ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:
«ΔΙΕΘΝΗΣ ΙΑΤΡΙΚΗ-ΔΙΑΧΕΙΡΙΣΗ ΚΡΙΣΕΩΝ ΥΓΕΙΑΣ»

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ: Καινοτόμο Ιατρικό Λογισμικό : Δυνατότητες & Προκλήσεις

Υπότιτλος : Συστηματική Ανασκόπηση Μελετών Παρεμβάσεων mHealth στη Θεραπεία του Σακχαρώδους Διαβήτη σε Αναπτυσσόμενες Χώρες.

ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ : Μαστοράκης Κωνσταντίνος

ΑΘΗΝΑ

Ιούνιος 2020

MASTER'S COURSE IN:

«INTERNATIONAL MEDICINE – HEALTH CRISIS MANAGEMENT»

NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF MEDICINE

THESIS

OBJECT OF STUDY: Innovative Medical Software : Potential & Challenges

Subtitle : A systematic review of studies of mHealth interventions in the management of Diabetes Mellitus in developing countries

POSTGRADUATE STUDENT: Mastorakis Konstantinos

ATHENS

June 2020

ΠΡΑΚΤΙΚΟ ΚΡΙΣΕΩΣ

ΤΗΣ ΣΥΝΕΔΡΙΑΣΗΣ ΤΗΣ ΤΡΙΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ ΓΙΑ ΤΗΝ ΑΞΙΟΛΟΓΗΣΗ ΤΗΣ ΔΙΠΛΩΜΑΤΙΚΗΣ ΕΡΓΑΣΙΑΣ

Του Μεταπτυχιακού Φοιτητή Μαστοράκη Κωνσταντίνου

Εξεταστική Επιτροπή

□ ....., Επιβλέπων

□ ....., Μέλος

□ .....,Μέλος

Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε απο την ΓΣΕΣ της Ιατρικής Σχολής του Πανεπιστημίου Αθηνών Συνεδρίαση της ….ης ……... 20…. για την αξιολόγηση και εξέταση του υποψηφίου κ……, συνεδρίασε σήμερα …./…../…..

Η Επιτροπή διαπίστωσε ότι η Διπλωματική Εργασία του κ……..... με τίτλο…… …… …… …… είναι πρωτότυπη, επιστημονικά και τεχνικά άρτια και η βιβλιογραφική πληροφορία ολοκληρωμένη και εμπεριστατωμένη.

Η εξεταστική επιτροπή αφού έλαβε υπ’ όψιν το περιεχόμενο της εργασίας και τη συμβολή της στην επιστήμη, με ψήφους ..... προτείνει την απονομή στον παραπάνω Μεταπτυχιακό Φοιτητή την απονομή του Μεταπτυχιακού Διπλώματος Ειδίκευσης (Master's).

Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους……., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους……, και για τον βαθμό «ΚΑΛΩΣ» ψήφους…….

Κατά συνέπεια, απονέμεται ο βαθμός «(Άριστα/Λίαν Καλώς/Καλώς) & (Βαθμός) ……»

Τα Μέλη της Εξεταστικής Επιτροπής

- ....., Επιβλέπων (Υπογραφή) ——————
- ....., Μέλος (Υπογραφή) ——————
- ....., Μέλος (Υπογραφή)

Abstract

Background: Diabetes mellitus is a major public health problem that is globally widespread, especially in the developing countries. Taking advantage of the exponential growth in mobile phone usage, the lives of those living with the disease can be substantially improved. The aim of this systematic review is the critical appraisal of existing evidence on the effectiveness of mHealth projects in the management of diabetes mellitus in low – and middle – income countries, the main implementation barriers and other contextual factors.

Methods: A literature search of randomized controlled trials of the last decade was performed at MEDLINE and EMBASE databases. English – language articles that quantitatively examined the impact of mHealth interventions over glycaemic control (ΔHbA1c) were included. A plethora of qualitative secondary health outcomes and scientific, practical and financial aspects of the studies that influenced the management of diabetes mellitus were, also, taken into consideration. Risk of bias assessment within articles was conducted with the CONSORT for non – pharmacologic treatments checklist.

Results: Eighteen studies were included in this review (n = 7481 patients – predominantly T2 diabetics –, mean duration = 8,1 months, main location = Asia, major mHealth modality : SMS). Ten trials demonstrated significant improvement on primary outcome by reducing HbA1c value among study groups pre – and post – intervention. Mixed results were yielded for the rest of secondary outcomes (lifestyle change, medication adherence, self-monitoring blood glucose, knowledge and self – efficacy). No effect was observed at the quality of life and the perception/ attitude of the patients. Positive acceptability and utility scores were observed in the intervention recipients.

Discussion: A marginally moderate to higher risk of bias was found. Short duration, small sample sizes, confounding co – interventions/ comparator group care, questionable self – reporting data and heterogeneity of study design and implementation were the most important limitations. Nonetheless, the potential of mHealth interventions on diabetes mellitus lifelong management in undeserved populations was unanimously agreed upon across the studies and remains to be proven by the results of future methodologically robust trials.

Other:

- **Funding:** None.
- **Registration:** At the scientific board of the Master's course.

Keywords: mHealth, Diabetes Mellitus, developing countries, mobile health, glycaemic control, low and middle income countries

Introduction

The human and socioeconomic consequences of Non Communicable Diseases (NCDs) pose a major public health challenge for health systems worldwide, that are obliged to accomplish their mission under difficult circumstances, like staff shortages and limited budget, among others. The rising burden of NCDs is quite heavy for every country, but, particularly, for lower and middle income countries, whose capacity to address them is overwhelmed.

Diabetes Mellitus (DM) comprises one of the leading causes of mortality and morbidity from NCDs, is associated with financial hardship and, currently, is on the rise. However, DM presents specific features, as a condition that makes DM an ideal tool for assessing the performance of a health system or intervention. It is common, well – defined and easy to diagnose. Above all, effective management of DM requires organized cooperation of health care providers at multiple levels of health services, regular follow-up, access to essential medications and active patient involvement. Thus, recommendations for improving DM management could provide lessons for management of other NCDs.

Mobile Health (mHealth) is a relatively new, emerging field that utilizes the advancement of mobile and wireless Information and Communication Technologies (ICTs) to incorporate them into processes and services for the benefit of health and well – being medical care. Taking into consideration the accelerating spread of smartphones and the massive growth of wireless network coverage, it is an unprecedented opportunity that is imperative to be seized, to harness the power of mobile technology to revolutionize the delivery of healthcare services. At the moment, mHealth is restricted to several small scale projects, since it lacks strong evidence to verify its impact on health outcomes, explaining why funding is allocated to competing health system programmes and reflecting the lack of interest or even understanding of the field.

The objective of this thesis is to conduct a systematic review of the research literature, investigating the effectiveness of mHealth interventions in promoting the management of DM in the developing world. The purpose of this thesis is to determine the status of mHealth in the developing countries, by examining five aspects : a) types of initiatives b) health outcomes c) user participation d) evaluation of applicability and e) barriers to implementation. In this way, the findings from this thesis can provide solid evidence, on which governments, policy – makers, Non Governmental Organizations (NGOs),

academics, industry and other stakeholders can base their decisions, maximizing the efficiency of mHealth interventions. Furthermore, it will contribute to raise awareness concerning the possible applications, while the field of mHealth matures, leading to the recognition of this key innovation's complete potential. In conclusion, the research question that this thesis will attempt to answer is if there are any mHealth interventions focusing on DM management that have, under practical (availability, accessibility, adequacy, appropriateness, and adaptability), economical (affordability) and scientific (accountability) criteria, achieved positive health outcomes and can, by extension, be carried out in order to deal with public health issues.

The choice of the subject of the thesis was made with conviction that new technologies can prove themselves to be an invaluable asset reversing health inequalities and reshaping the face of health care delivery. It is up to the all the relevant actors to experiment on the optimal applications of this recently developed and, therefore, unexplored field and up to the academic community to document, analyze critically these efforts, draw conclusions and propose solutions.

The Master's Course of "International Medicine – Health Crisis Management" has always been training health professionals so that they can approach complex public health challenges in a scientific manner and under an interdisciplinary perspective, with ultimate goal to improve access and equity in health care.

Background

Description of the condition

Diabetes mellitus is a major global public health problem that, although, has long since become an epidemic, continues to be underrated. According to the Global Health Estimates Technical Paper of the WHO (World Health Organization), DM has climbed from the 13th to the 7th position as the leading cause of death globally between 2000 and 2016. The same report underscores the fact that DM is no longer a disease of the wealthy countries. Mortality from DM is constantly increasing everywhere, but more remarkably in the world's low- (LICs) and middle income countries (MICs). In terms of absolute numbers, 83% of global deaths caused directly by DM occurred in LIC and MIC.(1) Consistent with current trends of DM statistics, the projections of WHO for years 2017 – 2060 suggest that the cost in human lives will rise further, since as many as 1 out of every 20 deaths globally will be attributed to DM in 2060 and the death toll is expected to be paid predominantly by LICs and MICs.(2)

Apart from the evident relationship between DM mortality and country income levels, the number of diabetic patients has almost quadrupled from 108 million (global prevalence of 4,7%) in 1980 to 422 million (8,5%) in 2014.(3)

