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Do mobile phone applications improve the glycemic control (HbA1c) in self-management of patients with diabetes: A systematic review, meta-analysis and GRADE of the evidence of 14 randomized trials

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Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes: A systematic review and meta-analysis and GRADE of 14 randomized trials

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ABSTRACT

OBJECTIVES: To investigate the effect of mobile phone applications on glycemic control (HbA1c) in the self -management of diabetes.

RESEARCH DESIGN AND METHODS: Relevant studies that were published between 1996 to June 1st, 2015 were searched from five databases: Medline, CINAHL, The Cochrane Library, Web of Science, and EMBASE. Randomized controlled trials that evaluated diabetes apps were included. We conducted a systematic review with meta-analysis and GRADE of the evidence.

RESULTS: 1360 participants from 14 studies were included and quality assessed. Whilst there may have been clinical diversity, all type 2 diabetes studies reported a reduction in HbA1c. The mean reduction in participants using an app compared to control was 0.49% (95% CI 0.30%-0.68%; I^2=10%), with a moderate GRADE of evidence. Subgroup analyses indicated that younger patients were more likely to benefit from the use of diabetes apps and the effect size was enhanced with healthcare professional feedback. There was inadequate data to describe the effectiveness of apps for type 1 diabetes.

CONCLUSIONS: Apps may be an effective component to help control HbA1c, and could be considered as an adjuvant intervention to the standard self-management for patients with type 2 diabetes. Given the reported clinical effect, the access and nominal cost of this technology, it is likely to be effective at the population level. The functionality and use of this technology needs to be standardized, but policy and guidance is anticipated to improve diabetes self-management care.

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What this study adds

- There is a moderate level of evidence that the self-management of type 2 diabetes is improved by using smart phone applications to reduce HbA1c
- Apps may offer a clinically effective component in the self-management of type 2 diabetes
- Younger users were associated with the largest reduction in HbA1c

Background

The number of diabetes patients globally is expected to rise to over 500 million by 2030 (1), there is an urgent need for an improved self-management suite of interventions. For self-management to be effective it needs to be structured and cost effective (2), and be widely accessible across all health economies, including the developing world (2).

As a newly emerging technology, diabetes mobile phone applications (hereafter referred to as diabetes apps) are a promising tool for self-management. We define diabetes apps as mobile phone software that accepts data (transmitted or manual entry), and provides feedback to patients on improved management (automated or by health care profession [HCP]). This technology combines the functions of the mobile phone, wireless network for data transmission and sometimes HCPs for providing feedback. Due to its ubiquitous, low cost, interactive, and dynamic health promotion, there is potential for diabetes apps to provide an effective intervention in diabetes self-care.

In terms of diabetes self-management, numerous studies have proven the effectiveness of other telemedicine technologies, such as short message service (3), computer-based interventions (4), and web-based interventions (3; 5). Compared with these telemedicine interventions, diabetes apps are advantageous in that they are global, cheaper, convenient, and more interactive. There is however, current uncertainty on the clinical effectiveness of diabetes apps in diabetes self-management (6-9).

METHODS

Data sources and search strategy

The PRISMA statement and checklist was followed. Five electronic databases were searched (Medline, CINAHL, The Cochrane Library, Web of Science, and EMBASE) for studies published between January 1st, 1996 to June 1st, 2015. Included studies' references were hand searched to identify any additional articles. The following terms and medical subject headings (MeSH) were used during the search: (mobile OR mHealth OR cell phone OR MeSH "Cellular Phone" OR MeSH "Smartphone" OR app OR MeSH "Mobile Applications") AND (MeSH "Diabetes Mellitus" OR diabete*

OR T2DM OR T1DM OR IDDM OR NIDDM).

Inclusion and exclusion criteria

The inclusion criteria were: the participants were over 18 years old and had type 1 or type 2 diabetes; the studies were randomized controlled trials (RCTs); the control group in the study received usual diabetes care without any telehealth programs; baseline and follow-up mean for HbA1c were reported (or could be calculated).; Exclusion criteria were: simulated or self-reported HbA1c data; computer or other mobile terminal-based diabetes apps; diabetes apps were exclusively designed for HCPs; and diabetes apps were exclusively designed for providing general education, or allowing communication between patients and HCPs.

Two reviewers (CH, TF) searched the literature and assessed the studies independently. Any disagreements were resolved through discussion with a third reviewer (BC). No language restrictions were applied.

Data extraction

Participant demographics, study design considerations and context were extracted from the included studies. Two reviewers independently carried out the data extraction (CH, TF). Study authors were contacted to provide additional data, and missing standard deviations were estimated by calculation (10).

Quality assessment

The quality assessment was conducted by two reviewers independently (CH, TF), using the quality rating tool proposed by the US Preventive Service Task Force (11). Seven criteria were used to assess quality: baseline comparability of the groups; the maintenance of comparability of the groups; differential or high loss to follow-up; reliable and valid measurement; clear definition of the intervention; consideration of important outcomes; and an intention-to-treat analysis. The quality of each study was graded as Good, Fair, or Poor. To be rated as good studies needed to meet all the criteria. A study was rated as poor if one (or more) domain was assessed as having a serious flaw. Studies that met some but not all of the criteria was rated as fair quality.

Data analysis

Changes in HbA1c, or HbA1c at follow-up were compared between groups using a mean difference, and were presented with an associated 95% confidence interval (95% CI). When studies investigated interventions and contexts that were both deemed clinically similar, and free from statistical heterogeneity, pooling was carried using an inverse variance random effects model (12). Meta-analyses were conducted using the Comprehensive Meta-Analysis Software (version 2.2). The level of evidence was applied to the GRADE criteria and reported.

Heterogeneity and subgroup analyses

Heterogeneity was assessed and quantified using the I^2 statistic. When substantial heterogeneity was found (I^2>50%), further exploration using subgroup analysis was undertaken. For type 2 diabetes studies, subgroup analyses were: follow-up duration (less than six months, versus more than six months); length of time with diabetes (less than nine years, versus more than nine years); age of participants (mean age less than 55 years old, versus more than 55 years old); number of self-monitoring tasks supported by the diabetes apps (up to three, versus greater than three); and types of feedback provided. No type 1 diabetes subgroup analyses were performed due to the small number of studies.

Sensitivity analyses and publication bias

Additional analyses were carried out on studies with: good or fair quality; complete information; and studies with a baseline HbA1c level less than 9.0%. A funnel plot was used to visually inspect publication bias where 10 or more studies were pooled.

Results

Identified and included studies

Searches identified 5209 articles, 4238 were screened after removing duplicate records and 4178 were excluded. Sixty studies were eligible for full text review and 42 were excluded (Figure 1) resulting in 14 included studies. Four studies examined type 1 diabetes and 10 studies examined type 2 diabetes.

Characteristics of the included studies and quality assessment

In the 14 studies, there were 1360 participants, 509 and 851 with type 1 and type 2

diabetes respectively (Online Table 1). In the type 1 diabetes studies, the mean age of participants ranged from 34 (13) to 36 years old (14), and the mean duration of diabetes ranged from 16 (13-15) to 19 years (16). Two studies were undertaken in Europe (13; 14), one in Australia (16) and one was multinational (15). In the type 2 diabetes studies, the mean age of the participants was much higher, ranging from 51 (17) to 62 years old (18) and the mean duration of diabetes ranged from five (19) to 13 years (20) from six studies. Four studies were undertaken in Europe (18; 20-22), three in the USA (17; 23; 24), two in Asia (19; 25) and one in Africa (26).

One type 1 diabetes study was assessed as good quality (14), two were rated as fair (13; 15), and one was rated as poor (16), for further details see Online Table 2. For type 2 diabetes studies, one was rated as good quality (21), six were rated as fair (17-19; 22; 24; 25) and three were rated as poor (20; 23; 26) (Online Table 2).

INCLUDE FIGURE 1 HERE

Apps featured in the included studies

Twelve diabetes apps were identified and examined in this review, with six domains of functionality (Online Table 3), details of the feedback provided by each can be seen in Online Table 4

Type 1 diabetes apps

Three apps were used for participants with type 1 diabetes and aimed to help patients to calculate the most appropriate insulin bolus, on the basis of patient blood glucose levels, food intake and physical activity. Data for all three apps were manually entered. One study reported that there was little impact of the app on the total time spent on face-to-face or telephone follow-up and concluded that the software did not require more time for patients to manage their diabetes (13). A further study estimated the average cost to patients and educators time was £38 per patient, attributed to the app over a 9 month period (16). HCP feedback was provided in all apps, with a frequency ranging from every week to every three weeks (Online Table 4).

Type 2 diabetes apps

Nine apps were used for participants with type 2 diabetes. The apps were designed

to improve patient self-management, by providing personalized feedback on self-monitoring data, such as blood glucose, food intake, and physical activity. In eight of the apps, BG was automatically transferred and other data manually entered., with one exception where BP, body weight and pedometer was also automatically transferred (25),. Quinn et al. (17) reported that the app was associated with shorter consultation times. Among seven apps with HCP feedback, three provided feedback when needed (eg patient data were considered abnormal). In the other apps, the frequency of feedback ranged from once a week to once every three months (Online Table 4).

Effectiveness of the apps:

Type 1 diabetes

There were mixed results from the type 1 diabetes studies. Two studies (14; 15) found no difference between the intervention group and the control group and two studies (13; 16) reported statistically significant results that favored the apps. There was a statistically insignificant difference in HbA1c between the apps and control group of -0.36% (95% CI -0.87% to 0.14%, P = 0.16, I^2 = 87%; Figure 2). No subgroup analyses were reported.

