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Effect of healthcare personnel in e-health interventions on glycated haemoglobin in adults with type 2 diabetes - a systematic review

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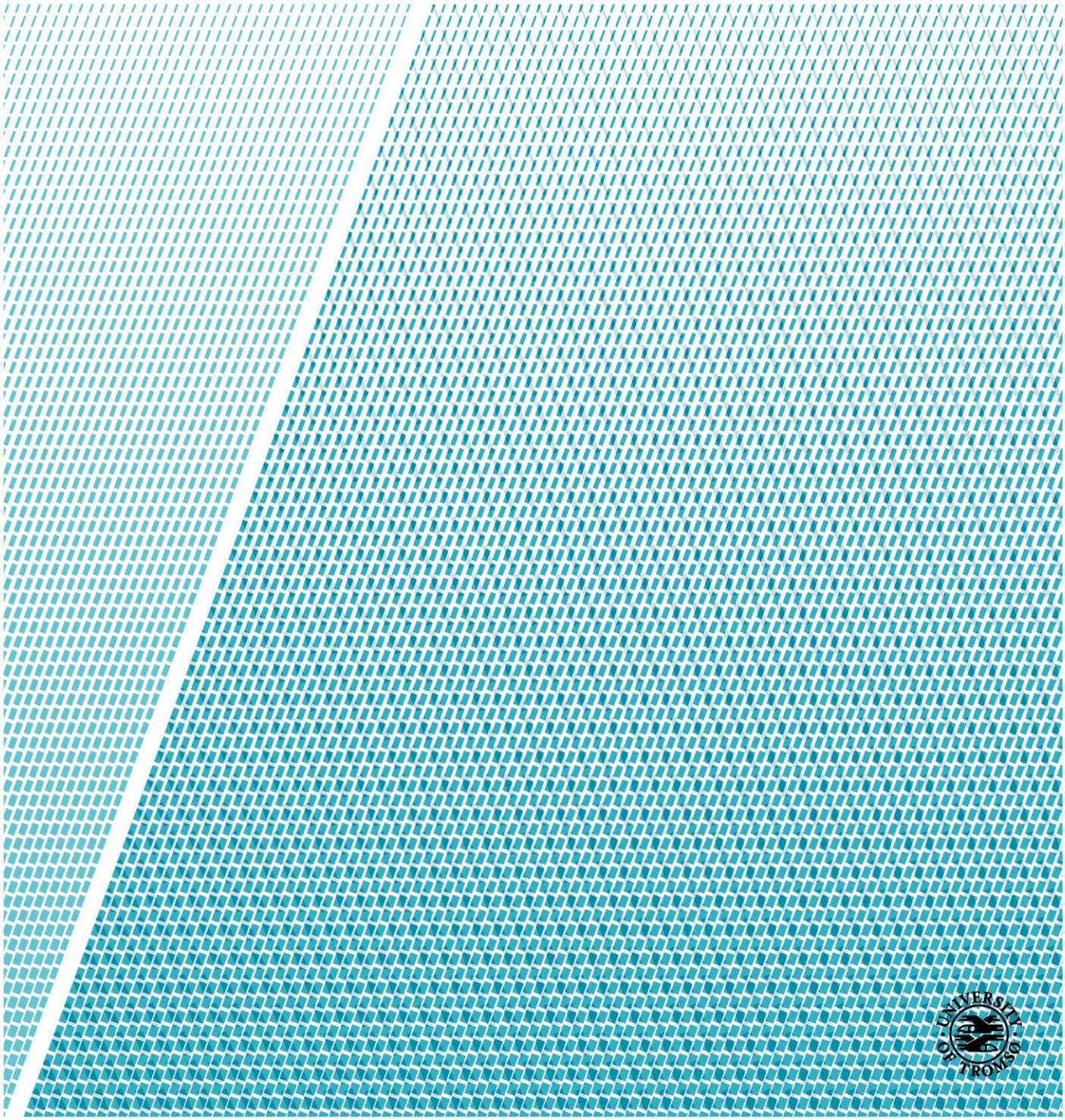

Acknowledgement

We would like to give special thanks to our supervisor Rigmor Berg for guiding and motivating us through this systematic review. We would also like to thank the librarian at University of Tromsø, Eirik Reierth for guiding us through our systematic search. Finally, we would like to thank our family and friends for their patience and support during the last year.