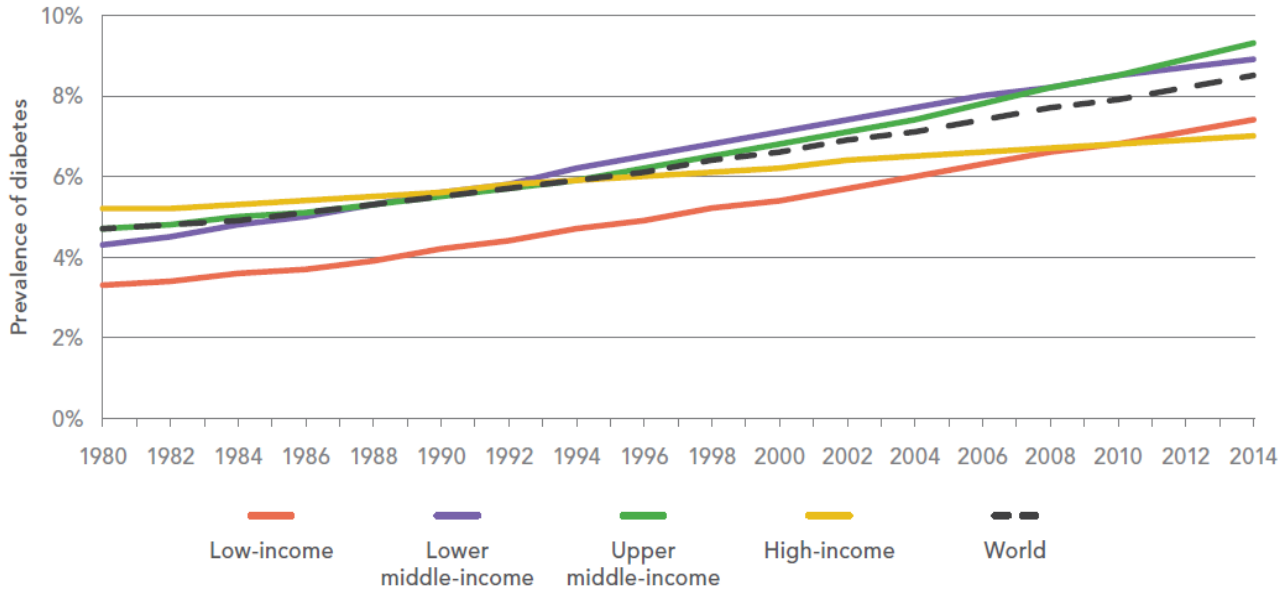

Figure 1. Trends in prevalence of diabetes, 1980-2014, by country income group
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The burden of DM, in terms of direct and indirect medical expenditure, is enormous for national economies, healthcare systems and individuals. Direct medical expenses include inpatient/outpatient-emergency/long term hospital care of DM and its complications and medications – medical supplies. On the other hand, indirect medical costs have to do with productivity loss due to morbidity and premature mortality. Of course, it is complicated to quantify the economic dimension of DM, but Bommer and colleagues (5) attempted to calculate the international DM – associated cost, that reached, approximately, a total of US$1,3 trillion in 2015, one third (34,7%) of which accounts for indirect costs. In agreement with the epidemiological shifts of DM and their implications, MICs carry a larger proportion of the considerable financial impact of the disease in comparison with the rest of the world, as an average 1,8% of every country's gross domestic product (GDP) is allocated for this purpose.(5) A parameter, that is often neglected, is the cost borne and the economic difficulty faced by patients themselves or families with a member with DM. Often, health care payments are covered by their own savings, if they can afford them, and, additionally, there is the subsequent loss of income, that arises from disability and premature loss of life associated with DM.(3) The natural progression reduces medication adherence and utilization and influences treatment-seeking behavior leading to a vicious circle of poverty and disease.(6)

Description of the intervention

Mobile technologies could play a key role by supporting the delivery of health care services at an individual level. The enhanced capabilities and infrastructure of ICTs, that continue advancing rapidly, could provide alternative means of prevention, diagnosis and treatment by facilitating the participation of patients and health professionals in several aspects of healthcare. The feature, which makes mobile technologies particularly appropriate for improving the health indicators especially of LICs and MICs, is their widespread acceptance.(7) Despite that saturation rates are being reached in developed countries, the proliferation of cell phones across the rest of the world has led to the fact that more than three quarters (76,4%) of the world population now owns a mobile phone and the number of mobile-cellular telephone subscriptions exceeds world population. Given the automation of delivery of text/picture messages and the interaction via phone calls and mobile apps, interventions carried out through a mobile phone can be proven to be a cost-effective public health strategy. Finally, the inherent characteristic of portability/mobility is accommodated by the growth in coverage of mobile cellular networks,

having 96% of global population living within their limits, overcoming geographical and temporal barriers and, thus, facilitating their participation.(8)

The aforementioned situation has paved the way, so that decisive steps forward can be made as regards the integration of ICTs into health systems and clinical care in the form of mHealth services as detailed below:

a. Communication between individuals and health services
    1. health call centers
    2. emergency toll-free telephone services
b. Communication between health services and individuals
    1. treatment compliance
    2. appointment reminders
    3. community mobilization and health promotion,
    4. health awareness raising
    5. prevention – detection – healthcare delivery
c. Consultation between healthcare professionals
    1. mobile telemedicine
d. Intersectoral communication
    1. managing emergencies and disasters
e. Health monitoring and surveillance
    1. patient monitoring and alerting
    2. health surveys and data (clinical and administrative) collection,
    3. surveillance,
f. Access to information for health care professionals at point of care
    1. patient records,
    2. information and decision support systems.
g. Supply chain management
    1. provision of medication, devices and consumables(9,10)

These types of mHealth can be implemented by various tools like Short Message Service (SMS), Multimedia Message Service (MMS), phone calls, smartphone applications (Apps) or other wireless devices like Personal Digital Assistants (PDAs) or patient monitoring devices. The prevailing delivery channel in developing world appears to be SMS in combination or not with phone calls, voice messages or smartphone apps, as proven by a

recent review, that identified SMS as a core component in the majority of articles analyzed (28/30 articles) & as the only means in 16 out of 26 interventions.(11) SMS is anticipated to be the most-used and, as a natural consequence, tested mHealth modality in LMICs. SMS programmes are presumably rendered more suitable because of instant transmission and availability for any type of phone and because messages are low cost, more discreet to daily lives (especially when a phone is shared between family members), less likely of being misplaced (vs. printed material), and can be sent, stored, retrieved and answered at user's convenience.(12,13) A point that needs clarification is on what extent SMS can be uni- or bidirectional. Bidirectional messaging costs more if extra charges, human resources and man-hours needed for the interaction are counted in and as Haider et al. correctly notes, bidirectional messaging, in the final analysis, "is no different to individual clinical guidance". On the contrary, unidirectional messaging can be applied on a large scale, as public health measures dictate and requires as less funding as possible, which is a variable that cannot be overlooked in less privileged parts of the world.(14)

Literature review

The potential of mHealth initiatives is generally acknowledged.(15) However, it is yet to be capitalized into the achievement of health objectives for several reasons, let alone in the resource – constrained settings of developing countries. First, the existing body of literature lacks a satisfactory amount of mHealth studies conducted in LMICs in contrast to HICs, and second, the small sample size of most of the studies hinders a more precise hypothesis of applicability of the results to larger LMICs populations.(16 – 19) Of course, this corresponds to the relative activity shown by each regions, with HICs highly surpassing LMICs.(9) Another factor is the questionable validity of the methodology followed by the authors of the published studies, as with all types of research.(19–22) The last, but most important, point for consideration is that the evidence on the effectiveness of mHealth interventions, as it is reported by the systematic reviews, is largely descriptive and inconclusive, albeit promising.(17,18, 20 – 22) These flaws can mislead and discourage candidate players, who have an interest on mHealth, to adopt novel technologies on DM management.

Such positive evidence that, nonetheless, has been pooled together from multiple trials and processed statistically is demonstrated by only a few systematic reviews/meta-analyses, regardless of study location. These report a moderate and short-term but

measurable improvement on glycaemic control compared to conventional care or other non mHealth approaches by reducing the value of post interventional glycosylated haemoglobin (HbA_{1c}), which is the standard of care and reflects the cumulative blood glucose history of the past trimester.(23–25)

Apart from health indicators, prior research has, also, evaluated the mHealth interventions on DM management per se and their ramifications-implications on several other fields. One of these is the users' perspectives on acceptability and their level of engagement. Hanauer et al. brought up that there was a marked decline in the interest in mHealth services, after the initial enthusiasm.(26) While this may be true, another study supported that nine out of ten participants declared their wish to continue to receive messages and eight out of ten believed that their DM self-management skills had improved.(27) The same study compared, as well, healthcare services utilization between mHealth intervention group and conventional control group with no significant difference at the number of clinic visits and the use of the emergency hotline.(27)

As can be seen from the above mentioned data, they represent prominent and secondary issues that need to be assessed prior to the implementation, or even design phase, of a mHealth project in order to have a positive impact on populations and individuals.

Rationale for the review

The successful and sustainable development of a mHealth strategy lies within the high-quality evidence that lacks, at the moment, and only rigorous research can contribute it. I aimed to add to the body of knowledge by critical appraising and synthesizing any piece of information that determines the feasibility and effectiveness of mobile-based services for improving DM management, compared to usual care. Mobile health itself can advance through reasoned analysis that can shape the future and assist becoming standard practice and taking a position in the fight against DM; hence against the rest of NCDs.

Main body of the thesis

Methods

The study was designed, conducted, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. (28) The review protocol was registered at the scientific board of the Master's course but not in the

PROSPERO International prospective register of systematic reviews, that can be done retrospectively.

Search strategy and information sources

MEDLINE (through PubMed search engine) and EMBASE (through Cochrane Library advanced search) databases were searched to identify Randomized Controlled Trials (RCTs) of mHealth interventions for DM published between January 1, 2010 and the day, when the search was conducted (April 12, 2020). Search was extended to hand-reviewing of reference lists of relevant Systematic Reviews (SRs). The search strategy comprised variations and combinations of multiple technology, medical and geographical specific keywords (e.g. mHealth, Diabetes Mellitus and developing world etc.). Language (English) type restriction was applied. The full search strategy for all databases is available in Appendix.

Study eligibility criteria

Studies were included if they i) quantitatively or qualitatively examined the impact of a mHealth intervention on the management of DM ii) took place in a developing country; iii) were published in English; iv) were designed as RCT. Only studies in which the mHealth component was the main or a major intervention type were included, i.e. via messages, calls, smartphone applications, patient monitoring devices, personal digital assistants and other wireless devices. The primary outcome of interest was defined in terms of objective and measurable changes in glycemic control (mean percentage HbA1c value difference pre – and post - intervention) in the intervention group, compared to control group. Difference in HbA1c levels was mandatory to be reported by a study, in order to be an eligible candidate for this SR. Other clinical outcomes (blood pressure, lipids, weight/BMI) were not included. Secondary outcomes were defined as changes regarding behavior/lifestyle, knowledge, self-management and attitude towards DM that have direct and sound impact on health improvement. The UN classification (2014) was used to determine each country status (developed economies, economies in transition and developing economies) and to further categorize them (low income, lower-middle income, upper-middle income and high income groups).(29) Exclusion criteria were: Projects that were not located in LICs and MICs of developing world and non-mHealth (telemedicine, other types of eHealth and use of other telecommunication technologies, such computers, internet or e-mail) interventions or co-interventions (as they can prove to be confounding

factors and no causal relationship can be established). Furthermore, we focused on adult Type 1 and 2 DM, which means that prediabetes, gestational diabetes or pediatric diabetes, were ruled out. Desirable data provided from the studies, which are also reported in this SR, were information associated with practical, economical and scientific aspects of the intervention.

Data extraction

Based on the research questions and objectives, data from full text articles was summarized, extracted and collected manually in a table format with the following contents:

1. General information: title, authors, date published
2. Study methods: study design, geographic location, purpose/(mHealth) service
3. Providers & Setting: description
4. Participants: description, number (included in the analysis), age. If applicable: principal health problem or diagnosis, stage of illness, treatment received
5. Intervention: description/type, duration of intervention, including multiple timings for measurements, control/usual or routine care, co-interventions.
6. Outcomes: primary and secondary outcomes.
7. Results: qualitative summary all reported measurements for the primary and secondary outcomes.