INCLUDE FIGURE 2 HERE

Type 2 diabetes

All ten studies of type 2 diabetes reported a reduction of HbA1c in participants using an app, with a median reduction of 0.55% (range 0.15% to 1.87%). After pooling the mean reduction in HbA1c was 0.49% (95% CI 0.30%, to 0.68%; P < 0.001; I^2=10%; Figure 3). These results exhibited consistent findings with no heterogeneity. One study reported a reduction larger than clinically anticipated which raised debate over the legitimacy of their findings (26). After excluding the subgroup of studies that were assessed as poor quality, we found a mean reduction of 0.41% (95% CI 0.22%, to 0.61%; P<0.001; I^2=0%; Figure 3). The level of evidence by GRADE was moderate, due to the findings being downgraded due to quality.

INSERT FIGURE 3 HERE

Type 2 diabetes subgroup analyses

The subgroup analysis by follow-up duration showed that five studies with a shorter follow-up duration (less than six months) displayed a larger (but non-significant) HbA1c reduction than those with a longer duration (greater than six months) 0.62% versus 0.40% (P = 0.33) respectively. There was no difference in the reduction of HbA1c in three studies with a mean diabetes duration of less than nine years (0.53%) compared to those with a duration ≥ 9 years (0.55%; P = 0.93). Studies of younger participants with a mean age of ≤ 55 years reported a larger and clinically significant reduction in HbA1c level of 1.03% compared to those with an average age greater than 55 of 0.41%, but the result was not found to be statistically significant (P = 0.10).

In the subgroup analysis by number of self-monitoring tasks six diabetes apps supported at most three self-monitoring tasks, and had similar results to those studies with more than three self-monitoring tasks (mean reduction of 0.44% versus 0.58%; P = 0.56). Two studies of diabetes apps with only automated feedback had a small and statistically non-significant reduction in HbA1c of 0.26% (95% CI 0.09%, to -0.62%). When diabetes apps included HCP feedback were pooled, eight studies reported a reduction of 0.56% (95% CI 0.35%, to 0.78%). There was no statistically significant difference between HCP verses automatic feedback subgroup (P = 0.16).

Four sensitivity analyses were undertaken to test the robustness of the results. Removing three studies (20; 23; 26) with poor quality reported a mean reduction of 0.41% (95% CI 0.22%, to 0.61%, Figure 3). The removal of one study (17) with incomplete statistical information was associated with a mean reduction of 0.48% (95% CI 0.28%, to 0.67%), and the exclusion of one study (20) conducted on mixed participants with type 1 and type 2 diabetes had an attendant mean reduction of 0.48% (95% CI 0.27%, to 0.69%). Finally, the exclusion of two studies (17; 23) with baseline HbA1c levels > 9.0% was associated with a mean reduction of 0.47% (95% CI 0.25%, to 0.69%).

Discussion

Ten studies were included for type 2 diabetes, predominately of fair quality. The results of these indicated a consistent reduction in HbA1c of 0.5%. Although there

was no indication of heterogeneity, the study conducted by Takenga et al. (26) introduced a large effect, that was likely to be caused by poor study quality (high attrition rate, differential loss to follow-up and high baseline HbA1c level). Thus, studies were stratified into subgroup determined by their quality assessment (27). No differences were found between the subgroups, and the studies of poor quality were included for completeness, and to highlight the challenges in study design.

Five subgroup analyses showed that the effect did not differ significantly by follow-up duration, mean diabetes duration of participants, mean age of participants, number of self-monitoring tasks supported by the diabetes apps, or types of feedback. Compared to studies that have investigated alternative interventions to improve their diabetes self-management, such as: text messaging, mobile device, computer based and convention self-management, we have found that apps offer promising results and reinforce the message argued by other authors (3; 4; 28-30). The evidence for this finding by GRADE was moderate, after down grading due to quality.

The subgroup analysis by follow-up duration suggested that the effect of diabetes apps on blood glucose control may attenuate over time. A possible rationale for this subgroup effect is a lack in user-friendliness, a lack in perceived additional benefits and a lack of use of gamification elements, resulting in a lack of efficacy following use (31). The subgroup analysis by mean age of participants indicated that younger patients were more likely to benefit from the use of the diabetes apps. It may be speculated that younger patients are more amenable to new technologies and more familiar with the use of mobile phones. The subgroup analysis by personalized feedback system highlighted the gap between automated feedback and healthcare professional feedback. Although automated feedback has the advantage of being interactive and dynamic, there is a limit to presupposed scenarios, whereas feedback provided by healthcare professionals was more individual, especially in emergency situations. Feedback options ranged widely between the apps, but it is postulated that it was the feedback that triggered improved lifestyle choices, which in turn lowered HbA1c. None of the five sensitivity analyses changed the overall effect size significantly, which suggests that the findings are not sensitive to these scenarios. The results of our meta-analysis lend support to the use of diabetes apps in diabetes self-management, especially for type 2 diabetes. However, we have

highlighted a number of limitations of current diabetes apps.

For type 1 diabetes, there was little difference in HbA1c between intervention and control groups and the results were associated with considerable heterogeneity. The level of evidence by GRADE was downgraded to very low due to: study quality; inconsistency; and uncertainty; so the findings should be interpreted as very uncertain and likely to be change following future research. Furthermore, none of the apps in the included type 1 diabetes studies had an automatic data uploading functionality. In future studies for type 1 diabetes, we encourage investigators to include apps with this functionality, not only for the purpose of being user-friendly, but also for safety concerns by reducing the risk of data entry errors.

Two studies reported on the cost effectiveness of the apps for type 1 diabetes with inconclusive findings (15; 16). Of three studies on type 2 diabetes that discussed compliance, two reported poor compliance with only 35% of patients regular app users (21; 24). One study (25) reported a decline in patient use over time, from 70% in the first week to 50% in the last two weeks. Four studies tried to explore the mechanisms behind the effects, but the conclusions were inconsistent (16; 17; 21; 24). We postulate that diabetes apps influence lifestyle choice, but how this occurs is unclear. One hypothesis is that the reminder and feedback features of diabetes apps can lead to improvement in health beliefs, self-efficacy and social support (32).

By the end of the decade, worldwide mobile phone usage is anticipated to exceed 5 billion (33). Therefore apps may be able to offer an affordable and widely available adjunct to diabetes self-management. We have included studies across a variety of healthcare systems, from both the developed and developing world, so we argue the apps are currently available and could form the basis of improved health promotion on diabetes education and self-management.

This study had several limitations. Since this review was restricted to published studies and so publication bias cannot be ruled out as highlighted by other investigators (30) All included study designs were not blinded, so were downgraded in the quality assessment tool, (highlighting the increased risk of ascertainment bias). Furthermore, patient-important outcomes and behavioral mechanisms and outcomes

were not considered and is a clear gap to be addressed in future studies. A further weakness is that some of the effect attributed to the apps could be explained by health care providers. Finally, there is no clear definition of diabetes apps and study authors defined their interventions in different ways as a result. In this review, we defined diabetes apps as software that is designed for use on a mobile phone allowing patients to enter data into the app and receive feedback.

The implications for future research include establishing a common standardized platform of functionality. Investigators of future studies need to consider adequately powered pragmatic RCTs with secure sequence generation, concealed allocation, use of an active control app, and comparable access to HCP. Features such as these might reduce the impact of ascertainment bias and effects due to HCP. RCTs with longer duration of follow up (> 6 months) using standardized app technology may well demonstrate beneficial clinical effect in type 2 diabetes. Furthermore, there is significant scope for research in the use of apps in other areas of self-management, such as increasing physical activity, weight loss and smoking cessation.

In a clinical context, we recommend that HCP feedback should be central in all future app design and supplemented with dynamic automated feedback. Future technology should also be underpinned by behavior change theories and gamification elements to achieve a larger effect on blood glucose control and improve compliance of patients in using diabetes apps. Finally, future technology should also consider the needs of older patients.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J: IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice 2011;94:311-321
2. Polonsky WH, Fisher L: Self-monitoring of blood glucose in noninsulin-using type 2 diabetic patients: right answer, but wrong question: self-monitoring of blood glucose can be clinically valuable for noninsulin users. Diabetes care 2013;36:179-182
3. Liang X, Wang Q, Yang X, Cao J, Chen J, Mo X, Huang J, Wang L, Gu D: Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabetic medicine : a journal of the British Diabetic Association 2011;28:455-463
4. Pal K, Eastwood SV, Michie S, Farmer AJ, Barnard ML, Peacock R, Wood B, Inniss JD, Murray E: Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. The Cochrane database of systematic reviews 2013;3:CD008776
5. Angeles RN, Howard MI, Dolovich L: The effectiveness of web-based tools for improving blood glucose control in patients with diabetes mellitus: a meta-analysis. Canadian Journal of Diabetes 2011;35:344-352
6. Tatara N, Arsand E, Nilsen H, Hartvigsen G: A Review of Mobile Terminal-Based Applications for Self-Management of Patients with Diabetes. International Conference on Ehealth, Telemedicine, and Social Medicine: Etelemed 2009, Proceedings 2009:166-175
7. Baron J, McBain H, Newman S: The impact of mobile monitoring technologies on glycosylated hemoglobin in diabetes: a systematic review. Journal of Diabetes Science & Technology 2012;6:1185-1196
8. El-Gayar O, P. T, N. N, Eid W: A systematic review of IT for diabetes self-management: are we there yet? International journal of medical informatics 2013;82(8):637-652
9. Klonoff DC: The current status of mHealth for diabetes: will it be the next big thing? Journal of diabetes science and technology 2013;7:749-758
10. Ma J, Liu W, Hunter A, Zhang W: Performing meta-analysis with incomplete statistical information in clinical trials. BMC Medical Research Methodology 2008;8:56
11. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D, Methods Work Group TUSPSTF: Current methods of the US Preventive Services Task Force: a review of the process. American journal of preventive medicine 2001;20:21-35
12. Deeks JJ, Higgins JPT, Altman DG: Chapter 9: Analysing data and undertaking meta-analyses. In *Cochrane handbook for systematic reviews of interventions* Higgins JPT, Green S, Eds., Wiley Online Library, 2008
13. Charpentier G, Benhamou P-Y, Dardari D, Clergeot A, Franc S, Schaepelynck-Belicar P, Catargi B, Melki V, Chaillous L, Farret A: The Diabeo Software Enabling Individualized Insulin Dose Adjustments Combined With Telemedicine Support Improves HbA1c in Poorly Controlled Type 1 Diabetic Patients A 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes Care 2011;34:533-539
14. Rossi MC, Nicolucci A, Lucisano G, Pellegrini F, Di Bartolo P, Miselli V, Anichini R, Vespasiani G, Did Study G: Impact of the "Diabetes Interactive Diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. Diabetes Technology & Therapeutics 2013;15:670-679
15. Rossi MC, Nicolucci A, Di Bartolo P, Bruttomesso D, Girelli A, Ampudia FJ, Kerr D, Ceriello A, Mayor Cde L, Pellegrini F, Horwitz D, Vespasiani G: Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 2010;33:109-115
16. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ: Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. Journal of medical Internet research 2013;15
17. Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A: WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. Diabetes technology & therapeutics 2008;10:160-168
18. Orsama AL, Lahteenmaki J, Harno K, Kulju M, Wintergerst E, Schachner H, Stenger P, Leppanen J, Kaijanranta H, Salaspuro V, Fisher WA: Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. Diabetes technology & therapeutics 2013;15:662-669
19. Yoo HJ, Park MS, Kim TN, Yang SJ, Cho GJ, Hwang TG, Baik SH, Choi DS, Park GH, Choi KM: A ubiquitous chronic disease care system using cellular phones and the internet. Diabetic Medicine 2009;26:628-635
20. Istepanian RS, Zitouni K, Harry D, Moutosammy N, Sungoor A, Tang B, Earle KA: Evaluation of a mobile phone telemonitoring system for glycaemic control in patients with diabetes. Journal of Telemedicine & Telecare 2009;15:125-128