Description of each student's effort

Each student has contributed equally to the master thesis. Both students have put in the same amount of time and effort, and both students have been involved in conducting all sections in this systematic review.

Abstract

Background:

Diabetes mellitus has been labelled as a global epidemic by the World Health Organization, and it is emerging as one of the greatest public health challenges worldwide in the twenty-first century. Type 2 diabetes is a chronic disease that requires continuous follow-up throughout the lifespan by the healthcare system. As a medium of delivering care to those with chronic conditions e-health has attracted considerable interest. E-health allows for long term follow-up outside the primary care setting by enabling patients to better manage their disease at home. Additionally, e-health as an extension of usual care allows for interactive two-way communication between patients and healthcare personnel besides their regular consultations. For patients with diabetes, the effect of healthcare personnel involvement in e-health interventions when the comparisons also receive e-health has not yet been evaluated in a systematic review.

Objectives:

The objective is to conduct a systematic review on the question: Is there added health benefit when healthcare personnel are involved in the provision of e-health for adults with type 2 diabetes? The primary outcome is HbA1c and secondary outcomes are weight, blood pressure and low density lipoprotein.

Method:

We searched EMBASE, MEDLINE, CINAHL, reference lists of included publications and relevant systematic reviews to identify randomised controlled trials published between January 2012 and January 2019. This was supplemented with a grey literature search in

Google Scholar. Study selection, data extraction and risk of bias assessment were carried out independently by two reviewers. Due to the heterogeneity of diabetes related measurements, outcome data were synthesised narratively. GRADE was used to assess the certainty in effect estimate for each outcome.

Results:

We included five randomized controlled trials from three countries with a total of 831 participants. We had moderate to low certainty in the effect estimate for the outcomes. The narrative synthesis indicated that only one study had significant change in HbA1c and the other studies showed no evidence of relevant clinical effect. There seem to be a small but beneficial effect in weight reduction when healthcare personnel are involved. There was no significant improvement in low density lipoprotein and blood pressure when healthcare personnel were involved.

Conclusions:

This systematic review shows that providing e-health with tailored healthcare personnel feedback to patients with type 2 diabetes, does not seem to have added health benefits when the control condition also receives e-health. However, there is a need for additional high quality RCTs and subsequently systematic reviews in order to draw firm conclusions about the effect of including healthcare personnel in e-health interventions for patients with diabetes.

Abbreviations

App(s)	Application(s)
BMI	Body Mass Index
CBAs	Controlled before-after
CHW	Community health workers
CI	Confidence interval
CVD	Cardiovascular disease
E-health	Electronic health
E-mail	Electronic mail
FTA	Few Touch Application
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HbA1c	Glycated haemoglobin
HCP	Healthcare personnel
HTA	Health technology assessment
ICT	Information and communication technology
ITT	Intend to treat analysis
lb	Pounds
LDL	Low density lipids
MD	Mean difference
MeSH	Medical Subject Headings
M-health	Mobile health
mg/dL	Milligrams per deciliter
mmHg	Millimetres of mercury
N/A	Not applicable
N-RCT	Non-randomized controlled trials
PICO	population (P), intervention (I), comparison (C), outcome (O)

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trials
SD	Standard deviation
SMBG	Self-measured blood glucose
SPSS	IBM SPSS software
T2DM	Type 2 diabetes mellitus
UiT	University of Tromsø
U.S	United States
USD	United States Dollar
WHO	World health organization

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Background

Description of the condition

Diabetes mellitus has been labelled as a global epidemic by the World Health Organization (WHO) (1), and it is emerging as one of the greatest public health challenges worldwide in the twenty-first century (2). Type 2 diabetes accounts for around 90% of all diabetes cases (3), while type 1 diabetes accounts for the majority of the remaining 10%. The prevalence of type 2 diabetes in adults is rapidly increasing worldwide and has nearly doubled from 1980 to 2014. In 2014, it was estimated that 422 million people were affected by the disease (4), and the global prevalence of diabetes is projected to increase to 592 million affected individuals by 2035 (5).

