Mobile phone applications and self-management of diabetes: a systematic review with meta-analysis, meta-regression of 21 randomized trials, and GRADE
Mobile phone applications and self-management of diabetes: a systematic review with meta-analysis, meta-regression of 21 randomized trials, and GRADE

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ABSTRACT

AIMS: To evaluate the growing evidence base of mobile phone applications for the self-management of type 1 and 2 diabetes mellitus. Then, to investigate the impact of app functions as moderating effects, including the impact of health care professional (HCP) feedback incorporated in the apps.

MATERIALS AND METHODS: A systematic review with meta-analysis, meta-regression and GRADE of the evidence. Relevant randomized controlled trials that were published between 1 January 1996 and 1 May 2017 and reported either HbA1c or severe hypoglycemic episodes as outcomes were searched in five databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase.

RESULTS: 1550 participants from 21 studies were included in the review. For type 1 diabetes, a significant 0.49% reduction in HbA1c was seen (95%CI 0.04 to 0.94; I²=84%), with unexplained heterogeneity and a low GRADE of evidence. For type 2 diabetes, using diabetes apps was associated with a mean reduction of 0.57% in HbA1c (95%CI 0.32 to 0.82, I²=77%). The results had severe heterogeneity that was explained by the frequency of HCP feedback. In studies with: no HCP feedback, a mean reduction of 0.24% (95% CI-0.02 to 0.49; I²=0%); low frequency, mean reduction of 0.33% (95% CI 0.07 to 0.59; I²=47%); and high frequency a mean reduction of 1.12% (95%CI 0.91 to 1.32; I²=0%), with high GRADE of evidence.

No evidence was found of excess severe hypoglycemic episodes associated with diabetes apps (seven studies).
CONCLUSIONS: There is evidence that diabetes apps improve glycemic control in type 1 diabetes patients. A reduction of 0.57% in HbA1c was found in type 2 diabetes patients. However, HCP involvement is critical functionality to achieve clinical effectiveness. A cost-effectiveness study is needed to evaluate whether diabetes apps should be used routinely.
INTRODUCTION

In the past three decades, the number of people with diabetes worldwide has risen from 153 million in 1980 [1] to 382 million in 2013 [2], and is expected to rise to 592 million by 2035 [2]. The high prevalence of diabetes gives rise to the increased global healthcare costs on diabetes and, more importantly, its complications. The estimated health expenditure on diabetes worldwide increased from 548 billion US dollars in 2013 to over 612 billion US dollars in 2014 [3], imposing a huge economic burden to healthcare systems.

Nevertheless, there are overwhelming evidence that intensive glycated hemoglobin (HbA\textsubscript{1c}) control can significantly reduce the risk of diabetes complications [4, 5]. But nowadays, the percentage of diabetes patients achieving the recommended HbA\textsubscript{1c} target remains low [6, 7]. The importance of patients’ self-management in achieving HbA\textsubscript{1c} level of below 6.5% is well-recognized. Traditional diabetes self-management education (DSME) that aimed to improve diabetes self-management has shown to be associated with approximately 0.5% reductions in HbA\textsubscript{1c} [8, 9]. However, the wide implementation of these self-management strategies is unrealistic in current over-burdened healthcare systems, as these strategies are historically resource-intensive and requires time from healthcare professionals (HCPs) and patients.

Diabetes mobile phone applications (diabetes apps) is a newly emerging technology for diabetes self-management. Due to its ubiquitous, cheap, interactive, and dynamic health promotion [10], diabetes apps may provide effective diabetes self-care by supporting diabetes patients in all the self-care behaviors and overcome the weakness of the current self-management strategies at the meantime. Our previous systematic review demonstrated that diabetes apps are effective in
controlling HbA1c in type 2 diabetes patients [10], this conclusion was supported by three later
systematic reviews [11-13]. However, there is still uncertainty on whether diabetes apps are effective
in the self-management of type 1 diabetes, and which aspects of the apps are associated with better
self-management. There is current debate to what extent the effect of diabetes apps on HbA1c should
be attributed to Health Care Professionals (HCP) [14].

The primary objective of this study is to determine the effectiveness and safety of the apps, and
secondary objectives are to establish which features are likely mediating effects.

MATERIALS AND METHODS

Literature searching, selection criteria and data extraction

This study is an update of a systematic review following a pre-specified protocol and follows the
PRISMA statement and checklist (PROSPERO reg. no. CRD42017067774). We searched relevant
peer-reviewed studies published between June 1\textsuperscript{st}, 2015 and May 1\textsuperscript{st}, 2017 in five electronic
databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase. The following terms
and medical subject headings (MeSH) were used: mobile, mHealth, cell phones, cellular phone,
smartphone, app, mobile applications, iphone, phone, diabetes mellitus, T2DM, T1DM, IDDM,
NIDDM, DM, T1D, T2D, or MODY (Supplementary Table 1). The references of the included
studies were hand searched to identify additional articles.

The inclusion and exclusion criteria used were: \( \geq 18 \) years old participants with type 1 or type 2
diabetes; the studies adopted randomized controlled trials (RCTs) design and reported HbA1c or
severe hypoglycemic episodes as an outcome; the control group in the study received usual care
without any telehealth interventions. We define severe hypoglycemic episodes as any hypoglycemic episodes that require third-party assistance. For data extraction, participant demographics, study design considerations, and context were extracted from each included study (Supplementary tables 2 and 3). Corresponding authors were contacted to provide missing data, and where necessary, we used statistical methods to impute missing data [15, 16]. Literature searching, screening (including rescreening of previous search results for hypoglycemic episodes) and data extraction were conducted by two reviewers independently (CH and QX). Any disagreements were resolved by discussion with a third reviewer (JYL).

Risk of bias (RoB) assessment

The nine Cochrane RoB domains were categorized as ‘low risk of bias’, high risk of bias, or ‘unclear’ of each study [17]. Risk of bias will be independently evaluated by two authors (CH and SD) and any discrepancies in bias coding were resolved by a third reviewer (BC). Studies were classified with a high RoB if they determined as having a high RoB for both blinding and incomplete outcome data domains. If all domains were a low RoB the study was described with a low RoB, and unclear if a combination of low and unclear domains.

Data analysis and synthesis

The primary outcome is HbA$_1c$, and secondary outcome is severe hypoglycemic episodes. For the primary outcome, we used the inverse variance random effects model [18] to pool mean differences (MD) in HbA$_1c$ changes from baseline or post-intervention HbA$_1c$ for type 1 and type 2 diabetes studies separately [18]. The $I^2$ statistic was used to assess and quantify heterogeneity. When substantial heterogeneity was found ($I^2>50$%), we explored the source of heterogeneity using
Subgroup analysis and meta-regression. For the secondary outcome, DerSimonian & Laird random-effects model [18] was used to carry out the pooling of risk ratios (RR) with the estimate of heterogeneity being taken from the Mantel-Haenszel model [19].

For cluster randomized controlled trial, effect size abstracted from an analysis that properly accounts for the cluster design is preferred [17]. Otherwise, an effective sample size will be used instead:

\[ N_{\text{effective}} = \frac{N}{1 + \left(\frac{m-1}{m}\right) \cdot ICC} \]

where parameter ICC was calculated from one of the included cluster randomized controlled studies [21]. All the statistical analyses were conducted using STATA (version 14.1) and Comprehensive Meta-Analysis (version 3).

**Subgroup analyses and meta-regression**

Subgroup analyses by HCP intensity were carried out for both type 1 and type 2 diabetes studies to explain heterogeneity. Random-effects meta-regressions were further carried out for type 2 diabetes studies to explore the factors that may influence the efficacy of apps on glycemic control. We applied a modification to the variance of the estimated coefficients as suggested by Knapp and Hartung [22] and used the residual maximum likelihood (REML) method to estimate between-study variance [23]. Univariable meta-regression analyses by length of the study follow up, baseline HbA1c levels, and ages of the participants were carried out first. We then conducted multivariable meta-regression analyses to investigate what functions of the apps could influence HbA1c control after adjusting for the predictors that found to be statistically significant (p<0.05) in the univariable meta-regressions. In the multivariable meta-regression analyses, Tau² was used to reflect
between-study variance while $I^2$-residual was calculated to reflect residual variation due to heterogeneity.

**Sensitivity analyses and publication bias**

For the primary outcome we removed studies with: a high RoB; had missing data imputation; and studies conducted on mixed participants. When 10 or more studies were pooled, we used funnel plot to visually inspect publication bias.

