Effectiveness of digital interventions for improving glycemic control in persons with poorly controlled type 2 diabetes: A systematic review, meta-analysis, and meta-regression analysis

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Effectiveness of Digital Interventions for improving Glycemic Control in Persons with Poorly Controlled Type 2 Diabetes: A Systematic Review, Meta-analysis and Meta-regression analysis

Running head: Effectiveness of Digital Interventions

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Abstract

Background: Digital interventions may assist patients with type 2 diabetes in improving glycaemic control. We aimed to synthesize effect sizes of digital interventions on glycated hemoglobin (HbA1c) levels and to identify effective features of digital interventions targeting patients with poorly controlled type 2 diabetes.

Methods: MEDLINE, ISI Web of Science and PsycINFO were searched for randomized controlled trials (RCTs) comparing the effects of digital interventions with usual care. Two reviewers independently assessed studies for eligibility and determined study quality, using the Cochrane risk of bias assessment tool. The Behavioural Change Technique Taxonomy v1 was employed to identify behavior change techniques (BCTs) employed in interventions. Mean HbA1c differences were pooled using Analysis of Covariance to adjust for baseline differences and pre-post correlations. To examine effective intervention features and to evaluate differences in effects sizes across groups, meta-regression and subgroup analyses were performed.

Results: Twenty three arms of 21 RCTs were included in the meta-analysis (n= 3787 patients, 52.6% in intervention arms). The mean HbA1c baseline differences ranged from –0.2% to 0.64%. The pooled mean HbA1c change was statistically significant (-0.39 (95%CI: [-0.51, -0.26]) with substantial heterogeneity (I-squared statistic, 80.8%)) and a significant HbA1c reduction was noted for web-based interventions. A baseline HbA1c-level above 7.5%, β=-0.44 (95%CI: [-0.81, -0.06]) and the BCTs 'problem solving', β=-1.30(95%CI: [-2.05, -0.54]) and 'self-monitoring outcomes of behavior', β=-1.21 (95%CI: [-1.95, -0.46]) were significantly associated with reduced HbA1c levels.

Conclusions

Digital interventions appear effective for reducing HbA1c-levels in patients with poorly controlled type 2 diabetes.

Background

In 2017, more than 425 million adults were living with diabetes. This number is estimated to reach 629 million cases by 2045. More than 90% of this burden is due to type 2 diabetes (1-3). Type 2 diabetes is the second highest cause for obesity related deaths, accounting for more than half a million deaths and 30.4 million disability adjusted life years in 2015 (4) .

Type 2 diabetes is a multifactorial metabolic disease linked with obesity, dietary behavior, and a sedentary lifestyle (5; 6). A recent trial conducted in the United Kingdom demonstrated remission to a non-diabetic state after changes in dietary behavior and significant weight loss in persons with type 2 diabetes (7). Hence, type 2 diabetes has recently been recognized as a potentially reversible metabolic state (8). However, the likelihood of a remission of the reversed state of the disease is still unclear. In addition, remission is less likely among persons with longer duration of type 2 diabetes (7; 9). Therefore, regular monitoring of blood glucose levels, as well as an optimal adherence to glucose lowering medications, a healthy diet, and moderate to high intensity physical activity (PA) remain important factors contributing to the prevention of macrovascular and microvascular complications of the disease (10-13).

Failure to strictly adhere to medication, nutrition, and PA recommendations leads to hyper- and hypoglycaemic levels (12; 14; 15) which worsen quality of life and increase the risk of mortality (16; 17). Ideally, tight glycaemic control or maintaining glycated haemoglobin (HbA1c)-levels between 5.7% and 6.5% is generally recommended to prevent complications and comorbidities. To help patients achieve tight glycaemic control targets of HbA1c-levels of 5.7% to 6.5% (18), the American Association of Diabetic Educators (AADE) identified seven self-care behaviors (AADE7). Healthy eating, being physically active, monitoring, taking medication, problem solving, reducing risks and healthy coping are the listed AADE7 self-care behaviors to guide diabetes education and care (19). The uptake of these self-care

behaviors among patients can be strongly supported with digital interventions, such as text messaging, web-based, and telemedicine interventions (20-23). By integrating digital technologies, eHealth interventions help patients change their behavior towards regular monitoring of blood-glucose levels, regular PA, a balanced diet, and other healthy lifestyle behaviors (23-29). Hence, diabetes-related behavioral and clinical outcomes can be improved through active engagement in e- and mHealth interventions. In general, diabetes care is increasingly incorporating interactive digital e- and mHealth interventions because the use of modern information and communication technologies comes with many advantages regarding the self-monitoring of the disease and self-regulation of lifestyle behaviors (30-32) .

HbA1c remains a surrogate marker of diabetes interventions after Stratton and colleagues demonstrated an independent log linear relationship between HbA1c and diabetes related complications (26). Further, recent reports suggest that interventions leading to a reduction in HbA1c of at least 0.3% among persons with type 2 diabetes are considered clinically significant (24; 29). Findings of several systematic reviews and meta-analyses on the effectiveness of digital interventions have reported clinically significant HbA1c reductions, with varying level of effectiveness. For example, HbA1c reductions of -0.63%, -0.5%, -0.43% have been documented for videoconferencing (25), mobile-based interventions (33), and interactive self-management interventions (28), respectively.

Meta-analysis results also suggest that the changes in HbA1c levels were different across duration and mode of interventions (21; 32). A review on the effects of health information technology self-management interventions reported an aggregated HbA1c reduction of 0.36% at six and 0.27% at twelve months (21). In another review, all information-technology based interventions led to a reduction of 0.33% (34). Participation in telemedicine, telecare, teleconsultation, and videoconferencing interventions was associated with HbA1c reductions of 0.31% (35), 0.37% (36), 0.54% (37), and 0.63 % (25), respectively. Furthermore, meta-

analysis results suggest a reduction of HbA1c when participating in interactive self-management interventions by 0.43% (28), whereas participation in computer-based interventions was only associated with a reduction of 0.2% (32) and mobile-based interventions with a reduction of 0.5% (33). Two different reviews on the effects of mobile short message services reported a HbA1c level reduction of 0.22% (30) and 0.60% (38). It can be argued that these HbA1c changes are small (32) but, in the long run, these small changes can help patients attain the target HbA1c level of less than 6.5% and thus prevent the risk of microvascular complications and diabetic related deaths (39; 40).

One limitation of the existing evidence of systematic reviews on the topic is the disregard of the influence of baseline HbA1c, the baseline mean HbA1c difference between control and intervention groups, and the pre-post correlation in the overall estimates of effect sizes for interventions. Results of subgroup and meta-regression analysis indicate that baseline HbA1c is associated with overall pooled effect sizes (33; 41). Available methodological literature on the meta-analysis of a continuous outcome emphasizes the importance of accounting for baseline imbalance and pre-post correlations to determine precise and unbiased effect size estimates of a continuous outcome, such as HbA1c. However, the methodology to account for baseline imbalance and pre-post correlations is complex in the absence of Individual Participant Data (IPD) and necessary summary data from published RCTs. Nevertheless, if relevant summary data is reported in randomized control trials (RCTs), it is recommended to use Analysis of Covariance (ANCOVA) rather than change scores and final values effect size estimators (42-45).

Importantly, eHealth interventions targeting persons with type 2 diabetes are generally multi-component behavioral interventions and complex in nature (46). One way to simplify the complexity of reporting and analysing the effect size of such interventions is by describing the active ingredients of the interventions by using the Behavioural Change Technique taxonomy

V1(BCTTv1) (47; 48). The effectiveness of the active ingredients for reducing HbA1c levels in patients with poorly controlled type 2 diabetes has, to our knowledge, not yet been investigated. The results of our previous scoping review suggested the need for a detailed investigation of the individual and combined effects of BCTs on HbA1c and their role as mediators in Hba1c change (49). Therefore, this systematic review and meta-analysis aimed to synthesize the effectiveness of digital interventions and identify BCTs associated with reductions of HbA1c levels.

Materials and Methods

The design, conduct, and reporting of this systematic review was guided by the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) 2015 guideline (50). The protocol of this systematic review was registered a priori (PROSPERO registration number 42016049940). The full description of the protocol for this systematic review can be accessed elsewhere (51).

Study inclusion criteria

Type of studies

Studies were included if 1) the design of the studies examining intervention effects was a RCT including multiple-arms or a cluster RCT; 2) patients in the intervention having documented poorly controlled type 2 diabetes defined by an HbA1c level of >7.0%; 3) interventions were technology-based, such as mHealth (mobile Health) interventions, web-based interventions, interventions delivered through the use of a Personal Digital Assistant, a tablet, a computer, the internet, telemedicine, videoconferencing, telehealth or other forms of eHealth; 4) HbA1c was reported as an outcome; 5) the control group received usual care, standard care or existing care, and 6) if the study results were published in English. We used the American Diabetes Association (ADA) definition to define poorly controlled type 2 diabetes. Hence, having an HbA1c value of greater than 7.0% was considered as poorly

controlled type 2 diabetes (52). Studies examining interventions which targeted either persons with type 1 diabetes or both type 1 and 2, and those including control groups receiving interventions other than usual care were excluded from the review.