Results

Study screening and selection

The initial search yielded a total of 8647 citations for review. The titles of the articles were screened by the author (single reviewer) and 8565 references were excluded, that clearly did not meet our inclusion criteria. The abstracts and, if needed, the full-text versions of the remaining 84 (12 from MEDLINE and 72 from EMBASE) articles were retrieved. After close examination, 69 articles were removed because they did not meet our eligibility criteria or their full-text versions could not be found. Duplicate citations from across databases weren't excluded but 27 out of the 72 selected reports, that were identified through Cochrane Library advanced search at EMBASE (restriction: source), were also labelled to be contained at MEDLINE. Interestingly, none of these came up when PubMed search engine was used for the MEDLINE database. In addition, reference lists of

relevant SRs were screened manually to identify any trial that was not captured by the initial search strategy. This process yielded another 3 articles. A combined total of 18 trials resulted from the study selection process that was included in the SR. A flow diagram of the search and selection process is shown in Figure 2. The exported results of the search at the corresponding databases presented in separate .txt files and a reasoned list with all the excluded studies are contained at the electronic folder of the thesis that is submitted to the secretariat of the Master's Program.

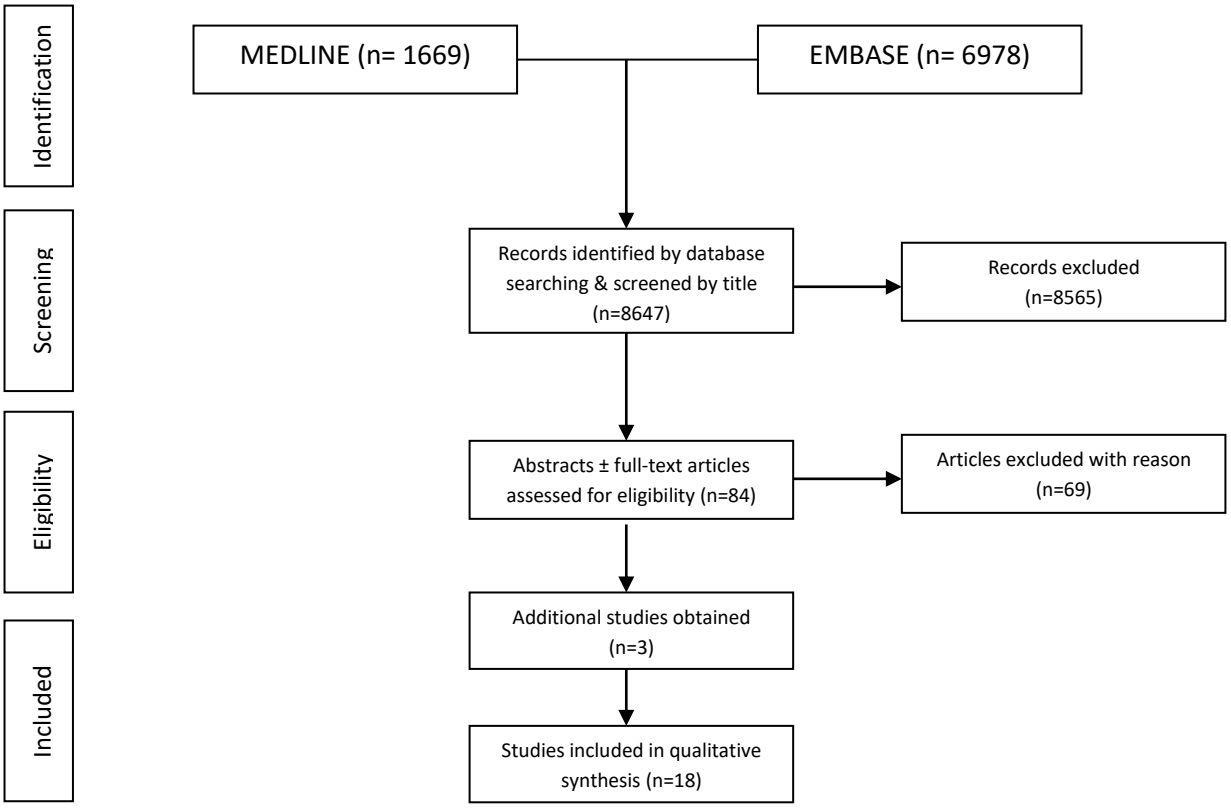

Figure 2. Flowchart for study identification, screening and selection.

Study characteristics

Table 1 provides an in-depth overview of the study characteristics. Reviews included in our sample were published between 2011 and 2020. Four studies were published before 2015 (34,44 – 46), one in 2015 (39) and the remaining thirteen studies were published from 2016 onward (30 – 33, 35 – 38, 40 – 43, 47). The majority (n = 12) were RCTs with two group study designs (34, 35, 37 – 42, 44 – 47), two were cluster RCTs (30,33), three were

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator -Control Group Intervention	Outcomes	Results
1.	Telemonitoring and Team-Based Management of Glycemic Control on People with Type 2 Diabetes: a Cluster-Randomized Controlled Trial. (30)	Lee JY et al. (2020)	Cluster RCT	Malaysia	12	Disease management, patient monitoring and surveillance	Healthcare providers from 11 primary healthcare centers	Pt monitoring device (Gluco - telemeter) + Team- Based management (Adjustments of therapy, group education on self - management, medication adherence, healthy lifestyle etc.)	T2 Diabetics for > 6 mo prior, aged 18-75 yo, with 11.0% ≤ HbA1c ≥ 7.5% within the past 3 mo (I:120, C:120)	Usual care (routine healthcare service)	HbA1c changes at 24 & 52 wks vs. baseline, health-related quality of life self-efficacy and SMBG.	No statistically significant difference in glycemic control, QoL or self-efficacy between intervention and comparator groups was demonstrated. ↓ Avg. # of SMBG in both groups throughout and especially after the study.
2.	Effects of Face-to-Face and Telephone-Based Family-Oriented Education on Self-Care Behavior and Patient Outcomes in Type 2 Diabetes: a Randomized Controlled Trial.(31)	Maslak-pak et al. (2017)	Multi-arm RCT	Iran	3	Patient/ Family education on self - management, medication adherence, blood glucose monitoring, lifestyle change, foot ulcer prevention	Authors at Diabetes Association	Telephone calls for family oriented education (x2/week in the first two months and x1/week in the 3rd month)	T2 Diabetics , aged 18-55 yo, with no underlying health problems (Ia:30, Ib:30, C:30)	1. Face to face family oriented education 2. Usual care (monthly training class and educational pamphlet)	Summary of Diabetes Self Care Activities (SDSCA) measure & HbA1c	↑ Overall self-care scores, mean dietary adherence score and physical activity scores In the intervention groups, with face-to-face group outcompeting significantly the telephone-based group - HbA1c & medication adherence scores: no significant differences among study groups pre or - post intervention - Comparable results at the rest SDSCA domains (foot care, blood glucose monitoring) between the intervention groups.
3.	Dulce Wireless Tijuana: a Randomized Control Trial Evaluating the Impact of Project Dulce and Short-Term Mobile Technology on Glycemic Control in a Family Medicine Clinic in Northern Mexico.(32)	Anzaldo-Campos et al. (2016)	Multi-arm RCT	Mexico	10	Disease management, patient education	Physicians and nurses from a family medical unit and local peer educators (All received Project Dulce training)	Project Dulce - Technology Enhanced (PD-TE) Pt monitoring device (Glucometer) + mHealth app (educational material, health surveys, alerts for abnormal glucose levels & appointments)	T2 Diabetics, aged 18-75 yo, with HbA1c ≥ 8.0% (PD:99, PD-TE:102, CG:100)	1. Project Dulce (PD) : Care by a multidisciplina-ry team 2.(CG) Usual care (monthly group or one-on-one medical visits with a family physician, following local technical guidelines)	HbA1c changes at 4 & 10 months vs. baseline - Self - efficacy, lifestyle, QoL, DM knowledge at 10 months vs. baseline	Significant ↓ of HbA1c and ↑ of DM knowledge in PD & PD -TE groups but no difference between intervention groups and not for any of the other self-reported outcomes.

Abbreviations: Pt: patient, T2: Type 2, mo: months, yo: years old, I: Intervention Group, C: Control Group, wks: weeks, QoL: Quality of Life. SMBG : Self Monitoring Blood Glucose

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator - Control Group Intervention	Outcomes	Results
4.	Effectiveness of an mHealth-Based Electronic Decision Support System for Integrated Management of Chronic Conditions in Primary Care: The mWellcare Cluster Randomized Controlled Trial.(33)	Prabha-karan et al. (2018)	Cluster RCT	India	12	Electronic information & decision support (EDS) system, disease management, patient records, medication adherence and appointment reminders - quality of care surveillance, supply chain management	Physicians and nurses from 40 community health centers	mHealth App (mWellcare) + physician and nurse training + nurse-led lifestyle advice + educational pamphlets + on-site simplified management charts	T2 Diabetics, aged ≥ 30 yo (I:1842, C:1856)	(EUC) Enhanced Usual Care (physician and nurse training + on-site simplified management charts + nurse-explained and –provided lifestyle advice pamphlets	HbA1c differences at 12 months vs. baseline	Significant ↓ of HbA1c at 1 year observed in both EUC & mWellcare arms - no difference in the change in HbA1c between the 2 arms.
5.	Use of Short Message Services (SMS) for the Management of Type 2 Diabetes Mellitus: A Randomized Controlled Trial.(34)	Tamban et al. (2013)	RCT	Philippines	6	Disease management, patient education, lifestyle change adherence, follow-up appointment reminder	University of the Philippines-Philippine General Hospital Diabetes Clinic : Endocrinologists and DM educators	SMS (x3/week) + Standard of DM care	T2 Diabetics, aged 19-50 yo, (I:52, C:52)	Standard of DM care (consultation with an endocrinologist + lecture by DM educator on proper diet and exercise.	HbA1c changes at 3 and 6 months vs. baseline & adherence to diet and exercise	Significant ↓ of HbA1c after 3 and 6 months, ↑ adherence to diet (mean # of meals) and exercise (mean # of minutes/exercise) after 6 months, in favour of the SMS group. Improved adherence to diet or exercise (mean # of days/week) for both groups without statistically significant difference.
6.	Effectiveness of mobile phone text messaging in improving glycaemic control among persons with new ly detected type 2 diabetes.(35)	Vinitha et al. (2019)	RCT	India	24	Disease management, patient education, medication adherence, health lifestyle	Physicians from 5 hospital centers	SMS (x2-3/week)	Newly diagnosed and treatment naïve T2 Diabetics, aged 20-60 yo w/ HbA1c >6.5% (I:122, C:126)	Advice at an individual level on healthy behavioral changes (healthy diet and physical activity)	HbA1c changes at 3,6,12,18 and 24 months vs. baseline and across groups & dietary intake, physical exercise and QoL	Intragroup significant ↓ of HbA1c vs baseline & Intergroup significant ↓ of HbA1c, favoring the intervention group. Significant ↓ of total calories and fat intake + significant ↑ of fibre intake in both groups w/ no intergroup difference. No improvement observed in physical activity and QoL.