**RESULTS**

The literature search in five databases resulted in 4467 records, plus 5211 records identified on June 2015. Thirty-two manuscripts (21 studies) were included and 116 were excluded (Figure 1). In the 21 included studies [21, 24-43], three studies enrolled both type 1 and type 2 diabetes patients, of these, two studies provided additional data and could be included in both type 1 and type 2 syntheses [32, 34], and the third study included predominantly type 2 diabetes patients (>90%) so was classified as type 2 [30]. In total, 1550 participants were included in the meta-analysis, of which 516 were type 1 diabetes patients (average 35.3 ys old and 18.4 years of diabetes duration) and 1034 were type 2 diabetes patients (average 55.2 years old and 9.5 years of diabetes duration) (Supplementary Table 2). The median follow-up period is 6 months (range 3-9 months) and 6 months (range 1.5-12 months) in type 1 and type 2 diabetes studies respectively.

INCLUDE FIGURE 1 HERE
One type 1 diabetes study [42] and three type 2 diabetes studies [30, 31, 33] were at high RoB, while the risk of bias in the remaining studies was unclear (Supplementary Figure 1 and 2). Studies with a high RoB were largely due to: blinding; use of fixed permuted-block randomization (in open-label trials); and high loss to follow up.

A total of 19 diabetes apps were assessed in 21 included studies, of which, four apps were assessed in type 1 diabetes patients, 12 in type 2 diabetes patients and three in both type 1 and type 2 diabetes patients. We examined diabetes apps in the following nine domains of functionality: self-monitoring tasks supported, data entry method, CHO/insulin bolus calculator, medication adjustment support, real-time personalized feedback (automated feedback provided by apps), structured display (display of blood glucose and other self-monitoring data), HCP feedback, frequency of HCP feedback and other functionalities (Supplementary Table 3). We further categorized HCP feedback into three groups according to the frequency of HCP feedback: no HCP feedback (did not support or provide additional HCP feedback in the intervention group), low frequency HCP feedback (when necessary or less than or equal to once per month) and high frequency HCP feedback (more than once per month). Among type 1 diabetes apps, two apps aimed to help patients with insulin bolus calculation and the others were designed to improve self-management by providing automated feedback or HCP feedback. None of type 1 diabetes apps supported real-time personalized feedback while wireless self-monitoring data transmission was supported in only one apps. As for HCP feedback, it was provided in four apps, with the frequency ranging from once per week to once per month. On the contrary, majority of the type 2 diabetes apps were designed to support diabetes self-management by providing personalized feedback on self-monitoring data (blood glucose, physical activity et al.). Besides, wireless data transmission and real-time personalized feedback was supported in
approximately half of the apps. In terms of HCP feedback, four studies of diabetes apps had no HCP feedback. In the remaining 12 studies of diabetes apps, seven provided low frequency HCP feedback and five had high frequency HCP feedback.

For primary outcome, seven studies on type 1 diabetes reported controversial results. After pooling, we found a mean reduction of 0.49% in HbA$_1c$ that favored the intervention (95% CI 0.04 to 0.94; P=0.03, Figure 2), (hereafter, the reported values always refer to absolute reduction in HbA$_1c$), but exhibited considerable heterogeneity ($I^2 = 84\%$), which was partially explained by HCP feedback (Figure 2). The differences between the subgroups were insignificant (P=0.26). We conducted two sensitivity analyses. Removing one study with incomplete data [43] reported an insignificant reduction of 0.49% (95% CI -0.04 to 1.01). When one study with high RoB was removed [42], the mean reduction decreased to 0.35% (95% CI -0.11 to 0.81). The level of evidence by GRADE is low, downgraded due to blinding and imprecision.

For type 2 diabetes, five studies reported statistically significant HbA$_1c$ reduction that favored the apps, nine studies found improvements in HbA$_1c$ but did not reach statistical significance, and two studies did not find any difference between the intervention and control groups. The pooled results indicated that compared with control, using diabetes apps was associated with a mean reduction of 0.57% in HbA$_1c$ (95% CI 0.32 to 0.82; P < 0.01; Figure 3). Although these results exhibited significant heterogeneity ($I^2 = 77\%$), it was explained by the HCP intensity (Figure 3). Studies with no HCP feedback reported a mean reduction of 0.24% (95% CI -0.02 to 0.49), whereas studies included low and high frequency HCP feedback had mean reductions of 0.33% (95% CI 0.07 to 0.59) and 1.12% (0.91 to 1.32) respectively. The level of evidence by GRADE for diabetes apps is high, based on downgrading for blinding but upgrading for dose-response.
For type 2 diabetes studies, three sensitivity analyses were conducted. Removing studies [30, 31, 33] with high risk of bias resulted in a mean reduction of 0.56% (95% CI 0.28 to 0.84). Exclusion of one study [30] that enrolled both type 1 and 2 patients reported a mean reduction of 0.57% (95% CI 0.30 to 0.83). Finally, we removed one study with incomplete data [29] and the mean reduction did not change distinctly (0.53%, 95% CI 0.28 to 0.79). There is no indication of publication bias in Supplemental Figure 3.

Although seven studies looked at severe hypoglycemic episodes [27, 28, 31, 36, 39-41], only one type 1 diabetes study [41] reported a total of four episodes of severe hypoglycemic in the intervention and control groups (one in the intervention group and three in the control group). Therefore, pooling of severe hypoglycemic episodes was not conducted as planned.

**INCLUDE FIGURE 2 AND FIGURE 3 HERE**

**Meta-regression analysis**

In the univariable meta-regression analyses (Supplementary Figure 4), we found a statistically significant relationship between baseline HbA$_1c$ levels and effect size (P=0.02), suggesting the reduction in HbA$_1c$ was likely to increase with the baseline HbA$_1c$ levels. We also found that mean ages of the participants was inversely associated with effect size, indicating studies with younger participants may report larger effect size compared with trials with older participants (P=0.03). As for study length, its relationship to effect size was not statistically significant (P=0.82).

Based on the results from single covariate meta-regressions, we conducted series of multivariable meta-regressions that adjusted for ages and baseline HbA$_1c$ values respectively. After adjusting for baseline HbA$_1c$ levels, we found a significant dose-response relationship between HCP feedback and
effect size (P=0.02, \( \tau^2=0.04, I^2\text{-res}=37.22\% \), Supplementary Figure 5). This dose-response relationship remained to be significant when we adjusted for mean ages of the participants (P=0.01, \( \tau^2=0.05, I^2\text{-res}=45.85\% \)). As for the other functionalities of the diabetes apps, their effect on glycemic control was insignificant in both models (Supplementary Figure 6).

**DISCUSSION**

This systematic review updated the body of evidence of diabetes apps to improve glycemic control in the self-management of diabetes. A total of 21 studies were included in this review, of which 8 studies were newly identified. For type 1 diabetes, a statistically significant reduction in HbA1c that favored the use of diabetes apps is reported for the first time. The results reaffirmed that apps for type 2 diabetes help with self-management, but also demonstrated a HCP dose-response with HbA1c. The magnitude of the effect in the diabetes apps group with a highest level of HCP was higher than that in our previous meta-analysis [10].

Compared with three recent similar meta-analysis [11-13], the strengthens of our meta-analysis are most updated searching of the literatures, strict following of a registered protocol, exclusion of studies conducted on participants aged <18 years old and studies that used other kinds of electronic devices. Furthermore, out analysis were conducted separately for type 1 and type 2 diabetes patients. One of the novel findings of our review is that we reported a statistically significant reduction in HbA1c among type 1 diabetes patients for the first time. Although previous reviews also revealed that diabetes apps that incorporated HCP feedback may be more effective, their conclusions are based on subgroup analysis and omit the potential effect of confounders. In our review, we used multivariable
meta-regression analyses to adjust for potential confounders and revealed a significant dose-response relationship between HCP feedback and HbA$_1$c reduction, which makes our conclusion more robust.

Nevertheless, our study has some limitations. Firstly, for the purpose of obtaining detailed information on the diabetes apps, we restricted the review to published articles, which may introduced publication bias. Due to the characteristics of the diabetes apps interventions, double-blind study design is not applicable, which raised the issue of high risk of ascertainment bias in all the included studies. Meanwhile, the assessment of risk of bias of included studies was inadequate for some domains, due to the lack of important information in some of the studies. Fourthly, the covariates included in the meta-regression models were study level data rather than patient level data, making our findings vulnerable to the ecological fallacy. Finally, because of insufficient numbers of studies, we were not able to investigate interactions between different functionalities of the apps.

