-up yielded larger effect sizes compared to studies with six months or more of follow-up. These findings are consistent with those found elsewhere[30] and may indicate that the effect of the intervention decreases over time. It may be necessary to intensify provider contact and implement motivational strategies to maintain gains made in glycemic control.[71] Another consideration is the natural history of diabetes which can impact the effectiveness of mHealth interventions in certain patients. The sensitivity of receptors to medication may decline over time so despite compliance with the treatment regimen the effect of the intervention on glycemic control is reduced.[31]

This review found that reductions in HbA1c were more pronounced in interventions that used automatic data entry. One of the barriers to diabetes self-management is the burden of tracking and collating BG data.[73] mHealth interventions that automatically transfer BG data

from a glucometer to an app streamline the BG testing process and facilitate compliance with treatment. Additionally, patients with little technology experience find such interventions very easy to use.[62] Studies with weekly provider feedback were found to have the largest effect on HbA1c but feedback on as needed basis also saw a significant effect. These findings suggest that regular provider feedback may not be necessary for intervention success. The process of recording and tracking BG data could be the key factor that increases patients' awareness, understanding, and motivation to self-manage their condition.[50] Knowledge that the data are accessible to a provider may also be an incentive for patients to follow a treatment regimen. Interventions that provide graphical and automated feedback, e.g. Mobil Diab[51] and Monica[61], might also be effective incentives by engaging patients and helping them identify relationships between lifestyle and BG patterns.[50]

The findings of this review indicate that there is insufficient evidence to determine whether mHealth interventions based on behavioral change theories are more effective. Four RCTs in this review specified the use of a behavioral theory in the design of the intervention. It should be noted that even when interventions are said to be guided by theory, in practice often they are not or only minimally so.[74] However, two [58, 61] of the four studies did attempt to explain the impact of the theory-based intervention on clinical outcomes. mHealth interventions can benefit from a greater application of health behavior theories in their design.[33] Interventions are often designed without sufficient knowledge about the target behavior and without a theoretical framework.[74] Therefore, those designing mHealth interventions for diabetics must know how to support and motivate this population's readiness for behavioral change. Future

research must include patients as part of the team when developing appropriate interventions tailored to their needs.[58]

B. Overall Completeness and Applicability of the Evidence

The use of information and communication technologies to track and transmit BG values in adults with type 2 diabetes is increasing and has been found to be highly acceptable to patients in several studies.[75-78] Patient feedback indicated that acceptance was facilitated by ease of use, perceived usefulness, and practicality.[79] However, type 2 diabetes is more common in older adults and compared to younger adults, these patients report greater anxiety and less confidence in their technological abilities.[71] A previous study[54] found a lack of intervention effect with increasing age while others have suggested that compliance may be higher in older patients.[30, 58] These conflicting results should compel researchers to identify which sub-populations of type 2 diabetics would benefit most from mHealth interventions. The incorporation of patient education into type 2 mHealth interventions should be explored in future studies to assess the impact on patient understanding of their illness and ability to perform self-care.[58, 61] Future trials should also explore the use of social media for patient support and as a low-cost approach to maintain behavior change. [56]

Diabetologists consider adolescents a difficult-to-treat age group.[64] The Diabetes Control and Complications Trial (DCCT) showed that adolescents had the worst glycemic control of all age groups and it remains unacceptably high despite close monitoring and patient education programs. [53, 64, 80, 81] It is critical to establish a regular BG monitoring regimen for

patients in this age group since it has been shown that poorly controlled type 1 diabetics carry such behaviors into adulthood, placing them at greater risk for complications.[57, 82] The reasons for poor BG control include coping with the constraints of the disease, competing social and developmental needs, hormonal fluctuations, resistance to parental and healthcare provider involvement, and difficulty determining the correct dose of insulin.[18, 53, 57, 64] As a result, mHealth interventions that simply perform BG monitoring functions may have a limited impact on glycemic control. Young patients with type 1 diabetes likely require more sophisticated interventions that offer features such as decision-support aids that have the capacity to effectively contextualize a BG result and then take appropriate action to optimize glycemic control.[75] Other strategies to improve patient engagement, such as gamification and social media, should be systematically explored in future studies.[18] All of the type 1 diabetes interventions in this review employed manual data transmission; future interventions should include automatic data transmission to facilitate data transfer and improve patient compliance.[64]

C. Overall Quality of the Evidence

Quality of evidence refers to the extent which one can be confident that the estimate of effect approaches the true value for an outcome and depends upon the validity of the included studies.[26] An assessment of validity of the included studies should emphasize the ROB in their results and indicate the extent to which they overestimate or underestimate the true intervention effect.[26] Using the Cochrane Collaboration criteria for ROB as outlined in Higgins and Green[26], it was determined that the body of evidence supporting the use of mHealth

interventions in diabetes was of moderate quality for the outcome of HbA1c, mainly due to deficits in sequence generation and allocation concealment. Half of the included studies did not describe a method for sequence generation and only four studies reported allocation concealment. Blinding of participants and study personnel was not feasible in any of the studies due to the nature of the intervention, but this is expected to have a minimal impact on the effect size given the objective methods used to determine changes in HbA1c. Visual inspection of the funnel plots (Figures X and XI) reveals a gap in the lower right-hand section of both graphs. This suggests publication bias towards larger studies with positive and statistically significant results.[49, 72, 73]

D. Limitations of this Review

This systematic review has several limitations. Non-English papers were not reviewed which may introduce language bias. There is no clear definition of what constitutes a diabetes app, and study authors defined their interventions in different, unique ways.[69] There was an attempt to identify unpublished studies but no unpublished RCTs satisfied the inclusion criteria, thus this review contains published data only. There is no gold standard of calculating missing standard deviations, so there may be random errors in the imputations.[30] Finally, small study sizes and the heterogeneity of findings make it difficult to determine the true effect size of the intervention.[31]

E. Implications for Future Research

Future randomized controlled trials should consider adequately powered sample sizes of patients with longer durations of follow-up (> 12 months) to improve the generalizability of

findings. [18, 31] These studies should include features such as adequate sequence generation and allocation concealment to reduce the impact of bias on internal validity.[69] Future research should identify those patient characteristics that predict intervention success; these findings can then be used to infer which populations would benefit most from mHealth interventions.[27, 29] Especially for the younger type 1 diabetes patients, future studies should examine the role of caregivers in the context of mHealth interventions as it is likely that the majority of the patient's healthcare is still monitored by a patient or other primary caregiver.[28] Future research should also explore the impact of behavioral change theories and gamification elements on BG control and the compliance of patients using diabetes apps.[69]