21. Holmen H, Torbjørnsen A, Wahl AK, Jenum AK, Småstuen MC, Årsand E, Ribu L: A Mobile Health Intervention for Self-Management and Lifestyle Change for Persons With Type 2 Diabetes, Part 2: One-Year Results From the Norwegian Randomized Controlled Trial RENEWING HEALTH. JMIR mHealth and uHealth 2014;2
22. Nagrebetsky A, Larsen M, Craven A, Turner J, McRobert N, Murray E, Gibson O, Neil A, Tarassenko L, Farmer A: Stepwise self-titration of oral glucose-lowering medication using a mobile telephone-based telehealth platform in type 2 diabetes: a feasibility trial in primary care. Journal of diabetes science and technology 2013;7:123-134
23. Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL: Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care 2011;34:1934-1942
24. Faridi Z, Liberti L, Shuval K, Northrup V, Ali A, Katz DL: Evaluating the impact of mobile telephone technology on type 2 diabetic patients' self‐management: the NICHE pilot study. Journal of evaluation in clinical practice 2008;14:465-469
25. Waki K, Fujita H, Uchimura Y, Omae K, Aramaki E, Kato S, Lee H, Kobayashi H, Kadowaki T, Ohe K: DialBetics: A Novel Smartphone-based Self-management Support System for Type 2 Diabetes Patients. Journal of diabetes science and technology 2014;8:209-215
26. Takenga C, Berndt R-D, Musongya O, Kitero J, Katoke R, Molo K, Kazingufu B, Meni M, Vikandy M, Takenga H: An ICT-based diabetes management system tested for health care delivery in the african context. International journal of telemedicine and applications 2014;2014:6
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928
28. Steinsbekk A, Rygg L, Lisulo M, Rise MB, Fretheim A: Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. BMC health services research 2012;12:213
29. De Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R: Mobile phone messaging for facilitating self-management of long-term illnesses. The Cochrane database of systematic reviews 2012;12
30. Su D, Zhou J, Kelley MS, Michaud TL, Siahpush M, Kim J, Wilson F, Stimpson JP, Pagán JA: Does telemedicine improve treatment outcomes for diabetes? A meta-analysis of results from 55 randomized controlled trials. Diabetes Research and Clinical Practice 2016;116:136-148
31. Scheibe M, Reichelt J, Bellmann M, Kirch W: Acceptance Factors of Mobile Apps for Diabetes by Patients Aged 50 or Older: A Qualitative Study. Medicine 20 2015;4
32. Nundy S, Dick JJ, Solomon MC, Peek ME: Developing a behavioral model for mobile phone-based diabetes interventions. Patient education and counseling 2013;90:125-132
33. http://www.statista.com/statistics/274774/forecast-of-mobile-phone-users-worldwide/: Accessed January 2016;

Role of the funding source: This was an unfunded study

A declaration of competing interests.

"All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that (1) CH, SM, JM, TF, or BC have no support from any companies for the submitted work; (2) CH, SM, JM, TF, or BC have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) CH, SM, JM, TF, or BC have no non-financial interests that may be relevant to the submitted work."

Author Contribution:

Can Hou (CH) designed the protocol, searched the literature, extracted the data, carried out the analysis, and drafted the manuscript

Sharon Mayor (SM) designed the protocol, interpreted the results, and contributed to the manuscript

Jonathan Hewitt (JH) reviewed the manuscript and advised on the clinical context of the review

Trevor Francisa (TF) searched the literature, extracted the data

Ben Carter (BC) interpreted the results, drafted to the manuscript and is the guarantor of the review.

Guarantor's statement

Dr. Ben Carter is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis

A transparency declaration:

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1: PRISMA Flowchart of included studies

Figure 2: Pooled Type 1 diabetes studies of HbA1c comparison of apps versus control

Figure 3: Pooled Type 2 diabetes studies of HbA1C comparison of apps versus control

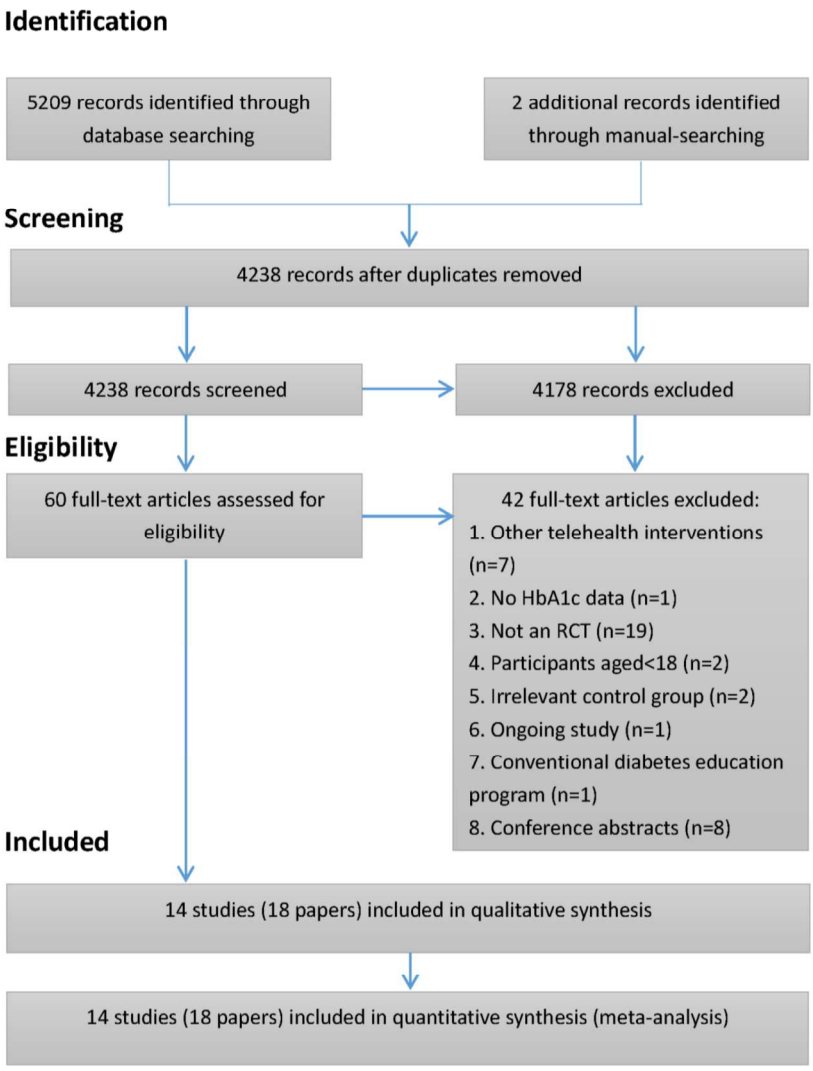

Figure 1: PRISMA Flowchart of included studies
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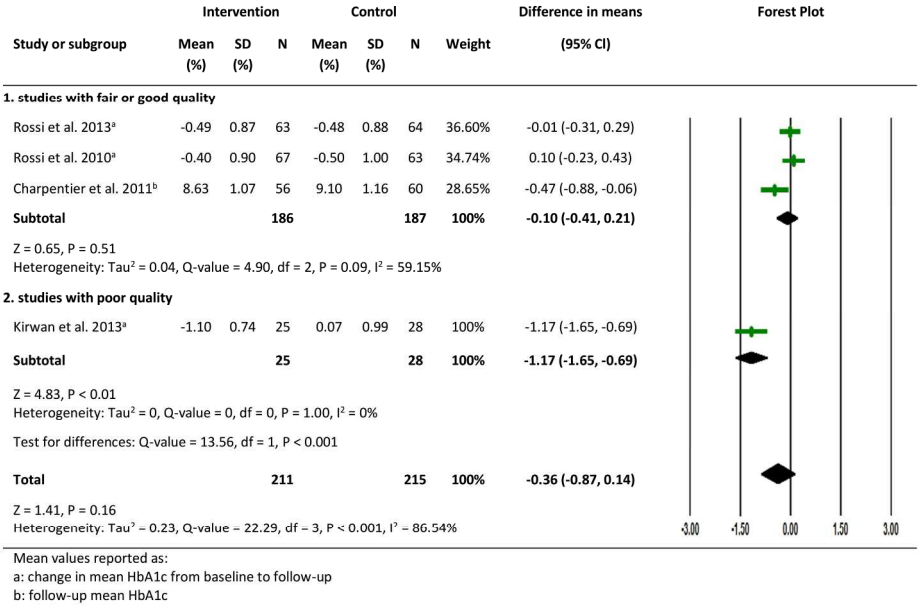