Although the results in type 2 diabetes were associated with significant heterogeneity, it was significantly decreased after we stratified the studies by HCP intensity. The residual heterogeneity is acceptable for complex interventions like diabetes apps. The results from univariable meta-regressions suggested that baseline HbA$_1$c levels was a significant mediator for the effect of diabetes apps. The positive association between baseline HbA1c levels and reductions in HbA$_1$c is anticipated and accordant with findings in other diabetes researches [44, 45], as patients with higher baseline HbA1c levels generally have poorer glycemic control and are therefore more likely to benefit from interventions. The inverse linear relationship between mean ages of the participants and reductions in HbA$_1$c agrees with our previous hypothesis that younger patients were more likely to benefit from the use of diabetes apps [10]. Since it has been reported that older patients were less
interested in the use of diabetes apps [46], it is plausible that diabetes apps is less effective among
older patients. However, there is no convincing external evidence supporting such hypothesis [47],
and future researches need to investigate into this relationship more deeply. Our results revealed no
significant association between follow-up duration and this finding is also supported by four studies,
in which the HbA\textsubscript{1c} reductions in the intervention groups kept stable at different follow-up visits [31,
33, 34, 38]. However, whether the effect of diabetes apps can sustain for a longer period of time (>1
year) is still largely unknown.

Results from multivariable meta-regressions statistically confirmed the hypothesis that the effect of
diabetes apps in glycemic control is largely attributed to the effect of HCPs [12]. Although diabetes
apps is projected to increase patients’ self-efficacy and promote behavior change through features
like reminder and real-time personalized feedback [14, 48], the effect of sole use of diabetes apps is
likely to be small. There are two possible explanations for this finding. First, vast majority of the
apps were not based on behavior change theory and had little impact on influencing lifestyle choice
of the patients. Second, due to the limitations of technology, automated feedback can only provide
limited support on self-management. Compared with diabetes apps with low frequency HCP
feedback, those with high frequency feedback have significantly larger effect size. We speculate this
difference is not only the result of different HCP intensity, but also the result of different types of
HCP feedback. Among the four studies with high HCP intensity, all of them provided medication
adjustment support. Whereas in the eight studies with low HCO intensity, medication adjustment
support from HCPs was included in less than half of the studies. Our speculation is consistent with
the findings from previous meta-analysis investigating other diabetes telemedicine interventions and
diabetes quality improvement strategies [45, 49]. Therefore, we believe it is medication adjustments
support that plays a crucial role in the effect of HCP feedback. Based on these results, we postulate two main mechanisms behind the effects of diabetes apps on HbA$_{1c}$ reduction (Supplementary Figure 7): (a) HCP feedback provide patients with medication adjustments and lifestyle modifications support (b) Self-monitoring using apps facilitates the HCP feedback.

For studies on type 1 diabetes, although we found a statistically significant reduction of 0.49%, the result was not robust and had some heterogeneity. Compared with the very low level of evidence we reported previously [10], the current level of evidence was rated up to low by GRADE, meaning future research is likely to change the estimate. It is notable that only one type 1 diabetes apps supported automatic data uploading functionality, therefore, we encourage more diabetes apps that include this functionality to be designed for type 1 diabetes patients.

Although there is some indication that the use of diabetes apps is associated with no excess severe hypoglycemia episodes, current evidence for the safety of diabetes apps is scarce. Future studies of diabetes apps should pay more attentions to the safety issues, especially for apps with bolus calculator functionality [50].

In recent years, the enthusiasm for diabetes apps is increasing with the worldwide smartphone usage rate. The purpose of our findings is not to dampen such enthusiasm, but to highlight the gaps in current diabetes apps and suggest future researches in this area. The population-wide implementation of diabetes apps need the support from both clinicians and payers. For clinicians, their primary consideration is not only the clinical effect of using diabetes apps for diabetes patients, but more importantly whether the time spent on adapting the technology and sending feedback justify the perceived benefit [51]. Hence, for future researches, we appeal that the intensity and types of HCP
feedback should always be reported with enough detail, so that clinicians can have a more comprehensive look at the study results. In order to fulfil HCPs’ needs, future diabetes apps need to reduce dependencies in HCP feedback. We suggest that future diabetes should be underpinned by behavioral principles and diabetes self-management guidelines and incorporate gamification elements [52] and social medial function [46]. As for payers, cost-effectiveness of the intervention is their primary concern. Future investigators should consider conducting a comprehensive economic evaluation that takes into account both the direct and indirect cost of the diabetes apps. Meanwhile, investigators need to pay more attentions to evaluating the safety of diabetes apps. Furthermore, the long-term effects (>1 year) of diabetes apps are still unknown and need to be investigated in more pragmatic observational studies.

Conclusion

This systematic review and meta-regression reveals a robust 0.57% reduction in HbA1c for diabetes apps compared with usual care in type 2 diabetes. However, this reduction in HbA1c is largely dependent on the effect of health care professionals, which highlights the importance of comprehensive economic evaluation and developing more effective apps in the future. As for type 1 diabetes, we found a statistically significant reduction in HbA1c that supported the use of diabetes apps, but the level of evidence was low. There is some indication that using diabetes apps will not increase the risk of severe hypoglycemic episodes. But the evidence is limited and more studies are needed.
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Author Contributions: CH designed the protocol, searched the literature, extracted the data, assessed the risk of bias, carried out the analysis, and drafted the manuscript. QX searched the literature, extracted the data and drafted the manuscript. SD assessed the risk of bias and contributed to the manuscript. JH interpreted the manuscript. JYL interpreted the results and contributed to the manuscript. BC designed the protocol, interpreted the results and contributed to the manuscript.

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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Legends to figures

Figure 1—PRISMA flowchart of included studies

Figure 2: Pooled type 1 diabetes studies of HbA1c comparison of apps vs. control (subgroup by HCP feedback)

Figure 3: Pooled type 2 diabetes studies of HbA1c comparison of apps vs. control (subgroup by HCP feedback)
**Figure 1**

**Identification**
- 5211 records identified (search conducted on June 2015)
- 4467 records identified (search conducted on May 2017)

**Screening**
- 7433 records after duplicates removed

**Eligibility**
- 148 full-text articles assessed for eligibility
  - 116 full-text articles excluded
    - Conference abstracts (n=38)
    - Other interventions (n=31)
    - Ineligible control group (n=3)
    - No relevant outcome reported (n=4)
    - Not an RCT (n=32)
    - Ongoing study (n=4)
    - Participants aged <18 years (n=3)
    - Simulated HbA1c (n=1)

**Included**
- 21 studies (32 papers) included in qualitative synthesis

- 21 studies (32 papers) included in quantitative synthesis (meta-analysis)
### Figure 2

<table>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference in means</th>
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<td>Mean (%)</td>
<td>SD (%)</td>
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</tr>
<tr>
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<tr>
<td>Rossi et al. 2013[9]</td>
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<td>Zhou et al. 2016[13]</td>
<td>3.24</td>
<td>1.66</td>
<td>10</td>
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<td>Subtotal</td>
<td>168</td>
<td>168</td>
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<tr>
<td>Z = -1.27, P = 0.20</td>
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<tr>
<td>Heterogeneity: Tau² = 0.26, Q-value = 21.31, df = 4, P &lt; 0.001, I² = 81.74%</td>
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<td>2. Studies without HCP feedback</td>
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<td>Subtotal</td>
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<td>Z = -3.88, P &lt; 0.001</td>
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<td>Heterogeneity: Tau² = 0.04, Q-value = 1.67, df = 1, P = 0.20, I² = 40.04%</td>
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<tr>
<td>Test for between groups differences: P = 0.26</td>
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</table>

Total: 256 | 260 | 100% | -0.49 (-0.94, -0.04) |

Z = -2.12, P = 0.03

Heterogeneity: Tau² = 0.26, Q-value = 37.02, df = 6, P < 0.001, I² = 83.79%

Mean values reported as: a: change in mean HbA1c from baseline to follow-up; b: follow-up mean HbA1c
Figure 3

<table>
<thead>
<tr>
<th>Study</th>
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<tr>
<td>Wayne et al. 2015</td>
<td>-0.82</td>
<td>1.05</td>
<td>48</td>
</tr>
<tr>
<td>Waki et al. 2014</td>
<td>6.70</td>
<td>0.70</td>
<td>27</td>
</tr>
<tr>
<td>Holmen et al. 2014</td>
<td>-0.31</td>
<td>1.11</td>
<td>39</td>
</tr>
<tr>
<td>Faridi et al. 2009</td>
<td>-0.10</td>
<td>0.30</td>
<td>15</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>129</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z = -1.83, P = 0.07</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² &lt; 0.001, Q-value = 1.36, df = 3, P = 0.71, I² &lt; 0.001%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Studies with low frequency HCP feedback