Search strategy for identification of studies

Studies published up to June 30, 2017 were searched in MEDLINE via PubMed, ISI Web of Science via Thomson Reuters, and PsycINFO via OvidSP using a comprehensive search strategy. The search terms suiting the different databases were created in collaboration with a research librarian. MeSH terms, keywords and Boolean operators were used to develop the search strategy. The search was first completed in June 07, 2016 and updated on June 30, 2017

Article screening

Two authors (MK and MP) screened titles and abstracts, as well as full-texts independently. If the two authors could not reach consensus, a third author (CP) was consulted to resolve disagreement. Covidence, a web-based screening tool, was used to document the screening process (53). Information regarding the search and screening process is displayed in Fig 1.

Data extraction process

Two authors extracted the following information: citation information (authors, titles, journals, year of publication), study location, study population (ethnicity, sex, age), study objectives, interventions type and delivery mode, AADE7 self-care behavior targeted, inclusion criteria, information on whether the intervention was guided by the use of behavioral science models or theories, individualization or tailoring of the interventions, and BCTs included in interventions were extracted. Moreover, sample size, intervention period, HbA1c-values and respective standard deviations (SD), p-values, and 95% confidence intervals were extracted for each study. The mean HbA1c change scores (SD), mean HbA1c difference (SD), type of statistical test (e.g., t-test, z-test), data on intention-to-treat analysis were collected for each study. If not reported in the articles, mean HbA1c change scores for

both, control and intervention groups, were calculated for a particular time point (3, 4, 6, 8, 9 and 12 months). Based on the full description of the interventions in the articles reporting the study results or in study protocols, BCTs were identified and coded using the BCTTv1 (54). Two authors (MK and TLH) read the description of the interventions to collect data about the seven AADE7 self-care behaviors addressed in each intervention. Two reviewers (MK and CP) experienced in using the BCTTv1 (54) coded the description of intervention contents independently and meetings were held to reach consensus on which BCTs were coded for each individual intervention.

Quality assessment

The Cochrane Risk of Bias Assessment tool for Randomized Control Trials (55) was used to assess the quality of the included studies. Two authors (MK and MP) independently assessed the risk of bias, resolving differences with consensus. Covidence was used to semi-automate the process (53). Using this tool, seven domains of risk of bias can be identified: allocation concealment, sequence generation, blinding of participants and personnel, blinding of outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. The terms low, high or unclear risk of bias were used to label the quality of studies for each domain. The seventh domain, "*other sources of bias*", was assessed following the recommendation by Fu and colleagues. Hence, baseline balance of HbA1c levels between control and intervention groups, information on loss to follow up, retention and attrition rates and reported competing interests were considered (42). Finally, the consensus quality ratings were exported to RevMan (56) to receive the final graphical representation of all risk of bias ratings.

Missing data

Missing data were obtained by contacting corresponding authors or computed based on the reported data. Using excel functions, SD values which were initially not reported for some of the studies were calculated based on the reported 95% confidence intervals, standard error

(SE), or p-values (42; 57). Contacting corresponding author and computing missing SD values with reported data did not work fora study by Wakefield and colleagues (58). Therefore, this missing SD value was imputed using arithmetic means by following an existing methodological guideline (42). For one study (59), the mean and SD values were calculated based on the reported median and range using Hozo's formula (60). The pre-post correlation values, both for control and intervention groups, were calculated based on formulas described in previous methodological studies and formulas by Fu et.al (42) and Morris et.al (44).

Data syntheses and analysis

Simple analysis of final values (SAFV), simple analysis of change scores (SACS) and ANCOVA effect size estimator are the main methods used to calculate effect sizes of a continuous outcome with a similar scale of measurement (42-45). Methodological guidelines shows that adjusting for baseline imbalance and pre-post correlation is important in meta-analysing continuous outcomes. The baseline HbA1c differences in the studies included in our review ranged from 0% to 0.64%, with only two RCTs having a mean HbA1 difference of 0% (61; 62). Assuming publication bias is negligible, meta-analysis of the baseline differences should be close to zero if the two treatment groups are balanced (42). In our case, meta-analysis of baseline HbA1c mean difference was 0.14% (95% CI –0.31, 0.59). Additionally, pre-post correlation ranged from 0.06 (63) to 0.74 (64). For this reason, accounting for baseline imbalance and pre-post correlation was essential. In this review, the ANCOVA effect size estimator was preferred because it helps to adjust for baseline imbalance and pre-post correlations (42-45). Therefore, the effect size estimates were computed using the "black-belt" ANCOVA approach using the following equation: $ANCOVA = (Yint - Yctr) - \beta(Xint - Xctrl)$, where β is a regression coefficient computed from pooled SD of the treatment (SDy) and control groups (SDx). Hence, $\beta = r\frac{SDy}{SDx}$ (42; 43). Equations by Jo

McKenzie et.al (43) and Riley et.al (45) were used to calculate the variances of the final values, change scores, and ANCOVA effect size estimates. If there was no possibility to compute ANCOVA effect size estimates from the reported data, the estimate with smaller effect size obtained from change score and final values estimates were pooled with the ANCOVA effect size estimates following existing methodology (42; 43; 45).

Meta-analyses

Stata version 13 statistical software was used to perform the meta-analyses. The outcome data reported at study closure were used to perform the overall meta-analysis. HbA1c reductions of at least 0.3% were labelled as clinically significant (24; 29; 65). For studies reporting the results of RCTs with three or more arms, relevant arms were considered in the pooled analysis if they were deemed combinable.

Following Cochrane recommendations, observed statistical heterogeneity was assessed with the Cochrane's X^2-test (a p-value of less than 0.1 indicates statistically significant heterogeneity) and quantified by using I^2. With I^2 value of $\geq$50%, a random-effects model was used, else a fixed-effect model (66).

Sensitivity analyses were performed by excluding studies judged as having a "high risk" of bias for more than three dimensions of the risk of bias assessment tool. Several subgroup analyses were performed to estimate the effects of various intervention features (e.g. tailoring, mode of intervention, and BCTs included). The differences across subgroups were assessed using the random-effects model.

A series of univariate meta-regression analyses were performed by regressing intervention effect sizes across studies on intervention features [i.e., duration of intervention, mode of delivery, theory-based, tailoring, baseline HbA1c inclusion criterion (HbA1c >7.0% vs. >7.5%), type of BCT (present or absent) and total number of BCTs included in the interventions]. Then, multivariate meta-regression analyses were performed to identify effective BCTs and intervention features associated with HbA1c level. Following the

recommendation by Borenstein et.al (67), BCTs were added in the subgroup and meta-regression analyses if they were included in at least two studies.

Visual inspection of contour funnel plot was used to detect publication bias. In addition, Egger's test using a p-value of less than 0.1 was conducted to assess publication bias (68). If publication bias was suspected, the "trim and fill" imputation method was used to estimate the number of missing studies in the funnel plot (69). Finally, the quality of evidence generated through meta-analysis was classified as high, moderate and low using the GRADE approach (70; 71). The GRADEpro online tool was used to systematically evaluate the synthesized evidence (72).

Results

Study selection and characteristics

In the database search, 1669 titles and abstracts were retrieved, with only 22 studies fulfilling the inclusion criteria (58; 59; 61-64; 73-88). Two studies (64; 79) were three-arm RCTs, 20 of them were two-arm RCTs. Because of this, 24 arms of 22 RCTs were considered in the meta-analysis. However, one RCT (74) had most of the required data missing, and was excluded from the quantitative syntheses. Finally, 23 arms of the 21 RCTs were used in the meta-analyses (Fig 1).

Studies were published between the years 2009 and 2017, with the majority conducted in the USA (n=9). A total of 3787 subjects were included in the 23 arms of the 21 RCTs and followed for a mean duration of 7.29 months (SD=3.05). 1991(52.6%) participants were assigned to the intervention arms. The mean number of participants randomized to control and intervention groups was 82.6 (SD=62.7) and 83.9 (SD=62.12) respectively. On average, treatment retention rate at study closure was 89.4% (SD=9.97, range = 75 to 100%).

Nearly two-thirds of interventions (n=15; 65.22%) were web-based delivered via smartphones, tablets, PDA and computers. Five interventions implemented telehealth (21.74%) and three (13.04%) text messaging. 11 of the 21 RCTs (52.4%) targeted patients

with baseline HbA1c values greater than 7.5% while the rest was targeted patients having an HbA1c level of greater than 7.0%.

Quality of studies

Less than half of the included studies described intention-to-treat analysis (ITT) with 12 studies not stating ITT procedures. Only one study was judged as having a low risk of bias on all of the risk of bias assessment dimensions (88). Four studies (18.2%) were judged as having a high risk of bias on three out of seven dimensions (74; 76; 81; 83). Eighteen (81.2%) studies adequately described the randomization procedure and were judged as having a low risk of bias with regard to this dimension (58; 59; 61-64; 73-80; 82; 84; 85; 88). Seven studies (31.2%) did not adequately describe how the allocation was performed and were unclear for judgement (59; 61; 75; 81; 85-87) (Fig 2).

Regarding intervention-related adverse events, only eight studies (58; 62-64; 75; 79; 84; 88) reported that adverse events were assessed. All of these studies reported that there were no intervention-related adverse events. One study reported two deaths but not due to intervention participation (64) and one reported trouble among intervention participants with regard to using the digital devices or connecting with Bluetooth (79).