Importantly, future studies should examine healthcare providers' acceptance and intention to incorporate mHealth interventions into their practices.[18, 29] Future research should clarify the actual long-term and overall impact of these interventions on providers' workloads, since that will influence the extent to which this technology is accepted and used in healthcare.[18] Future studies also need to examine the impact of mHealth interventions on the utilization of healthcare services.[18] Healthcare organizations are under intense pressure to reduce costs and as a result are shifting care from hospitals to ambulatory care centers and home settings which are lower cost, more accessible alternatives.[74] mHealth represents a promising approach to care in these settings but requires further study to evaluate whether its widespread adoption is warranted. None of the included studies in this review provided information about the cost of the interventions nor did they include evaluations of cost effectiveness. Without this information, it is impossible to confirm whether implementing mHealth interventions are economically viable.[18, 27]

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APPENDICES

APPENDIX A

MEDLINE Ovid Search Strategy December 2015

1. exp Diabetes Mellitus/
2. diabet*.tw.
3. (IDDM or NIDDM or T1DM or T2DM or T1D or T2D). tw.
4. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*).tw.
5. (insulin* depend* or insulin?depend*).tw
6. ((typ* 1 or typ* 2) adj6 diabet*). tw.
7. ((typ* I or typ* II) adj6 diabet*).tw.
8. or/ 1-7
9. exp Cellular Phone
10. ((car or cell* or smart or mobile) adj6 phone*).tw
11. (carphone* or cellphone* or cell-phone* or smartphone* or smart-phone* or smart phone* or mobilephone* or mobile phone*).tw.
12. (iphone* or i-phone* or ipod* or i-pod* or podcast* or pod-cast or ipad* or i-pad* or android* or blackberr* or palm pilot* or palm-pilot* or nokia or HTC).tw.
13. (google adj3 phone*).tw.
14. (nexus adj3 phone*).tw.
15. Text Messaging/
16. ((mms or sms) and (text* or messag*)).tw.
17. (text messag* or texting).tw.
18. (multimedia messag* service* or short messag* service*).tw.
19. Computers, Handheld/
20. (pda* or personal digital assistant*).tw.
21. tablet adj6 (comput*or pc or device*). tw.
22. (palm* adj3 computer*).tw.
23. ((wireless or handheld or hand-held) adj6 (device* or technolog*)). tw.
24. Telemedicine/
25. Remote Consultation/
26. (telemed* or telehealth* or tele-health* or telemonitor* or tele-monitor* or telecare or tele-care or mhealth or m-health or ehealth or e-health).tw.
27. (mobile health).tw.
28. (remote$ adj3 (consult$ or monitor$)).tw.
29. Electronic Mail/
30. (electronic mail or e-mail* or email*).tw.
31. Internet/
32. (web* or website* or internet).tw.
33. (social adj3 (media or network*)).tw.
34. or/ 9-33

35. randomized controlled trial.pt.
36. controlled clinical trial.pt.
37. randomized.ab.
38. placebo.ab.
39. drug therapy.fs.
40. randomly.ab.
41. trial.ab.
42. groups.ab.
43. or/35-42
44. exp animals/ not humans.sh.
45. 43 not 44
46. 8 and 34 and 45

EMBASE search February 2016

1. 'diabetes mellitus'/exp
2. diabet*:ab,ti
3. iddm:ab,ti OR niddm:ab,ti OR t1dm:ab,ti OR t2dm:ab,ti OR t1d:ab,ti OR t2d:ab,ti
4. 'non insulin* depend*':ab,ti OR 'noninsulin* depend*':ab,ti OR 'non-insulin* depend*':ab,ti
5. 'insulin* depend*':ab,ti
6. ((typ*1 OR typ*2) NEXT/3 diabet*):ab,ti
7. ((typ*i OR typ*ii) NEXT/3 diabet*):ab,ti
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. 'mobile phone'/de
10. ((car OR cell* OR smart OR mobile) NEXT/3 phone*):ab,ti
11. iphone*:ab,ti OR ipod*:ab,ti OR ipad*:ab,ti OR android*:ab,ti OR blackberr*:ab,ti OR 'palm-pilot*':ab,ti OR 'palm pilot*':ab,ti OR 'palm-top*':ab,ti OR 'palm top*':ab,ti OR nokia:ab,ti OR htc:ab,ti
12. (google NEXT/3 phone*):ab,ti
13. (nexus NEXT/3 phone*):ab,ti
14. 'text messaging'/de
15. mms:ab,ti OR sms:ab,ti
16. 'text messag*':ab,ti OR texting:ab,ti
17. 'multimedia messag* service*':ab,ti OR 'short messag* service*':ab,ti
18. 'wireless communication'/de
19. 'microcomputer'/de
20. pda:ab,ti OR 'personal digital assistant*':ab,ti
21. (tablet NEXT/3 (comput* OR pc OR device*)):ab,ti
22. (palm* NEXT/3 computer*):ab,ti
23. ((wireless OR handheld OR 'hand held') NEXT/3 device*):ab,ti
24. 'telemedicine'/de

25. 'teleconsultation'/de
26. 'telemonitoring'/de
27. 'telehealth'/exp
28. telemed*:ab,ti OR telehealth*:ab,ti OR telemonitor*:ab,ti OR telecare:ab,ti OR mhealth:ab,ti OR 'm-health':ab,ti
29. 'mobile health':ab,ti
30. (remote NEXT/3 (consult* OR monitor*)):ab,ti
31. #9 OR #10 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
32. random*:ab,ti
33. factorial*:ab,ti
34. crossover*:ab,ti
35. 'cross over*':ab,ti or 'cross-over':ab,ti
36. placebo:ab,ti
37. (doubl* NEXT/3 blind*):ab,ti
38. (singl* NEXT/3 blind*):ab,ti
39. assign*:ab,ti
40. allocat*:ab,ti
41. volunteer*:ab,ti
42. 'crossover procedure'/exp
43. 'double blind procedure'/exp
44. 'randomized controlled trial'/exp
45. 'single blind procedure'/exp
46. #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45
47. #8 AND #31 AND 46 AND [embase]/lim

CINAHL (EBSCO*host*) Search Strategy December 2015

1. (MH "Diabetes Mellitus, Type 1") OR (MH "Diabetes Mellitus, Type 2")
2. TX diabet*
3. TX (IDDM or NIDDM or T1DM or T2DM or T1D or T2D)
4. TX (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*)
5. TX (insulin* depend* or insulin?depend*)
6. TX ((typ* 1 or typ* 2) N6 diabet*)
7. TX ((typ* I or typ* II) N6 diabet*)
8. or/ 1-7
9. (MH "Cellular Phone +")
10. (MH "Smartphone +")
11. TX ((car or cell* or smart or mobile) N6 phone*)
12. TX (carphone* or cellphone* or cell-phone* or smartphone* or smart-phone* or smart phone* or mobilephone* or mobile phone*)
13. TX (iphone* or i-phone* or ipod* or i-pod* or podcast* or pod-cast or ipad* or i-pad* or android* or blackberr* or palm pilot* or palm-pilot* or nokia or HTC)
14. TX (google N3 phone*)