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference in means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Istepanian et al. 2009</td>
<td>7.76</td>
<td>32</td>
<td>8.40</td>
</tr>
<tr>
<td>Nagrebetsky et al. 2013</td>
<td>6.90</td>
<td>0.70</td>
<td>7</td>
</tr>
<tr>
<td>Yoo et al. 2009</td>
<td>7.10</td>
<td>0.80</td>
<td>57</td>
</tr>
<tr>
<td>Bee et al. 2016</td>
<td>-1.59</td>
<td>1.62</td>
<td>29</td>
</tr>
<tr>
<td>Kardas et al. 2016</td>
<td>0.04</td>
<td>0.52</td>
<td>30</td>
</tr>
<tr>
<td>Baron et al. 2017</td>
<td>-0.53</td>
<td>1.45</td>
<td>37</td>
</tr>
<tr>
<td>Ursma et al. 2015</td>
<td>-0.37</td>
<td>0.83</td>
<td>23</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td><strong>215</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z = -2.51, P = 0.01</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.05, Q-value = 11.40, df = 6, P = 0.08, I² = 47.33%</td>
<td></td>
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</tbody>
</table>

3. Studies with high frequency HCP feedback

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference in means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinn et al. 2014</td>
<td>-1.90</td>
<td>1.58</td>
<td>62</td>
</tr>
<tr>
<td>Zhou et al. 2014</td>
<td>1.03</td>
<td>0.95</td>
<td>40</td>
</tr>
<tr>
<td>Aloia et al. 2016</td>
<td>-0.91</td>
<td>0.63</td>
<td>10</td>
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<tr>
<td>Kleinman et al. 2017</td>
<td>-1.50</td>
<td>1.10</td>
<td>41</td>
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<tr>
<td>Quinn et al. 2009</td>
<td>-2.02</td>
<td>1.3</td>
<td>23</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td><strong>166</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Z = -10.60, P &lt; 0.001</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Heterogeneity: Tau² &gt; 0.001, Q-value = 2.45, df = 4, P = 0.65, I² &lt; 0.001%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for between groups differences: P &lt; 0.001</td>
<td></td>
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</tbody>
</table>

| **Total**              | 510          |         |                     | 517          |         |         | **100.00%** |
| **Z = -4.42, P < 0.001** |              |         |                     |              |         |         |               |
| Heterogeneity: Tau² = 0.19, Q-value = 65.25, df = 15, P < 0.001, I² = 77.01% |

* Effective sample size

Mean values reported as: a: change in mean HbA1c from baseline to follow-up; b: follow-up mean HbA1c
Supplementary Figure 1. ‘Risk of bias’ graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.
Supplementary Figure 2. ‘Risk of bias’ summary: review authors’ judgements about each risk of bias item for each included study.
Supplementary Figure 3: Funnel plot of type 2 diabetes studies
Supplementary Figure 4: Univariate meta-regressions of mean ages, mean baseline HbA1c levels and length of follow-up.
Supplementary Figure 5: Multivariate meta-regressions of HCP feedback after adjustment for mean ages or baseline HbA1c levels

<table>
<thead>
<tr>
<th>Meta-regression models</th>
<th>Number of studies</th>
<th>Heterogeneity</th>
<th>P-value</th>
<th>Estimated difference in means (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCP feedback (adjusted for mean ages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With no HCP feedback</td>
<td>4</td>
<td></td>
<td></td>
<td>-0.16 (-0.52, 0.20)</td>
</tr>
<tr>
<td>With low frequency HCP feedback</td>
<td>7</td>
<td>45.85%</td>
<td>0.05</td>
<td>-0.54 (-0.72, -0.35)</td>
</tr>
<tr>
<td>With high frequency HCP feedback</td>
<td>5</td>
<td></td>
<td>0.01</td>
<td>-0.91 (-1.23, -0.60)</td>
</tr>
<tr>
<td>HCP feedback (adjusted for mean baseline HbA1c levels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With no HCP feedback</td>
<td>4</td>
<td></td>
<td></td>
<td>-0.14 (-0.48, 0.20)</td>
</tr>
<tr>
<td>With low frequency HCP feedback</td>
<td>7</td>
<td>37.22%</td>
<td>0.04</td>
<td>-0.51 (-0.69, -0.32)</td>
</tr>
<tr>
<td>With high frequency HCP feedback</td>
<td>5</td>
<td></td>
<td>0.02</td>
<td>-0.87 (-1.22, -0.52)</td>
</tr>
</tbody>
</table>

*The estimated difference in means were derived from meta-regression models given a mean age of 55 years old or a 8.0% mean baseline HbA1c level*
Supplementary Figure 6: Multivariate meta-regressions of the other functions of diabetes apps after adjustment for mean ages or baseline HbA1c levels

<table>
<thead>
<tr>
<th>Meta-regression models</th>
<th>Number of studies</th>
<th>Heterogeneity</th>
<th>P-value</th>
<th>Estimated difference in means (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reminder (adjusted for the mean ages)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>With reminder</td>
<td>8</td>
<td>61.12%</td>
<td>0.05</td>
<td>-0.65 (-0.96, -0.33)</td>
</tr>
<tr>
<td>Without reminder</td>
<td>8</td>
<td>0.48 (-0.83, -0.14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reminder (adjusted for the baseline HbA1c levels)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With reminder</td>
<td>8</td>
<td>48.68%</td>
<td>0.07</td>
<td>-0.62 (-0.92, -0.33)</td>
</tr>
<tr>
<td>Without reminder</td>
<td>8</td>
<td>-0.39 (-0.68, -0.09)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of self-monitoring tasks supported (adjusted for the mean ages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supporting only one self-monitoring task</td>
<td>4</td>
<td>66.57%</td>
<td>0.10</td>
<td>-0.58 (-0.81, -0.35)</td>
</tr>
<tr>
<td>Supporting 2-4 self-monitoring tasks</td>
<td>7</td>
<td>54.26%</td>
<td>0.08</td>
<td>-0.45 (-0.76, -0.13)</td>
</tr>
<tr>
<td>Supporting &gt;4 self-monitoring tasks</td>
<td>5</td>
<td>56.57%</td>
<td>0.09</td>
<td>-0.62 (-0.92, -0.32)</td>
</tr>
<tr>
<td>Number of self-monitoring tasks supported (adjusted for the baseline HbA1c levels)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supporting only one self-monitoring task</td>
<td>4</td>
<td>65.16%</td>
<td>0.10</td>
<td>-0.45 (-0.73, -0.18)</td>
</tr>
<tr>
<td>Supporting 2-4 self-monitoring tasks</td>
<td>7</td>
<td>54.26%</td>
<td>0.08</td>
<td>-0.45 (-0.76, -0.13)</td>
</tr>
<tr>
<td>Structured display</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With structured display</td>
<td>11</td>
<td>66.23%</td>
<td>0.10</td>
<td>-0.51 (-0.79, -0.24)</td>
</tr>
<tr>
<td>Without structured display</td>
<td>5</td>
<td>-0.70 (-1.10, -0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Structured display (adjusted for the baseline HbA1c levels)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With structured display</td>
<td>11</td>
<td>56.57%</td>
<td>0.09</td>
<td>-0.45 (-0.73, -0.18)</td>
</tr>
<tr>
<td>Without structured display</td>
<td>5</td>
<td>-0.45 (-0.73, -0.18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Data entry method</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wireless data transmission</td>
<td>11</td>
<td>65.16%</td>
<td>0.10</td>
<td>-0.61 (-0.89, -0.33)</td>
</tr>
<tr>
<td>Manual data entry</td>
<td>5</td>
<td>-0.51 (-0.91, -0.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wireless data transmission</td>
<td>11</td>
<td>53.44%</td>
<td>0.07</td>
<td>-0.59 (-0.85, -0.34)</td>
</tr>
<tr>
<td>Manual data entry</td>
<td>5</td>
<td>-0.29 (-0.70, 0.12)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*The estimated difference in means were derived from meta-regression models given a mean age of 55 years old or a 8.0% mean baseline HbA1c level.
Supplementary Figure 7: Postulated mechanisms behind the effects of diabetes apps
**Supplementary Table 1: Detailed search strategy used in each database.**