Diabetes type 2 is a chronic disease caused by a deficiency in the production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. Insulin is not able to transfer and store glucose in the cells as normal. This leads to increased concentrations of glucose in the blood. If left untreated, this could damage the blood vessels and nerves in the body, and cause severe diabetes complications (3). Diabetes is a major cause of myocardial infarctions, strokes, blindness, kidney failure and amputations. The consequences of these complications can for many people be fatal. WHO estimates that diabetes was the seventh leading cause of death in 2016 (3). However, diabetes is more often listed as an associated cause of death than a direct cause. Which means that diabetes related deaths may be grossly underestimated (6). Thus, diabetes is a serious disease with high comorbidity that must be handled properly in regards to disease management in order to reduce the disease burden for the patient.

The increasing prevalence of diabetes heavily impacts the healthcare systems and individuals both in developed and developing countries and imposes a serious economic impact (1). In 2017, USD 727 billion was spent by individuals with diabetes aged 20-79 years worldwide (7). 80% of the health expenditures used on diabetes are spent on treating diabetes related complications as a result of poorly controlled diabetes. However, many of these complications are highly preventable (2).

Traditionally, type 2 diabetes occurs in middle aged adults and seniors, but is now seen in younger adults and children as a consequence of increased obesity among this age group (8). Consequently, the extent of type 2 diabetes is now making a severe impact in all age groups. Type 2 diabetes is caused by a combination of environmental factors and genetics. Previous research has shown that relatives of people with diabetes has a greater risk of developing the disease (9). Environmental factors include obesity, overeating, physical inactivity, stress and aging (10). Due to an increasing prevalence of obesity and an aging population globally, diabetes incidence is predicted to rise (11). This especially in developing countries where there is an urbanization and transition to a more westernized diet together with a sedentary lifestyle (12).

An unhealthy lifestyle contributes in a great extent to the development of diabetes type 2, and one of the key components for treatment and prevention of diabetes is adopting a healthy lifestyle (13). Since there is no cure for diabetes, it requires constant monitoring of blood glucose, adherence to the national treatment regime for diabetes and personal engagement and participation (14). In addition, self-management is found to play a vital role in minimizing the long-term complications of diabetes and improving quality of life (15). Self-management involves measuring and recording of blood glucose, physical activity, dietary regulations and

medication management.

In Norway, around 216 000 people have a diabetes type 2 diagnosis (16). This is approximately 4.1% of the population, which is lower than the European average of 10% (17). However, it is likely that there is a large number of people living with undiagnosed diabetes, therefore the extent of the disease could be underreported (1). It is common to be diagnosed with diabetes when complications start to arise. However, the onset of diabetes is often present years before the diagnosis. As a result, by the time someone is diagnosed with type 2 diabetes they have already lost 50-70% of their capacity to produce insulin (18). Thus, lowering and controlling glycated haemoglobin (HbA1c) is the most important treatment target in order to delay and reduce diabetes complications. The level of HbA1c reflects the average blood glucose level over the past 2-3 months by measuring the amount of glucose attached to haemoglobin in the red blood cells (19). According to Norwegian guidelines, the treatment target is HbA1c <7% for individuals without comorbidities and HbA1c between 7-8% for individuals with high degree of comorbidities (20).

Diabetes complications share many of the same risk factors. Therefore, one complication can worsen the other complications. E.g. many people with diabetes suffer from hypertension which in turn further increases the risk of heart disease and diabetes blindness (21). Long term observations have shown that the risk of developing cardiovascular disease is thought to be 18% per unit (%) HbA1c increase (22). In diabetes research, it is therefore common to complement HbA1c measurements with other biometrical and physiological measurements in order to assess the risk for cardiovascular disease. These measurements can include weight, blood pressure and cholesterol, such as low density lipoprotein (14).