Figure 2: Pooled Type 1 diabetes studies of HbA1c comparison of apps versus control
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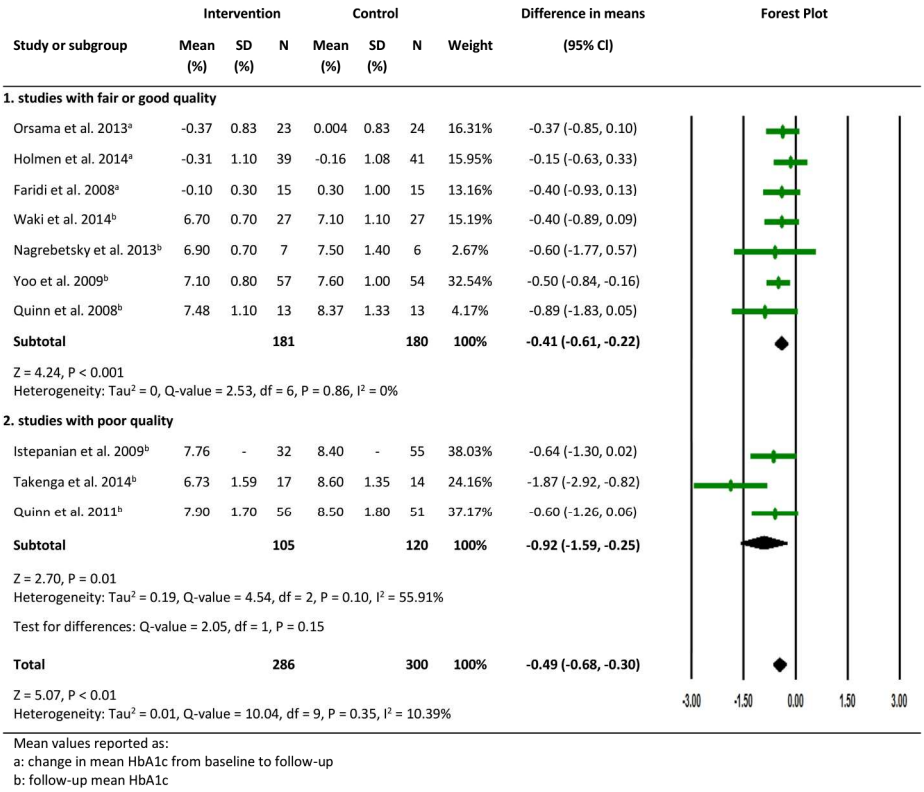

Figure 3: Pooled Type 2 diabetes studies of HbA1C comparison of apps versus control
529x501mm (120 x 120 DPI)

Online Table 1: Baseline characteristics of the included studies and participants

Study					Participants			HbA1c (%, mean and SD)		
Name (year)	Length (mths)	N	Setting	Control group	Age (years, mean and SD)	Duration of diabetes (years, mean and SD)	Ethnic groups	Baseline	Post-intervention	change from baseline
Type 1 diabetes										
Rossi et al. (2013)[14]	6	I:63 C:64	Diabetes clinics	Standard educational approach based on CHO counting	I:38.4 (10.3) C:34.3 (10.0)	I: 16.2 (10.0) C: 15.0 (8.4)	N/A	I: 8.4 (0.79) C: 8.5 (0.80)	I: 7.9 (0.79) C: 8.1 (0.80)	I: -0.49 (0.87) C: -0.48 (0.88)
Rossi et al. (2010)[15]	6	I:67 C:63	Diabetes outpatient clinics	Standard carbohydrate counting education	I:35.4 (9.5) C:36.1 (9.4)	I: 17.1 (10.3) C: 15.8 (10.7)	N/A	I: 8.2 (0.8) C: 8.4 (0.7)	I: 7.8 (0.87)* C: 7.9 (1.04)*	I: -0.4 (0.9) C: -0.5 (1.0)
Charpentier et al. (2013)[13]	6	I:56 C:60	Hospital	Patients kept their paper logbook and attended two follow-up visits	I:32.9 (11.7) C:36.8 (14.1)	I: 17.6 (8.9) C: 16.9 (10.5)	N/A	I: 9.2 (1.1) C: 8.9 (0.9)	I: 8.63 (1.07) C: 9.10 (1.16)	I: -0.5 (0.9) C: 0.2 (0.8)
Kirwan et al. (2013)[16]	9	I:25 C:28	Diabetes Australia in New South Wales and Queensland	Patients continued usual care	I:36.0 (10.7) C:34.4 (10.3)	I: 19.7 (9.6) C: 18.2 (9.8)	N/A	I: 9.08 (1.18) C: 8.47 (0.86)	I: 7.80 (0.75) C: 8.58 (1.16)	I: -1.10 (0.74) C: 0.07 (0.99)

I=Intervention; C=Control; *SDs were imputed;

	Study				Participants			HbA1c (%, mean and SD)		
Name (year)	Length (mths)	N	Setting	Control group	Age (years, mean and SD)	Duration of diabetes (years, mean and SD)	Ethnic groups	Baseline	Post-intervention	change from baseline
Type 2 Diabetes										
Orsama et al. (2013)[18]	10	I:23 C:24	Community health center	Standard medical care	I:62.3 (6.5) C:61.5 (9.1)	N/A	N/A	I: 6.86 (1.56) C: 7.09 (1.51)	N/A	I: -0.37 (0.83) C: 0.00 (0.83)
Holmen et al. (2014)[21]	12	I:39 C:41	Primary care	Usual care according to clinical guidelines	I: 59 (12) C: 56 (12)	N/A	N/A	I: 8.1 (1.1) C: 8.3 (1.2)	I: 7.8 (0.99) C: 8.2 (1.36)	I: -0.31 (1.11) C: -0.16 (1.08)
Faridi et al. (2008)[24]	3	I:15 C:15	Community health center	Standard diabetes self-management	I:55.3 (8.7) C:56.7 (10.6)	N/A	N/A	I: 6.4 (0.6) C: 6.5 (0.7)	N/A	I: -0.1 (0.3) C: 0.3 (1.0)
Waki et al. (2014)[25]	3	I:27 C:27	Hospital	Patients continued their self-care regimen	I:57.1 (10.2) C: 57.4 (9.4)	I: 9.6 (7.0) C: 8.5 (8.0)	N/A	I: 7.1 (1.0) C: 7.0 (0.9)	I: 6.7 (0.7) C: 7.1 (1.1)	N/A
Nagrebetsky et al. (2013)[22]	6	I:7 C:6	General practices	Usual care and supportive lifestyle intervention	I:56 (8) C:60 (13)	I: 3.0 (0.6-4.7) C: 2.3 (0.4-8.0)	White: 100%	I: 8.0 (1.0) C: 8.2 (1.2)	I: 6.9 (0.7) C: 7.5 (1.4)	N/A
Yoo et al. (2009)[19]	3	I:57 C:54	Hospital and community health center	Usual out-patient treatment	I:57.0 (9.1) C:59.4 (8.4)	I: 6.0 (5.4) C: 7.2 (6.0)	N/A	I: 7.6 (0.9) C: 7.4 (0.9)	I: 7.1 (0.8) C: 7.6 (1.0)	N/A
Quinn et al. (2008)[17]	3	I:13 C:13	Community endocrinology and community primary care practice	Patients continued usual standards of care	51.0 (11.03)	I: 7.61 C: 11	African American: 62% White: 38%	I: 9.51 (1.22)* C: 9.05 (1.21)*	I: 7.48 (1.10)* C: 8.37 (1.33)*	N/A
Istepanian et al. (2009)[20]	9	I:32 C:55	Hospital	Patients received care from the diabetes center	I:60 (12) C:57 (13)	I: 13.3 (8.6) C: 11.7 (8.0)	Caucasian: 34% African-Caribbean: 31% Indo-Asian: 31% Other: 4%	I: 7.9 (1.5) C: 8.1 (1.6)	I: 7.76 D: 8.4	N/A
Takenga et al. (2014)[26]	2	I:17 C:14	Not specified	Conventional therapy	I:53.3 (10.7) C:53.4 (9.6)	N/A	N/A	I: 8.67 (1.22)* C: 8.59 (1.21)*	I: 6.73 (1..59) C: 8.6 (1.35)	N/A
Quinn et al. (2011)[23]	12	I:56 C:51	Primary care practices	Patients were provided care as usual	I:52.0 (8.0) C:53.2 (8.4)	I: 8.2 (5.3) C: 9.0 (7.0)	Black: 39% White: 53% Other: 8%	I: 9.9 (2.1) C: 9.2 (1.7)	I: 7.9 (1.7) C: 8.5 (1.8)	I: -1.9 C: -0.7

I=Intervention; C=Control; *SDs were imputed;

Online Table 2: Quality Assessment of the included studies

Study or subgroup	1	2	3	4	5	6	7	Overall quality
Type 1 diabetes								
Rossi et al. (2013)[14]	✓	✓	✓	✓	✓	✓	✓	Good
Rossi et al. (2010)[15]	✓	✓	×	✓	✓	✓	✓	Fair
Charpentier et al. (2011)[13]	×	✓	✓	✓	✓	✓	✓	Fair
Kirwan et al. (2013)[16]	×	×	×	✓	✓	✓	×	Poor[&]
Type 2 diabetes								
Orsama et al. (2013)[18]	×	✓	✓	×	✓	✓	×	Fair
Holmen et al. (2014)[21]	✓	✓	✓	✓	✓	✓	✓	Good
Faridi et al. (2008)[24]	×	×	×	✓	✓	✓	✓	Fair
Waki et al. (2014)[25]	×	✓	✓	✓	✓	✓	✓	Fair
Nagrebetsky et al. (2013)[22]	×	×	✓	✓	✓	✓	×	Fair
Yoo et al. (2009)[19]	×	✓	✓	✓	✓	✓	✓	Fair
Quinn et al. (2008)[17]	×	✓	✓	✓	✓	×	×	Fair
Istepanian et al. (2009)[20]	✓	×	×	✓	✓	✓	✓	Poor*
Takenga et al. (2014)[26]	×	×	×	×	✓	×	×	Poor[#]
Quinn et al. (2011)[23]	×	×	×	✓	✓	✓	✓	Poor^