<table>
<thead>
<tr>
<th>Data sources</th>
<th>Databases</th>
<th>Search Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVID</td>
<td>Medline: Ovid MEDLINE(R) 1996 to Present with Daily Update, Ovid MEDLINE(R) Epub Ahead of Print, Ovid MEDLINE(R) In-Process &amp; Other Non-Indexed Citations</td>
<td>(mobile.af. or mHealth.af. or exp Cell Phones/ or cellular phone*.af. or exp Smartphone/ or app.af. or apps.af. or exp Mobile Applications/ or iphone*.af. or phone*.af.) and (exp Diabetes Mellitus/ or diabet*.af. or T2DM.af. or T1DM.af. or IDDM.af. or NIDDM.af. or DM.af. or T1D.af. or T2D.af. or MODY.af.)</td>
</tr>
<tr>
<td>EMBASE</td>
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<td></td>
</tr>
<tr>
<td>EBSCO</td>
<td>CINAHL Plus</td>
<td>((TX mobile) OR (TX mHealth) OR (TX cellphone*) OR (MM &quot;Cellular Phone+&quot;) OR (MM &quot;Smartphone+&quot;) OR (TX app) OR (TX apps) OR (MM &quot;Mobile Applications&quot;) OR (TX iPhone*) OR (TX phone*)) AND ((MM &quot;Diabetes Mellitus+&quot;) OR (TX diabet*) OR (TX T2DM) OR (TX T1DM) OR (TX IDDM) OR (TX NIDDM) OR (TX DM) OR (TX T1D) OR (TX T2D) OR (TX MODY))</td>
</tr>
<tr>
<td>Web of Science</td>
<td>Web of Science</td>
<td>(TS=(mobile OR mHealth OR cellphone* OR smartphone* OR cell phone* OR app OR apps) OR mobile application* OR phone*) OR TI=(mobile OR mHealth OR cellphone* OR smartphone* OR app OR apps OR mobile application* OR iphone* OR phone*)) AND (TS=(diabetes mellitus OR diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY)) OR TI=(diabetes mellitus OR diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY)); Timespan=2015-2017; Search language=Auto</td>
</tr>
</tbody>
</table>
| Cochrane     | The Cochrane Library | Search all text: mobile OR mHealth OR cellular phone* OR app OR apps OR iphone* OR phone* (#1)  
MeSH descriptor: [Cell Phones] explode all trees (#2)  
MeSH descriptor: [Smartphone] explode all trees (#3)  
MeSH descriptor: [Mobile applications] explode all trees (#4)  
Search all text: diabet* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D (#5)  
MeSH descriptor: [Diabetes Mellitus] explode all trees (#6)  
(#1 or #2 or #3 or #4) and (#5 or #6) Publication Year from 2015 to 2017 |
## Supplementary Table 2: Baseline characteristics of the included studies and participants

### Type 2 diabetes studies

<table>
<thead>
<tr>
<th>Name (year)</th>
<th>Design</th>
<th>Length (mths)</th>
<th>Number of participants</th>
<th>Number of participants randomized</th>
<th>Population characteristics</th>
<th>Country</th>
<th>Setting</th>
<th>Intervention group(s)</th>
<th>Treatment regimen</th>
<th>Exclusion criteria</th>
<th>Study outcomes</th>
<th>Age (years, mean and SD)</th>
<th>Gender (male %)</th>
<th>Duration of diabetes (years, mean and SD)</th>
<th>Ethnic groups</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Change from baseline</th>
<th>Baseline comparison to</th>
<th>Supplementary Table 2: Baseline characteristics of the included studies and participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>NA</td>
<td>NA</td>
<td>Study population naive to diabetes management and monitoring of blood glucose levels</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA: diet 0% oral 100%</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
<td>NA</td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
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<td>Korea</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>USA</td>
<td>Community health center</td>
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<td>Usual care</td>
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<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
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<td>Istepanian et al. (2014)</td>
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<td>Usual care</td>
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<td>Istepanian et al. (2014)</td>
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<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
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<td>USA</td>
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<tr>
<td>Istepanian et al. (2014)</td>
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<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
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<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
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<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
<td>NA</td>
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<tr>
<td>Istepanian et al. (2014)</td>
<td>RCT</td>
<td>12</td>
<td>USA</td>
<td>Community health center</td>
<td>Patients randomized to intervention group</td>
<td>USA</td>
<td>Usual care</td>
<td>FTA-HC: diet 10% oral 42%, insulin 46%</td>
<td>NA</td>
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<tr>
<td>Study et al. (2017)</td>
<td>Cluster RCT</td>
<td>Number</td>
<td>Country</td>
<td>Primary care setting</td>
<td>Population characteristics</td>
<td>Primary outcomes</td>
<td>Other outcomes</td>
<td>Type 2 diabetes studies</td>
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<tr>
<td>I: insulin 22.2%, oral</td>
<td>NA</td>
<td>NA</td>
<td>Primary care patients</td>
<td>Patients were screened for diabetes complications (e.g., chronic kidney disease, nephropathy or proliferative diabetic retinopathy, and at the time of baseline</td>
<td>Diabetes complications</td>
<td>Diabetes complications</td>
<td>Type 2 diabetes studies</td>
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<tr>
<td>NA</td>
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<td>Primary care patients</td>
<td>Patients were screened for diabetes complications (e.g., chronic kidney disease, nephropathy or proliferative diabetic retinopathy, and at the time of baseline</td>
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<td>Type 2 diabetes studies</td>
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</tbody>
</table>

**Interventions:**
- **Control:**
  - P=0.08 for between-group differences.
- **Intervention:**
  - Studies conducted on mixed populations of type 1 and type 2 diabetes patients (majority of which are type 2).
  - Studies included both children and adults.
- **Objectives:**
  - To evaluate the efficacy and safety of the intervention in improving HbA1c and other diabetes-related outcomes.
  - To compare the intervention with standard care in terms of diabetes control and complications.

**Type 1 diabetes studies:**

| Study et al. (2017) | Cluster RCT | Number | Country | Primary care setting | Population characteristics | Primary outcomes | Other outcomes |
|------------------|-------------|--------|---------|----------------------|---------------------------|-----------------|---------------|-------------------------|
| I: insulin 22.2%, oral | NA | NA | Primary care patients | Patients were screened for diabetes complications (e.g., chronic kidney disease, nephropathy or proliferative diabetic retinopathy, and at the time of baseline | Diabetes complications | Diabetes complications | Type 2 diabetes studies |
| NA | NA | NA | Primary care patients | Patients were screened for diabetes complications (e.g., chronic kidney disease, nephropathy or proliferative diabetic retinopathy, and at the time of baseline | Diabetes complications | Diabetes complications | Type 2 diabetes studies |
| NA | NA | NA | Primary care patients | Patients were screened for diabetes complications (e.g., chronic kidney disease, nephropathy or proliferative diabetic retinopathy, and at the time of baseline | Diabetes complications | Diabetes complications | Type 2 diabetes studies |

**Interventions:**
- **Control:**
  - P=0.08 for between-group differences.
- **Intervention:**
  - Studies conducted on mixed populations of type 1 and type 2 diabetes patients (majority of which are type 2).
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- **Objectives:**
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  - To compare the intervention with standard care in terms of diabetes control and complications.
<table>
<thead>
<tr>
<th>Study</th>
<th>RCT</th>
<th>Authors</th>
<th>Design</th>
<th>Setting</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ross</td>
<td>2010</td>
<td>Drion et al.</td>
<td>Parallel RCT</td>
<td>France</td>
<td>Patients with type 1 and type 2 diabetes</td>
<td>Personal web portal linked to Diabeo</td>
<td>Primary: HbA1c, Secondary: FBS, body weight</td>
<td>Pooled SD=2.27 (imputed using Prognostic Method)</td>
</tr>
<tr>
<td>Rossi</td>
<td>2010</td>
<td>Rossi et al.</td>
<td>Parallel RCT</td>
<td>Italy, Spain, and England</td>
<td>Patients with type 1 diabetes</td>
<td>Personal web portal linked to Diabeo</td>
<td>Primary: HbA1c, Secondary: FBS, body weight</td>
<td>Pooled SD=2.27 (imputed using Prognostic Method)</td>
</tr>
<tr>
<td>Zhou</td>
<td>2016</td>
<td>Zhou et al.</td>
<td>Parallel RCT</td>
<td>China</td>
<td>Patients with type 1 diabetes</td>
<td>Personal web portal linked to Diabeo</td>
<td>Primary: HbA1c, Secondary: FBS, body weight</td>
<td>Pooled SD=2.27 (imputed using Prognostic Method)</td>
</tr>
</tbody>
</table>

**Notes:**
- SDs were calculated from SEs or 95% CIs.
- Statistical significance was set at p < 0.05 for individual studies.
- The meta-analysis was performed using Review Manager (RevMan) Version 5.3 for Windows. meta-analysis was performed using Review Manager (RevMan) Version 5.3 for Windows.