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator - Control Group Intervention	Outcomes	Results
7.	Effectiveness of short message service-based intervention (SMS) on self-care in type 2 diabetes: a feasibility study.(36)	Peimani et al. (2016)	Multi-arm RCT	Iran	3	Disease management, patient education, medication adherence, blood glucose monitoring	GP, DM nurse educator, endocrinologist, nutritionist from an outpatient DM clinic (Endocrinology & Metabolism Research Institute affiliated to Tehran University of Medical Sciences)	Individually tailored (specifically on barriers obtained from diabetes self-care barriers assessment scale for older adults) & non-tailored SMS (x7/week for 3 months)	T2 Diabetics (Ia:50, Ib:50, C:50)	None	HbA1c changes at 3 months vs. baseline - Adherence to self-care tasks - Self efficacy	HbA1c: no significant differences at 3 months - Statistically significant post intervention difference (improvement) at promoting self-efficacy, adherence to self-care and overcoming its barriers among and within study groups
8.	Effects of Mobile Text Messaging on Glycemic Control in Patients With Coronary Heart Disease and Diabetes Mellitus.(37)	Huo et al. (2019)	RCT	China	6	Disease management, patient education, medication usage, blood glucose monitoring, healthy lifestyle.	Multidisciplinary team of cardiologists, endocrinologists, psychologists, nurses, linguists, and patients from 34 hospitals	SMS (x6/week for 6 months) + standard treatment	Patients aged ≥18 yo, w/ documented discharge Dx of CHD (acute MI or PCI) and DM within the prior 3 years (I:251, C:251)	Standard treatment + 2 thank you SMS /month	HbA1c changes at 6 months vs. baseline - Physical activity [METs (min × week)] at 6 months – Health status	Significant ↓ of HbA1c between baseline and 6 months in the intervention vs the control group. - Self reported physical activity and health status did not differ between groups..
9.	Impact of pharmacist-directed counseling and message reminder services on medication adherence and clinical outcomes in type 2 diabetes mellitus.(38)	Goruntla et al. (2019)	RCT	India	6	Disease management, patient education, medication adherence	Pharmacists from an outpatient medical department of a secondary care referral hospital	SMS (every day for 6 months) + pharmacist directed counseling	T2 Diabetics, aged 18-75yo,on glucose-lowering oral and/or injectable drugs (I:151, C:155)	Usual care by a physician	HbA1c changes and medication adherence at 3,6 months vs. baseline	Significant ↓ of HbA1c between baseline and 3,6 month follow-up in the intervention vs the control group - The mean difference of medication adherence from baseline to first and second follow-up visit was significantly more in intervention group compared to that in control group.

Abbreviations : METs : Metabolic Equivalents, min : minutes.

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator - Control Group Intervention	Outcomes	Results
10.	Mobile phone intervention to improve diabetes care in rural areas of Pakistan: a randomized controlled trial.(39)	Shadid et al. (2015)	RCT	Pakistan	4	Disease management, patient education, medication adherence, blood glucose monitoring, lifestyle change.	Physicians, DM educationist, nutritionist at Dpt of Endocrinology (Liaquat National Hospital, Karachi)	Telephone calls every 15 days for 4 months + Standard of DM care by physician + training by DM educationist on SMBG + diet information leaflet prepared by nutritionist	T2 Diabetics for > 3 mo prior, aged 18-70yo, with HbA1c ≥ 8.0% (I:220, C:220)	Standard of DM care by physician + training by DM educationist on SMBG + diet information leaflet prepared by nutritionist	HbA1c changes at 4 months vs. baseline	Significant ↓ of HbA1c at 4 months observed in both groups, but more pronounced in intervention group. Significant improvement in following diet plan and physical activity only in the intervention group at endline.
11.	The Influence of the Smart Glucose Manager Mobile Application on Diabetes Management.(40)	Gunawardena et al. (2019)	Pilot RCT	Sri Lanka	6	Disease management, patient education, medication adherence, blood glucose monitoring, lifestyle change.	Endocrinology clinic staff from a university hospital	mHealth App (Smart Glucose Manager - SGM)	T2 Diabetics for > 6 mo prior, aged 18-80 yo, with HbA1c ≥ 8.0% (I:35, C:32)	Usual care	HbA1c changes at 3 and 6 months vs. baseline	Both groups showed significant ↓ of HbA1c levels by 3months but the intervention group's HbA1c continued to ↓ while the control group's HbA1c levels plateaued.
12.	DM-calendar app as a diabetes self-management education on adult type 2 diabetes mellitus: a randomized controlled trial.(41)	Kusnanto et al. (2019)	RCT	Indonesia	3	Disease management, patient education, blood glucose monitoring, lifestyle change.	Primary health care nurses	mHealth app (DM-calendar app) + 4 x 30' DSME sessions	T2 Diabetics, dx within the last 12 months, w/ HbA1c ≥ 7.0% & under the same drug regimen for ≥ 3 months (I:15, C:15)	Leaflets + + 4 x 30' DSME sessions	Self-efficacy and HbA1c levels pre- and post-intervention	Both groups showed significant improvement of self-efficacy, but, comparatively, the intervention group achieved a statistically significant, absolute higher mean score. HbA1c values were significant only at the experimental group and comparatively lower.

Abbreviations : Dpt: Department, DSME : Diabetes Self Management Education.

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator - Control Group Intervention	Outcomes	Results
13.	SMS-based intervention in type 2 diabetes: clinical trial in Senegal. (42)	Wargny et al. (2018)	RCT	Senegal	6	Disease management, patient education	ITU,WHO, Endocrinolo-gists/ Diabetologi-sts in two primary care centers	SMS (daily/ week every 2 weeks for 3 months)	T2 Diabetics aged ≥18 (S: 92, P: 94)	Usual care	HbA1c changes at 3 months vs. baseline (impact on glycemic control) and at 6 months vs. at 3 months (residual effect – validation) between centers	Significantly higher ↓ of HbA1c at 3 months at S center. Improvement persisted in glycemic control at S center after SMS sending had been discontinued. Positive impact confirmed in the other center (P) after the intervention was applied.
*Randomized time allocation of the intervention between two centers: the S center participants received SMS during the first three months, then no SMS during the three following months. It was the reverse for P center participants.												
14.	The effect of text message support on diabetes self-management in developing countries – A randomised trial.(43)	Van Olmen et al. (2017)	3 sub – studies (RCTs)	Democratic Republic of Congo (DRC), Cambodia (CA) and the Philippines (P)	24	Disease management, patient education. -DRC : Faith-based primary care -CA: NGO-supported, community	Program manager + assistant, educator and DM trained GP	Routine Care + (DSME) + Diabetes Self Management Support (DSMS) with SMS -DRC : x5/wk -CA : x6/wk -P : x2/wk	Diabetics aged ≥18 DRC : (I: 160, C: 155) CA : (I: 198, C: 184) P : (I: 43, C: 41)	Routine Care (Consultations, with doctors) + DSME	Change in HbA1c levels between groups after 2 years – Knowledge, Perceptions, Utilization of care, SMBG.	The majority of the subjects did not change HbA1c categories (<7.0%; 7.0-7.9%; 8.0-8.9%; >9.0%) over 2 years. The % of subjects that improved by at least one category was significantly larger in the intervention group (aggregate analysis). No effect on the rest outcomes.
15.	Impact of distance education via mobile phone text messaging on knowledge, attitude, practice and self efficacy of patients with type 2 diabetes mellitus in Iran.(44)	Goodarzi et al. (2012)	RCT	Iran	3	Disease management, patient education.	Authors at a Diabetes Association	SMS (x4/week for 3 months)	T2 Diabetics for > 12 mo prior, aged > 30 yo, with HbA1c > 7.0% (I: 43, C: 38)	None	HbA1c changes at 3 months vs. baseline - Knowledge, Attitude, Practice and Self-Efficacy	↓ of HbA1c and ↑ of DM knowledge, practice and self-efficacy levels : Significant difference between intervention groups . No comparative improvement in attitude was observed.

Abbreviations : GP : General Physician, NGO : non- Governmental Organization, CHWs : Community Health Workers

No.	Title	Authors (Year)	Study Design	Study Location (Country)	Study Duration (Months)	Purpose / (mHealth) Service	Providers & Setting	Type of Intervention	Participants (n)	Comparator - Control Group Intervention	Outcomes	Results
16.	An ICT-Based Diabetes Management System Tested for Health Care Delivery in the African Context.(45)	Takenga et al. (2014)	RCT	Democratic Republic of Congo	2	Electronic information system (data collection/ transfer and reporting), disease management, patient education, self-monitoring, patient surveillance therapy adjustments	Medical doctors, nurses and nutritionists of four local hospitals	mHealth app (Mobil Diab)	T2 diabetics, aged 35 - 75 yo (I:20, C:20)	Conventional therapy	HbA1c changes at 2 months vs. baseline, usability, efficiency and acceptability (among patients and medical staff)	↓(in absolute values) of HbA1c at 2 months in intervention group vs. control group, moderate usability and efficiency and higher acceptability scores in both groups.
17.	Reinforcement of Adherence to Prescription Recommendations in Asian Indian Diabetes Patients Using Short Message Service (SMS)-A Pilot Study.(46)	Shetty et al. (2011)	Pilot RCT	India	12	Disease management, patient education, medication adherence, lifestyle change	Healthcare personel from a diabetes clinic	SMS reminder (x1/3 days) to follow the treatment plan (dietary modification, physical activity and drug regimen) + education program during the quarterly clinic visits	T2 Diabetics for ≥ 5 years, aged 30-65yo, with 10.0% ≤ HbA1c ≥ 7.0% (I:78, C:66)	Standard care (prescriptions of drugs and advice on diet and physical activity + education program during the quarterly clinic visits	HbA1c changes at 3,6,9,12 months vs. baseline, physical activity,diet & drug adherence, acceptability	No significant difference in the mean HbA1C values in both groups, no significant intergroup difference in adherence to diet, physical activity and drug prescriptions. The SMS intervention was evaluated as highly acceptable due to the high # of messages and their frequency requested by the patients.
18.	SMS education for the promotion of diabetes self-management in low & middle income countries: a pilot randomized controlled trial in Egypt.(47)	Abaza et al. (2017)	Pilot RCT	Egypt	3	Disease management, patient education, medication adherence, blood glucose monitoring reminders	Study's researcher, diabetes specialist, internal medicine doctors, and clinic & lab nurses from a teaching hospital's outpatient clinic of internal and general medicine	SMS (x1/day for 3 months) + Booklet of DM care instructions + Blood glucose monitoring table	T2 Diabetics (I:34, C:39)	Booklet of DM care instructions + Blood glucose monitoring table	HbA1c changes at 3 months vs. baseline *	After 3 months no significant difference was demonstrated in the mean HbA1C values in both groups and all secondary outcomes appeared to be in favor of the intervention group

*Non - clinical secondary outcomes : treatment and medication adherence, diabetes self-efficacy, diabetes knowledge, rate of hospital/ER visits and stays, average frequency of blood glucose measurement, rate of regular exercise, patients' confidence in healthcare provider, patient satisfaction, and healthcare provider's reputation.

multi – arm (with three group study designs) RCTs (31,32,36) and one was a multicentre RCT (43). Fifteen trials originated in Asia [Malaysia, Iran, India, Philippines, China, Pakistan, Sri Lanka, Indonesia and Cambodia) (30, 31, 33 – 41, 43, 44, 46), four in Africa (Senegal, Democratic Republic of Congo and Egypt) (42, 43, 45, 47) and one in Central America (Mexico) (32). India and Iran were the most represented countries, with 4 (33, 35, 38, 46) and 3 (31, 36, 44) trials respectively. Philippines (34, 43) and Democratic Republic of Congo (43, 45) followed with two trials. Each one of the rest trials took place in a different country. The studies lasted between 2 and 24 months (median = 6 months, mean = 8,1 months).