✓: criteria met; ×: criteria NOT met or unclear

Methodological Domains

1, Initial assembly of comparable groups (eg Initial assembly of comparable groups: adequate randomization, including concealment and whether potential confounders were distributed equally among groups)
2, The maintenance of comparable groups (eg Maintenance of comparable groups (includes attrition, crossovers, adherence, and contamination)
3, No important loss to follow-up (eg Important differential loss to follow-up or overall high loss to follow-up)
4, Equal, reliable, and valid measurement
5, Clear definitions of intervention
6, All the important outcomes were considered
7, Intention-to-treat analysis

Studies determined as poor quality

[&]**Kirwan et al (2013)**: The study had a very high dropout rate in the intervention group compared to the control group. The groups were not suitably comparable (eg the baseline HbA1c was higher in the intervention group compared to control) and reported a healthier diet. The randomisation mechanism was inadequate

***Istepanian et al 2009:** The study had a very high dropout rate and differential loss to follow-up rate (55.6% in the intervention group and 15.4% in the control group).

^Quinn et al (2011): the study had a high dropout rate which was differential between groups. The randomisation mechanism was inadequate and the two groups were not comparable (CPDS patients had higher baseline glycated haemoglobin than UC (9.9 vs. 9.2%, P = 0.04).

[#]**Takenga et al 2014:** The study provided limited information on the randomisation methods and measurement. The study had neither intention-to-treat analysis nor sample size calculation.

Online Table 3: Functionality of the featured apps included

Type 1 Diabetes

Study	App used in the study	Self-monitoring tasks	Data entry method	CHO/ insulin bolus calculator	Medication adjustment support	Graphical feedback	Automated feedback	HCP feedback	Freq. of HCP feedback	Other functionalities
Rossi et al. (2013)[14]	Diabetes Interactive Diary	BG, food intake (CHO and calories), dose of insulin, physical activities, and specific events	Data were manually entered	✓	✓	✗	✓	✓	Every one to three weeks	Glycaemic target setting
Rossi et al. (2010)[15]	Diabetes Interactive Diary	BG, dose of insulin injections, food intake, physical activity, and specific events	Data were manually entered	✓	✓	✗	✓	✓	N/A	Glycaemic target setting
Charpentier et al. (2011)[13]	Diabeo	BG, carbohydrate intake and physical activity	Data were manually entered	✓	✓	✗	✓	✓	N/A	BG target setting
Kirwan et al. (2013)[16]	Glucose Body	Blood glucose levels, insulin dosages, other medications, diet (food item in grams), and physical activities (minutes)	Data were manually entered	✗	✓	✓	✗	✓	Weekly	N/A

Type 2 Diabetes

Study	App used in the study	Self-monitoring tasks	Data entry method	CHO/ insulin bolus calculator	Medication adjustment support	Graphical feedback	Automated feedback	HCP feedback	Freq of HCP feedback	Other functionality
Orsama et al (2013)[18]	Monica	BP, body weight, physical activity (pedometer), BG measurement only for six participants with high HbA1c level	All data were manually imputed	✗	Not specified	✓	✓	✓	When necessary	N/A
Holmen et al. (2014)[21]	FewTouch	Food habits registration, BG, and physical activity	BG data were automatically transferred to the app; activity data and food habits were entered manually	✗	✗	✓	✓	✗	NA	Personal goal setting system, general diabetes education system
Faridi et al. (2008)[24]	NICHE	BG, exercise (pedometer) and weight	BG data were automatically transmitted; weight and pedometer counts were manually entered	✗	✗	✓	✓	✗	N/A	N/A
Waki et al. (2014)[25]	DiaBetics	BG, BP, body weight and pedometer counts, voice/text messages about meals and exercise, photos of meals	BG,BP, body weight and pedometer data were transmitted automatically to the app; meals and exercise were input by voice/text message or photos	✗	Not specified	✓	✓	✓	When necessary	The database triggered alerts for missed or late readings (reminder)
Nagrebetsky et al. (2013)[22]	t+Diabetes	BG	BG data were automatically transmitted to the app	✗	✓	✓	✗	✓	Monthly	N/A
Yoo et al. (2009)[19]	Ubiquitous Chronic Disease Care	BG, BP, exercise, and body weight	BG data were automatically transmitted to the app; BP and weight data were manually entered	✗	Not specified	✗	✓	✓	When necessary	Reminder

Quinn et al. (2008)[17]	Diabetes Manager	BG, medication dosage and carbohydrates intake	BG data were automatically sent to the app, other data were manually input	✗	✓	✗	✓	✓	NA	Direct patients to test BG at optimal times (reminder)
Istepanian et al. (2009)[20]	Not specified	BG	Automatically transmitted to the app	✗	✓	✗	✗	✓	NA	The mobile phone alerted the patient when a measurement was due (reminder)
Takenga et al. (2014)[26]	Mobil Diab	BG, insulin take, sport done, BP, and body weight and body size	BG data were automatically transmitted to the app; other data were manually entered	✗	✓	✓	✗	✓	N/A	The app is integrated into a telemedicine platform directly
Quinn et al. (2011)[23]	Diabetes Manager	BG, carbohydrates consumed, diabetes medications taken, and miscellaneous comments regarding diabetes self-care	BG data were automatically sent to the app, other data were manually input	✗	✓	✗	✓	✓	From every two months to weekly	N/A

Online Table 4: Feedback provided by the featured apps

Type 1 Diabetes

Study	Data inputted	Feedback received
Rossi et al. (2013)[14]	BG, food intake (CHO and calories), dose of insulin, physical activities, and specific events	1. CHO/insulin bolus calculator: DID can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predefined carbohydrate-to-insulin ratio and the glycaemic correction factor, together with other information already filled out in the DID (e.g., physical activity, glycaemic target, insulin dose, and specific events). 2. All the recorded data were sent to the physician on average each 1–3 weeks. Any new therapeutic and behavioural prescriptions were sent from the diabetes clinic computer to the patient's mobile phone.
Rossi et al. (2010)[15]	BG, dose of insulin injections, food intake, physical activity, and specific events	1. CHO/insulin bolus calculator: DID can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predefined carbohydrate-to-insulin ratio and the glycaemic correction factor, together with other information already filled out in the DID (e.g., physical activity, glycaemic target, insulin dose, and specific events). 2. Data stored in the mobile phone are periodically sent to the personal computer of the physician. Then, any new therapeutic and behavioural prescription can be sent from the computer to the mobile phone.
Charpentier et al. (2011)[13]	BG, carbohydrate intake and physical activity	1. Bolus calculators using validated algorithms, taking into account carbohydrate intake, pre-meal blood glucose, and anticipated physical activity reported by the patient. 2. Automatic algorithms for the adjustment of carbohydrate ratio and basal insulin or pump basal rates when the postprandial or fasting plasma glucose levels are off target 3. Data transmission to medical staff computers to allow easy telemonitoring and teleconsultations.
Kirwan et al. (2013)[16]	Blood glucose levels, insulin dosages, other medications, diet (food item in grams), and physical activities (minutes)	1. Patients can view their data on a customizable graph. 2. Data were reviewed by an educator and all patients in the intervention arm were sent a minimum of 1 personalized text-message communication per week for the first 6 months of the study.

Type 2 Diabetes		
Orsama et al. (2013)[18]	BP, body weight, physical activity (pedometer), BG measurement only for six participants with high HbA1c level	1. Real-time graph display reflecting the uploaded data in relation to individual target value generated by app. 2. Automatically generated, theory-based, health promotion-rich information, motivation, and behavior skills feedback messages, linked to patients' remote reports of their health parameters. 3. Study nurses scanned through the status of all intervention patients each week and contacted patients if warranted by their remote data reports. 4. A web portal (Medinet) enabled participants to view their uploaded data.
Holmen et al. (2014)[21]	Food habits registration, BG, and physical activity	1. Real-time feedback from the app on how the individually set goals were met within the defined period. 2. Motivational feedback through symbols such as smiling faces and color codes in the app. 3. Patients can also access related tips and look up words and concepts related to their diseases.
Faridi et al. (2008)[24]	BG, exercise (pedometer) and weight	1. Real-time, automated, graphical and texts feedback and reminders based on patient-specific data. 2. A web-based portal for patients and clinicians to view measurement data and prior messages received from the system.
Waki et al. (2014)[25]	BG, BP, body weight and pedometer counts, voice/text messages about meals and exercise, photos of meals	1. Data were automatically evaluated following the Japan Diabetes Society (JDS) guideline's targeted values, DialBetics determined if each reading satisfies guideline requirements, then immediately sent those results to each patient's smartphone. 2. Readings defined as abnormal were reported to a doctor as "Dr Call," meaning a physician will check the data and interact with the patient if necessary. 3. Voice input was converted to text and matched with text in the DialBetics database; advice on lifestyle modification, matched to the patient's input about food and exercise, was sent back to each patient immediately after the patient's input. 4. Patients' photos of meals were sent to the server; the nutritional value of those meals was calculated by dieticians, then sent back to each patient. 5. Patients can view their measurement data as well as graphic outputs of their measurements with diet and exercise history.
Nagrebetsky et al. (2013)[22]	BG	1. Real-time graphical feedback on glucose levels. 2. BG reading were also monitored by research nursing twice a week via a web-based portal, and support and encourage patients using standardized text messages and telephone calls monthly. 3. Patients used the phone application to review their glucose levels every 3 weeks and, if necessary, titrate their oral glucose-lowering medication.
Yoo et al. (2009)[19]	BG, BP, exercise, and body weight	1. Real-time automated SMS feedback of encouragement, reminders, and recommendations according to the data input. 2. Participants received information via SMS three times a day regarding healthy diet and exercise methods, along with general information about diabetes, hypertension and obesity. 3. A web-based portal for physicians to view patient data and send individualized recommendations to patients when needed.
Quinn et al. (2008)[17]	BG, medication dosage and carbohydrates intake	1. Real-time feedback about the BG level related to the patient-specific target level and was shown HCP-prescribed medication instruction. 2. If BG levels were above or below target levels, patients received real-time feedback on how to correct the BG level. 3. Data were sent to server and analyzed by automated algorithms and research team; patients would receive positive feedback if no problems detected; if problems detected, patients were given further feedback and education, or even referral if needed. 4. Suggestions of medical changes to patients (approved by HCP first). 5. HCPs were provided with logbook to review, attached with analysis of the patient data and trend.
Istepanian et al. (2009)[20]	BG	1. The research clinicians reviewed the recordings via a web-based application. Letters were sent from the clinician to the patients and their general practitioners with details of the amalgamated readings and treatment recommendations.
Takenga et al. (2014)[26]	BG, insulin take, sport done, BP, and body weight and body size	1. Doctors can view the clear graphical representation of trends and statistics of patient data from a web portal. 2. Therapy plans, instructions and recommendations sent from the doctor portal were received directly in the app. 3. Results of the input data were presented directly in app using different graphs.