15. TX (nexus phone*)
16. (MH “Instant Messaging”)
17. TX ((mms or sms) and (text* or messag*))
18. TX (text messag* or texting)
19. TX (multimedia messag* service* or short messag* service*)
20. TX (electronic mail or e-mail* or email*)
21. (MH “Computers, Portable +”)
22. TX (pda* or personal digital assistant*)
23. TX tablet N6 (comput*or pc or device*)
24. TX (palm* N3 computer*)
25. TX ((wireless or handheld or hand-held) N6 (device* or technolog*))
26. (MH “Telehealth +”)
27. TX (telemed* or telehealth* or tele-health* or telemonitor* or tele-monitor* or telecare or tele-care or mhealth or m-health or ehealth or e-health)
28. TX (mobile health)
29. TX (remote N3 (consult* or monitor*))
30. (MH “Internet”)
31. TX (web* or website* or internet)
32. TX (social N3 (media or network*))
33. Or/ 9-32
34. (MH "Clinical Trials+")
35. PT Clinical trial
36. TX clinic* n1 trial*
37. TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
38. TX randomi* control* trial*
39. (MH "Random Assignment")
40. TX random* allocat*
41. TX placebo*
42. (MH "Placebos")
43. (MH "Quantitative Studies")
44. TX allocat* random*
45. Or/34-44
46. 8 and 33 and 45
47. limit 46 to human

The Cochrane Library Search Strategy December 2015

1. MeSH descriptor: [Diabetes Mellitus, Type 1] this term only

2. MeSH descriptor: [Diabetes Mellitus, Type 2] this term only

3. diabet*:ti,ab,kw

4. (IDDM or NIDDM or T1DM or T2DM or T1D or T2D): ti, ab, kw

5. (non insulin* depend* or noninsulin* depend* or non insulin?depend* or noninsulin?depend*): ti, ab, kw

6. (insulin* depend* or insulin?depend*): ti, ab, kw

7. ((typ* 1 or typ* 2) NEAR diabet*): ti, ab, kw

8. ((typ* I or typ* II) NEAR diabet*): ti, ab, kw

9. or/ 1-8

10. MeSH descriptor: [Cell Phones] explode all trees

11. MeSH descriptor: [MP3-Player] this term only

12. ((car or cell* or smart or mobile) NEAR phone*): ti, ab, kw

13. (carphone* or cellphone* or cell-phone* or smartphone* or smart-phone* or smart phone* or mobilephone* or mobile phone*): ti, ab, kw

14. (iphone* or i-phone* or ipod* or i-pod* or podcast* or pod-cast or ipad* or i-pad* or android* or blackberr* or palm pilot* or palm-pilot* or nokia or HTC): ti, ab, kw

15. (google NEAR/3 phone*): ti, ab, kw

16. (nexus NEAR/3 phone*): ti, ab, kw

17. ((mms or sms) and (text* or messag*)): ti, ab, kw

18. (text messag* or texting): ti, ab, kw

19. (multimedia messag* service* or short messag* service*): ti, ab, kw

20. MeSH descriptor: [Computers, Handheld] this term only

21. (pda* or personal digital assistant*): ti, ab, kw

22. tablet NEAR (comput*or pc or device*): ti, ab, kw

23. (palm* NEAR/3 computer*): ti, ab, kw

24. ((wireless or handheld or hand-held) NEAR (device* or technolog*)): ti, ab, kw

25. MeSH descriptor: [Telemedicine] this term only

26. MeSH descriptor: [Remote Consultation] this term only

27. (telemed* or telehealth* or tele-health* or telemonitor* or tele-monitor* or telecare or tele-care or mhealth or m-health or ehealth or e-health): ti, ab, kw

28. (mobile health): ti, ab, kw

29. (remote NEAR/3 (consult* or monitor*)): ti, ab, kw

30. MeSH descriptor: [Electronic Mail] this term only

31. (electronic mail or e-mail* or email*): ti, ab, kw

32. MeSH descriptor: [Internet] explode all trees

33. (web* or website* or internet): ti, ab, kw

34. (social adj3 (media or network*)) in All Text

35. or/ 10-34

36. 9 and 35

APPENDIX B

CHARACTERISTICS OF STUDIES	
Characteristics of included studies *(ordered by study ID)*	
<u>Baron 2016</u> Study design & duration	RCT (2 arm, study duration 9 months)
Participants	Adult patients (age over 18 years) with either Type 1 or Type 2 diabetes mellitus, poorly controlled (HbA1c ≥ 7.5% within last 12 months), on insulin treatment who are fluent and literate in English (n=81). Excluded were patients a) with previous experience with mobile telehealth; b) regular extended travel (≥ 3 weeks) outside the UK; c) home visits by a nurse for blood glucose monitoring and/or insulin administration; d) kidney failure: e) sickle cell disease; f) pregnancy; g) dexterity or visual problems
Intervention	Participants in the Intervention group received mobile telehealth equipment: BG meter, BP monitor, mobile phone, Bluetooth cradle, and training on the equipment. Patient data was stored in the mobile phone and transmitted via Bluetooth to the Web server. Participants followed their usual routine of BG self-monitoring. The data display is color-coded and is automatically displayed after each data transfer. Nurses access the patient data on the server via a Web portal (which was also accessible to patients). The nurses provided feedback on out-of-range clinical readings as needed, education on lifestyle changes (for a total of 6 weekly educational calls), and supported insulin titration. If more substantial support was required, participants were instructed to follow up with a diabetes specialist nurse (DSN) in clinic. Participants in the control group received usual care with face-to-face clinic appointments every 3-4 months and 1-2 semi-annual appointments with diabetes consultants.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was carried out by a (selection bias) member of the research team upon receipt of the completed baseline questionnaire, and independently of DSNs, using an online sequence generator that generated randomised block allocations (blocks of 20)." Comment: Allocation sequence was genuinely randomized.
Allocation concealment (selection bias)	Unclear risk	No details are provided regarding how the allocation sequence was implemented.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Low risk	Quote: " [HbA1c] was measured and analysed blind to group sing high-performance liquid chromatography" (Baron 2016).
Incomplete outcome data (attrition bias)	Low risk	Quote: "There were less than 5% of missing data. Data were missing completely at random (Little's test), suggesting the imputation method used was unlikely to influence results." Comment: Total attrition was 13.5%, balanced between the 2 groups.
Selective reporting (reporting bias)	Low risk	The protocol for this study is available. No differences found between the protocol and reported outcomes and results.
Other bias	Unclear risk	No evidence of other sources of reporting bias.