For patients with diabetes, disease management requires daily glucose monitoring, following a medication regimen, regular physical activity, dietary adjustments and medical check-ups. The many aspects of diabetes treatment can be demanding for patients to manage. As a result, many patients will not engage in the necessary behaviours to reach appropriate glycaemic control. Previous research has shown that patients who struggle with diabetes management have poorer glycaemic control and are therefore at higher risk of developing diabetes related complications. As a result, we are in need of new ways to support patients in their diabetes management and treatment regimen (1).

Description of the intervention

Electronic health (e-health) interventions are recognized as a potentially effective platform for health delivery and delivering diabetes self-management programmes to individuals with type 2 diabetes (23). By the use of e-health it is possible to transfer health information and deliver healthcare by electronic means. This includes remote monitoring of patients, information exchange, treatment at a distance, education and self-management (24). Commonly used methods of e-health delivery include use of social media, telephone calls, text-messages, videoconferencing, e-mail, web-based resources, online portals and mobile applications.

E-health is the use of information communication technology (ICT) to exchange information between patient and healthcare personnel (HCP) (25). A large variety of terms and definitions in research are applied to define the use of ICT. When referring to the use of ICT for health, this systematic review uses the term e-health. This includes prevention, diagnosis, treatment, monitoring and management of medical conditions and diseases (26). The goal of e-health is to improve the quality, safety and efficiency within the healthcare sector (27).

The conventional outpatient care offered to diabetes patients generally occurs less than three times a year, and is found insufficient for many patients due to the lack of engagement in self-management and the occurrence of health disparities (2). Health disparities among those with diabetes is illustrated by higher prevalence, more diabetes-related complications and poorer glycaemic control seen among ethnic minorities. The same is seen among residents in rural areas and those with low education and income. These groups represents medically underserved subgroups of the population in the need of more suitable treatment options (28).

Type 2 diabetes as a chronic disease needs a long-term approach to healthcare, which implies integration of healthcare services outside of the primary care setting (29). E-health allows for long term follow-up outside the primary care setting by enabling patients to better manage their disease at home (5). E-health has the advantage that it could be designed to allow patients to tailor the solution according to their own needs (30). This allows for patient participation in the intervention, which research previous has shown to improve adherence and health outcomes (15).

Different regions use e-health with various practises, mostly prompted by the technological development within these areas. Remote patient monitoring enables monitoring of patients outside of their conventional clinical setting, e.g. delivering patient data to HCP by electronic means. The use of remote patient monitoring is a common practice being used today. However, there is a trend towards increasing the self-management for patients with diabetes through the use of e-health. This by increasing the individual's ability to better manage symptoms, treatment and lifestyle changes in the comfort of their own home. This development is prominent in the North-European countries (31).

E-health has the potential to reduce barriers such as geographical distances and access to healthcare services for the patient. However, e-health still has many underlying challenges. For the patients, some of the most pressing challenges is usability issues that comes from poorly designed software, technical difficulties or usability errors made by the patients themselves. This together with safety concerns when patient share personal data through a e-health unit (32,33).

How the intervention might work

It has been debated whether we need a more comprehensive e-health intervention offering more than delivery of patient data to HCP, in order to improve glycaemic control. The reason is that many patients lack proper education about the disease process and the necessary skill-set to handle it (34). Implementing education about diabetes and diabetes management could therefore be vital in order for e-health to be successful.

E-health has the potential to be an important contributor to the existing healthcare sector. It is important to note that e-health interventions are not a substitute for functioning healthcare systems, but is rather intended to complement and enhance healthcare systems. This by increasing the amount of information exchange and monitoring of patients, as an extension of usual care in the healthcare sector (33).