The mHealth interventions served several purposes in order to optimize disease management. Almost all had educational orientation by providing simplified piece of scientific information and the greater part aimed at supporting medication compliance, blood glucose monitoring and encouraging the adoption of a healthier lifestyle through physical activity and a suitable diet. Of note, two studies (33,45) presented electronic decision and information systems, that offered appointment reminder, electronic health record, therapy modification and supply chain management supplementary services. SMS was the main ICT tool used accounting for 10 out of 18 studies (34 – 38, 42 – 44, 46, 47), that chose this manner to implement their intervention (8/10 entirely unidirectional & 2/10 bidirectional (37, 43) . Immediately next were the mHealth apps, that were preferred by authors of four studies (33, 40, 41, 45) as communication channel. Two studies used telephone calls (31, 39), one a Glucotelemeter (30) and one a combination of a portable and interconnected blood glucose monitoring device with a mHealth app (32). The frequency of the SMS sent by the researchers started from once every three days (46) or twice a week (35, 43) that reached daily messaging (36, 38, 47). Correspondingly, phone calls ranged from once in fifteen days (39) to twice a week (31). It is worth mentioning that mHealth interventions were often complemented either by standard care like consultations and educational sessions or printed material (booklets, pamphlets). On the other hand, comparator group intervention wasn't restrictred to conventional therapy/ routine care but was intensified by similar means.

A wide variety of healthcare providers (physicians, nurses, researchers, peer educators, nutritionists, educationists, pharmacists, psychologists, linguists and others) in mixed group synthesis committed to perform all the necessary actions so that the interventions are completed successfully. The settings differed, as well. A half of the total happened at

hospital level departments (34 – 40, 45, 47), two thirds of which showed some degree of specialisation in endocrinology disorders (34, 36, 37, 39, 40, 47). One third of all the studies took place in primary health care centers or equivalent (30, 32, 33, 41 – 43). Finally, the remaining three studies (31, 44, 46) reported being held at DM focused establishments like associations or DM dedicated clinics, that wasn't very clear if they were independent or part of a bigger healthcare facility. The number of participants ranged from a combined sum of 30 (31) to 3698 (33). In total, data from 7481 patients were analyzed all studies included. All studies targeted adults with T2 DM except for two (37, 43) studies, that did not make any discrimination between T1 and T2 DM and another one (47) whose candidates could be both T1 and T2 diabetics, but only T2 diabetics were eventually recruited.

All studies, as it was prespecified in the eligibility criteria, assessed the difference in HbA1c values between endline and baseline. Eight studies conducted intermediate HbA1c measurements, while the intervention was still in progress (30, 32, 34, 35, 38, 40, 42, 46). Apart from three studies (33, 40, 42), whose central clinical outcome was HbA1c, all the rest reported several other health outcomes. Self efficacy (psychological concept – used when evaluating the potential to modify behaviour on adoption of healthier practices – "how well one can execute courses of action required to deal with prospective situations" (48,49) was measured in six studies (30, 32,36, 41, 44, 47). Diet and physical activity adherence were assessed together in three studies (34, 39, 46). Dietary intake was analysed (35) and physical activity (in kJ/kg/day and METs min/week) was calculated in additional studies (35, 37). Medication adherence and SMBG (average frequency of self blood glucose testing) were examined three times each (38, 46, 47 and 30, 43, 47, respectively).Quality of life (30, 32, 35) and health status (37) with DM were also investigated pre – and post – intervention. Terms, like Self – Care or Lifestyle, covering a broad category of DM management sectors simultaneously were other research topics (31 and 32). Finally, both DM knowledge and perceptions/ attitude towards DM were studied in two studies (43 ,44) but DM knowledge concerned authors in another two studies (32, 47). Secondary outcomes were assessed subjectively in various ways using self – reporting tools like questionnaires, interviews, recall sheets/tables.

Risk of bias within studies

All studies were assessed for risk of bias using the Consolidated Standards of Reporting Trials (CONSORT) statement for randomized trials of nonpharmacologic treatments. (50)

The detailed CONSORT risk of bias assessment sheet of the individual studies is contained at the electronic folder along with the rest supplementary files. On average, the studies fulfilled 66,9% of the criteria (range between 33% and 95%). Thus, overall the studies had a marginally moderate risk of bias. Five studies achieved low risk of bias (≥80% of the criteria) (30, 33, 37, 43, 47). Six studies had moderate risk of bias (≥65%, <80%) (32, 35, 38, 40, 41, 44). Four studies had higher risk of bias (≥50%, <65%) (31, 34, 36, 42). Three studies failed to achieve the minimal passing level and fulfilled less than 50% of the criteria set (39, 45, 46). Weakest points of the reports proved to be giving adequate information on the implementation phase of the trials and the intervention harms. Blinding was another issue but it is partially explained by the nature of the intervention.

Limitations of studies

The problems that reduce the importance of the studies are related either to the methodology of the study or to the participants. The necessity for larger numbers of participants (31, 32, 35, 40, 41, 44, 46, 47) and longer (30 – 32, 37, 39, 41, 44, 47) duration of studies was common ground for researchers. The difficulty with sample size further influences the validity of the trial, if the losses to follow up (due to inability to attend, relocation, personal matters), which were substantial, are taken into consideration (32, 34, 41 – 44). To make matters worse, authors turned to per protocol analysis as a solution, compromising randomisation that may have led to bias (38, 41 – 44, 46, 47). Moreover, various studies reported the problem of co – interventions (30, 32, 35) and lack of standardised comparator group care (30, 32, 33, 43, 47) as the effect cannot be easily interpreted and attributed either exclusively (or at which extent) to the mHealth intervention or health coaching. A factor that made results questionable was also the uncertainty in data that were self – reported by study's subjects and may have inserted reporting, recall or social desirability biases (30, 34, 36, 37). Finally, non – controllable confounding variables like participant's educational level (36, 42, 47), sex (37), sustained motivation/engagement (poor blood glucose measurements recording for example) in the study (30, 31), psychological and cultural profile (31) technological barriers confronted (43, 47) cannot be avoided, but should be expected and the outcomes appropriately adjusted.

Intervention effectiveness

Of the 18 studies included, significant improvement of HbA1c between intervention and control group was observed in ten (34, 35, 37 – 42, 44, 45) and eight demonstrated no significant effect on primary outcome (30 – 33, 36, 43, 46, 47). No clear patterns emerged between them. As far as the secondary outcomes are concerned, inconclusive data were reported, as well. The exceptions to the rule were quality of life (30, 32, 35) and perceptions/attitude towards DM (43, 44) that remained consistently unchanged after the interventions. Diet and physical activity went hand in hand, since they were commonly examined together, being in a balanced state, that means benefit in half of the studies (34, 39) and no difference in the other half (35, 46). As regards self – efficacy and knowledge the results seemed more positive (36, 41, 44, 47 & 32, 44, 47 respectively) than negative (or to put it more accurately, neutral) (30, 32 & 43). Medication adherence increased in two studies (38, 47) and showed comparable score in one (46), while for SMBG the reverse is true (47 & 30, 43).

Discussion

Summary and related work

The potential of mHealth interventions on DM lifelong management that requires lifestyle modification and medication treatment was unanimously agreed upon across the studies. Nevertheless, the heterogeneity in type of interventions applied, participants and settings the mixed results and the controversial quality of methodology and evidence inevitably constrain the added value this systematic review aims to confer on mHealth practices by disseminating experiences in LMICs of underrepresented populations in health research. Scarce relevant studies statistically confirmed the significant positive impact of mHealth interventions on glycaemic control (HbA1c) (14,18,51–53) and other diseases (18). In particular, according to a comparison made by Arambepola et al. (52), “the proportion of studies reporting positive effects was consistently higher for trials carried out in LMICs compared to HICs in all domains examined”, even though the calculated decline in HbA1c values was similar. On the other hand, this should be interpreted bearing in mind the different type of care and outcome a patient can expect in LMICs and HICs (7) and there were studies that contradicted the conclusions of the above mentioned studies (54,55). Probably, a future meta – analysis that will produce an overall effect size on the basis of the main clinical outcome could clarify the role of mHealth, as it was depicted in the

included studies, in circumventing the all kinds of barriers of traditional DM management. For the time being, the observations made had been presented narratively. Independently of where the balance will tip, it is quite sad that almost ten years later, mHealth studies face the same limitations and very few steps ahead have been made (51).

Points for consideration

No matter how much the big picture shouldn't be missed, I would like to dwell on several equally important points that were raised by individual studies and, in my opinion, need to be shared, so that ideas worth spreading are shared and errors are not repeated.

First of all, a better understanding of the intervention recipients is warranted. Only after listening carefully their needs and priorities and considering differences in cultural, social and demographic determinants can any suitably tailored intervention be implemented (30, 37). It is reasonable to anticipate that a horizontal intervention in different settings might not have the desirable effects (43). Another example is the influence of Fasting or Ramadan on a diabetic's nutrition plan and the implications on glycaemic control (46). In the same manner, illiteracy – health, technological or simple – is another issue that poses practical obstacles of mHealth services (30, 47). Confidentiality, security and privacy were another three parameters that were made prominent by an equal number of studies (32, 37, 45). A mHealth intervention might introduce risks that could easily result in data breach and exposure of sensitive personal health information, so extra protection should be enforced. Furthermore, the conflict of opinions over uni – and bidirectional messages (52) and tailored and non – tailored messages (36) should be resolved, as the available evidence points towards no effect difference in between them. Last, but not least, is the fact that DM is a chronic and progressive disease, that, as time goes by, can be associated with diabetics becoming careless (47) or less compliant (32) over health matters and health status (43) or medication regimen modifications (30, 35, 37). Abandoning static and initiating dynamic interventions is the proper path to avoid diminishing their effectiveness. Despite all that, the SMS interventions measured acceptability and utility that showed more than satisfactory results (37, 46, 47). Almost all identified messages as understandable, useful and readable and showed willingness to continue to receive messages. Encouraging as these data may be, they cannot mask the necessity of cost – effectiveness for the sustainability of mHealth services. The cost of programmes may seem low (Less than 1,5$ (37) or 3,1$ (42) per participant) but always

should be correlated with utilization of care, the long – term cost saving from averting diabetes – related complications and per capita income (and/or country's gross domestic product per capita).