Only seven interventions were designed following behavioral health theories. The theories used were the "health belief model" (73; 82), the "trans-theoretical model of behavioural change" (73), the "health action process approach", the "theory of planned behaviour", and the "Bandura's theory of self-efficacy" (82). In addition, "Green and Kreuter's PRECEDE-PROCEED model" (80), "cognitive behavioural therapy", the "Reach Out" problem-solving model, and "motivational interviewing" (64; 79) were used to guide intervention design. Seventeen interventions (58; 61-64; 75; 76; 78-82; 84-88) were tailored according to individual patient characteristics (Table 1).

AADE7 seven self-care behaviours targeted in the interventions

Inter-rater agreement determined by using Cohen's Kappa and prevalence adjusted bias kappa (PABAK) was 0.6 and 0.8 respectively, suggesting a high reliability. A mean of 4 (SD=1.74, range 1-7) AADE7 self-care behaviors were addressed in interventions. Of the seven AADE7 self-care behaviors, "monitoring" was the most frequently included (in 21 of 24 intervention arms) followed by "healthy eating" and "taking medication", which were addressed 16 and 15 times, respectively. However, "healthy coping" was included in only nine intervention arms.

Of the 22 interventions included in this review, only one intervention addressed seven of the AADE7 self-care behaviors (87). Four interventions targeted six self-care behaviors each (61; 74; 75; 84) (Table 1).

BCTs used in eHealth interventions targeting persons with poorly controlled type 2 diabetes

Inter-rater agreement determined by using percent agreement was 96.5% and prevalence adjusted bias kappa (PABAK) was 0.93, suggesting a very good agreement. A total of 27 BCTs with a minimum of four (62; 83; 88) and a maximum of eleven BCTs (73) were addressed in interventions. Of the 27 BCTs, "instruction how to perform behaviour" was employed most frequently, included in 21 intervention arms (58; 59; 61-64; 73-75; 77-81; 83-85; 87; 88). Eight BCTs were included only once. None of the intervention arms had a similar combination of BCTs (Supplementary Table S1).

Impact of interventions in terms of reducing HbA1c

The pooled mean HbA1c difference suggests a statistically significant HbA1c reduction, -0.39 (95%CI: -0.51, -0.26), favouring digital intervention groups. However, heterogeneity was high (I-squared statistic: 80.8%).

Publication bias

Visual inspection of the contour funnel plot shows that the majority of the effect sizes of the interventions are in the significant region as well as in the upper left part of the plot which suggests the predominance of published significant findings (Supplementary Fig 1). However,

Egger's test indicated that there is not enough evidence of small-study effects (Coefficient=-1.13, p-value = 0.182). Performing the "trim and fill" test also did not result in changes suggesting that the influence of publication bias was negligible.

Sensitivity analyses

Sensitivity analyses was conducted excluding four studies judged as having a "high risk" of bias in more than three dimensions of the risk of bias assessment. The pooled HbA1c MD and heterogeneity I-square statistics were not substantially changed, resulting in a pooled HbA1c MD of -0.38% (95%CI: [-0.51, -0.24]) and I-squared of 77.9%. However, removing eight studies having a "high" and an "unclear" risk of bias for allocation concealment resulted in a lower effect size estimate, -0.30% (95%CI: [-0.45, -0.15]). I-squared statistic was also lowered to 68.4%. Further sensitivity analysis conducted by removing the four studies with inadequate description of randomization yielded a lower effect size estimate, -0.29% (95% CI: -0.41, -0.17).

Subgroup analyses by intervention features and BCTs

The pooled mean HbA1c difference was -0.52% (95%CI: [-1.04, 0.00]), -0.41% (95%CI: -0.55, -0.27), -0.21% (95%CI: [-0.65, 0.22]) for text message-delivered, web-based, and telehealth interventions, respectively. Statistically significant pooled HbA1c reductions favoring the intervention group were only noted for web-based interventions. However, there was substantial statistical heterogeneity across the three intervention subgroups (Figure 3).

A subgroup analysis on the duration of interventions yielded an ANCOVA adjusted mean HbA1c difference of -0.30 (95%CI: -0.495, -0.11), -0.59(95%CI: -0.78, -0.39), and -0.21 (95%CI: -0.35, -0.075) for interventions having outcome end-points after 3 to 4 months, 6 to 8 months, and 9 to 12 months, respectively. However, there was substantial heterogeneity in the

3 to 4 months (I-squared = 89%) and 6 to 8 months (I-squared = 85%) sub-groups (Supplementary Figure 2).

Additional subgroup analysis was performed to investigate the differences in mean HbA1c reduction for interventions that "included" vs. "did not include" a specific BCT. Hence, we noted HbA1c mean differences favouring the intervention group for the presence of the following BCTs: 'information about health consequences' (-0.77%), 'instruction on how to perform behaviour' (-0.35%), 'self-monitoring of behaviour' (-0.27%), 'self-monitoring outcomes of behaviour' (-0.15%), 'adding objects to the environment' (-0.13%) and 'feedback on outcomes of behaviour' (-0.12%). However, as can be seen above, only two BCTs led to clinically significant HbA1c changes (delta > -0.3%) (Supplementary Table S2).

Further, subgroup analysis on the effect size differences shows that interventions which were implemented among patients with HbA1c levels of greater than 7.5% led to higher reductions (delta=-0.12%) of HbA1c levels relative to interventions among patients with HbA1c of greater than 7.0% (Supplementary Table S3).

Subgroup analysis on the baseline HbA1c inclusion criteria resulted in relatively bigger effect size for interventions targeting patients with HbA1c-levels greater than 7.5% (i.e., -0.46% (95% CI: [-0.70, -0.21]) vs. -0.33% (95% CI: [-0.478, -0.18]) (Supplementary Fig 3).

Identifying intervention features and BCTs associated with HbA1c reductions

The univariate meta-regression analysis, obtained by regressing the effect sizes of interventions on intervention features indicated that none of the features, except for duration of interventions, was significant. Interventions with 3- to 4-months duration (β=0.42, p-value=0.016, tau2=0.085, R2= 21.7%) and a 6- to 8-months duration (β=-0.29, p value=0.03, tau2=0.089, R2= 17.7%), displayed significant associations with the effect size indicating that 6 to 8 months of intervention duration resulted in a pronounced reduction of HbA1c levels. Only two BCTs, 'feedback on behaviour' (β=0.29, p-value=0.037, tau2=0.092, R2= 15.4%) and 'social support practical' (β=0. 42, p-value=0.016, tau2=0.0085, R2= 21.6%), were significantly associated with the effect size. Because the beta coefficients were positive, the use of these BCTs did not demonstrate HbA1c reductions.

Multivariable meta-regression revealed that the presence/absence of nine BCTs and other intervention features in the model explained 79.8% of the variance in the effect size. Tailoring the interventions, β=1.15 (95%CI: [0.14, 2.17]), baseline HbA1c higher than 7.5, β=-0.44 (95%CI: [-0.81, -0.06]), and the presence or absence of 4 BCTs were significantly associated with HbA1c levels. Hence, the BCTs 'problem solving' (β=-1.30 (95%CI: [-2.05, -0.54])), 'feedback on outcomes of behaviour'(β=0.68 (95%CI: [0.08, 1.28]), 'self-monitoring outcomes of behaviour'(β=-1.21(95%CI: -1.95, -0.46)) and 'prompts/cues'(β=0.44 (95%CI: [0.03, 0.85]) were significantly associated with the HbA1c levels. Of these, baseline HbA1c

higher than 7.5%, ‘problem solving’ and ‘self-monitoring outcomes of behaviour’ were associated with reduced HbA1c-levels (Table 2).

Grading the quality of evidence generated from the meta-analyses

Applying the GRADE principles (72), the quality of evidence generated through this meta-analysis can be considered as “moderate quality” (Supplementary Table S4 and Supplementary Table S5).

Discussion

This systematic review is the first to demonstrate the effectiveness of digital interventions for reducing HbA1c levels in patients with poorly controlled type 2 diabetes. It is also the first review to account for baseline imbalance and pre-post correlations using an available robust statistical method, ANCOVA. The review also used a reliable taxonomy (48) to identify effective BCTs employed in digital interventions targeting persons with type 2 diabetes, as well as the well-established AADE7 (19) to unravel the effects of intervention components on HbA1c-levels. These tools offer a great opportunity to handle heterogeneity across multicomponent and complex interventions (47; 49).

In this review, we report clinically and statistically significant effects of PDA-, mobile phone- or computer-delivered web-based interventions on HbA1c. A clinically significant HbA1c reduction is associated with lower rates of deaths, myocardial infractions, and reduced microvascular complications (24).

Similar to our results, clinically and statistically significant pooled HbA1c reductions were reported for internet-based interactive self-management interventions (28), and mobile

phone-based internet interventions, (33). Our findings thus support the previously reported evidence on beneficial effects of web-based interventions (34). However, we could not show a statistical significant reduction of HbA1c-levels after participation in text message and telehealth interventions. Contrary to our findings, previous results of meta-analyses reported significant HbA1c reductions after participation in telehealth (35; 89) and text-message interventions (38). This may possibly be due to the number of telehealth and text message interventions included in our meta-analyses which was relatively low.