E-health as an extension of usual care allows for interactive two-way communication between patients and HCP besides their regular consultations (5). This interactive communication can be concurrent (e.g. real-time communication by telephone consultation or videoconferencing) or non-concurrent (e.g. feedback delivered by email or through an online portal) (15). By allowing for communication in e-health interventions, patients can reach out to the HCP with

their question of concern in the moment that it worries them. For HCP it will be possible to deliver tailored feedback and self-management support to a large number of diabetes patients simultaneously when the HCP find it convenient (15). This makes health services more available for chronically ill patients and maximizes the efficiency among HCP. Thus, e-health has the potential of decreasing the HCP shortage, which worldwide is predicted to be 12.9 million healthcare workers by 2035 (35).

There is expected a substantial increase in the development of mobile applications and online resources for diabetes patients in the future (36). Today, searching online for tools to achieve better diabetes management will give patients a lot of options, without the patient knowing the risk or benefits of its usage. We do not have enough knowledge about the effect of the different e-health interventions being used today (2). There is a need for health authorities to develop and implement guidelines for the use and evaluations of e-health resources in order to make it safe and beneficial for patients (37).

Why it is important to do this review

Compared to usual care, e-health interventions with and without HCP has shown to have a significant and clinical impact on HbA1c for patients with diabetes (2). For diabetic patients, the effect of HCP involvement in e-health interventions when the comparisons also receive e-health has not yet been evaluated in a systematic review. Therefore, the added effect of HCP in e-health interventions for patients with diabetes are still unknown. This knowledge gap is important to investigate, as this could affect the utilization of e-health for patients with type 2 diabetes.

For policymakers to propose future healthcare services, being able to distinguish between the effectiveness of e-health with and without HCP is important. Policy makers need to know if including HCP-patient communication in e-health interventions could optimize patient treatment, and further increase health benefits when patients already receives e-health. If there are no added health benefits when including HCP in e-health, this could save decision makers and stakeholders from unnecessary use of resources and reduce the workload for HCP.

This systematic review aims to investigate added health benefits when healthcare personnel are involved in the provision of e-health for adults with type 2 diabetes. This when the control condition also receives e-health. HCP involvement in this review refers to HCP and patient communication in e-health solutions. The primary outcome is change in HbA1c. Since a large number of people affected by diabetes experiences cardiovascular complications, weight, blood pressure and LDL are included as secondary outcomes to assess if HCP in e-health can reduce these risk factors involved in type 2 diabetes.

Method

The systematic review followed a pre-specified protocol (not published but available upon request), the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (38) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and checklist (39). The PRISMA checklist is presented in appendix 1. We included research that reported on HbA1c outcome associated with healthcare personnel involvement in e-health. Specifically, we included randomized controlled trials with type 2 diabetes adults who had been subjected to any type of e-health intervention with healthcare personnel involvement. Eligible comparisons were adults with type 2 diabetes who received e-health interventions without healthcare personnel involvement. This systematic review had no specific funding and no funders were involved in any aspect of the review.

Objective

The objective was to conduct a systematic review on the question: Is there added health benefit when healthcare personnel are involved in the provision of e-health for adults with type 2 diabetes?

Literature search

We searched MEDLINE, EMBASE and CINAHL in January 2019 for studies meeting our inclusion criteria. The search strategies are presented in appendix 2. In addition, we searched i) google scholar, ii) the reference lists of 12 relevant systematic reviews identified in the electronic searches, iii) the reference lists of included studies in this systematic review. Due to lack of resources and rapid development of e-health solutions, we limited our search to English publications between January 2012 to January 2019. We note that an added search

revealed no eligible studies published between 2009 and 2012 in the databases mentioned above.

A search specialist at the University of Tromsø (UiT), Eirik Reierth, advised us on how to search databases. However, we developed the search strategies and performed the electronic searches independently. To investigate our objective, we divided our search into two categories; i) related to our population, diabetes type 2, ii) related to use of e-health interventions. However, given the extent of e-health we used a variety of search terms in order to obtain all relevant studies, see appendix 2.