**Interventions:**
- C: Control
- P: Intervention

**Outcomes:**
- Primary: HbA1c
- Secondary: FBS, body weight, BP, lipid profile, quality of life, symptoms of depression and anxiety

**Analysis:**
- Pooled SD=2.27 (imputed using Prognostic Method)
### Supplementary Table 3: Characteristics of the apps in the included studies

<table>
<thead>
<tr>
<th>Name (year)</th>
<th>Type 2 diabetes studies</th>
<th>App used in the study</th>
<th>Self-monitoring tasks</th>
<th>Data entry method</th>
<th>CHD/DM calculator</th>
<th>Medication adjustment support</th>
<th>Real-time personalized feedback</th>
<th>Structured display</th>
<th>HCP feedback</th>
<th>Freq. of HCP feedback</th>
<th>Categories of freq. of HCP feedback</th>
<th>Other functionalities</th>
<th>Feedback received</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osame et al. (2013) (24)</td>
<td>diabetes studies</td>
<td>Monica</td>
<td>BG, BP, body weight, and physical activity (pedometer)</td>
<td>All data were manually input</td>
<td>NO</td>
<td>NA</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>When necessary (study nurses scanned through patients’ status each week)</td>
<td>Low frequency</td>
<td>NA</td>
<td>1. Real-time graph display reflecting the uploaded data in relation to individual target values generated by app. 2. Automatically generated, theory-based, health promotion-rich information, motivation, and behaviour skills feedback messages, linked to patient’s 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 (MedConfidant) enabled participants to review their uploaded data.</td>
</tr>
<tr>
<td>Holmen et al. (2014) (25)</td>
<td>diabetes studies</td>
<td>FewTouch</td>
<td>Food habits registration, BG, and physical activity</td>
<td>BG data were automatically transmitted (individually); pedometer counts were manually entered</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>No HCP feedback</td>
<td>Personal goal setting system, general diabetes education system</td>
<td>1. Real-time feedback from the app on how the individually set goals were met within the defined period. 2. Observational feedback through symbols such as smiling faces and colour codes in the app. 3. Patients can also access related links and look up words and concepts related to their diseases.</td>
</tr>
<tr>
<td>Yoo et al. (2009) (26)</td>
<td>diabetes studies</td>
<td>Niche</td>
<td>BG, exercise (pedometer) and weight</td>
<td>BG and weight data were automatically transmitted (individually); pedometer counts were manually entered</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NA</td>
<td>No HCP feedback</td>
<td>1. Real-time, automated, graphical trend feedback and reminders based on patient-specific data. 2. Upon receipt of newly submitted patient data, the Confidant server software will generate and send one or more feedback messages directly to the patient’s cell phone. 3. A web-based portal for patients and clinicians to view measurement data and prior messages received from the system.</td>
<td></td>
</tr>
<tr>
<td>Waki et al. (2014) (27)</td>
<td>diabetes studies</td>
<td>DiabeDiet</td>
<td>BG, BP, body weight and pedometer counts, photos of meals</td>
<td>BG, BP, body weight and pedometer data were transmitted automatically to the app; meals and exercise were input by voice/text message or photos</td>
<td>NO</td>
<td>NA</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
<td>When necessary (if readings were defined as abnormal, a health care provider’s time was not required)</td>
<td>No HCP feedback</td>
<td>The database triggered alerts for missed or late readings (reminder)</td>
<td>1. Data were automatically evaluated following the Japan Diabetes Society (JDS) guideline’s targeted values. DiabeDiet 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. Visions input was converted to text and matched with text in the DiabeDiet database: advice on lifestyle modifications, matched to the patient’s input about food and exercise. 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.</td>
</tr>
<tr>
<td>Negrobiaty et al. (2013) (28)</td>
<td>diabetes studies</td>
<td>H+Diabetes</td>
<td>BG</td>
<td>BG data were automatically transmitted to the app</td>
<td>NO</td>
<td>NA</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
<td>Monthly</td>
<td>Low frequency</td>
<td>NA</td>
<td>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 test 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.</td>
</tr>
<tr>
<td>Tai et al. (2009) (29)</td>
<td>diabetes studies</td>
<td>Ubiquitous Chronic Disease Care</td>
<td>BG, BP, exercise, and body weight</td>
<td>BG data were automatically transmitted to the app; BP and weight data were manually entered</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>When necessary</td>
<td>Low frequency</td>
<td>Reminder</td>
<td>1. Real-time, automated feedback of encouragement, reminders, and recommendations according to the data input. 2. Participants received information via SMS twice 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.</td>
</tr>
<tr>
<td>Quinn et al. (2009) (30)</td>
<td>diabetes studies</td>
<td>Diabetes Manager</td>
<td>BG, medication dosage and carbohydrates intake</td>
<td>BG data were automatically sent to the app; other data were manually input</td>
<td>NO</td>
<td>NA</td>
<td>YES</td>
<td>NO</td>
<td>No</td>
<td>When necessary (by study team) plus feedback from HCP every four weeks</td>
<td>High frequency</td>
<td>Direct patients to test BG at optimal times (reminder)</td>
<td>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 below 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 refed if needed. 4. Suggestions of medical changes to patients (approved by HCP first). 5. HCPs were provided with logins to review, attached with analysis of the patient data and trend.</td>
</tr>
<tr>
<td>Sapjani et al. (2006) (31)</td>
<td>diabetes studies</td>
<td>Not specified</td>
<td>BG</td>
<td>Automatically transmitted to the app</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
<td>NO</td>
<td>Low level contact</td>
<td>Low frequency</td>
<td>1. The researchers 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.</td>
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<tr>
<td>Quinn et al. (2011) (32)</td>
<td>diabetes studies</td>
<td>Diabetes Manager</td>
<td>BG, carbohydrates consumed, diabetes medications taken, and medication compliance regarding diabetes self-care</td>
<td>BG data were automatically sent to the app, other data were manually input</td>
<td>NO</td>
<td>NA</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
<td>Average one phone call per month plus intermittently electronic messages (from every week to every 2-3 months)</td>
<td>High frequency</td>
<td>Learning library</td>
<td>1. Real-time educational, behavioral and motivational feedback regarding patients input data, trend of recent entered data and physician prescription instruction. 2. Patients and P/OHs had access to a web-portals consisted of secure messaging centre for patient-provider communication, personal health record with additional diabetes information, learning library and regular review of historical data (analyzed). 3. Diabetes educators intermittently reviewed patient data and communicated with patients electronically or via phone (frequency: high risk level patients: at least 4 times a month; others every 2-3 months).</td>
</tr>
</tbody>
</table>
Zhou et al. (2016) (34)
Wattling
BG, carbohydrate intake, medications, physical activity, blood pressure, and weight/height
Data were manually entered
NO YES NO YES YES
Every one to two weeks; average 3-10 min of time spent; mean number of contacts was 11 (once every week)
High frequency
1. Real-time graphical feedback on glucose levels.
2. The study team provided feedback on the blood glucose levels of patients, their target goals, and their individualized medication regimens based on the data they entered once a week or every 2 weeks.
3. Readings outside threshold limits would automatically trigger a message to be sent to patients and notify clinicians.
4. Patients received an electronic action plan as pre-visit summaries for physician visits once a month.

Wayne et al. (2015) (33)
New/Health Coach
BG, exercise, food intake, weight/BMI and mood
Data were manually entered
NO NA NO YES YES
Average 37 minutes/week of interaction (29 min of interaction in the control group)
No HCP feedback
Reminder and health library
1. Real-time graphical feedback on patient reported data.
2. The HC co-monitored the client’s mobile phone input and directed immediate attention (on a 24-hour/day and 7-day/week basis) to episodes of desirable progress, medication issues, or illness.
3. Patients could communicate with their health coach at any time in the 24-hour cycle via secure messaging, scheduled phone contact, and/or during in-person meetings.

Baron et al. (2017) (24)
Not specified
BG, BP, physical activity, insulin dose and weight
BG and BP data were automatically transmitted, other data were manually entered
NO YES NO YES YES
When necessary plus six weekly educational calls
Low frequency
NA
1. Color-coded graphical feedback on the data recorded was automatically displayed following each data transfer.
2. MTH nurses provided feedback on out-of-range clinical readings (as needed).
3. MTH nurses made six weekly educational calls to deliver diabetes education.
4. MTH nurses supported insulin injection.