Coming to the end of this thesis, the contribution of behavioural sciences to mHealth should be recognised. Management of DM far exceeds the prescription of medication and urging to engage on healthier lifestyle. Attention should be shifted away from the hospital – based treatment towards patient's education, because patients are the central players in day to day health care. Understanding the mechanisms how behavioural changes are translated into improvement of self – care actions and how these can be reflected in study designs will be a huge step in maximizing the effectiveness and establishing mHealth as integral part of standard care. Two studies report on a frame of specific behavioural theories. Anzaldo – Campos (32) et al. explained through control and goal setting theory the significance conceived by the participants of the feedback given, as blood glucose levels changed in relation to modifications of certain aspects of their lifestyle and the way this might have influenced them. Van Olmen et al.(43), on the other side, quotes theory of planned behaviour to explain how the transition from knowledge and attitude to actualized behaviour can be done.

Conclusions

This up – to – date and comprehensive study aimed to make readers aware of the mHealth landscape, to assess the processes and contextual factors that influenced the implementation of mHealth interventions against DM in underserved populations and document insights for future research development. This SR underlines that the dominant form of mHealth today is still characterized by limited quality projects. It would be imprudent to overestimate its effectiveness, since conclusions on our hypothesis can only be drawn with relevant uncertainty. There are no simple solutions for managing DM. However, we advocate of mHealth interoperability with conventional care and strongly believe that this new therapeutic option will mature capitalizing on the results of methodologically robust studies. By that time, a multifaceted intervention with mHealth as an adjunct will be able to make a significant difference against the silent pandemic of diabetes mellitus.

Appendix

Definitions – Abbreviations – Terminology

Diabetes Mellitus (DM) is a chronic medical condition, that consists of a group of metabolic disorders and is defined as a fasting plasma glucose (FPG) value of ≥ 7mmol/l (≥ 126mg/dl) or a two- hour, 75-gram oral glucose tolerance test (OGTT) of ≥ 11,1 mmol/l (≥ 200 mg/dl) or Hemoglobin A1c (HbA1c) ≥ 6,5% or a patient with classic symptoms of hyperglycemia or hyperglycemic crisis and random plasma glucose ≥200 mg/dL (≥11.1 mmol/L) or being on medication (insulin or oral hypoglycemic drugs) for raised blood glucose or with a history of diagnosis of diabetes (3,56). For the purpose of this thesis, the separate types (Type 1 & 2) of diabetes are not distinguished and the term Diabetes Mellitus is used as an umbrella term.

Diabetes Mellitus Management is composed of the following cluster of pillars:

a) use of a small set of generic medicines (insulin and oral hypoglycaemic agents – integrated management of DM and other diseases/NCDs)
b) interventions to support a healthy lifestyle (diet, physical activity, avoidance of harmful use of tobacco/alcohol)
c) patient education to facilitate self care (agreed and continually updated DM care plan)
d) regular screening for early detection (comprehensive eye examination/measurement of urine protein/feet assessment for signs of neuropathy – standard criteria for referral) and
e) treatment of complications through a multidisciplinary team (follow – up : periodic review of metabolic control and complications) (4)

Mobile Health (mHealth) , according to the Global Observatory of eHealth (GOe) and since no standardized definition has been established , is considered as a subset of electronic health (eHealth) and specified as medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices. (7)

NCDs : Non Communicable Diseases
WHO : World Health Organization

Database Search Strategy

Search (in title, abstract and keywords, 12.04.2020)

Limits: Databases : MEDLINE, EMBASE; Publication dates : 2010-2020; Languages : English; Species : Humans; Article Types : Randomized Controlled Trial, Controlled Clinical Trial, Clinical Trial

Sorted by: “Best match” and “Relevance” option

All Technology (Intervention) Terms combined with OR
ICT, Information technology, Communication technology , Mobile health, mHealth, Mobile phone, Short message service ,SMS, Multimedia messaging service ,MMS ,Text message, Application , App ,Smartphone, Cell phone, Cellular phone, Wireless, Device, Tablet, Personal digital assistant, Patient monitoring device.
All Disease Terms combined with OR
Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus , Blood glucose, Glycaemic control, Glycemic control, Management, Complications, Neuropathy, Nephropathy, Retinopathy, Micro vascular disease Treatment Adherence, Insulin, Insulin pump, Metformin, Oral Hypoglycemic Agents, Diet, Physical Activity, Non communicable diseases, NCDs, Glycosylated Haemoglobin, HbA1c, BMI, Body weight, Waist circumference, Hypoglycemia, Hyperglycemia, Impaired fasting glucose, Impaired glucose tolerance, Sugar
All Geographical Terms combined with OR
Developing country, Developing world, Low-income country, Middle-income country, Lower-middle income country, Upper-middle income country, Emerging country, Resource limited, Algeria, Angola, Argentina, Bahrain, Bangladesh, Barbados, Benin, Bolivia, Botswana, Brazil, Brunei Danas Salam, Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Chile, China, Colombia, Comoros, Congo, Costa Rica, Cote d’Ivoire, Cuba, Djibouti, Dominican Republic, DR Congo, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guatemala, Guinea, Guinea-Bissau, Guyana, Honduras, Hong Kong SAR, India, Indonesia, Iran, Iraq, Israel, Jamaica, Jordan, Kenya, Kuwait, Lebanon, Lesotho, Liberia, Libya, Madagascar, Malawi, Malaysia, Mali, Mauritania, Mauritius, Mexico, Morocco, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Niger, Nigeria, Oman, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Qatar, Republic of Korea, Rwanda, Sao Tome & Principe, Saudi Arabia, Senegal, Sierra Leone, Singapore, Somalia, Sri Lanka, Sudan, Syrian Arab Republic, Taiwan Province of China, Thailand, Togo, Trinidad and Tobago, Tunisia, Turkey, Uganda, United Arab Emirates, United Republic of Tanzania, Uruguay, Venezuela, Viet Nam, Yemen, Zambia, Zimbabwe
All Terms combined
#1 AND #2 AND #3

Tables

Classification of developing countries by region

Africa		Asia	Latin America and the Caribbean
North Africa	Southern Africa	East Asia	Caribbean
Algeria	Angola*	Brunei Danassalam	Barbados
Egypt	Botswana	China	Cuba
Libya	Lesotho*	Hong Kong SAR	Dominican Republic
Mauritania*	Malawi*	Indonesia	Guyana
Morocco	Mauritius	Malaysia	Jamaica
Sudan*	Mozambique*	Myanmar*	Trinidad and Tobago
Tunisia	Namibia	Papua New Guinea	Mexico and Central America
Central Africa	South Africa	Philippines	Costa Rica
Cameroon	Zambia*	Republic of Korea	El Salvador
Central African Republic*	Zimbabwe	Singapore	Guatemala
Chad*	West Africa	Taiwan Province of China	Honduras
Congo	Benin*	Thailand	Mexico
Equatorial Guinea*	Burkina Faso*	Viet Nam	Nicaragua
Gabon	Cape Verde	South Asia	Panama
Sao Tome & Principe*	Cote d'Ivoire	Bangladesh*	South America
East Africa	Gambia*	India	Argentina
Burundi*	Ghana	Iran	Bolivia
Comoros*	Guinea*	Nepal*	Brazil
DR Congo*	Guinea-Bissau*	Pakistan	Chile
Djibouti*	Liberia*	Sri Lanka	Colombia
Eritrea*	Mali*	Western Asia	Ecuador
Ethiopia*	Niger	Bahrain	Paraguay
Kenya	Nigeria*	Iraq	Peru
Madagascar*	Senegal*	Israel	Uruguay
Rwanda*	Sierra Leone*	Jordan	Venezuela
Somalia*	Togo*	Kuwait	
Uganda*		Lebanon	
United Republic of Tanzania*		Oman	
		Qatar	
		Saudi Arabia	
		Syrian Arab Republic	
		Turkey	
		United Arab Emirates	
		Yemen*	
High – income	Upper middle income	Lower middle income	Low - income

*Least developed countries

Reproduced and recombined by the World Economic Situation and Prospects annex that was prepared by the Development Policy and Analysis Division of the Department of Economic and Social Affairs of the United Nations Secretariat in 2014.

List of excluded studies and reasons for exclusion

No.	Title	Author(s) (Date of publication)	Rejection Reason(s)
1.	The effect of case management model based on mobile health on self-management and blood glucose control of type 2 diabetes patients.	Li (2018)	Publication type: Conference abstract – Full text version could not be retrieved.
2.	Randomized trial of technology-assisted self-monitoring of blood glucose by low-income seniors: improved glycemic control in type 2 diabetes mellitus.	Levine et al. (2016)	Study Location: USA – ICT used: PC.
3.	"Mellitusone.", a new technological approach to record, access, share and improve the glycemic control.	Jacomassi et al. (2016)	Publication type: Conference abstract – Full text version could not be retrieved – ICT used: PC.
4.	Utility of a multi-model bot enabled and doctor led intervention for diabetes management-clinician and patient perspectives.	Kesavadev et al. (2018)	Publication type: Conference abstract – Full text version could not be retrieved – Outcomes: Irrelevant.
5.	Implementation of foot thermometry plus mHealth to prevent diabetic foot ulcers: study protocol for a randomized controlled trial.	Lazo-Porras et al. (2016)	Publication type: Study Protocol – Report of completed trial was retrieved – Outcomes: Irrelevant.
6.	Lifestyle changes and glycemic control in type 1 diabetes mellitus: a factorial design approach	Siddiqui et al. (2019)	Publication type: Conference abstract – Full text version could not be retrieved.
7.	Impact of self-management on metabolic control indicators of diabetes patients.	Moattari et al. (2012)	Non – mHealth intervention.
8.	The impact of smartphone-based body cloud application on diabetes self-care behaviors and glycemic control: a randomized controlled trial.	Xia et al. (2017)	Publication type: Conference abstract - Full text version could not be retrieved - Study location: Singapore.
9.	Efficacy of mobile diabetes care based on a newly developed patient decision support system (PDSS).	Kim et al. (2014)	Publication type: Conference abstract – Full text version could not be retrieved – Study location: Republic of Korea (South).
10.	Adherence level and blood sugar control of type 2 diabetes mellitus patients who gets counseling and short messages service as reminder and motivation.	Adikusuma et al. (2018)	Study design: Quasi experimental.
11.	Effectiveness of digital health using the trans theoretical model to prevent or delay type 2 diabetes in impaired glucose tolerance patients: protocol for a randomized control trial.	Alzeidan et al. (2019)	Publication type : Protocol – Aim of study: Prevention – Study location: Saudi Arabia.
12.	Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial.	Ramachand-ran et al. (2013)	Aim of study: Prevention.
13.	Randomized Controlled Trial of Technology - Assisted Case Management in Low Income Adults with Type 2 Diabetes.	Egede et al. (2017)	Study location: USA.
14.	Mobile based intervention for reduction of coronary heart disease risk factors among patients with diabetes mellitus attending a tertiary care hospital of India.	Patnaik et al. (2014)	Outcomes: Irrelevant.
15.	The effect of short message service (SMS) on knowledge and preventive	Moradi et al. (2019)	Aim of study: Prevention