Berndt 2014	
Study design & duration	RCT (2 arm, study duration 4 weeks)
Participants	Children between the ages of 8-18 years with Type 1 diabetes with disease duration of at least 6 months, were following either intensified conventional insulin therapy (ICT) or insulin pumps (continuous subcutaneous insulin infusion, CSII), and who could read and write. Participants should have no other disease besides diabetes. (n = 68)

Intervention	MobilDiab enables diabetic patients to self-manage their blood glucose monitoring using their mobile device (Android, iPhone, iPad) and/or web-based applications. The MobilDiab system is composed of a mobile application (Android/iOS), web-based portals, and the platform. The system provides risk monitoring with automated alarm messages. Clinicians can access the patients' data via the protected doctor portal and have a clear view of patients' diabetes-related data. Clear graphical representation of trends and statistics enable them to make appropriate decisions about therapy adjustments. The mobile application had an intuitive user interface which is self-explanatory. Data are automatically synchronized with the central server to allow the medical staff access in real time.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	Many of the authors are from Infokom GmBH which is a company that provides consulting, software development, IT training, distribution of hard/software, networks, and their management (see Infokom.de).

Risk of bias

Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "For classification and evaluation purpose, the cohort was divided randomly into a control group (conventional therapy without the use of telemedicine system) and an intervention group (treatment with the use of telemedicine system "Mobil Diab")." Comment: No details provided regarding the randomization process.
Allocation concealment (selection bias)	Unclear risk	No description of how assignments were distributed or that concealment of the allocation sequence was adequate
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided.
Incomplete outcome data (attrition bias)	Low risk	Quote: "All 68 patients took part until the end of the study." Comment: No evidence of attrition bias.
Selective reporting (reporting bias)	Low risk	No differences found between the methods section and reported results. Data from all participants reported.
Other bias	Low risk	Quote: " Rolf-Dietrich Berndt, Claude Takenga, Petra Preik, Sebastian Kuehn and Luise Berndt from the Infokom GmbH conceived and developed the mobile and web applications used during the study....All [study]

		authors critically reviewed and revised the manuscript, and gave final approval." Comment: There is no evidence that the sponsor either owns the data or needs to approve the manuscript.

<u>Bowes 2009</u> Study design & duration	RCT (2 arm, study duration 6 months)
Participants	Adult Type 1 diabetes patients, average age 40 years (range 21-52 years) (n= 13).
Intervention	Diabetes Interactive Diary (DID) is a mobile phone-based interactive education program. The software is installed on a patient's mobile phone and it automatically calculates insulin dose and has a photographic database of different foods with corresponding carbohydrate and calorie content. Patients sent BG data via text messaging; this data was downloaded to a computer and the researcher (AB) suggested changes to their treatment plan based on that data. Patients could view their data as graphs and charts.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No explicit method of randomization was described.
Allocation concealment (selection bias)	Unclear risk	No details provided regarding how the randomization sequence was implemented, i.e., how participants were assigned to their study groups.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind study participants or personnel in these types of trials.
Blinding of outcome assessment	Unclear risk	No details provided.

(detection bias)		
Incomplete outcome data (attrition bias)	Unclear risk	Unknown if there was any attrition of participants.
Selective reporting (reporting bias)	Unclear risk	Unclear if there is any selective reporting of outcomes.
Other bias	Unclear risk	No evidence of any other bias.

Charpentier 2011 Study design & duration	RCT (3 arm, study duration 6 months)
Participants	Adult Type 1 diabetes patients, diagnosed with diabetes for at least one year, treated with basal bolus insulin regime for at least 6 months, and HbA1c values ≥ 8.0% the year before and at study entry (n=180). Excluded were patients who participated in a diabetes education program in the 3 months prior to the study or those patients with a health condition that required follow up more frequently than the quarterly visits scheduled.
Intervention	Participants randomized to Group 3 (electronic logbook and teleconsultation) received a smartphone with Diabeo software. The Diabeo software is a bolus calculator; personalized insulin doses are entered into the system for each patient. If BG results do not meet target levels, the system can suggest adjustments for carbohydrate ratio, insulin dose, or pump rates. No follow up hospital visits were scheduled until the endpoint at month 6. Participant BG data, diet, and insulin treatment data were automatically uploaded by the smartphone to a secure website where they were available to investigators. Teleconsultations were conducted with patients and doctors using computers or phones displaying last week's data and focused on insulin dose adjustments and motivational support. Participants in Group 2 (electronic logbook alone) received a smartphone loaded with Diabeo software, did not use teleconsultations. Clinic visits were scheduled for months 3 and 6. Participants in Group 1 (control group, usual paper logbook) were asked to attend two clinic visits, after 3 and 6 months.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c

Notes	This study was funded by sanofi-aventis, Orange, and CERTID

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization was carried out using a Web-based system." Comment: No specific details provided regarding how randomization was achieved.
Allocation concealment (selection bias)	Unclear risk	Quote: " We randomly assigned 180 participants to groups G1 (n = 61), G2 (n = 60), and G3 (n = 59)." Comment: No details provided regarding how the allocation sequence was implemented.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind study participants or personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	No evidence provided that outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Quote: "Seven participants were lost to follow-up and/or had missing HbA1c data at month 6 (Fig. 1). Thus we analyzed 173 participants for their main end point result at month 6." Comment: Attrition 4% (7/180), balanced between groups.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Dafoulas 2015	
Study design & duration	RCT (2 arms, study duration 12 months)
Participants	Adult Type 2 diabetes patients with HbA1c > 7.0% and capable of using a telemonitoring device (n = 823). All patients were located in a cluster from 3 European regions: Venuto, Italy; Berlin, Germany; or Thessaly, Greece; a different age group was the focus in each country.