There is a large interdisciplinary range of healthcare personnel involved in e-health interventions and therefore it was not justifiable to include HCP in the search strategy. We manually screened for HCP and primary outcomes in accordance with our inclusion criteria.

Inclusion and exclusion criteria

Study design: We included randomized controlled trials (RCT). In the event that few RCTs met the inclusion criteria we would include also non-randomized controlled trials (N-RCTs) and controlled before-after studies (CBAs). Protocols were excluded.

Study setting: We enforced no restrictions on type of settings in which the interventions took place: both primary care, hospital care, and outpatient settings were allowed. Studies could be carried out in low-, middle-, and high-income countries.

Population: We included adults (18 years and above) with type 2 diabetes mellitus, using any recognized diagnostic criteria. All levels of HbA1c were eligible. Studies where 75% of the participants had diabetes type 2 were allowed. We excluded participants with gestational diabetes, and people living in institutions.

Intervention: Interventions were use of e-health with healthcare personnel involvement. Healthcare personnel was any healthcare worker who had received training on diabetes. HCP involvement was either individual follow-up on diabetes, diabetes and lifestyle education or tailored motivational support to achieve treatment target. Individually tailored feedback on blood glucose measurement or health behaviour, or answering general question from the patient regarding diabetes was also eligible for inclusion. Communication methods could be phone calls, video conferencing, text messaging, email, mobile applications or internet and web-based resources. Feedback from HCP to patients was at least once a month in order to ensure a minimum amount of contact. In order to detect a change in HbA1c, duration of intervention was of at least three months. There was no limitation with respect to follow-up.

Comparison: The comparison condition could be any use of e-health services without healthcare personnel involvement.

Outcome: The primary outcome was change in HbA1c, or fasting blood glucose if HbA1c was not available. In order to detect diabetes comorbidities, we included change in weight, blood pressure, and LDL as secondary outcomes whenever reported in the included studies.

Article selection

We imported the retrieved references into EndNote 9.1 and checked for and subsequently removed duplicates. Identified records were first screened based on titles and abstracts in accordance with the inclusion criteria. The two authors screened titles and abstracts independently of each other, and publications found to be relevant were promoted to full text reading. A pre-designed form was used to assess eligibility of the studies promoted to full text reading, see appendix 3. Disagreements between the authors were resolved by re-examination of the study and mutual discussion. In case of no consensus we consulted our supervisor (Rigmor Berg) for an objective third party opinion.

When key-information to decide upon inclusion was lacking, we contacted the study authors by email. A reminder was sent within two weeks if the author did not reply to the initial email. We contacted five study authors for further information, and four authors answered our request (40–43). Wongrochananan et al. (44) did not reply to our emails and Onoue et al. (43) was a protocol where our request for the full text article was declined. Of those contacted, by email Lutes et al. (41) was the only study that met the inclusion criteria.

Data extraction and management

We extracted study data onto a pre-designed data collection form made by the authors, see appendix 4. One author collected data while the other author checked for accuracy. After the data were collected from the first three studies the authors changed tasks. Thus, the author who collected data then checked for accuracy and vice versa. Any disagreement between the authors was resolved by discussion and re-examination of the study until agreement was achieved. When key-information was lacking we contacted the study authors by email. A

reminder was sent within two weeks if the author did not reply to the initial email. We contacted two authors regarding data imputation (41,45). Both study authors sent us the requested information.

The following characteristics were retrieved from the included studies: i) Study characteristics: year, author, study setting, and aim, ii) Study methods: inclusion, exclusion and withdrawals from study, iii) Population description: number of participants, age, sex, socio economic status, ethnicity, and mean HbA1c at inclusion, iv) Information regarding the intervention: description, duration, frequency, HCP information, and medium of delivery, v) Information regarding the comparison: description, duration, frequency, and medium of delivery, vi) Primary outcome and data analysis: change in HbA1c, timepoints measure, and imputation of missing data, vii) Secondary outcomes: change in weight, blood pressure, and low density lipoprotein. A complete description is presented in appendix 5. In addition, we created descriptive tables, which we presented in the result section when applicable.