	behaviors of diabetic foot ulcer in patients with diabetes type 2.		
16.	A pragmatic and scalable strategy using mobile technology to promote sustained lifestyle changes to prevent type 2 diabetes in India-Outcome of screening.	Priscilla et al. (2015)	Aim of study: Screening – Prevention.
17.	Efficacy, feasibility and acceptability of mHealth technology (SMS) for promoting glycaemic status and self-management among low-income earning adults in Eastern Cape, South Africa.	Owolabi et al. (2019)	Outcomes: Irrelevant.
18.	Text messaging versus usual care for weight loss in patients with pre-diabetes.	Fischer et al. (2015)	Condition: Prediabetes – Outcomes: Irrelevant.
19.	The effectiveness of interactive multi-modality intervention on self-management support of type 2 diabetic patients in Thailand: a cluster randomized controlled trial.	Wongrocha-nanan et al. (2013)	Non – mHealth co-interventions.
20.	Efficacy of a virtual assistance-based lifestyle intervention in reducing risk factors for Type 2 diabetes in young employees in the information technology industry in India: LIMIT, a randomized controlled trial.	Limaye et al. (2017)	Aim of study: Prevention – Non – mHealth co-interventions.
21.	Study of the supportive care program effects of a home nursing platform based on mobile internet technology in adolescent patients with type 1 diabetes mellitus.	Li et al. (2018)	Publication type: Conference abstract – Full text version could not be retrieved – Pediatric diabetes.
22.	Digital Diabetes Management Application Improves Glycemic Outcomes in People With Type 1 and Type 2 Diabetes..	Offringa et al. (2017)	Study Location: USA – Outcomes: Irrelevant.
23.	Comprehensive electronic data capture of diabetes management information in a diverse population across 25 countries.	Chang et al. (2014)	Publication type: Conference abstract – Full text version could not be retrieved – Outcomes: Irrelevant
24.	Evaluation, intervention, and follow-up of patients with diabetes in a primary health care setting in Brazil: the importance of a specialized mobile consultancy.	Eik Filho et al. (2016)	Non – mHealth intervention
25.	Engagement and Weight Loss: results from the Mobile Health and Diabetes Trial.	Muralidha-ran et al. (2019)	Outcomes: Irrelevant – Aim of study: Prevention.
26.	How do Smart Device Apps for Diabetes Self-Management correspond with Theoretical Indicators of Empowerment? An Analysis of App Features.	Brew-Sam et al. (2019)	Outcomes: Irrelevant – Aim of study: Irrelevant.
27.	TRIal to slow the Progression of Diabetes (TRIPOD): study protocol for a randomized controlled trial using wireless technology and incentives.	Lim et al. (2019)	Publication type : Protocol - Study location : Singapore.
28.	Acceptability and feasibility of an mHealth self-management intervention in underserved hispanics with poorly controlled type 2 diabetes.	Fortmann et al. (2015)	Study Location: USA – Outcomes: Irrelevant.
29.	Mobile phone text messaging and Telephone follow-up in type 2 diabetic patients for 3 months: a comparative study.	Zolfaghari et al. (2012)	Study design: Quasi experimental

30.	The effect of community groups and mobile phone messages on the prevention and control of diabetes in rural Bangladesh: study protocol for a three-arm cluster randomised controlled trial.	Fottrell et al. (2016)	Publication type: Study Protocol – Report of completed trial was retrieved – Outcomes: Irrelevant.
31.	Protocol of economic evaluation and equity impact analysis of mHealth and community groups for prevention and control of diabetes in rural Bangladesh in a three-arm cluster randomised controlled trial.	Haghparast - Bidgoli et al. (2018)	Publication type: Study Protocol – Report of completed trial could not be retrieved – Outcomes: Irrelevant.
32.	A randomized trial using mobile short-text messaging to improve cardiovascular risk profile in poorly controlled diabetes in Kenya.	Soin et al. (2018)	Publication type: Conference abstract – Full text version could not be retrieved.
33.	Community groups or mobile phone messaging to prevent and control type 2 diabetes and intermediate hyperglycaemia in Bangladesh (DMagic): a cluster-randomised controlled trial.	Fottrell et al. (2019)	Outcomes: Irrelevant.
34.	Cost Effectiveness of a Technology-Enhanced Diabetes Care Management Program in Mexico	Gilmer et al.(2019)	Outcomes : Irrelevant.
35.	Community-and mHealth-based integrated management of diabetes in primary healthcare in Rwanda (D2;Rwanda): the protocol of a mixed-methods study including a cluster randomised controlled trial.	Lygidakis et al. (2019)	Publication type: Study Protocol – Report of completed trial could not be retrieved.
36.	Cost-effectiveness of technology-assisted case management in low income adults with diabetes.	Egede et al. (2018)	Publication type: Conference abstract – Report of original trial was retrieved – Study Location: USA.
37.	A Smartphone App to Improve Medication Adherence in Patients With Type 2 Diabetes in Asia: feasibility Randomized Controlled Trial.	Huang et al. (2019)	Study Location: Singapore.
38.	A randomized controlled trial of a smart phone-based diabetes management application to improve blood glucose control in Chinese people with diabetes.	Zhang et al. (2018)	Publication type: Conference abstract – Full text version could not be retrieved.
39.	Design and patient characteristics of the randomized controlled trial TExT-MED + FANS A test of mHealth augmented social support added to a patient-focused text-messaging intervention for emergency department patients with poorly controlled diabetes.	Burner et al. (2019)	Publication type: Research support – Study location: USA.
40.	Effects of mobile text messaging on glycemic control in patients with coronary heart disease and diabetes mellitus: a randomized controlled trial.	Huo et al. (2019)	Publication type: Conference abstract – Full text was retrieved – Already included in the SR.
41.	Efficacy, acceptability and feasibility of daily text-messaging in promoting glycaemic control and other clinical outcomes in a low-resource setting of South Africa: a randomised controlled trial.	Owolabi et al. (2019)	Outcomes: Irrelevant.
42.	Dulce Digital: an mHealth SMS-Based Intervention Improves Glycemic Control in	Fortmann et al. (2017)	Study location: USA.

	Hispanics With Type 2 Diabetes.		
43.	Evaluation of a mobile social networking application for improving diabetes Type 2 knowledge: an intervention study using WhatsApp.	Alanzi et al. (2018)	Study location: Saudi Arabia – Outcomes: Irrelevant.
44.	'MOVEdiabetes': a cluster randomized controlled trial to increase physical activity in adults with type 2 diabetes in primary health in Oman.	Alghafri et al. (2018)	Study location: Oman.
45.	Trial to examine text message-based mHealth in emergency department patients with diabetes (TExT-MED): a randomized controlled trial.	Arora et al. (2014)	Study location: USA.
46.	DTEXT - text messaging intervention to improve outcomes of people with type 2 diabetes: protocol for randomised controlled trial and cost-effectiveness analysis.	Waller et al. (2019)	Study location: Australia.
47.	Using Mobile Health to Improve Social Support for Low-Income Latino Patients with Diabetes: a Mixed-Methods Analysis of the Feasibility Trial of TExT-MED + FANS.	Burner et al. (2018)	Study location: USA.
48.	The effect of a smartphone-based, patient-centered diabetes care system in patients with type 2 diabetes: a randomized, controlled trial for 24 weeks.	Kim et al. (2019)	Publication type : Letter – Full text was retrieved – Study location : Republic of Korea (South).
49.	Effect of mobile learning (application) on self-care behaviors and blood glucose of type 2 diabetic patients.	Hooshmand-ja et al. (2019)	Study design: Quasi experimental.
50.	Process evaluation of a mobile health intervention for people with diabetes in low income countries - the implementation of the TEXT4DSM study.	Van Olmen et al. (2017)	Article type: Evaluation study.
51.	Comparison of multimedia and SMS education on the physical activity of diabetic patients: an application of health promotion model.	Lari et al. (2018)	Primary outcome (difference in HbA1c levels) was not included.
52.	Mobile phone use and willingness to pay for SMS for diabetes in Bangladesh.	Islam et al. (2015)	Publication type: Conference abstract - Full text version was retrieved - Outcomes : Irrelevant
53.	Effects of mobile phone sms to improve glycemic control among patients with type 2 diabetes in Bangladesh: a prospective, parallel-group, randomized controlled trial.	Islam et al. (2015)	Publication type: Journal note – Report of completed trial could not be retrieved.
54.	A mobile phone message reminder to improve adherence of diabetic patients for scheduled eye care in Rural China: a randomized clinical trial.	Chen et al. (2017)	Publication type: Conference abstract – Full text version was retrieved – Primary outcome (difference in HbA1c levels) was not included.
55.	Distance education and diabetes empowerment: a single-blind randomized control trial.	Zamanza-deh et al. (2016)	Outcomes: Irrelevant.
56.	Development of mWellcare: an mHealth intervention for integrated management of hypertension and diabetes in low-resource settings.	Jindal et al. (2018)	Publication type: Research support.
57.	The influence of mobile health on patient	Yasmin et al.	Publication type: Conference