Sensitivity analyses performed by removing studies with a high risk of bias for more than three dimensions suggests that there was no change in the direction of the overall effect estimate. However, the two additional meta-analyses performed after dropping studies with an inadequate description of randomization and a high or unclear risk of bias regarding allocation concealment resulted in a lower effect size estimate. This supports the finding that studies with inadequate or unclear allocation concealment may report inflated treatment effect estimates (90; 91).

Results of the subgroup analyses by duration of intervention suggest higher effect size estimates for longer intervention periods. This is likely due to the fact that it takes time for behavioral interventions to change patterns of thoughts and feelings towards behavior change and behavior itself which, in turn, leads to a change in HbA1c. Yet, the effect size estimate decreased nine to twelve months into the intervention. This is in line with other recent meta-analyses results that reported similar effects of digital interventions on HbA1c reduction by duration (28; 65; 92). However, a review by Cradock and colleagues reported a higher HbA1c reduction at month 3 compared to month 6 during the intervention period (65). It should be noted though that only a small number of studies (four) were included and that baseline HbA1c-levels were not taken into account in the subgroup-analyses performed by Cradock and colleagues (65). Previous literature also suggests that more pronounced reductions of HbA1c occur among patients with higher HbA1c-levels at the beginning of the intervention

(31; 41; 93). This was confirmed in both of our subgroup and meta-regression analyses. Patients with an HbA1c-level greater than 7.5% displayed higher effect estimates. Clinically, this supports the usefulness of digital interventions, particularly among patients with poor initial glycaemic control.

Only interventions addressing the following two BCTs, 'information about health consequences' and 'instruction on how to perform behaviour' led to clinically significant HbA1c changes in patients with poorly controlled type 2 diabetes. Cradock et al also reported a clinically significant effect of employing the BCT 'instruction on how to perform behaviour' (65), as did another meta-analysis reported by Avery and colleagues (94). Future meta-analyses including more studies and larger study populations as well as concise intervention descriptions are needed to validate these findings.

The results of the multivariable meta-regression analysis indicate that nine BCTs, as well as additional intervention features in the model explained more than three-fourths of the variance in the effect size. Baseline HbA1c above 7.5%, the presence of the two BCTs 'problem solving' and 'self-monitoring outcomes of behaviour' were associated with significant reductions in HbA1c levels. Contrary to the results of a meta-analysis by Kassavou and colleagues, our results suggest that interventions employing the BCT 'problem solving' had a higher beneficial pooled effect (95). It is known that meta-regression models provide robust results when a greater number of studies and fewer covariates are taken into account (96). Future meta-regression analyses therefore ought to pool larger number of trials to develop relatively stable and precise meta-regression results.

Although tailoring the interventions and 'feedback on outcomes of behaviour' were significantly associated, these associations were inverse which indicates that the presence of tailoring and this BCT does not lead to reductions in HbA1c-levels. There was also no evidence of an association between HbA1c-levels and the use of theories for designing interventions. Although the use of theories ideally offers scientific explanations of the process

of change and is helpful for linking observed changes in outcomes with active intervention ingredients, the existing evidence regarding the benefits of theory use for intervention development is mixed (97).

Our results did not suggest an association between the number of BCTs addressed in interventions and changes in HbA1c. In contrast, two previous systematic reviews demonstrated an association between a greater number of BCTs included in behavioral and self-management interventions and reductions in HbA1c-levels (65; 94). The substantial variation in the breadth and depth of BCT descriptions included in the articles could partially explain this finding. Greater quality of intervention descriptions enhance reliability and validity of characterization of the multi-component interventions and improve reliability and the power of results (49; 98).

Limitations

The study has several limitations. Our search was limited to three main databases. However, during the preliminary search, we did not observe major differences in search results when using EMBASE, CINAHL and Cochrane library. Therefore, we concluded that our search in PubMed, ISI Web of Science and PsycINFO covered the relevant articles. We also did not search in un-indexed databases and the grey literature.

Previous research suggest that each additional intervention increases the unspecific "attention factor" for patients. Testing a digital intervention against a standard care might therefore overestimate the specific effect of digital interventions, since the "attention factor" is not well controlled. Additionally, higher dropout rates were reported from previous digital interventions. This might be due to self-selection indicating that people who like digital media stay in the interventions and people who have difficulties with digital interventions may drop out from the study which leads to overestimation of the results. However, in this review high retention rate was observed from individual studies.

Mapping and differentiating the intervention content to determine which BCTs were addressed in interventions relies on the quality and depth of descriptions available for various interventions (99). In addition, it is based on a subjective judgement. We tried to minimize this limitation by taking online training in using the BCTTv1, applying consensus ratings, and using a third experienced reviewer to resolve any disagreement.

Conclusions

In conclusion, the results of this systematic review and meta-analysis indicate that participation in digital interventions, particularly web-based interventions, favourably influences HbA1c levels among patients with poorly controlled type 2 diabetes. Intervention effects were more pronounced among patients with higher baseline HbA1c-levels and greater effects were observed six to eight months into an intervention. Moreover, the results of the meta-regression analyses suggest that baseline HbA1c >7.5%, and the two BCTs 'problem solving', and 'self-monitoring outcomes of behaviour' were associated with a reduction of HbA1c-levels. Hence, considering these two BCTs in future interventions may lead to clinically meaningful reductions in HbA1c.

The effort to adjust for baseline imbalance and pre-post correlation relies on the level of detail of reporting available for individual studies. We suggest to authors of future intervention studies, particularly with baseline imbalance, to report detailed information that allows authors of systematic reviews to calculate ANCOVA effect size estimates or, ideally, to provide access to IPD.

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Author's contributions

MK conceptualized and designed the study, conducted the systematic literature search with the help of research librarian, performed the title and abstract screening, quality assessment, data extraction, data analysis and interpretation of the data and wrote the manuscript.

HZ: participated in the conception and the design of the study and the development of the methodology, and critically revising the manuscript for important intellectual content.

MP: conducted the title and abstract screening, quality assessment and participated in the draft of the manuscript.

TH: contributed to the extraction of the data and critically revised the manuscript.

CP: participated in the conception, data extraction, and critically revised the manuscript for important intellectual content.

All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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Tables and Figures

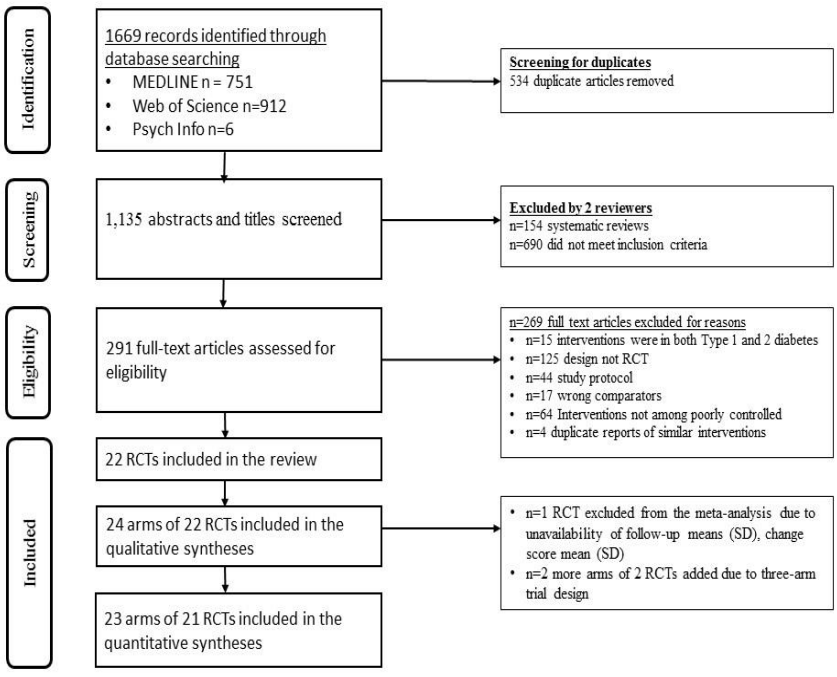
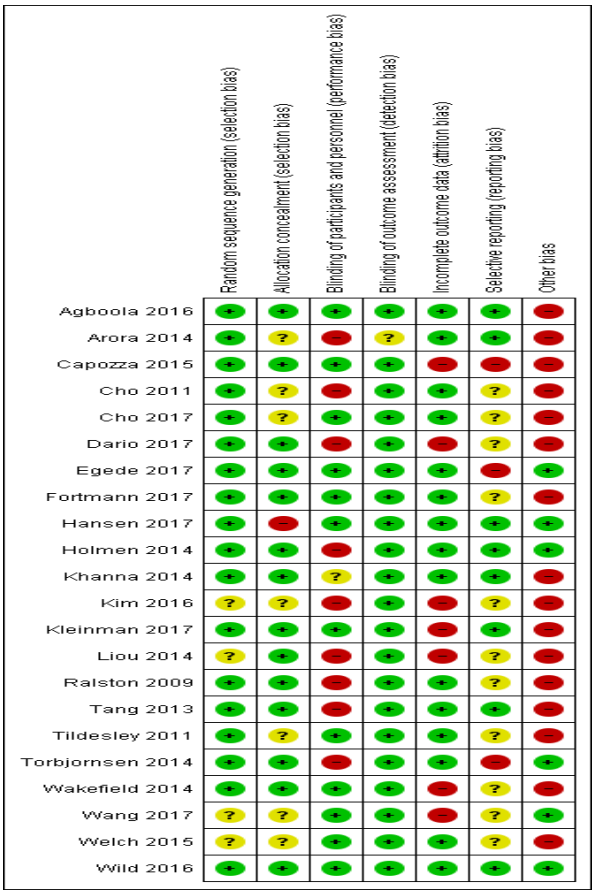