Arnaud et al. (2016) (35)
SAED
BG
BG data were automatically transmitted
NO YES YES YES YES
Patient can send messages to HCP at any time, HCP monitored and reviewed patients’ condition and advice on treatment
High frequency
1. The medical staff monitored and reviewed the patient’s condition using the data collected and stored in the database to plan and advise on the treatment.
2. Based on the blood glucose and HbA1c readings from the database, automated feedback was securely transmitted in real-time to the patient’s smart phone.
3. SMS education program wherein the patients received weekly messages to keep them informed about diabetes and other related information.
4. Real-time graphical feedback on patient reported data.

See et al. (2016) (36)
Diabetes Pal
BG
Data were manually entered
YES YES NO NO YES
When necessary (hypoglycaemic episodes)
Low frequency
General diabetes education system
1. Patients in the intervention group entered FBG readings into the app daily; the app responded with a suggested insulin dose.
2. An administrative module where the research staff could remotely monitor glucose readings submitted and flag issues to the endocrinologist.
3. Generates graphs from the daily readings, so patients can see their progress in managing their diabetes.

Kubes et al. (2016) (37)
COMMODITY
2
BG, ECG, heart rhythm, respiratory movements, activity, weight, BP and adherence
Data were automatically transmitted
No YES NO YES YES
When necessary (hypoglycaemic episodes)
Low frequency
NA
1. Artificial Intelligence Layer (AIL) proved to produce alerts according to the relevant algorithms for cases of hypon- and hyperglycaemias, tachy- and bradycardia cases, as well as on the supposed risk of the interspace. These alerts were presented in the system, and made ready for use by clinicians.
2. The data are interpreted by personal agents that use expert biomedical knowledge to derive important insights about the individual’s health status, which are then presented in the form of active feedback to the patient directly from the device, or via health professionals who assist in diagnosis, treatment, and life management.
3. Real-time graphical feedback on patient reported data.

Rahman et al. (2017) (38)
Gather Health
BG, medication
Data were manually entered
NA NA NO YES YES
sent 497 messages to 115 patients (mean 880 messages from provider)
High frequency
The app automatically reminded participants to complete tasks each day (remind).
1. BG tests submitted out of standard range had automated question follow-up to identify issues, and participants could message questions to providers.
2. Provider contact with participants outside the system was discouraged, except in cases of high-risk glycaemic data or technical troubleshooting.
3. Real-time graphical feedback on patient reported BG data.

* Studies conducted on mixed populations of type 1 and type 2 diabetes patients (majority of which are type 2).

Type 1 diabetes studies

Rossi et al. (2013) (39)
Diabetes Interactive Diary
BG, food intake (CHO and calories), dose of insulin, physical activity, and specific events
Data were manually entered
YES YES NO NO NO
Every one to three weeks; average 5-8 min of time spent; mean number of exchanged per week
High frequency
Food exchange, prevention of relapse, and resistance.
1. CHO/mmol calc.: calculator; DICE can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predicted 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 center computer to the patient’s mobile phone.

Rossi et al. (2010) (40)
Diabetes Interactive Diary
BG, dose of insulin injections, food intake, physical activity, and specific events
Data were manually entered
YES YES NO NO YES
Average 2 messages per week sent to the physician
High frequency
Food exchange, prevention of relapse, and resistance.
1. CHO/mmol calc.: calculator; DICE can automatically calculate the most appropriate insulin dose on the basis of entered BG, food intake (CHO and calories) and current insulin dose, and predicted 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. (2015) (41)
Diabetes
BG, carbohydrate intake and physical activity
Data were manually entered
YES YES NO NO NA
No HCP feedback
plasma glucose targets
1. Blood sugars 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.
<table>
<thead>
<tr>
<th>Studies conducted on mixed populations of type 1 and type 2 diabetes patients</th>
</tr>
</thead>
</table>
| **Kiron et al. (2013)**<sup>42</sup>  
Glucose Body  
Blood glucose levels, insulin dosages, other medications, diet (food item in grams), and physical activities (minutes)  
Data were manually entered  
NO NA NO YES YES  
First 6 months: approximately 2 text messages per patient per week; 5 minutes per patient (n=36) per week  
High frequency N/A  
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.  
| **Zhou et al. (2015)**<sup>34</sup>  
WellAct  
BG, carbohydrate intake, medications, physical activity, blood pressure, and weight/height  
Data were manually entered  
NO YES NO YES YES  
Every one to two weeks; average 9–10 min of time spent; mean number of contacts was 11 (once every week)  
High frequency  
1. Real-time graphical feedback on glucose levels.  
2. The study team provided feedback on the blood glucose levels of patients, their target goals, and their individualized medication regimens based on the data they entered once a week or every 2 weeks.  
3. Readings outside threshold limits would automatically trigger a message to be sent to patients and notify clinicians.  
4. Patients received an electronic action plan as pre-visit summaries for physician office visits once a month.  
| **Drion et al. (2015)**<sup>43</sup>  
DBEES  
BG, carbohydrate intake, medication and physical exercise  
Data were manually entered  
NO NO NO YES NO N/A No HCP feedback  
Alerts and reminders a diabetes forum  
1. Allows patients to use a number of charts and statistics that can visualize the recorded information.  
2. Data recorded can be made available to diabetes nurses.  
3. MTH nurses provided feedback on out-of-range clinical readings (as needed).  
4. MTH nurses made six weekly educational calls to deliver diabetes education.  
| **Baron et al. (2016)**<sup>34</sup>  
Not specified  
BG, BP, physical activity, insulin dose and weight  
BG and BP data were automatically transmitted, other data were manually entered  
NO YES NO YES YES  
When necessary plus six weekly educational calls  
Low frequency N/A  
1. Colour-coded graphical feedback on the data recorded was automatically displayed following each data transfer.  
2. MTH nurses provided feedback on out-of-range clinical readings (as needed).  
3. MTH nurses made six weekly educational calls to deliver diabetes education.  
4. MTH nurses supported insulin titration.  

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For Review Only
Mobile phone applications and self-management of diabetes: a systematic review and meta-analysis of randomised trials

Ben Carter, Jiayuan Li, Can Hou, Qian Xu

Citation


Review question

The aim of this systematic review is to update the evidence of the effect of mobile phone applications (apps) on glycemic control (HbA1c) in the self-management of diabetes and explore the factors that may influence the efficacy of apps on glycemic control.

Searches

In the previous study, we searched relevant studies that were published between 1 January 1996 and 1 June 2015 from five databases: Medline, CINAHL, Cochrane Library, Web of Science, and Embase. For details of the search strategy used, please refer to: "Do Mobile Phone Applications Improve Glycemic Control (HbA1c) in the Self-management of Diabetes? A Systematic Review, Meta-analysis, and GRADE of 14 Randomized Trials." Diabetes Care 39.11 (2016): 2089-2095. In this systematic review, we will update the searches in Medline, CINAHL, Cochrane Library, Web of Science, and Embase databases to find relevant studies that were published between 2015 and 2017. The search strategy used will be slightly modified to reflect some research progress in this area. The following terms and medical subject headings (MeSH) were used during the search: (mobile OR mHealth OR cellphone* OR MeSH "Cellular Phone" OR MeSH “Smartphone” OR app OR apps OR phone* OR iphone* OR MeSH “Mobile Applications”) AND (MeSH “Diabetes Mellitus” OR diabete* OR T2DM OR T1DM OR IDDM OR NIDDM OR DM OR T1D OR T2D OR MODY). The references of the included studies will also be hand searched to identify any additional articles.

Types of study to be included

Only the studies that evaluated the effect of diabetes mobile phone apps on diabetes self-management and adopted a randomised controlled trial (RCT) design will be included.

Condition or domain being studied

Diabetes mobile phone applications (diabetes apps) is a newly emerging technology for diabetes self-management. 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. Our previous systematic review with GRADE of the evidence demonstrated that diabetes apps could help type 2 diabetes patients to control HbA1c (Hou et al., 2016). This conclusion is also supported by a recent systematic review (Wu et al., 2017). However, several questions still remain to be answered:

1) Do diabetes apps improve glycemic control among type 1 diabetes patients?

2) What functions of the apps are associated with better efficacy?

3) Are there any other factors that may influence the effect of diabetes apps?
4) What is the evidence that using diabetes apps is safe for diabetes patients?

Participants/population

The participants were over 18 years old and had type 1 or type 2 diabetes. The self-management of participants aged younger than 18 years largely relies on their parents. Therefore, studies with participants age younger than 18 years were not included.

Intervention(s), exposure(s)

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 professional [HCP]).

Comparator(s)/control

The control group in the study received usual diabetes care without any telehealth program(s) linked to the management of diabetes.