Intervention	Participants randomized to the intervention group sent BG data weekly via a telemonitoring device (not specified) for a period of one year. Health professionals provided feedback via phone regarding lifestyle and medication adjustments. Patients in the control group received usual care with face-to-face consultations.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization was performed through the Center of Randomization at the Unit for Applied Clinical Research at the Norwegian University of Science and Technology in Trondheim using the Web Case Report" (Holmen 2014). Comment: Blocked randomization is a common form of restricted randomization (which is used to generate a sequence that ensures particular allocation rations to the intervention groups). Blocking ensures that the # of participants assigned to the comparison groups is balanced.
Allocation concealment (selection bias)	Low risk	Quote: " Immediately after randomization, the patients are told which group they have been placed." (Ribu 2013). Comment: Allocation concealment achieved.
Blinding of participants and personnel (performance bias)	High risk	Quote: "The study could not be blinded for the participants or GPs and health providers because of the nature of the intervention, which required overt participation."
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided.
Incomplete outcome data (attrition bias)	Low risk	Quote: " After the 1-year follow-up, there was a total dropout attrition rate of 21% (31/151), with an equal distribution in the groups...For the primary outcome (HbA1c level), data were obtained for a total of 120 participants after the 1-year follow-up: 39 in the FTA group (dropout attrition 24%, 12/51), 40 in the FTA-HC group (dropout attrition 20%, 10/50), and 41 in the

		control group (dropout attrition 18%, 9/50)." Comment: Attrition rate is high, ie, > 20%, but it is balanced across all the 3 study groups.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of any other bias.

Garcia 2014 Study design & duration	RCT (2-arm, study duration 3 months)
Participants	Low-income Latinos living in San Diego, CA, diagnosed with type 2 diabetes mellitus, HbA1c > 7.5% (n=71). Mean age 48.71 (± 9.25 years), 80% female.
Intervention	Dulce Digital is a mobile SMS messaging system. Participants in the intervention group received three types of text messages: educational/motivational, medication reminders, and blood glucose monitoring prompts. At the start of the study, 2-3 messages were sent each day, with the frequency tapering over 6 months. The study staff monitored blood glucose responses, assessed hyperglycemia, and encouraged participants to follow up with a provider as needed.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	Publication type is an abstract of an oral presentation. This is an ongoing study, reporting results at 3 months of a 6 month study.

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Following randomization and baseline assessment, all participants receive diabetes care-as-usual and repeat clinical and self report measures at months 3 and 6." Comment: No details provided regarding randomization process.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding of participants and study personnel not possible in these types of trials.

Blinding of outcome assessment (detection bias)	Unclear risk	No details provided.
Incomplete outcome data (attrition bias)	High risk	Article states 116 patients were recruited for the study but data from only 71 participants was analyzed (61% attrition). Authors did not state reasons for attrition.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence for other sources of bias.

Greenwood 2015 Study design & duration	RCT (2-arm, study duration 6 months)
Participants	Adult patients diagnosed with type 2 diabetes mellitus who were being treated with oral medications, noninsulin injectable medications, or lifestyle adjustments. Participants must have attended a diabetes management program for previous 12 months, age between 30-70 years, HbA1c 7.5-10.9% in previous 6 months, Internet or 3G connection with email access, landline or cell phone, English speaking, primary care provider in the system (n = 90). Excluded were patients on insulin, those who were unable to independently self-manage their diabetes, diagnosis of stroke, heart failure, end-stage renal disease, or legally blind.
Intervention	Participants randomized to the intervention group received a tablet computer that transmitted blood glucose data and facilitated a complete feedback loop to educate participants, analyze blood glucose data, amd provide clinical feedback. The tablet was connected via the Internet or 3G network to the Care Innovations Health Suite online portal. Participants also received a OneTouch Ultra 2 glucometer, and USB cables to connect the glucometer to the tablet. Data from paired glucose testing was analyzed using computer-assisted pattern analysis, this was shared with patients via the EFR weekly. Certified diabetes educators called participants monthly to discuss glucose trends and treatment changes.
Outcome	The primary outcome was the change in HbA1c between study groups after 6 months.
Notes	This study received funding from both industry and academia: LifeScan Corp., Intel-GE Care Innovations, Sutter Institute for Medical Research, Betty Irene Moore School of Nursing, Jonas Center for Nursing Excellence, and U of C Davis.

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "A permuted block, with blocks of 4 and 6, and a computer-generated random number table were utilized for randomization." Comment: Random permuted blocks is a common form of restricted randomization. Restricted randomization is used to ensure particular allocation ratios to each group.
Allocation concealment (selection bias)	Low risk	Quote: "The investigator matched the ID numbers to the random number table to assign study group." Comment: Allocation sequence adequate.
Blinding of participants and personnel (performance bias)	High risk	Quote: "Blinding of participants, providers, and the research team was not possible." Comment: Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	High risk	Quote: " Although a treatment fidelity plan was in place, the same CDEs were responsible for treatment and usual care groups, possibly contaminating the usual care group." Comment: Potential bias exists since the same CDEs assessed outcomes for both study groups.
Incomplete outcome data (attrition bias)	Unclear risk	Table 1 shows n= 90 at onset and n=80 at 6 months (11% decrease). No details provided regarding reasons for loss of participants.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	This study received funding from both industry and academia. No evidence that industry required review or approval of the manuscript or owned the data.

Hanauer 2009	
Study design & duration	RCT (2-arm, study duration 3 months)
Participants	Insulin-treated adolescents and young adults, 12-25 years of age, with an SMS-capable phone and home internet with email access (n = 40).

Intervention	The Customized Automated Reminder Diabetes System (CARDS) included a web-based module and a messaging/reminder module. Participants logged onto a system via a secure website to customize their schedule for reminder messages. If CARDS sent a reminder message either by text or email and did not receive a response, a single repeat reminder was sent. When a user submitted a blood glucose value, regardless of value, they received positive feedback. If the blood glucose value was out of range, CARDS advised the patient to take action per the healthcare team's recommendations and recheck his or blood glucose.
Outcome	Primary outcome: Glycemic control, assessed by HbA1c
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomized to receive reminders either via cell phone text messaging or by e-mail..." Comment: No explicit method of randomization was stated by the authors.
Allocation concealment (selection bias)	Unclear risk	No evidence that those who admitted participants to the study were shielded from knowing the upcoming assignments.
Blinding of participants and personnel (performance bias)	High risk	Blinding of participants and personnel not possible given the type of intervention.
Blinding of outcome assessment (detection bias)	Unclear risk	No evidence that outcome assessors were blinded.
Incomplete outcome data (attrition bias)	High risk	Quote: " 11 of the 40 (27.5%) enrolled participants never used the system, the majority of whom (seven of 11) were randomized to the e-mail group. Usage dropped off considerably after the first month, even in the more popular cell phone group." Comment: At the conclusion of the study, only 15% of participants remained, thus the final sample in the analysis

		consisted only of 6 participants - 1 in the email group and 5 in the cell phone group. The study authors attempted to explain that the high attrition rate was attributed to fatigue using the new CARDS system and use of the system over the summer months. Essentially all but a handful of participants remained until the end which indicates that there may have been issues related to the design of the intervention or problems conducting the study.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting of outcomes
Other bias	Low risk	No evidence for other sources of bias