Fig 1: Preferred Reporting Items for Systematic Reviews and Meta-analyses flowchart for database search and study selection



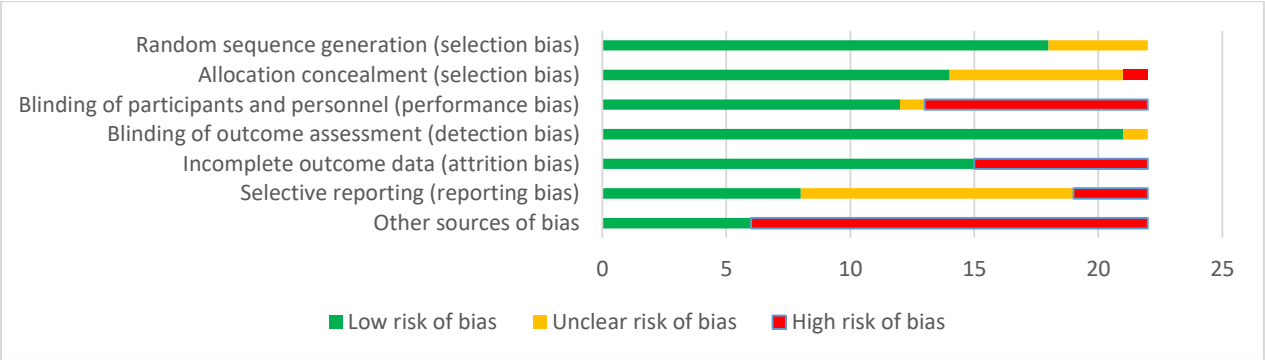


Fig 2: Risk of bias assessment graph and summary

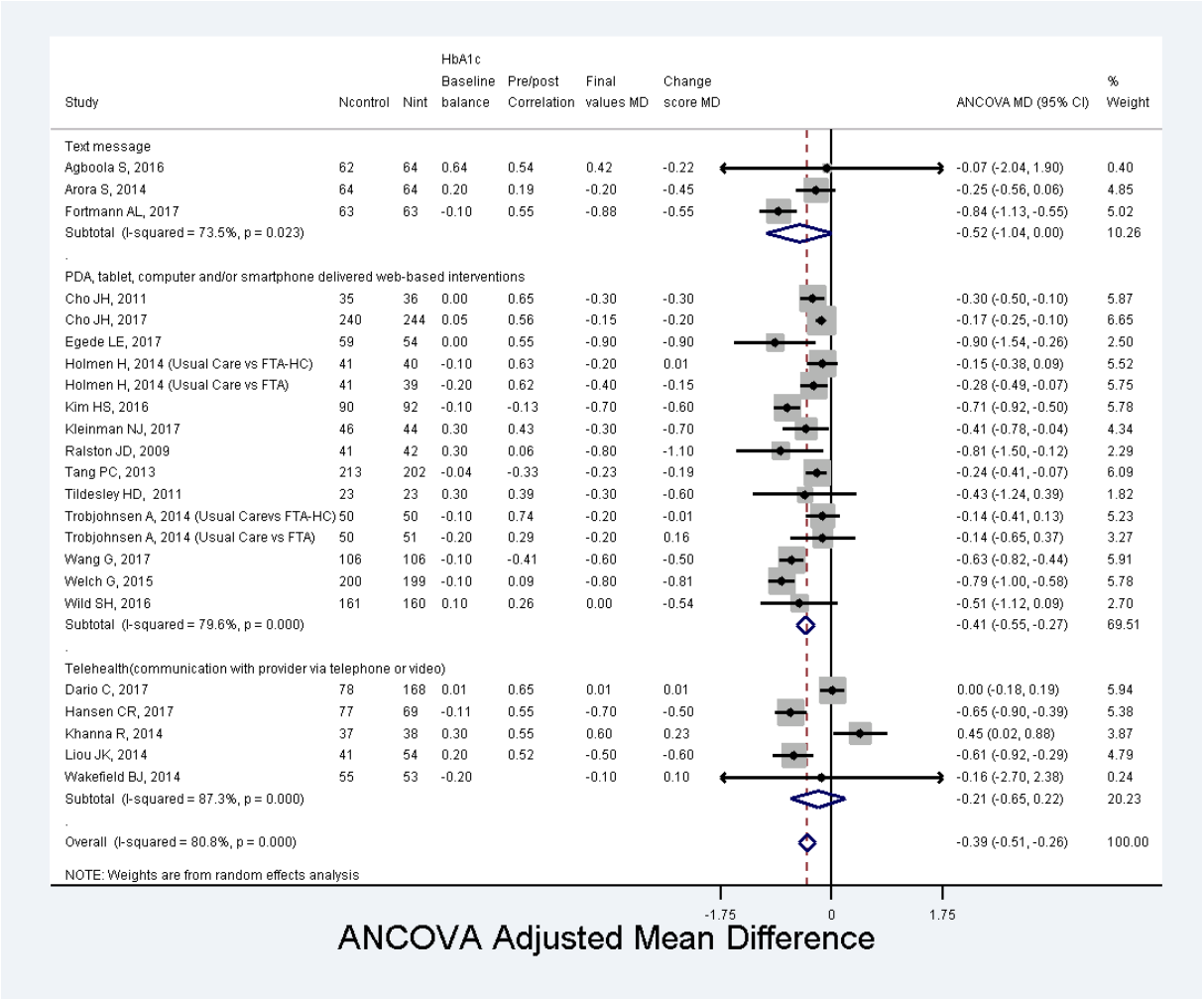


Figure 3: Subgroup analysis of effectiveness of digital interventions for reducing HbA1c-levels by mode of delivery.

Table 1: Characteristics of the included studies

Study	Location	Intervention	Intervention time end-points	Tailoring	Theory	Study population	Baseline HbA1c inclusion criteria (%)	AADE7 self-care behavior targeted	Adverse event
	Mobile phone-delivered text message interventions								
Agboola S, 2016	USA	Text to move (Text message)	6 months	No	Yes, trans theoretical model of behavior change	Spanish or English-speaking low-income and ethnic minorities, type 2 diabetes patients	> 7.0	Being active, healthy coping, taking medication, healthy coping	Not reported
Arora S, 2014	USA	2 daily text messages for 6 months. Education/motivation-1 text per day, medication reminders-3 per week, healthier living challenge-2 per week, trivia. Unidirectional text message	6 months	No	Yes, Health Belief Model	English or Spanish speaking Latino and black type 2 diabetes patients	>7.5	Being active, healthy eating, monitoring, taking medication, reducing risks	Not reported
Capozza K, 2015	USA	Text message (Care4Life program) for education & motivation, medication adherence, glucose control, weight and exercise	3 and 6 months	No, allowed patients to send text messages to providers	No	No specific population, adult patients with type 2 diabetes patients	>7.5	Being active, monitoring, taking medication, healthy coping, reducing risks, problem solving	Not reported
Fortmann AL, 2017	Canada	Dulce Digital: An mHealth SMS-Based Intervention	3 and 6 months	Culturally and ethnically tailored, but not tailored to individual characteristics	No	Under- served Hispanics with poor glycaemic control, type 2 diabetes patients	≥7.5	Healthy eating, monitoring, taking medication, problem solving	Not reported

	PDA, tablet, computer and/or smartphone delivered web-based interventions								
Cho JH, 2011	South Korea	Internet diabetes management	3 months	Yes	No	No specific population, type 2 diabetes patients, Koreans	>7.0	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks	Not reported
Cho JH, 2017	Korea	health-care provider mediated, remote coaching system via a PDA-type glucometer and the Internet	3 and 6 months	Tailored	No	Koreans, no specific population, patients with type 2 diabetes	7 to 10.0	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks	No adverse event detected
Egede LE, 2017	USA	Telehealth and clinical decision support system	3 and 6 months	Tailored	No	18 years or older, type 2 diabetes patients	≥8.0	Monitoring, taking medication, problem solving	No adverse event detected
Holmen H, 2014 (Usual Care vs FTA-HC)	Norway	Few Touch Application (diabetes diary app with health counselling(FTA-HC)	12 months	Tailored	Yes, cognitive behavioural therapy, the "Reach Out" problem-solving model, and motivational interviewing (MI)	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring, problem solving, healthy coping	No adverse event, but only trouble with use of the digital devices
Holmen H, 2014 (Usual Care vs FTA)	Norway	Few Touch Application (diabetes diary app without health counselling(FTA-HC)	12 months	Tailored	Yes, cognitive behavioral therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring	No adverse event, but only trouble with use of the digital devices
Kim HS, 2016	China	Internet based glucose monitoring system	3 and 6 months	Tailored	No	Male and female outpatients with type 2	7.0 to 10.0	Monitoring	Not reported

						diabetes patients			
Kleinman NJ, 2017	India	Smart phone app for patients and smart phone app and a web based portal for providers	3 months	Tailored	Health belief model, health action process approach, theory of planned behavior, Bandura's theory of self-efficacy	No specific population, type 2 diabetes patients for >6 months	7.5 to 12.5	Monitoring, problem solving, reducing risks, taking, medication	Not reported
Ralston JD, 2009	USA	Web-based care management	12 months	Tailored	Yes, Wagner's Chronic Care Model	No specific population, adults patients with type 2 diabetes	>7.0	Healthy eating, monitoring, taking, medication, problem solving	No adverse event
Tang PC, 2013	USA	Online disease management system	6 and 12 months	Tailored	Yes, Universal models of behavior change, MI and Chronic care model	No specific population, adult patients with type 2 diabetes	>7.5	Healthy eating, being active, monitoring, taking medication, reducing risks, problem solving	No adverse event
Tildesley HD, 2011	Canada	Internet-based glucose monitoring system (IBGMS)	3, 6 and 12 months	Tailored	No	No specific population, type 2 diabetes patients	>7.0	Monitoring, taking medication	Not reported
Trobjohnsen A 2014 (Usual Care vs FTA-HC)	Norway	Few Touch Application (diabetes diary app with health counselling(FTA-HC)	4 months	Tailored	Yes, cognitive behavioural therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring, problem solving, healthy coping	2 deaths, but unrelated with the interventions