	adherence in the case of effective management of type 2 diabetes in Bangladesh.	(2015)	abstract – Full text version could not be retrieved.
58.	Protocol for a clinical trial of text messaging in addition to standard care versus standard care alone in prevention of type 2 diabetes through lifestyle modification in India and the UK.	Thomson et al. (2018)	Publication type: Protocol – Full text version was retrieved – Condition: Prediabetes.
59.	A randomized controlled trial on a nurse-led smartphone-based self-management program for people with poorly controlled type 2 diabetes: A study protocol.	Wang et al. (2018)	Publication type: Protocol – Full text version could not be retrieved – Study location : Singapore.
60.	Protocol of economic evaluation and equity impact analysis of mHealth and community groups for prevention and control of diabetes in rural Bangladesh in a three-arm cluster randomised controlled trial.	Haghparast et al. (2018)	Outcomes: Irrelevant.
61.	A Mobile Lifestyle Management Program (GlycoLeap) for People With Type 2 Diabetes: Single-Arm Feasibility Study.	Koot et al. (2019)	Publication type: Single – arm feasibility study – Study location: Singapore – non – mHealth co-intervention.
62.	Feasibility study of automated interactive voice response telephone calls with community health nurse follow-up to improve glycaemic control in patients with type 2 diabetes.	Pichayapi-nyo et al. (2019)	Publication type: Single - arm feasibility study – non – mHealth co-intervention.
63.	Effectiveness of digital health using the transtheoretical model to prevent or delay type 2 diabetes in impaired glucose tolerance patients: protocol for a randomized control trial.	Alzeidan et al. (2019)	Study location: Saudi Arabia – Condition: Prediabetes – Aim of study: Prevention.
64.	A mobile and web-based clinical decision support and monitoring system for diabetes mellitus patients in primary care: a study protocol for a randomized controlled trial.	Kart et al. (2017)	Publication type: Study protocol - Full text version could not be retrieved.
65.	Modular ICT-based patient empowerment framework for self-management of diabetes: Design perspectives and validation results.	Lamprinos et al. (2016)	Oucomes: Irrelevant – non – mHealth co-intervention – Study location : Germany (partly).
66.	Determining Effective Diabetic Care; A Multicentre - Longitudinal Interventional Study.	Gillani (2016)	Full text version could not be retrieved.
67.	Evaluation of a mobile social networking application for improving diabetes Type 2 knowledge: an intervention study using WhatsApp.	Alanzi et al. (2018)	Study location: Saudi Arabia – Primary outcome (difference in HbA1c levels) was not included.
68.	Short-term trajectories of use of a caloric-monitoring mobile phone app among patients with type 2 diabetes mellitus in a primary care setting.	Goh et al. (2015)	Study location : Singapore – Primary outcome (difference in HbA1c levels) was not included.
69.	Cost-Effectiveness of Facilitated Access to a Self-Management Website, Compared to Usual Care, for Patients With Type 2 Diabetes (HeLP-Diabetes): Randomized Controlled Trial.	Li et al. (2018)	Study location : UK – Outcomes: Irrelevant – non – mHealth intervention.

Risk of Bias Assessment Using the CONSORT Checklist of Information to Include When Reporting Randomized Trials Assessing Non Pharmacologic Treatments

	Lee et al. (2020)	Maslakpak et al. (2017)	Anzaldo - Campos et al. (2016)	Prabhakaran et al. (2019)	Tamban et al., 2013	Vinitha et al. (2019)	Peimani et al. (2016)	Huo et al. (2019)	Goruntla et al. (2019)
1.Title and abstract	+ +	+ +	+ +	+ +	+ +	- +	- +	+ +	- +
a) identification as randomized trial in title; b) structured summary									
2.Introduction	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
a) scientific background rationale; b) specific objectives hypotheses									
3.Methods – *trial design*	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -
a) description of trial design (incl. allocation ratio), if applicable care providers allocation method b) changes in methods after trial commencement									
4.Participants	+ +	+ +	+ +	+ +	+ -	+ +	+ +	+ -	+ +
a) eligibility criteria, if applicable also for centres and for care providers b) settings and locations of data collection									
5.Interventions	+ + - +	+ - - -	+ + + +	+ + + +	+ - - +	+ + - +	+ + - +	+ + + +	+ + + +
Sufficient details of both the experimental treatment and comparator to allow replication (incl. how and when) a) description of components b) standardization c),d) adherence of care providers and participants									
6.Outcomes	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -
a) pre-specified primary and secondary outcomes; b) changes to outcomes after trial commencement									
7.Sample size	+	+	+	+	+	+ +	+	+	+
a) how sample size was determined, if applicable management of clustering by care providers or centers b) if applicable, interim analysis/ stopping guidelines									
8.Randomization – *sequence generation*	+ -	+ -	+ +	+ +	+ +	+ -	- +	+ +	+ +
a) method used; b) type of randomization including any type of restriction									
9.Allocation concealment mechanism	+	+	-	+	+	+	-	+	--
Implementation of random allocation sequence, including concealment									
10.Implementation	-	-	-	+	+	+	-	-	-
Who generated random allocation sequence, who enrolled participants, who assigned participants									
11.Blinding	+ - +	- - -	- - -	- - +	+ + +	- + +	+ + -	+ + +	- - -

a) if done, who was blinded and how; b) if relevant, similarity of interventions c)if not possible, attempts to limit bias									
12.Statistical methods	+ +	+ +	+ +	+ +	+ -	+ +	+ +	+ +	+ +
Statistical methods used a) for primary outcomes, if applicable management of clustering by care providers or centers, b) additional analyses									
13.Results – ***participant flow***	+ + + -	+ + + +	+ + + +	- + + +	+ + - -	+ - - +	+ + - +	+ + + +	+ + + +
a) number of participants randomized, receiving treatment, and analyzed, care providers/centers performing the intervention in each group and patients treated by each care provider or in each center b) losses and exclusions, with reasons c) delay between randomization and initiation d) details of the experimental treatment and comparator as they were implemented									
14.Recruitment	+ -	- -	+ -	+ -	- -	+ -	- -	+ -	+ -
a) dates of recruitment and follow-up b) why the trial ended									
15.Baseline data	+ -	+	+	+	+	+	+	+	+
A table with baseline demographic and clinical characteristics for each group and if applicable, description of care providers and centers									
16.Numbers analyzed	+	+	+	+	+	+	+	+	+
For each group, number of participants included in each analyses									
17.Outcomes and estimation	+ -	+ -	+ -	+ -	- -	+-	+ -	+ +	+ +
a) results for each group, and the estimated effect size and its precision; b) absolute and relative effect sizes for binary outcomes									
18.Ancillary analyses	+	-	+	+	-	+	+	+	-
Results of any other analyses performed, distinguishing pre-specified from exploratory									
19.Harms	+	-	-	-	-	-	-	-	-
Harms or unintended effects in each group									
20.Discussion - ***Limitations***	+	+	+	+	+	+	+	+	+
Trial limitations/ bias/ multiplicity of analyses									
21.Generalizability	+	-	+	-	-	-	-	+	+
Generalisability (external validity/ applicability) of findings according to the intervention, comparators, patients and care providers/centers involved									
22.Interpretation	+	+	+	+	+	+	+	+	+

Consistent with results and balanced									
23.Other information - ***Registration***	+	+	+	+	-	+	-	+	+
Registration number and name of registry									
24.Protocol	+	-	+	+	-	-	-	+	+
Where full trial protocol can be accessed									
25.Funding	+	-	+	+	+	+	-	+	+
Sources of funding/ role of funders									
Number of criteria satisfied (in percent)	20,25 (81%)	14,25 (57%)	19 (76%)	20,09 (80%)	15 (60%)	17,92 (72%)	13,67 (55%)	21 (84%)	18 (72%)

	Shahid et al. (2015)	Gunawarde-na et al. (2019)	Kusnanto et al. (2019)	Wargny et al. (2018)	Van Olmen et al. (2017)	Goodarzi et al. (2012)	Takenga et al. (2014)	Shetty et al. (2011)	Abaza et al. (2017)
1.Title and abstract	+ +	- +	+ +	- +	+ +	+ +	- -	- +	+ +
a) identification as randomized trial in title; b) structured summary									
2.Introduction	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
a) scientific background rationale; b) specific objectives hypotheses									
3.Methods – ***trial design***	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ -	+ +
a) description of trial design, if applicable care providers allocation method b) changes in methods after trial commencement									
4.Participants	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +	+ +
a) eligibility criteria, if applicable also for centres and for care providers b) settings and locations of data collection									
5.Interventions	+ - + +	+ + - +	+ + + +	+ + + -	+ + + +	+ + + +	+ - - -	+ - - -	+ + + +
Sufficient details of both the experimental treatment and comparator to allow replication (incl. how and when) a) description of components b) standardization c),d) adherence of care providers and participants									
6.Outcomes	+ -	+ -	+ -	+ +	+ -	+ -	+ -	+ -	+ -
a) pre-specified primary and secondary outcomes; b) changes to outcomes after trial commencement									
7.Sample size	+	-	+	+ -	+	+	-	-	+
a) how sample size was determined, if applicable management of clustering by care providers or centers b) if applicable, interim analysis/ stopping guidelines									
8.Randomization – ***sequence generation***	- -	+ +	+ +	- +	+ +	+ +	- -	+ -	+ +
a) method used; b) type of randomization including any type of restriction									

9.Allocation concealment mechanism	-	-	-	-	+	+	-	-	+
Implementation of random allocation sequence, including concealment									
10.Implementation	-	-	-	-	-	-	-	-	+
Who generated random allocation sequence, who enrolled participants, who assigned participants									
11.Blinding	- - -	- - -	+ + +	- - -	- + -	- - -	- - -	- - -	+ + -
a) if done, who was blinded and how; b) if relevant, similarity of interventions c)if not possible, attempts to limit bias									
12.Statistical methods	+ +	+ +	+ +	+ +	+ +	+ +	- -	+ +	+ +
Statistical methods used a) for primary outcomes, if applicable management of clustering by care providers or centers, b) additional analyses									
13.Results – ***participant flow***	- - - -	+ + + +	+ + + +	+ + + -	+ + - +	+ + + +	- - - -	+ - - +	+ + + +
a) number of participants randomized, receiving treatment, and analyzed, care providers/centers performing the intervention in each group and patients treated by each care provider or in each center b) losses and exclusions, with reasons c) delay between randomization and initiation d) details of the experimental treatment and comparator as they were implemented									
14.Recruitment	+ -	+ -	+ -	+ -	- -	+ -	- -	- -	+ -
a) dates of recruitment and follow-up b) why the trial ended									
15.Baseline data	+	+	+	+	+	+	+	+	+
A table with baseline demographic and clinical characteristics for each group and if applicable, description of care providers and centers									
16.Numbers analyzed	+	+	+	+	+	+	+	+	+
For each group, number of participants included in each analyses									
17.Outcomes and estimation	+ -	+ +	+ -	+ -	+ +	+ +	- -	- -	+ +
a) results for each group, and the estimated effect size and its precision; b) absolute and relative effect sizes for binary outcomes									
18.Ancillary analyses	-	+	+	+	+	+	-	-	+
Results of any other analyses performed, distinguishing pre-specified from exploratory									
19.Harms	-	-	-	-	-	-	-	-	+
Harms or unintended effects in each group									

20.Discussion - *Limitations*	+	+	+	+	+	+	+	+	+
Trial limitations/ bias/ multiplicity of analyses									
21.Generalizability	-	+	+	+	+	+	+	-	+
Generalisability (external validity/ applicability) of findings according to the intervention, comparators, patients and care providers/centers involved									
22.Interpretation	-	+	+	+	+	+	+	+	+
Consistent with results and balanced									
23.Other information - *Registration*	-	+	+	-	+	+	-	-	+
Registration number and name of registry									
24.Protocol	-	+	-	-	+	-	-	-	+
Where full trial protocol can be accessed									
25.Funding	-	+	-	+	+	-	-	-	+
Sources of funding/ role of funders									
Number of criteria satisfied (in percent)	10,25 (41%)	17,75 (71%)	18 (72%)	15,5 (62%)	20,09 (80%)	18,5 (74%)	8,25 (33%)	9,75 (39%)	23,66 (95%)

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