Holmen 2014	
Study design & duration	RCT (3-arm, study duration 12 months)
Participants	European adult type 2 diabetes patients with a HbA1c ≥7.1%, capable of completing questionnaires in the Norwegian language, able to cognitively participate (n = 151).
Intervention	The Few Touch Application (FTA) consisted of a blood glucose-measuring system with automatic wireless data transfer, as well as a diet manual, physical activity monitoring, and management of personal health goals, recorded on a diabetes diary app on a mobile phone. Participants measured blood glucose levels with a glucometer which enabled automatic transfer of the blood glucose data to the diary mobile app through a wireless Bluetooth connection. The app also provided graphs, trend reports, and feedback through color coding.
Outcome	The primary outcome was the HbA1c level.
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Block randomization was performed through the Center of Randomization at the Unit for Applied Clinical Research at the Norwegian University of Science and Technology in Trondheim using the Web Case Report" (Holmen 2014). Comment: Blocked randomization is a common form of restricted randomization (which is used to generate a sequence that ensures particular allocation rations to the intervention groups). Blocking ensures that the # of participants assigned to the comparison groups is balanced.
Allocation concealment (selection bias)	Low risk	Quote: " Immediately after randomization, the patients are told which group they have been placed." (Ribu 2013). Comment: Allocation concealment achieved.
Blinding of participants and personnel (performance bias)	High risk	Quote: "The study could not be blinded for the participants or GPs and health providers because of the nature of the intervention, which required overt participation" (Holmen 2014).
Blinding of outcome assessment (detection bias)	Unclear risk	No details provided.
Incomplete outcome data (attrition bias)	Low risk	Quote: " After the 1-year follow-up, there was a total dropout attrition rate of 21% (31/151), with an equal distribution in the groups...For the primary outcome (HbA1c level), data were obtained for a total of 120 participants after the 1-year follow-up: 39 in the FTA group (dropout attrition 24%, 12/51), 40 in the FTA-HC group (dropout attrition 20%, 10/50), and 41 in the control group (dropout attrition 18%, 9/50)" (Holmen 2014). Comment: Attrition rate is high, ie, > 20%, but it is balanced across all the 3 study groups.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of any other bias.

Istepanian 2009 Study design & duration	RCT (2-arm, study duration 9 months)
Participants	Ambulatory adult diabetic patients (mainly type 2 diabetics) who lived near St. George's Hospital, UK (n = 137). 22% belonged to a non-white minority group. Exclusion criteria included physical inability to self-monitor blood glucose, pregnancy, life-threatening or terminal illness, inability to provide written consent.
Intervention	Participants were trained to use a blood glucose meter which transmitted the readings wirelessly via Bluetooth to a mobile phone, then on to a server at St. George's Hospital. Clinicians were able to examine and respond to blood glucose readings via a web-based application.
Outcome	The primary outcome was HbA1c.
Notes	Per ITT analysis, the telemonitoring group did not have an advantage over usual diabetic care.

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization to usual care or the telemonitoring arm of the study was by computer-generated random numbers." Comment: Simple randomization used here to generate a randomized sequence of assignments.
Allocation concealment (selection bias)	Unclear risk	No details provided regarding how participants were told what group they were assigned to.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if outcome assessors were blinded.

Incomplete outcome data (attrition bias)	High risk	Quote: “The drop-out rate from the intervention arm in the study was higher than the 10–15% we predicted would occur. Patients cited technical issues related to operating the equipment as the main reason behind the protocol violations." Comment: Attrition not balanced between groups, there is a significant drop out rate in the telemonitoring group with only 32 of 72 completing the study. High attrition in this group could bias the effect estimate in favor of the intervention since those participants who were unable to use the system were excluded, making the intervention seem more useful than it truly was.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	Quote: “We are grateful for financial and technical support from the IDEN Group, Motorola, USA and the Motohealth team in UK." Comment: No evidence that sponsors own data or required approval of the manuscript.

Nagrebetsky 2013 Study design & duration	RCT (2-arm, study duration 6 months)
Participants	Adults type 2 diabetic patients recruited from several general practices in the UK. Inclusion criteria was ≥ 35 years of age, type 2 diabetes for at least 3 months, taking po meds, HbA1c 8.0 - 11.0% with no increase in po meds (n = 14). Exclusion criteria included physical, cognitive, or social limitations, on insulin, visual impairment, pregnancy, breast feeding, limited life expectancy.
Intervention	Participants received a cell phone and blood glucose meter; blood glucose readings were wirelessly transferred to the phone then uploaded to a server. The system also included a mobile phone diary app that provided real-time graphical feedback to patients on their blood glucose readings. The blood glucose readings were monitored by research nurses twice a week via a Web-based monitoring system; the nurses also encouraged patients via text messages and phone calls to adjust their medication based on their blood glucose data.
Outcome	Authors reported the 6-month data on changes of HbA1c.

Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Fourteen type 2 patients were randomly allocated to two groups." Comment: No details provided regarding how randomization was achieved.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding of participants and personnel (performance bias)	High risk	Blinding not possible due to nature of the intervention.
Blinding of outcome assessment (detection bias)	Low risk	No details provided.
Incomplete outcome data (attrition bias)	Low risk	All participants completed the study.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting of outcomes.
Other bias	Low risk	No evidence for other sources of bias.

<u>Orsama 2013</u>	
Study design & duration	RCT (2-arm, study duration 10 months)
Participants	Adult type 2 diabetes patients who attended the Sipoo, Finland Community Health Center. Inclusion criteria included age range 30-70 years, HbA1c > 6.5 %, SBP > 140 mmHg or DBP > 90 mmHg, and currently using diabetic medications (n =56). Exclusion criteria were poor study compliance, pregnancy, short life expectancy, major elective surgery in the past 6 months or planned in the next 6 months, and psychiatric issues.