Quinn et al. (2011)[23]	BG, carbohydrates consumed, diabetes medications taken, and miscellaneous comments regarding diabetes self-care	1. Real-time educational, behavioral and motivational feedback regarding patients input data, trend of recent entered data and physicians' medication instruction. 2. Patients and PCPs had access to a web-portal consisted of secure messaging center (for patient-provider communication), personal health record with additional diabetes information, learning library and logbook to review historical data (analyzed data). 3. Diabetes educators intermittently reviewed patient data and communicated with patients electronically or via phone (frequency: high risk level patents: at most 4 times a month; others every 2-3 months).

Do mobile phone applications improve glycemic control (HbA1c) in the self-management of diabetes: A systematic review and meta-analysis and GRADE of 14 randomized trials

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ABSTRACT

OBJECTIVES: To investigate the effect of mobile phone applications on glycemic control (HbA1c) in the self -management of diabetes.

RESEARCH DESIGN AND METHODS: Relevant studies that were published between 1996 to June 1st, 2015 were searched from five databases: Medline, CINAHL, The Cochrane Library, Web of Science, and EMBASE. Randomized controlled trials that evaluated diabetes apps were included. We conducted a systematic review with meta-analysis and GRADE of the evidence.

RESULTS: 1360 participants from 14 studies were included and quality assessed. Whilst there may have been clinical diversity, all type 2 diabetes studies reported a reduction in HbA1c. The mean reduction in participants using an app compared to control was 0.49% (95% CI 0.30%-0.68%;I^2=10%), with a moderate GRADE of evidence. Subgroup analyses indicated that younger patients were more likely to benefit from the use of diabetes apps and the effect size was enhanced with healthcare professional feedback. There was inadequate data to describe the effectiveness of apps for type 1 diabetes.

CONCLUSIONS: Apps may be an effective component to help control HbA1c, and could be considered as an adjuvant intervention to the standard self-management for patients with type 2 diabetes. Given the reported clinical effect, ~~and~~ the access and nominal cost of this technology, it is likely to be ~~cost~~ effective at the population level. The functionality and use of this technology needs to be standardized, but policy and guidance is anticipated to improve diabetes self-management care ~~and reduce healthcare cost~~.

Word Count Abstract = 235

Word Count Manuscript = 3002

What this study adds

- There is a moderate level of evidence that the self-management of type 2 diabetes is improved by using smart phone applications to reduce HbA1c
- Apps ~~for type 2 diabetes~~ may offer a clinically effective ~~adjuvant~~ component ~~to~~ in the self-~~medication~~management of type 2 diabetes
- Younger users were associated with the largest reduction in HbA1c

Background

The number of diabetes patients globally is expected to rise to over 500 million by 2030 (1), there is an urgent need for an improved self-management suite of interventions. For self-management to be effective it needs to be structured and cost effective (2), and be widely accessible across all health economies, including the developing world (2).

As a newly emerging technology, diabetes mobile phone applications (hereafter referred to as diabetes apps) are a promising tool for self-management. We define diabetes apps as mobile phone software that accepts data (transmitted or manual entry), and provides feedback to patients on improved management (automated or by health care profession [HCP]). This technology combines the functions of the mobile phone, wireless network for data transmission and sometimes HCPs for providing feedback. Due to its ubiquitous, low cost, interactive, and- dynamic health promotion, there is potential for diabetes apps to provide an ~~cost~~ effective intervention in diabetes self-care.

In terms of diabetes self-management, numerous studies have proven the effectiveness of other telemedicine technologies, such as short message service (3), computer-based interventions (4), and web-based interventions (3; 5). Compared with these telemedicine interventions, diabetes apps are advantageous in that they are global, cheaper, convenient, and more interactive. There is however, current uncertainty on the clinical effectiveness of diabetes apps in diabetes self-management (6-9).

METHODS

Data sources and search strategy

The PRISMA statement and checklist was followed. Five electronic databases were searched (Medline, CINAHL, The Cochrane Library, Web of Science, and EMBASE) for studies published between January 1st, 1996 to June 1st, 2015. Included studies' references were hand searched to identify any additional articles. The following terms and medical subject headings (MeSH) were used during the search: (mobile OR mHealth OR cell phone OR MeSH "Cellular Phone" OR MeSH "Smartphone" OR app OR MeSH "Mobile Applications") AND (MeSH "Diabetes Mellitus" OR diabete*

OR T2DM OR T1DM OR IDDM OR NIDDM).

Inclusion and exclusion criteria

The inclusion criteria were: the participants were over 18 years old and had type 1 or type 2 diabetes; the studies were randomized controlled trials (RCTs); the control group in the study received usual diabetes care without any telehealth programs; baseline and follow-up mean for HbA1c were reported (or could be calculated).; Exclusion criteria were: simulated or self-reported HbA1c data; computer or other mobile terminal-based diabetes apps; diabetes apps were exclusively designed for HCPs; and diabetes apps were exclusively designed for providing general education, or allowing communication between patients and HCPs.

Two reviewers (CH, TF) searched the literature and assessed the studies independently. Any disagreements were resolved through discussion with a third reviewer (BC). No language restrictions were applied.

Data extraction

Participant demographics, study design considerations and context were extracted from the included studies. Two reviewers independently carried out the data extraction (CH, TF). Study authors were contacted to provide additional data, and missing standard deviations were estimated by calculation (10).

Quality assessment

The quality assessment was conducted by two reviewers independently (CH, TF), using the quality rating tool proposed by the US Preventive Service Task Force (11). Seven criteria were used to assess quality: baseline comparability of the groups; the maintenance of comparability of the groups; differential or high loss to follow-up; reliable and valid measurement; clear definition of the intervention; consideration of important outcomes; and an intention-to-treat analysis. The quality of each study was graded as Good, Fair, or Poor. To be rated as good studies needed to meet all the criteria. ~~A study with a fair quality had to be free of fatal flaws and a study with at least one fatal flaw was recorded as having a poor quality.~~A study was rated as poor if one (or more) domain was assessed as having a serious flaw. Studies that met some but not all of the criteria was rated as fair quality.

Data analysis

Changes in HbA1c, or HbA1c at follow-up were compared between groups using a mean difference, and were presented with an associated 95% confidence interval (95% CI). When studies investigated interventions and contexts that were both deemed clinically similar, and free from statistical heterogeneity, pooling was carried using an inverse variance random effects model (12). Meta-analyses were conducted using the Comprehensive Meta-Analysis Software (version 2.2). The level of evidence was applied to the GRADE criteria and reported.

Heterogeneity and subgroup analyses

Heterogeneity was assessed and quantified using the I^2 statistic. When substantial heterogeneity was found (I^2>50%), further exploration using subgroup analysis was undertaken. For type 2 diabetes studies, subgroup analyses were: follow-up duration (less than six months, versus more than six months); length of time with diabetes (less than nine years, versus more than nine years); age of participants (mean age less than 55 years old, versus more than 55 years old); number of self-monitoring tasks supported by the diabetes apps (up to three, versus greater than three); and types of feedback provided. No type 1 diabetes subgroup analyses were performed due to the small number of studies.

Sensitivity analyses and publication bias

Additional analyses were carried out on studies with: good or fair quality; complete information; and studies with a baseline HbA1c level less than 9.0%. A funnel plot was used to visually inspect publication bias where 10 or more studies were pooled.

Results

Identified and included studies

Searches identified 5209 articles ~~(Figure 1)~~, 4238 were screened after removing duplicate records and 4178 were excluded. Sixty studies were eligible for full text review and 42 were excluded (Figure 1) resulting in 14 included studies. Four studies examined type 1 diabetes and 10 studies examined type 2 diabetes.

Characteristics of the included studies and quality assessment

In the 14 studies, there were 1360 participants, 509 and 851 with type 1 and type 2 diabetes respectively (Online Table 1). In the type 1 diabetes studies, the mean age of participants ranged from 34 (13) to 36 years old (14), and the mean duration of diabetes ranged from 16 (13-15) to 19 years (16). Two studies were undertaken in Europe (13; 14), one in Australia (16) and one was multinational (15). In the type 2 diabetes studies, the mean age of the participants was much higher, ranging from 51 (17) to 62 years old (18) and the mean duration of diabetes ranged from five (19) to 13 years (20) from six studies. Four studies were undertaken in Europe (18; 20-22), three in the USA (17; 23; 24), two in Asia (19; 25) and one in Africa (26).