Trobjohnsen A 2014 (Usual Care vs FTA)	Norway	Few Touch Application (diabetes diary app without health counselling(FTA-HC)	4 months	Tailored	Yes, cognitive behavioural therapy, the "Reach Out" problem-solving model, MI	No specific population, adult patients with type 2 diabetes	>7.0	Healthy eating, being active, monitoring	2 deaths, but unrelated with the interventions
Wang G, 2017	China	Monitoring via computer/web/mobile phone connected to glucometer via cable	3 and 6 months	Tailored	No	No specific population, type 2 diabetes patients confirmed for over 1 year	7 to 10.0	Healthy eating, being active, monitoring	Not reported
Welch G, 2015	USA	Internet-based integrated diabetes management system	6 months	Tailored	No	Latino, type 2 diabetes patients	>7.5	Healthy eating, being active, monitoring, taking medication, problem solving, reducing risks, healthy coping	Not reported
Wild SH, 2016	Scotland	Monitoring through computer/web based/mobile phone connected to glucometer via modem	9 months	Tailored	No	No specific population, type 2 diabetes aged over 17 years	>7.5	Monitoring, taking medication, reducing risks	Adverse events were equally distributed between in intervention & control groups
Telehealth(communication with provider via telephone or video)									
Dario C, 2017	Italy	Videoconferencing	12 months	Tailored	No	Italy, no specific population, type 2 diabetes patients	>7.0	Monitoring, reducing risks	Not reported
Hansen CR, 2017	Denmark	Videoconferencing	8 months	Tailored	No	Danish speaking type 2 diabetes patients	>7.5	Monitoring, problem solving, reducing risks	Not reported
Khanna, R. 2014	USA	Automated telephone support with dialogic telephone card	3 months	Tailored	Yes, Green and Kreuter's PRECEDE-	Spanish-speaking patients with type 2 diabetes	>7.5	Healthy eating	Not reported

					PROCEED model				
Liou JK, 2014	Taiwan	Web-based and videoconferencing	6 months	No	no	No specific population, adult type 2 diabetes patients	>7.0	Healthy eating, taking medication, reducing risks, healthy coping, problem solving	Not reported
Wakefield BJ, 2014	USA	Tele-monitoring	3 and 6 months	Tailored	No	No specific population, subjects with established type 2 diabetes	>8.0	Monitoring, taking medication	No adverse events

Table 2: Multivariable meta-regression analysis regressing ANCOVA adjusted MD on intervention features and BCTs.

ANCOVAestimate3	Coefficient	Std. Err.	t	P	[95% Confidence Interval]
Type of intervention					
Web-based interventions	-0.39	0.18	-2.23	0.076	[-0.85, 0.06]
Text message based	0.38	0.35	1.08	0.331	[-0.52, 1.28]
Duration of intervention					
3 to 4 months	-0.003	0.13	-0.02	0.987	[-0.35, 0.34]
6 to 8 months	-0.17	0.16	-1.11	0.318	[-0.58, 0.23]
Tailoring	**1.15**	**0.39**	**2.91**	**0.033**	[**0.14, 2.17**] **
Baseline HbA1c >7.5	**-0.44**	**0.15**	**-2.97**	**0.031**	[**-0.81, -0.06**] **
Theory use	0.05	0.15	0.33	0.752	[-0.33, 0.42]
Problem solving	**-1.30**	**0.29**	**-4.41**	**0.007**	[**-2.05, -0.54**]**
Review outcome goals	-0.44	0.20	-2.22	0.077	[-0.96, 0.07]
Self-monitoring of Behaviour	-0.22	0.24	-0.92	0.399	[-0.84, 0.40]
Self-monitoring outcomes of behaviour	**-1.21**	**0.29**	**-4.15**	**0.009**	[**-1.95, -0.46**] **
Feedback on outcomes of behaviour	**0.68**	**0.23**	**2.91**	**0.033**	[**0.08, 1.28**] **
Instruction how to perform behaviour	0.05	0.20	0.24	0.823	[-0.46, 0.55]
Salience of consequences	-0.14	0.12	-1.12	0.312	[-0.45, 0.18]
Prompts/cues	**0.44**	**0.16**	**2.77**	**0.040**	[0**.03, 0.85**] **
Adding objects to the environment	0.04	0.28	0.16	0.882	[-0.68, 0.76]
Total number of BCTs	-0.02	0.05	-0.42	0.695	[-0.14, 0.10]
Intercept	-0.40	0.36	-1.11	0.317	[-1.33, 0.53]

Number of studies included in the model =23, estimate of between study variance tau2=0.022, Adjusted R2=79.83, I^2=97.76%, Joint test for all covariates F (17.5) = 5.34, p = 0.037

**

Statistically significant at a p value of 0.05

Supplementary Table S1: BCTs included in interventions

BCT	Studies																								
	Agboola S	Arora S 2014	Capozza K 2015	Cho JH 2011	Cho JH 2017	Dario C 2017	Egede LE 2017	Fortmann AL 2017	Hansen CR 2017	Holmen H 2014 (Usual Care vs FTA [illegible])	Holmen H 2014 (Usual Care vs FTA)	Khanna R 2014	Kim HS 2016	Kleinman NJ 2017	Liou JK 2014	Ralston JD 2009	Tang PC 2013	Tildesley HD 2011	Torbjonsen A 2014 (Usual Care vs FTA HC)	Torbjonsen A 2014 (Usual Care vs FTA)	Wakefield BJ 2014	Wang G 2017	Welch G 2015	Wild SH 2016	Total
Goal Setting Behaviour	✓	✓	✓																						3
Problem Solving				✓												✓									2
Goal Setting Outcome						✓				✓	✓				✓	✓	✓		✓	✓					8
Action Planning	✓															✓	✓						✓		4
Review Behaviour Goals																						✓			1
Review Outcome Goals						✓							✓									✓			3
Discrepancy from Behaviour Goal	✓																✓								2
Feedback on Behaviour	✓				✓					✓	✓	✓	✓						✓	✓		✓			9
Self-monitoring of Behaviour	✓				✓								✓			✓						✓	✓		6
Self-monitoring Outcomes of Behaviour			✓		✓	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	18
Biofeedback			✓													✓									2
Feedback on Outcomes of Behaviour			✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓			✓		✓	✓	✓	✓	✓	✓	18
Social Support(unspecified)			✓																						1
Social Support(practical)				✓						✓		✓							✓						4
Social Support(emotional)	✓							✓		✓						✓	✓		✓						6

Instruction how to perform Behaviour	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	21
Information on Antecedents																								✓		1
Information about Health Consequences	✓	✓	✓	✓	✓			✓	✓			✓			✓	✓	✓	✓			✓			✓		14
Salience of Consequences		✓				✓			✓			✓		✓										✓		6
Demonstration of Behaviour																					✓					1
Prompts/Cues	✓	✓	✓		✓	✓		✓				✓	✓	✓		✓	✓	✓				✓	✓			14
Behavioural Substitution												✓														1
Graded Tasks	✓																									1
Social Reward												✓						✓								2
Pharmacological Support				✓																						1
Reduce Negative Emotions															✓											1
Adding Objects to the Environment	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓			✓	✓	✓	✓	✓	✓	✓	✓		20
Total Number of BCTs	11	5	9	7	8	7	4	7	6	8	6	7	8	6	4	9	10	6	8	6	6	8	10	4		

Supplementary Table S2: Subgroup analyses of effects of BCTs on HbA1c-levels.