Intervention	Participants in the intervention group were provided with a mobile phone, software, and a blood glucose meter. Blood glucose was measured 3x/week and patients were instructed to upload their data using the application Monica in the mobile phone. After each upload, the application displayed graphs based on the uploaded data in relation to individual target values and provided informational/motivational/behavioral skills feedback designed to support self-care. Study nurses scanned through the data of all intervention patients each week and contacted them as necessary.
Outcome	The primary outcome was HbA1c.
Notes	Study arms similar except: 1. SBP was significantly higher in the intervention arm 2. BMI was lower in the intervention arm

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote:" Stratified randomization was used to allocate patients to control and intervention study arms. Patients were stratified by sex and dichotomized age (<65 years and ‡65 years).Using Microsoft (Redmond, WA) Excel-generated random numbers, patients were then assigned to either the control (n = 29) or intervention study arms (n = 27)." Comment: Stratified randomization is an adequate method of sequence generation.
Allocation concealment (selection bias)	Unclear risk	No details provided regarding how the participants were told what group they were randomized to.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if the outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Attrition low and balanced between groups.
Selective reporting (reporting bias)	Unclear risk	
Other bias	Low risk	The study was partially funded by Bayer Healthcare LLC, Diabetes Care, and three of the authors were employees of same. However, there is no evidence that the sponsor owns the data or required approval of the manuscript

Quinn 2008 Study design & duration	RCT (2-arm, study duration 3 months)
Participants	Adult type 2 diabetics with a diagnosis of type 2 diabetes for at least 6 months, HbA1c ≥ 7.5 %, 18-70 years old, and on a stable diabetes therapeutic regimen for 3 months prior to study enrollment (n = 30).
Intervention	Participants randomized to the intervention group received a Bluetooth-enabled blood glucose meter and a cell phone loaded with WellDoc's proprietary DiabetesManager software. When the patient removed the test strip from the meter, the blood glucose value would be sent wirelessly and automatically to the patient's cell phone. Once the blood glucose value was received by the phone, the DiabetesManager software was triggered which prompted the patient to label the blood glucose data; subsequently the software sent the data to the WellDoc server. The software provided real-time feedback on blood glucose values. The system sent computer-generated logbooks with suggested treatment plans to patients' providers.
Outcome	The primary outcome was HbA1c.
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Eligible patients gave consent and were randomized to either the control or intervention group. Fifteen patients were randomized to each group." Comment: No further details provided to assess if allocation sequence was genuinely randomized.
Allocation concealment (selection bias)	Unclear risk	Quote: "Fifteen patients were randomized to each group." Comment: No details provided regarding how the participants were assigned to each group.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if outcome assessors were blinded.
Incomplete outcome data	Low risk	Quote: " Two subjects for each study group dropped out

(attrition bias)		of the study." Attrition low and balanced across groups.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Quinn 2011 Study design & duration	Cluster RCT (4-arm, study duration 12 months)
Participants	Adults age 18-64 years with a diagnosis of type 2 diabetes for at least 6 months and HbA1c ≥ 7.5 % within 3 months (n = 163). Excluded were Medicare or Medicaid patients, the uninsured, insulin pump users, patients not currently being managed by study physicians, pregnancy, history of substance abuse, psychiatric issues, hearing or visual impairment, no internet or email access.
Intervention	Patients randomized to the intervention groups received a glucose meter, mobile phone, mobile diabetes management software, and access to the web-based portal. The patient entered blood glucose data into the mobile phone and received automated real-time educational, behavioral, and motivational messages specific to the entered data. The web-based portal was a secure messaging center for patient-provider communication. The provider portal had 3 different views of patient data based on study group assignment. Diabetes educators supplemented the automated messages with electronic messages sent to the patient portal.
Outcome	The primary outcome was HbA1c (%) comparing usual care to intervention at baseline versus 12 months.
Notes	Primary care practices = unit of randomization (26)

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Practices were assigned to treatment groups according to a 1.5:1:1:1.5 (Group 1, UC:Group 2, CO:Group 3, CPP:Group 4, CPDS) ratio using a computer-generated list of random numbers." (Quinn 2011) Comment: Authors specify how assignments were randomly generated.
Allocation concealment	Unclear risk	No details provided regarding the method used to

(selection bias)		conceal the study group assignments to determine if the assignments could have been foreseen in advance.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	High risk	Quote: "Physicians are not told of their practice intervention (Groups 1–4) assignment until they agree to participate." (Quinn 2009a). Comment: Clinicians knew what group they were assigned to during the course of the study.
Incomplete outcome data (attrition bias)	Unclear risk	Attrition is rather high at 23% (note Table 1 in Quinn 2011). No details provided regarding reasons for participants to drop out.
Selective reporting (reporting bias)	Low risk	Quote: "Although not all participants provided data at all planned study visits, we addressed missing data in this study in two ways. First, the primary analysis used mixed-effects models, which have the effect of implicitly imputing missing observations (25). Second, we performed the WEE sensitivity analysis that used baseline characteristic data to upweight observations from participants who were most similar to participants with missing data." Comment: Adequate measure taken to ensure all results had been reported.
Other bias	Low risk	No evidence of any other bias.

Rami 2006	
Study design & duration	Cross-over RCT (2-arm, study duration 6 months)
Participants	Adolescents between the ages of 10-19 years of age with type 1 diabetes > 1 year, HbA1c ≥ 8%, who were willing to attend follow-up visits (n = 36).
Intervention	Patients in the telemedical phase of the study used the VIE-DIAB system (a telemedical system and program) to send their blood glucose data from their mobile phone to the study server. Diabetologists provided personalized clinical feedback with specific advice via weekly text messages as needed. The system generated automated text messages if blood glucose readings were in the normal range.
Outcome	The primary outcome was HbA1c (%) comparing telemedical care to paper diaries.

Notes	Results reported as medians.

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The study was designed as a randomized crossover trial for 6 months." Comment: No further details provided regarding how random sequence was generated.
Allocation concealment (selection bias)	Unclear risk	Unclear if study personnel were blinded from the assignments.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	Quote: "All 36 patients completed the 6-month trial." Comment: No attrition.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence the sponsor, Telecom Austria, owned the data or required review of the manuscript.

Rodriguez-Idigoras 2009	
Study design & duration	RCT (2-arm, 12 month duration)
Participants	Adult patients > 30 years of age diagnosed with type 2 diabetes and who had been self-monitoring for at least 6 months prior to the study (n = 328). Excluded were patients with difficulties using the system due to the number and severity of the complications of diabetes and those who required a caregiver.
Intervention	All patients received a glucometer. Patients in the intervention group, and their family physicians, received a mobile phone. The patients' and physicians' mobile phones and a call center comprised the DIABECOM teleassistance system. Those patients in the intervention group sent their blood glucose via their mobile phones to the call center. If blood glucose levels were outside the normal range, the system sent an alarm to the call center. Physicians had real-time access to any information patients sent

	through the DIABECOM system.
Outcome	The primary outcome in this study was the HbA1c level.
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "...participants were selected through a systematic sampling design with a random start. Patients remained in the same order in which they had been selected..In order to ensure that each physician's patients were randomly allocated in a balanced way, block randomization was used..." Comment: Blocked randomization is a common form of restricted randomization which is used to ensure that there is a balance in the number of participants assigned to each comparator group. The authors randomly varied the block size by using a random start that would reduce the likelihood of any foreknowledge of intervention assignment.
Allocation concealment (selection bias)	Low risk	Quote: "...block randomization was used, with an allocation sequence being generated by means of a table of random numbers." Comment: Allocation concealment was achieved.
Blinding of participants and personnel (performance bias)	High risk	Quote: "...given the nature of the intervention, it could not be blind to participating physicians." Comment: Blinding not possible due to the nature of the intervention.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "...analytical determinations required during the study were also made in the same reference laboratories. Therefore, all analytical measures were blind."
Incomplete outcome data (attrition bias)	Low risk	Quote: " 328 patients...were included in the study sample and randomly assigned to the study groups: 161 to the intervention group and 167 to the control group. During the trial seven patients died, and another 24 were lost to follow-up; therefore, in 1 year we followed 146 patients (91%) from the intervention group and 151 (90%) from the control group.' Comment: Only 9% attrition (31/328) and loss balanced between the 2 comparator groups.
Selective reporting (reporting bias)	Low risk	No differences found between methods and reported results. All missing participants were accounted for.