~~Our quality assessment of the~~One type 1 diabetes stud~~y was assessedies report one rated~~ as good quality (14), two were rated as fair (13; 15), and one was rated as poor (16), for further details see Online Table 2. For type 2 diabetes studies, one was rated as good quality (21), six were rated as fair (17-19; 22; 24; 25) and three were rated as poor (20; 23; 26) (Online Table 2).

INCLUDE FIGURE 1 HERE

Apps featured in the included studies

Twelve diabetes apps were identified and examined in this review, with six domains of functionality (Online Table 3), details of the feedback provided by each can be seen in Online Table 4

Type 1 diabetes apps

Three apps were used for participants with type 1 diabetes and aimed to help patients to calculate the most appropriate insulin bolus, on the basis of patient blood glucose levels, food intake and physical activity. Data for all three apps were manually entered. One study reported that there was little impact of the app on the total time spent on face-to-face or telephone follow-up and concluded that the software did not require more time for patients to manage their diabetes (13). A further study estimated the average cost to patients and educators time was £38 per patient, attributed to the app over a 9 month period (16). HCP feedback was provided in all apps, with a frequency ranging from every week to every three weeks (Online Table 4).

Type 2 diabetes apps

Nine apps were used for participants with type 2 diabetes. The apps were designed to improve patient self-management, by providing personalized feedback on self-monitoring data, such as blood glucose, food intake, and physical activity. In eight of the apps, BG was automatically transferred and other data manually entered., with one exception where BP, body weight and pedometer was also automatically transferred (25),. Quinn et al. (17) reported that the app was associated with shorter consultation times. Among seven apps with HCP feedback, three provided feedback when needed (eg patient data were considered abnormal). In the ~~remaining~~ other apps, the frequency of feedback ranged from once a week to once every three months (Online Table 4).

Effectiveness of the apps:

Type 1 diabetes

There were mixed results f~~o~~rom the type 1 diabetes studies. Two studies (14; 15) found no difference between the intervention group and the control group and two studies (13; 16) reported statistically significant results that favored the apps~~.~~. There was a statistically insignificant difference in HbA1c between the apps and control group of -0.36% (95% CI -0.87% to 0.14%, P = 0.16, I^2 = 87%; Figure 2). No subgroup analyses were reported.

INCLUDE FIGURE 2 HERE

Type 2 diabetes

All ten studies of type 2 diabetes reported a reduction of HbA1c in participants using an app, with a~~and the~~ median reduction ~~from the studies was~~of 0.55% (range 0.15% to 1.87%). After pooling the mean reduction in HbA1c was 0.49% (95% CI 0.30%, to 0.68%; P < 0.001; I^2=10%; Figure 3). These results exhibited consistent findings with no heterogeneity. One study reported ~~results~~ a reduction larger than clinically anticipated which raised debate over the legitimacy of their findings (26). After excluding the subgroup of studies that were ~~quality~~ assessed as poor quality~~and only including those studies with good or fair quality~~, we found a mean reduction of 0.41% (95% CI 0.22%, to 0.61%; P<0.001; I^2=0%; Figure 3). The level of evidence by GRADE was moderate, due to the findings being downgraded due to quality.

INSERT FIGURE 3 HERE

Type 2 diabetes subgroup analyses

The subgroup analysis by follow-up duration showed that five studies with a shorter follow-up duration (less than six months) displayed a larger (but non-significant) HbA1c reduction than those with a longer duration (greater than six months) 0.62% versus 0.40% (P = 0.33) respectively. There was no difference in the reduction of HbA1c in three studies with a mean diabetes duration of less than nine years (0.53%) compared to those with a duration ≥ 9 years (0.55%; P = 0.93). Studies of younger participants with a mean age of ≤ 55 years reported a larger and clinically significant reduction in HbA1c level of 1.03% compared to those with an average age greater than 55 of 0.41%, but the result was not found to be statistically significant (P = 0.10).

~~The~~ In the subgroup analysis by number of self-monitoring tasks ~~found no difference. S~~ six diabetes apps ~~that~~ supported at most three self-monitoring tasks, and had similar results to those studies with more than three self-monitoring tasks (mean reduction of 0.44% versus 0.58%; ~~,~~P = 0.56). Two studies of diabetes apps with only automated feedback had a small and statistically non-significant reduction in HbA1c of 0.26% (95% CI 0.09%, to -0.62%). When diabetes apps included HCP feedback were~~as~~ pooled, eight studies reported a reduction of 0.56% (95% CI 0.35%, to 0.78%). There was no statistically significant difference between HCP verses automatic feedback subgroup (P = 0.16).

Four sensitivity analyses were undertaken to test the robustness of the results. Removing three studies (20; 23; 26) with poor quality reported a mean reduction of 0.41% (95% CI 0.22%, to 0.61%, Figure 3). The removal of one study (17) with incomplete statistical information was associated with a mean reduction of 0.48% (95% CI 0.28%, to 0.67%), and the exclusion of one study (20) conducted on mixed participants with type 1 and type 2 diabetes had an attendant mean reduction of 0.48% (95% CI 0.27%, to 0.69%). Finally, the exclusion of two studies (17; 23) with baseline HbA1c levels > 9.0% was associated with a mean reduction of 0.47% (95% CI 0.25%, to 0.69%).

Discussion

Ten studies were included for type 2 diabetes, ~~of~~ predominately of fair quality. The results of these indicated a consistent reduction in HbA1c of 0.5%. Although there was no indication of heterogeneity, the study conducted by Takenga et al. (26) introduced a large effect, that was likely to be caused by poor study quality (high attrition rate, differential loss to follow-up and high baseline HbA1c level). ~~Subgroup of study quality were used to stratify studies with a poor quality assessment, compared to those with a fair and good quality assessment~~ Thus, studies were stratified into subgroup determined by their quality assessment (27). No differences were found between the subgroups ~~based on quality~~, and the studies of poor quality were included for completeness, and to highlight the challenges in study design.

Five subgroup analyses showed that the effect did not differ significantly by follow-up duration, mean diabetes duration of participants, mean age of participants, number of self-monitoring tasks supported by the diabetes apps, or types of feedback. Compared to studies that have investigated alternative interventions to improve their diabetes self-management ~~of HbA1c~~, such as: text messaging, mobile device, computer based and convention self-management, we have found that apps offer promising results and reinforce the message argued by other authors (3; 4; 28-30). The evidence for this finding by GRADE was moderate, after down grading due to quality.

The subgroup analysis by follow-up duration suggested that the effect of diabetes apps on blood glucose control may attenuate over time. A possible rationale for this subgroup effect is a lack in user-friendliness, a lack in perceived additional benefits and a lack of use of gamification elements, resulting in a lack of efficacy following use (31). The subgroup analysis by mean age of participants indicated that younger patients were more likely to benefit from the use of the diabetes apps. It may be speculated that younger patients are more amenable to new technologies and more familiar with the use of mobile phones. The subgroup analysis by personalized feedback system highlighted the gap between automated feedback and healthcare professional feedback. Although automated feedback has the advantage of being interactive and dynamic ~~(and probably cost-effective)~~, there is a limit to presupposed

scenarios, whereas feedback provided by healthcare professionals wais more individual, especially in emergency situations. Feedback options ranged widely between the apps, but it is postulated that it was the feedback that triggered improved lifestyle choices, which in turn lowered HbA1c. None of the five sensitivity analyses changed the overall effect size significantly, which suggests that the findings are not sensitive to these scenarios. The results of our meta-analysis lend support to the use of diabetes apps in diabetes self-management, especially for type 2 diabetes. However, we have highlighted a number of limitations of current diabetes apps.

For type 1 diabetes, there was little difference in HbA1c between intervention and control groups and the results were associated with considerable heterogeneity. The level of evidence by GRADE was downgraded to very low due to: study quality; inconsistency; and uncertainty; so the findings should be interpreted as very uncertain and likely to be change following future research. Furthermore, none of the apps in the included type 1 diabetes studies had an automatic data uploading functionality. In future studies for type 1 diabetes, we encourage investigators to include apps with this functionality, not only for the purpose of being user-friendly, but also for safety concerns by reducing the risk of data entry errors.

Two studies reported on the cost effectiveness of the apps for type 1 diabetes with inconclusive findings (15; 16) on type 1 diabetes reported on the cost of the intervention. Although the data provided by the two studies seemed to favor the diabetes apps as a low-cost self-management intervention for type 1 diabetes, its effect on diabetes self-management is still questioned. Of tThree studies on type 2 diabetes that discussed compliance, described patient compliance, and two reported poor compliance of the patients, reporting compliance with only 35% of patients as regular app users (21; 24). One study (25) reported a decline in patient use over time, from 70% in the first week to 50% in the last two weeks. Four studies tried to explore the mechanisms behind the effects, but the conclusions were inconsistent (16; 17; 21; 24). We postulate that diabetes apps influence lifestyle choice, but how this occurs is unclear. One hypothesis is that the reminder and feedback features of diabetes apps can lead to improvement in health beliefs, self-efficacy and social support (32).

By the end of the decade, worldwide mobile phone usage is anticipated to exceed 5 billion (33). Therefore apps may be able to offer an affordable and widely available adjunct to diabetes self-management. We have included studies across a variety of healthcare systems, from both the developed and developing world, so we argue the apps are currently available and could form the basis of improved health promotion on diabetes education and self-management.

This study had several limitations. Since this review was restricted to published studies and so publication bias cannot be ruled out as highlighted by other investigators (30) All included study designs were ~~unblinded~~not blinded, so were downgraded in the quality assessment tool, (highlighting the increased risk of ascertainment bias). Furthermore, patient-important outcomes and behavioral mechanisms and outcomes were not considered and is a clear gap to be addressed in future studies. A further weakness is that some of the effect attributed to the apps could be explained by health care providers. Finally, there is no clear definition of diabetes apps and study authors defined their interventions in different ways as a result. In this review, we defined diabetes apps as software that is designed for use on a mobile phone allowing patients to enter data into the app~~, with response to the inputted data through either automatically generated feedback or patients' HCPs' feedback.~~ and receive feedback.