BCT	K present/ absent	Present					Absent					Difference
		Effect size (95%CI)	Q	P	I^2%	Test for effect size	Effect size (95%CI)	Q	P	I^2%	Test for effect size	
Goal Setting Behaviour	2/21	-0.25 (-0.55, 0.06)	0.03	0.86	0	0.12	-0.39(-0.53, -0.26)	114.27	0.000	82.5	0.000	0.15
Problem Solving	2/21	-0.45 (-0.90, 0.00)	1.98	0.16	49.4	0.054	-0.38 (-0.52, -0.24)	112.43	0.000	82.2	0.000	-0.07
Goal Setting Outcome	8/15	-0.23(-0.37, -0.09)	15	0.036	53.3	0.001	-0.47 (-0.65, -0.28)	91.34	0.000	84.7	0.000	0.24
Review Outcome Goals	3/20	-0.44(-0.89, 0.00)	2	0.000	93.7	0.053	-0.37(-0.50, -0.24)	78.17	0.000	75.7	0.000	-0.07
Discrepancy Between Current Behavior and Goal	2/21	-0.24(-0.41, -0.07)	0.03	0.864	0	0.005	-0.40(-0.54, -0.26)	113.72	0.000	82.4	0.000	0.16
Feedback on Behavior	9/14	-0.26(-0.45, -0.06)	49.85	0.000	84	0.011	-0.48(-0.66, -0.31)	54.5	0.000	76	0.000	0.23
Self-monitoring of Behavior	6/17	-0.58(-0.91, -0.26)	59.47	0.000	91.6	0.000	-0.31(-0.45,-0.18)	53.75	0.000	70.2	0.000	-0.27
Self-monitoring Outcomes of Behavior	17/6	-0.42(-0.57, -0.27)	96.67	0.000	83.4	0.000	-0.27(-0.58, 0.04)	17.69	0.003	71.7	0.08	-0.15
Feedback on Outcomes of Behavior	17/6	-0.41(-0.55, -0.27)	96.62	0.000	83.4	0.000	-0.29(-0.69, 0.12)	17.79	0.003	71.9	0.16	-0.12
Social Support (practical	4/19	-0.09(-0.33, 0.153)	9.87	0.020	69.6	0.474	-0.47(-0.61, -0.32)	97.85	0.000	81.6	0.000	0.38
Social Support (emotional)	6/17	-0.37(-0.63, -0.12)	18.65	0.002	73.2	0.005	-0.39(-0.54, -0.24)	95.82	0.000	83.3	0.000	0.02
Instruction How to Perform Behavior	**20/3**	**-0.43(-0.56, -0.30)**	**80.55**	**0.000**	**76.4**	**0.000**	**-0.08(-0.64, 0.48)**	**32.45**	**0.000**	**93.8**	**0.77**	**-0.35**
Information about Health Consequences	**13/10**	**-0.41(-0.60, -0.22)**	**70.88**	**0.000**	**83.1**	**0.000**	**0.36(-0.55, -0.17)**	**42.72**	**0.000**	**78.9**	**0.000**	**-0.77**
Salience of Consequences	6/17	-0.29(-0.64, 0.06)	50.42	0.000	90.1	0.1672	-0.41(-0.55, -0.28)	63.49	0.000	74.8	0.04	0.12
Prompts/Cues	13/10	-0.39(-0.58, -0.20)	96.81	0.000	87.6	0.000	-0.36(-0.50, -0.22)	17.26	0.045	47.9	0.000	-0.03
Social reward	2/21	0.08(-0.77, 0.93)	3.52	0.061	71.6	0.847	-0.42 (-0.55, -0.29)	102	0.000	80.4	0.000	0.50
Adding Objects to the Environment	4/19	-0.41 (-0.54, -0.27)	96.75	0.000	81.4	0.000	-0.28(-0.77, 0.21)	17.62	0.001	83	0.26	-0.13

Supplementary Table S3: Subgroup analyses of intervention features on HbA1c-levels.

Intervention features		Number of intervention arms	HbA1c reduction (95%CI)	Q	P	I^2%	Test for effect size
Delivery mode	Text message	3	-0.52(-1.04, 0.004)	7.54	0.023	73.5	0.052
	Telehealth(communication with provider via telephone or video)	5	-0.21(-0.65, 0.22)	31.58	0.000	87.3	0.338
	PDA, tablet, computer and/or smartphone delivered web-based interventions	15	-0.41 (-0.55, -0.27)	68.53	0.000	79.6	0.000
	Difference: Text message versus web-based interventions		-0.31				
	Difference: Text message versus Telehealth		-0.11				
Use of theory to guide intervention designs	Yes	10	-0.20(-0.33, -0.07)	14.49	0.106	37.9	0.003
	No	13	-0.52(-0.71, -0.33)	93.44	0.000	87.2	0.000
	Difference		0.32				
Tailoring	Yes	19	-0.36(-0.49, -0.22)	97.89	0.000	81.6	0.000
	No	4	-0.56(-0.87, -0.24)	7.6	0.055	60.5	0.001
	Difference		0.20				
Baseline HbA1c	> 7.5%	10	-0.46(-0.70, -0.21)	45.88	0.000	80.4	0.000
	> 7.0%	13	-0.33 (-0.48, -0.19)	54.18	0.000	77.8	0.000
	Difference		-0.12				

Supplementary Table S4: GRADE evidence profile exported from GRADEpro online tool

Author(s): Mihiretu M Kebede, Hajo Zeeb, Manuela Peters, Thomas L Heise, Claudia Pischke

Date: October 20/2017

Question: **Question**: Digital interventions compared to usual care for improving glycaemic control in patients with poorly controlled TYPE 2 DIABETES

Setting: Clinical

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Digital interventions	Usual care	Relative (95% CI)	Absolute (95% CI)		
Glycated haemoglobin level(HbA1c) (follow up: range 3 months to 12 months; assessed with: Mean difference)												
21	randomised trials	not serious [a]	serious [b]	not serious [c]	not serious [d]	none	1804	1632	-	MD **0.39 % lower** (0.51 lower to 0.26 lower)	⊕⊕⊕◯ MODERATE	CRITICAL
Serious adverse events (follow up: range 3 months to 12 months; assessed with: Number of adverse events)												
7	randomised trials	not serious	not serious [e]	not serious	not serious	none	0/854 (0.0%)	0/774 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Most of the studies had a “low risk of bias”. There were 11 studies having a “high risk of bias” in two dimensions of the risk of bias assessment tool. Only four studies had a "high risk of bias" in three domains of the tool. None of the included studies had a “high risk of bias” in more than three domains. Fifteen of the 21 RCTs had a "high risk of bias" in the other source of bias. For this reason, we did not downgraded this item

b. Heterogeneity remained unexplained even after several subgroup analyses

c. Interventions were delivered differently in different settings (downgraded by one level). The interventions also differed by design (text-message, web-based, video conferencing), and by intervention components

d. Most (15 of the 21) interventions had smaller sample sizes (less than 200). Four studies had relatively wider confidence intervals in the meta-analyses. We did not lower the rating for this item

e. Studies reporting on this outcome did not differ in event rates or reported any serious adverse events that could be explained by participation in the study

Supplementary Table S5: Summary of findings table exported from the GRADEpro online tool

Title: Digital interventions compared to usual care for improving glycaemic control in patients with poorly controlled type 2 diabetes