Other bias	Low risk	Quote: "The authors declare that Emminens, the company that finances the research on which this article is based, does not use the work system described in the mentioned article, and therefore there is no duality of interest." Comment: There does not appear to be any publication bias in this study. The sponsor does not own the data or require screening of the manuscript.

Takenga 2014 Study design & duration	RCT (2-arm, 2 month duration)
Participants	Adults between the ages of 35-75 years diagnosed with type 2 diabetes (n = 40).
Intervention	The Mobil Diab system enables diabetic patients to self-manage their condition using their mobile device. Clinicians access patient data through a web portal. Patients enter their data via intuitive screens; data is automatically synchronized so providers can receive data in real time. Feedback from the clinician is received directly in the mobile app.
Outcome	One of the main outcomes in this study was HbA1c (%).
Notes	No SDs or p values given.

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients diagnosed with type 2 diabetes and aged between 35 and 75 years were recruited randomly. A total of 40 patients were included in the trial phase. For classification and evaluation purpose, the cohort was divided into a control group (conventional therapy without the use of telemedicine system) and an intervention group (treatment with the use of telemedicine system Mobil Diab)." Comment: No details provided regarding the actual randomization sequence.
Allocation concealment (selection bias)	Unclear risk	Quote: "The randomization of all the 40 patients in control and intervention group was successful." Comment: No details provided regarding method of concealment and if participants or investigators could

		foresee assignments.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not clear if outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	All 40 patients completed the study.
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias, results from all participants reported.
Other bias	Low risk	No evidence of other bias.

Tang 2013	
Study design & duration	RCT (2-arm, 12 month duration)
Participants	Adults ≥ 18 years of age diagnosed with type 2 diabetes, HbA1c ≥ 7.5%, and seen within the last 12 months (n = 415). Excluded were patients with an initial diagnosis of diabetes within the last 12 months, inability to read or speak English, lack of internet access, unwillingness to perform self-monitoring, terminal illness, pregnancy or breastfeeding, currently enrolled in a care management program at the Palo Alto Medical Foundation (PAMF), family member enrolled in already enrolled in the study (the EMPOWER-D study), resident of a long-term care facility, plans to discontinue care at PAMF, and the uninsured.
Intervention	Glucometers were fitted with a Bluetooth adapter that wirelessly transmitted blood glucose readings to a smartphone. The smartphone then uploaded the data to the PAMF HER. Clinicians were able to view patient data and provide timely feedback via secure messaging regarding blood glucose levels, food intake, and medication doses.
Outcome	The primary outcome in this study was blood glucose as measured by HbA1c (%).
Notes	Intervention patients achieved greater decreases in HbA1c at 6 months than usual care, but the differences were not sustained at 12 months. More intervention patients than usual care patients achieved improvement in HbA1c (> 0.5% decrease).

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed by-patient. An analyst sequestered from the research assistants entered the participants into a randomization program based on Pocock's 'minimization' procedure, which assures better-than-chance group balance for the following key variables: primary care site, age, gender, A1C levels, systolic blood pressure, low-density lipoprotein (LDL) cholesterol, and pre-enrollment use of our patient portal." Comment: Method of randomization specified.
Allocation concealment (selection bias)	Low risk	Quote: " Participants were then sent letters about study assignment (intervention (INT) vs usual care (UC))..." Comment: Appears that adequate allocation sequence concealment achieved, however no mention of use of sealed, opaque envelopes.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "Clinical measurements, adverse event reports, and online questionnaires were collected from all participants at 6 and 12 months by a research assistant blinded to randomization status." Comment: Low risk of bias due to blinding of research assistant and objective measure of HbA1c.
Incomplete outcome data (attrition bias)	Low risk	193/213 (91%) in UC and 186/202 (92%) INT completed the study. Attrition low and balanced between groups.
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting.
Other bias	Low risk	No evidence of other bias.

Waki 2014	
Study design & duration	RCT (2-arm, 3 month duration)
Participants	Adult diabetic patients with type 2 diabetes with no severe complications such as proliferative retinopathy, a serum Cr < 1.5 mg/dL, and who were able to exercise (n = 54).
Intervention	Each participant in the intervention group received a smartphone and wireless-enabled glucometer which transmitted data wirelessly to the DialBetics server. Abnormal readings were reported as a "Dr. Call" meaning a physician would check the data and follow-up with the patient via text

	message or phone.
Outcome	The primary outcome in this study was the change in HbA1c (%).
Notes	

Risk of bias		
Bias	**Author's judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomly divided into a DialBetics group and non-DialBetics group using a computer-generated list of random numbers." Comment: Study used a randomized sequence of assignments.
Allocation concealment (selection bias)	Unclear risk	No details provided regarding the method of concealment of study group assignments.
Blinding of participants and personnel (performance bias)	High risk	Not feasible to blind the participants or study personnel in these types of trials.
Blinding of outcome assessment (detection bias)	Unclear risk	Not stated if outcome assessors were blinded.
Incomplete outcome data (attrition bias)	High risk	Quote: " ...the study's dropout rate was relatively high (9.3%): 3 DialBetics and 2 non-DialBetics group members. One in the DialBetics group (and both in the non-DialBetics group) dropped out for hospitalization. The other 2 DialBetics dropouts cited unwillingness to continue constant measurements as their main reason. Although interpretation should be cautious given the small sample size, dropout rate is a potential source of bias in the current study. "Comment: Could be biased in favor of the Dialbetic group since 2/3 participants who left that groups did not want to use the intervention, possibly making Dialbetics appear more useful than it truly is.
Selective reporting (reporting bias)	Unclear risk	No details provided regarding how missing data was handled. Table 2 shows n=27 for both groups even though 5 participants could not or did not complete the study.
Other bias	Low risk	No evidence of bias from other sources.

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