The implications for future research include establishing a common standardized platform of functionality. Investigators of future studies need to consider adequately powered pragmatic RCTs with secure sequence generation, concealed allocation, use of an active control app, and comparable access to HCP. Features such as these might reduce the impact of ascertainment bias and effects due to HCP. RCTs with longer duration of follow up (> 6 months) using standardized app technology may well demonstrate beneficial clinical effect in type 2 diabetes. Furthermore, there is significant scope for research in the use of apps in other areas of self-management, such as increasing physical activity, weight loss and smoking cessation.

In a clinical context, ~~the need to consider patient safety issues is of paramount~~

~~importance with apps aligned with current diabetes self-management guidelines.~~ ~~W~~we recommend that HCP feedback should be central in all future app design and supplemented with dynamic automated feedback. Future technology should also be underpinned by behavior change theories and gamification elements to achieve a larger effect on blood glucose control and improve compliance of patients in using diabetes apps. Finally, future technology should also consider the needs of older patients.

References

1. Whiting DR, Guariguata L, Weil C, Shaw J: IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice 2011;94:311-321
2. Polonsky WH, Fisher L: Self-monitoring of blood glucose in noninsulin-using type 2 diabetic patients: right answer, but wrong question: self-monitoring of blood glucose can be clinically valuable for noninsulin users. Diabetes care 2013;36:179-182
3. Liang X, Wang Q, Yang X, Cao J, Chen J, Mo X, Huang J, Wang L, Gu D: Effect of mobile phone intervention for diabetes on glycaemic control: a meta-analysis. Diabetic medicine : a journal of the British Diabetic Association 2011;28:455-463
4. Pal K, Eastwood SV, Michie S, Farmer AJ, Barnard ML, Peacock R, Wood B, Inniss JD, Murray E: Computer-based diabetes self-management interventions for adults with type 2 diabetes mellitus. The Cochrane database of systematic reviews 2013;3:CD008776
5. Angeles RN, Howard MI, Dolovich L: The effectiveness of web-based tools for improving blood glucose control in patients with diabetes mellitus: a meta-analysis. Canadian Journal of Diabetes 2011;35:344-352
6. Tatara N, Arsand E, Nilsen H, Hartvigsen G: A Review of Mobile Terminal-Based Applications for Self-Management of Patients with Diabetes. International Conference on Ehealth, Telemedicine, and Social Medicine: Etelemed 2009, Proceedings 2009:166-175
7. Baron J, McBain H, Newman S: The impact of mobile monitoring technologies on glycosylated hemoglobin in diabetes: a systematic review. Journal of Diabetes Science & Technology 2012;6:1185-1196
8. El-Gayar O, P. T, N. N, Eid W: A systematic review of IT for diabetes self-management: are we there yet? International journal of medical informatics 2013;82(8):637-652
9. Klonoff DC: The current status of mHealth for diabetes: will it be the next big thing? Journal of diabetes science and technology 2013;7:749-758
10. Ma J, Liu W, Hunter A, Zhang W: Performing meta-analysis with incomplete statistical information in clinical trials. BMC Medical Research Methodology 2008;8:56
11. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D, Methods Work Group TUSPSTF: Current methods of the US Preventive Services Task Force: a review of the process. American journal of preventive medicine 2001;20:21-35
12. Deeks JJ, Higgins JPT, Altman DG: Chapter 9: Analysing data and undertaking meta-analyses. In *Cochrane handbook for systematic reviews of interventions* Higgins JPT, Green S, Eds., Wiley Online Library, 2008
13. Charpentier G, Benhamou P-Y, Dardari D, Clergeot A, Franc S, Schaepelynck-Belicar P, Catargi B, Melki V, Chaillous L, Farret A: The Diabeo Software Enabling Individualized Insulin Dose Adjustments Combined With Telemedicine Support Improves HbA1c in Poorly Controlled Type 1 Diabetic Patients A 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). Diabetes Care 2011;34:533-539
14. Rossi MC, Nicolucci A, Lucisano G, Pellegrini F, Di Bartolo P, Miselli V, Anichini R, Vespasiani G, Did Study G: Impact of the "Diabetes Interactive Diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. Diabetes Technology & Therapeutics 2013;15:670-679
15. Rossi MC, Nicolucci A, Di Bartolo P, Bruttomesso D, Girelli A, Ampudia FJ, Kerr D, Ceriello A, Mayor Cde L, Pellegrini F, Horwitz D, Vespasiani G: Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care 2010;33:109-115
16. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ: Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. Journal of medical Internet research 2013;15
17. Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A: WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. Diabetes technology & therapeutics 2008;10:160-168
18. Orsama AL, Lahteenmaki J, Harno K, Kulju M, Wintergerst E, Schachner H, Stenger P, Leppanen J, Kaijanranta H, Salaspuro V, Fisher WA: Active assistance technology reduces glycosylated hemoglobin and weight in individuals with type 2 diabetes: results of a theory-based randomized trial. Diabetes technology & therapeutics 2013;15:662-669
19. Yoo HJ, Park MS, Kim TN, Yang SJ, Cho GJ, Hwang TG, Baik SH, Choi DS, Park GH, Choi KM: A ubiquitous chronic disease care system using cellular phones and the internet. Diabetic Medicine 2009;26:628-635
20. Istepanian RS, Zitouni K, Harry D, Moutosammy N, Sungoor A, Tang B, Earle KA: Evaluation of a mobile phone telemonitoring system for glycaemic control in patients with diabetes. Journal of Telemedicine & Telecare 2009;15:125-128

21. Holmen H, Torbjørnsen A, Wahl AK, Jenum AK, Småstuen MC, Årsand E, Ribu L: A Mobile Health Intervention for Self-Management and Lifestyle Change for Persons With Type 2 Diabetes, Part 2: One-Year Results From the Norwegian Randomized Controlled Trial RENEWING HEALTH. JMIR mHealth and uHealth 2014;2
22. Nagrebetsky A, Larsen M, Craven A, Turner J, McRobert N, Murray E, Gibson O, Neil A, Tarassenko L, Farmer A: Stepwise self-titration of oral glucose-lowering medication using a mobile telephone-based telehealth platform in type 2 diabetes: a feasibility trial in primary care. Journal of diabetes science and technology 2013;7:123-134
23. Quinn CC, Shardell MD, Terrin ML, Barr EA, Ballew SH, Gruber-Baldini AL: Cluster-randomized trial of a mobile phone personalized behavioral intervention for blood glucose control. Diabetes Care 2011;34:1934-1942
24. Faridi Z, Liberti L, Shuval K, Northrup V, Ali A, Katz DL: Evaluating the impact of mobile telephone technology on type 2 diabetic patients' self‐management: the NICHE pilot study. Journal of evaluation in clinical practice 2008;14:465-469
25. Waki K, Fujita H, Uchimura Y, Omae K, Aramaki E, Kato S, Lee H, Kobayashi H, Kadowaki T, Ohe K: DialBetics: A Novel Smartphone-based Self-management Support System for Type 2 Diabetes Patients. Journal of diabetes science and technology 2014;8:209-215
26. Takenga C, Berndt R-D, Musongya O, Kitero J, Katoke R, Molo K, Kazingufu B, Meni M, Vikandy M, Takenga H: An ICT-based diabetes management system tested for health care delivery in the african context. International journal of telemedicine and applications 2014;2014:6
27. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savović J, Schulz KF, Weeks L, Sterne JA: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj 2011;343:d5928
28. Steinsbekk A, Rygg L, Lisulo M, Rise MB, Fretheim A: Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. BMC health services research 2012;12:213
29. De Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R: Mobile phone messaging for facilitating self-management of long-term illnesses. The Cochrane database of systematic reviews 2012;12
30. Su D, Zhou J, Kelley MS, Michaud TL, Siahpush M, Kim J, Wilson F, Stimpson JP, Pagán JA: Does telemedicine improve treatment outcomes for diabetes? A meta-analysis of results from 55 randomized controlled trials. Diabetes Research and Clinical Practice 2016;116:136-148
31. Scheibe M, Reichelt J, Bellmann M, Kirch W: Acceptance Factors of Mobile Apps for Diabetes by Patients Aged 50 or Older: A Qualitative Study. Medicine 20 2015;4
32. Nundy S, Dick JJ, Solomon MC, Peek ME: Developing a behavioral model for mobile phone-based diabetes interventions. Patient education and counseling 2013;90:125-132
33. http://www.statista.com/statistics/274774/forecast-of-mobile-phone-users-worldwide/: Accessed January 2016;

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A declaration of competing interests.

"All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare that (1) ~~BC and~~ CH, SM, JM, TF, or BC have no support from any companies for the submitted work; (2) CH, SM, JM, TF, or BC ~~BC and CH~~ have no relationships with companies that might have an interest in the submitted work in the previous 3 years; (3) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (4) CH, SM, JM, TF, or BC~~BC and CH~~ have no non-financial interests that may be relevant to the submitted work."

Author Contribution:

Can Hou (CH) designed the protocol, searched the literature, extracted the data, carried out the analysis, and drafted the manuscript

Sharon Mayor (SM) designed the protocol, interpreted the results, and contributed to the manuscript

Jonathan Hewitt (JH) reviewed the manuscript and advised on the clinical context of the review

Trevor Francisa (TF) searched the literature, extracted the data

Ben Carter (BC) interpreted the results, drafted to the manuscript and is the guarantor of the review.

Guarantor's statement

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Dr. Ben Carter ~~BC~~ is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis ~~has full access to all the data in the study and had final responsibility for the decision to submit for publication~~

A transparency declaration:

The manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure 1: PRISMA Flowchart of included studies

Figure 2: Pooled Type 1 diabetes studies of HbA1c comparison of apps versus control

Figure 3: Pooled Type 2 diabetes studies of HbA1C comparison of apps versus control