Context

Primary outcome(s)

The primary outcome of interest will be HbA1c.

Secondary outcome(s)

The secondary outcome will be severe hypoglycemia events reported. Studies included should report either HbA1c as outcome or report hypoglycemia events in both intervention and control groups.

Data extraction (selection and coding)

Data will be extracted from each included study by one author (CH) and verified by a second author. Disagreement will be resolved by discussion with a third author (BC or Jiayuan Li). The following data will be extracted: author name, year of publish, study design, study length, setting, intervention group, control group, number of participants randomised, number of participants withdrew, number of participants in the analysis, imputation method, number of males and females, age, duration of diabetes, treatment regimen, ethnic group, baseline HbA1c, post-intervention HbA1c, HbA1c change from baseline, hypoglycemia, app used in the study, self-monitoring tasks supported, data entry method, and functions of the app (including CHO/insulin bolus calculator, number of self-monitoring tasks supported, medication adjustment support, structured feedback, target setting, reminders, HCP feedback, HCP feedback frequency and other functionalities).

Risk of bias (quality) assessment
Risk of bias will be independently evaluated by two authors using the Cochrane risk of bias tool and discussed if needed by a third. Risk of bias will be assessed in the following domains: selection bias, performance bias, detection bias (primary and secondary outcomes), attrition bias (primary and secondary outcomes), reporting bias, and other bias (Higgins and Green, 2011). A third reviewer resolved any discrepancies in bias coding. Studies will not be excluded on the basis of risk of bias. Studies will be categorized as ‘low risk of bias’, high risk of bias, or ‘unclear’.

Strategy for data synthesis

Measure of treatment effect

For primary outcome, the treatment effect will be either mean difference in HbA1c or mean HbA1c at follow-up, but mean difference in HbA1C is preferred.

For secondary outcome, the treatment effect will be risk ratios (RR).

Dealing with missing data

When required data is missing, we will first try to contact the corresponding authors of the studies. When necessary, we will use specific statistical methods to calculate missing data (Ma et al., 2008).

Meta-analysis

All the analyses will be conducted separately for type 1 and type 2 diabetes studies.

For primary outcome, pooling will be carried out using an inverse variance random effects model for type 1 and type 2 diabetes studies separately (DerSimonian and Laird, 1986). Heterogeneity will be assessed and quantified using the I^2 statistic. An I^2 of 0% to 40% might represent no important heterogeneity, 30% to 60% might represent moderate heterogeneity, 50% to 90% might represent substantial heterogeneity and 75% to 100% might represent considerable heterogeneity. When substantial heterogeneity is found (I^2>50%), we will try to explore the source of heterogeneity.

For secondary outcome, pooling will be carried out using DerSimonian & Laird random effects model with the estimate of heterogeneity being taken from the Mantel-Haenszel model (Mantel and Haenszel, 1959).

If studies were conducted on mixed participants with type 1 and type 2 diabetes, we will first contact the corresponding authors of the studies for additional data. If additional data is not available, the studies will be assigned to either type 1 or type 2 diabetes group according to the percentage of participants with type 1 and 2 diabetes.

For studies with multiple intervention groups, only the intervention group that are relevant to meta-analysis will be selected. If more than two groups are relevant, we will combine the groups to create a pair-wise comparison.

For cluster randomised controlled trial, effect size extracted from an analysis that properly accounts for the cluster design is preferred. Otherwise, an effective sample size will be used instead: Neffective = (k*m)/(1+(m-1)*ICC), where k indicates the number of clusters; m, the number of observations per cluster; and ICC, the intracluster correlation coefficient.

Analysis of subgroups or subsets

Based on our previous study, a small number of type 1 diabetes studies is anticipated. Therefore, we will only carry out few subgroup analyses on studies with type 1 diabetes to explore heterogeneity. The following
subgroup analyses will be carried out: by length of the study follow up (less than one month, between one and six months, and greater than 6 months), and by functions of the apps (with CHO/insulin bolus calculator vs without CHO/insulin bolus calculator, with HCP feedback vs without HCP feedback).

For type 2 diabetes studies, univariate meta-regression will be conducted first by length of the study follow up, baseline HbA1c level, age of the participants and medication regimen. Effects that found to be statistically significant (p<0.1) will be included in the next multivariate meta-regression. A multivariable meta-regression will then be conducted using restricted maximum likelihood (REML) random effect model (Van Houwelingen et al., 2002). This model will be used to explore which functions of the apps (HCP feedback, number of self-monitoring tasks supported, structured feedback, reminders, and data entry method) are associated with better efficacy after adjusting for effects that found to be statistically significant in the univariate meta-regression. I-squared – residual in the multivariate meta-regression will be calculated to reflect residual heterogeneity.

Meta-analyses and meta-regression will be conducted using the STATA (Version 14.0).

Sensitivity analysis

For primary outcome, sensitivity analyses will be carried out by removing studies with high risk of bias, changing the parameter ICC for cluster RCTs, changing the method of missing data imputation and removing studies conducted on mixed participants.

For secondary outcome, sensitivity analyses will be carried out by changing the statistical model to the Mantel and Haenszel and the inverse variance fixed effect model (Higgins and Green, 2011).

Publication bias

A funnel plot will be used to visually inspect publication bias where 10 or more studies are pooled (Higgins and Green, 2011).

Independent participant meta-analysis

Authors of all included studies will be contacted and asked to provide the individual data to carry out an individual participant meta-analysis (Riley et al., 2010). The outcomes will be analysed as per the traditional meta-analysis, however studies will be fitted as random effects and important and consistent covariates included will include: patient age; gender, and group allocated. As per previous analyses, the analyses will be carried out separately for type 1 and type 2 diabetes. All analyses will be carried out in Stata 14.

Contact details for further information

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Organisational affiliation of the review

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King's College London and West China School of Public Health, Sichuan University

Review team members and their organisational affiliations

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01 May 2017

Anticipated completion date
01 August 2017

Funding sources/sponsors
None

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None known

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English

Country
England, China

Stage of review
Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Cell Phones; Diabetes Mellitus; Humans; Mobile Applications; Self Care

Date of registration in PROSPERO
24 May 2017

Date of publication of this version
25 May 2017

Revision note for this version
Joint corresponding authors

Stage of review at time of this submission

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<th>Completed</th>
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<td>Yes</td>
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<td>Piloting of the study selection process</td>
<td>Yes</td>
<td>Yes</td>
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<td>Formal screening of search results against eligibility criteria</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Data extraction</td>
<td>No</td>
<td>No</td>
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<td>Risk of bias (quality) assessment</td>
<td>No</td>
<td>No</td>
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<td>Data analysis</td>
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Revision note
Joint corresponding authors

Versions
25 May 2017
24 May 2017

PROSPERO
This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.
## TITLE

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<tr>
<th>#</th>
<th>Checklist item</th>
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<tr>
<td>1</td>
<td>Identify the report as a systematic review, meta-analysis, or both.</td>
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## ABSTRACT

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>2</td>
<td>Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
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## INTRODUCTION

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<td>3</td>
<td>Describe the rationale for the review in the context of what is already known.</td>
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## METHODS

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<tr>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
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<tr>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
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<tr>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
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<tr>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
</tr>
<tr>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
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<tr>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
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<tr>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
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<tr>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
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<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
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<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis.</td>
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## PRISMA 2009 Checklist

<table>
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<th>Section/topic</th>
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<th>Reported on page #</th>
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<tbody>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
<td>Page 7</td>
</tr>
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<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
<td>Page 8-9</td>
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### RESULTS

| Study selection               | 17| Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.                                                   | Figure 1          |
| Study characteristics         | 18| For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.                                                                          | Supplementary Table 2 and 3 |
| Risk of bias within studies   | 19| Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).                                                                                                        | Supplementary Figure 1 and 2 |
| Results of individual studies | 20| For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Figure 2 and 3    |
| Synthesis of results          | 21| Present results of each meta-analysis done, including confidence intervals and measures of consistency.                                                                                                         | Page 11           |
| Risk of bias across studies   | 22| Present results of any assessment of risk of bias across studies (see Item 15).                                                                                                                                | Page 9            |
| Additional analysis           | 23| Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).                                                                                          | Page 11-13        |

### DISCUSSION

| Summary of evidence           | 24| Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).                       | Page 13-17        |
| Limitations                   | 25| Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).                                                   | Page 14           |
| Conclusions                   | 26| Provide a general interpretation of the results in the context of other evidence, and implications for future research.                                                                                           | Page 16-17        |

### FUNDING

| Funding                       | 27| Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.                                                                     | Page 18           |