Patient or population: Poorly controlled TYPE 2 DIABETES patients

Setting: Clinical

Intervention: Digital interventions

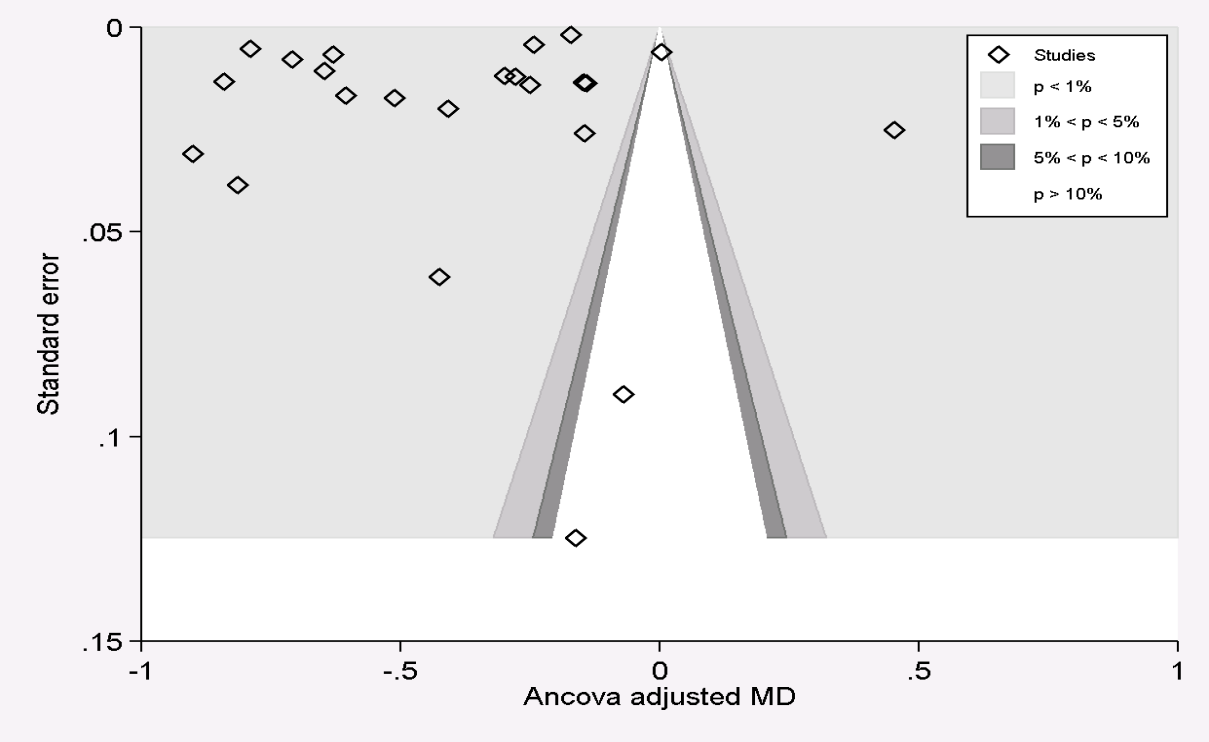
Comparison: Usual care

Outcome № of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty	What happens
		Without Digital interventions	**With Digital interventions**	**Difference**		
Glycated haemoglobin level (HbA1c) assessed with: Mean difference follow up: range 3 months to 12 months № of participants: 3436 (21 RCTs)	-	The mean glycated haemoglobin level (HbA1c) was **-0.28** %	The mean glycated haemoglobin level (HbA1c) was **-0.64** %	MD **0.39 % lower** (0.51 lower to 0.26 lower)	⨁⨁⨁◯ MODERATE [a,b,c,d]	21 out of 23 studies reported favourable effect estimates for digital interventions. However, heterogeneity was quite substantial (I^2 = 80.8%) and even remained unexplained by calculating subgroup analyses in order to investigate this issue. Interventions differed in content and delivery features.
Serious adverse events (Adverse events) assessed with: Number of adverse events follow up: range 3 months to 12 months № of participants: 1628 (7 RCTs)	not estimable	0.0%	**0.0%** (0.0 to 0.0)	**0.0% fewer** (0 fewer to 0 fewer)	⨁⨁⨁⨁ HIGH [e]	Only 7 studies reported on adverse events; "no adverse event" or "the adverse events do not differ between the control and the intervention groups". One study reported 2 deaths, but unrelated to the intervention

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

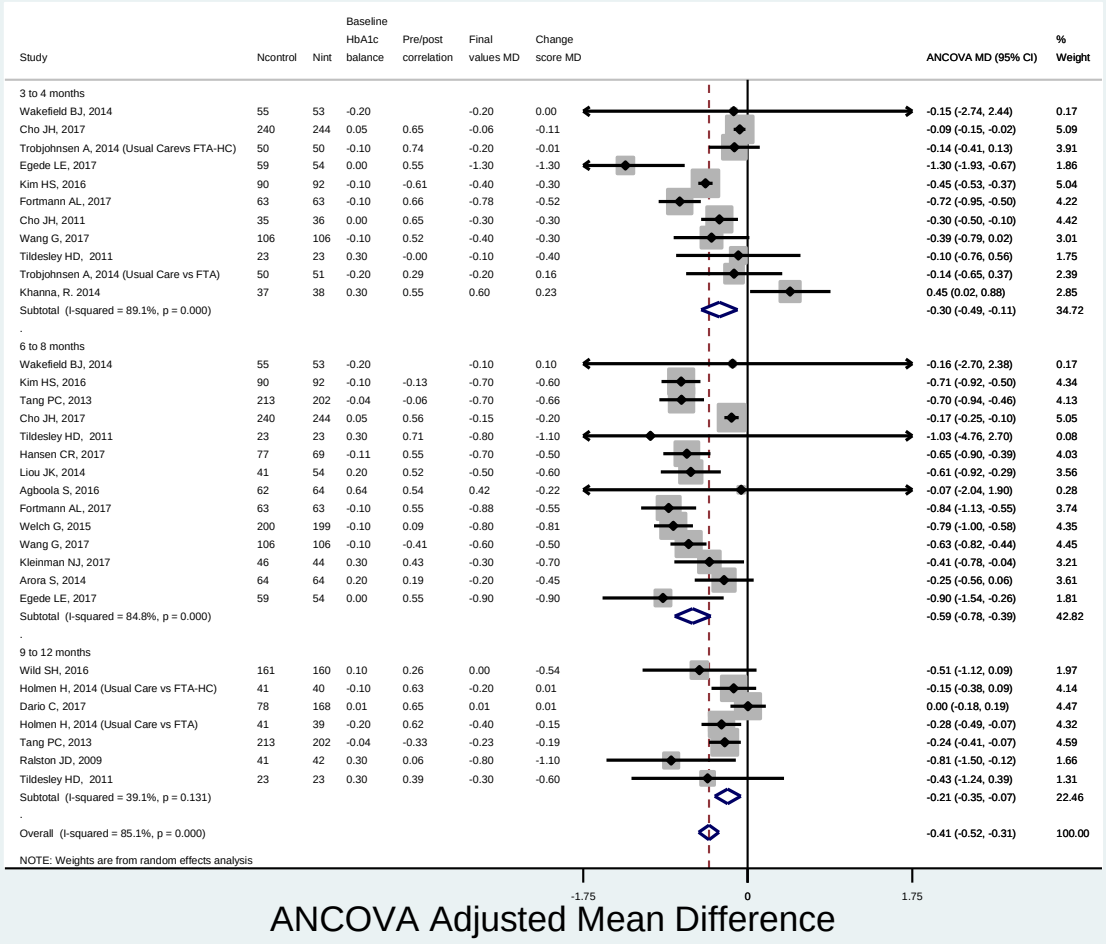
CI: Confidence interval; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

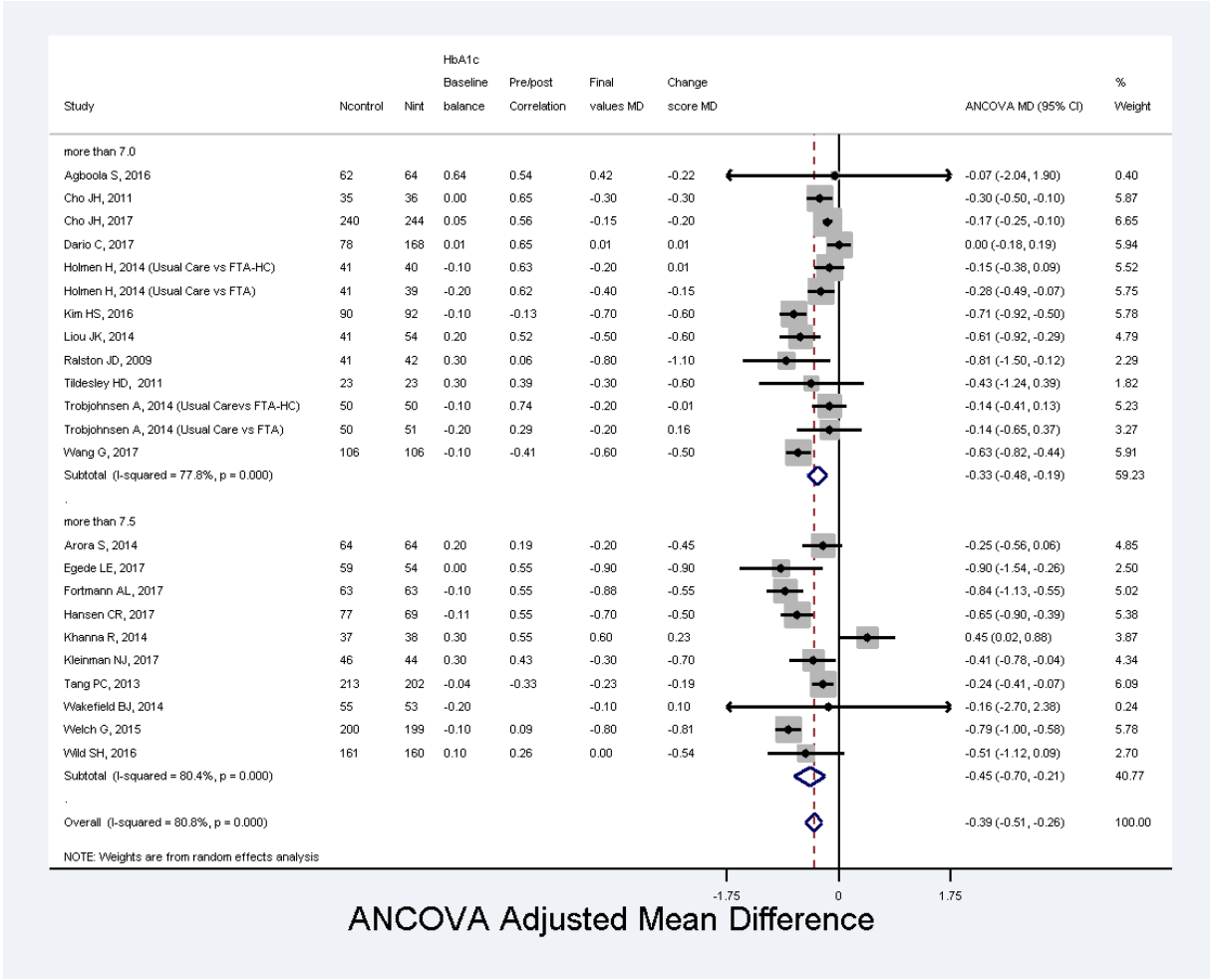


Legend: The dark grey and the white parts of the graph are the statistically non-significant regions (p-value > 0.05). Note that only one study falls on the non-significant region of the plot which suggests the probable presence of publication bias.

Supplementary Fig 1: Contour funnel plot depicting publication bias



Supplementary Figure 2: Subgroup analysis of effectiveness of digital interventions for reducing HbA1c-levels by intervention duration



Supplementary Figure 3: Subgroup analysis of effectiveness of digital interventions for reducing HbA1c-levels by baseline HbA1c-levels.