Risk of bias assessment

We assessed the methodological quality of the included studies with the Cochrane tool for assessing risk of bias (46). Review manager 5.3 was used to make a risk of bias assessment table. Bias was assessed as low, unclear or high in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We used the description regarding judgement for the low, unclear and high category, from the Cochrane tool for assessing risk of bias (46). Assessment of risk of bias of individual studies was done at the study level as all outcomes were biological or physiological measurements

and therefore considered to have similar risk of bias.

Similar to the data extraction, one author did the risk of bias assessment while the other author checked for accuracy. After risk of bias was done on the first three studies the authors changed tasks. Any disagreement between the authors was resolved by discussion and re-examination until agreement was achieved.

Lutes et al. (41) and Torbjørnsen et al. (45) had supplementary material where allocation, randomization, and blinding were described. We used the supplementary material in the assessment of methodological quality for these two studies presented in Cummings et al. (47) and Ribu et al. (48).

Data analysis

Continuous outcomes were expressed with mean difference (MD) and standard deviation (SD). No outcomes were presented as dichotomous. We planned to pool sufficiently similar outcomes. Thus, we examined the similarity and differences among the studies with respect to the characteristics of the population, intervention, comparison, and outcome. We planned to do a meta-analysis using inverse variance and a random effects model. This is because we considered that the included studies each would estimate a true effect, which derives from the same family of effects. I.e., that there are several possible real values for the treatment effect (depending on dose, duration, etc). We planned to pool data using the Review Manager 5.3 and examine heterogeneity. In accordance with the Cochrane Handbook for Systematic Reviews of Interventions, we specified that high heterogeneity was I^2 higher than 50% and p-value for the Chi^2 statistic of less than 0.05 was considered to be statistically significant. However, our inspection of the similarities and differences among the studies revealed that

there was considerable study specific heterogeneity among the studies. As a check, we conducted a meta-analysis of the main outcome, which showed an I^2 of 72%. Thus, we considered that heterogeneity was too high to justify conducting meta-analyses. We therefore created tables for each outcome specifying differences in mean change from baseline to closeout within all groups. We also presented differences in mean change between groups at closeout when applicable. Additionally, we created forest plots of each outcome to graphically display the information for each individual study. We did not include the average pooled effect estimate due to high heterogeneity.

GRADE

We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of the body of evidence. GRADE is a transparent and systematic approach used to assess the extent to which we can have certainty in the effect estimates and whether further research is likely to change these. Because we only had RCTs the evidence was assessed by the following criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias. Had we included observational studies, we could have used also large magnitude of effect, dose response, and effect of all plausible confounding factors to assess the evidence. Rating the certainty of evidence is from high, moderate, low to very low (49). A complete description of each rating is presented in table 1.

Table 1: Definitions for ratings of the certainty of the evidence

Ratings	**Definitions**
High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different is low.
Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different is moderate.
Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different (a large enough difference that it might have an effect on a decision) is high.
Very Low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different (a large enough difference that it might have an effect on a decision) is very high.

Results

Description of the search results

A total of 1998 references was obtained by electronic search in MEDLINE (487), EMBASE (1066) and CINAHL (445). We removed 772 duplicates in EndNote X9. In addition, we found 653 unique references in an advanced search in Google Scholar (figure 1). Thus, we assessed a total of 1879 references by title and abstract screening. We promoted 24 publications to full text reading according to the inclusion criteria. One ongoing trial was identified (43). Email correspondence with the author revealed that the trial is about to be published, but access to the article was not obtained. Of those 24 publications promoted to full text screening, four studies had insufficient information to decide if the study met the inclusion criteria (40–42,44). We emailed all the study authors, three of the study authors sent us sufficient information to decide upon inclusion. Of those, only Lutes et al. (41) met the inclusion criteria. Wongrochananan et al. (44) did not answer our email, and was therefore excluded since the available data were insufficient to allow inclusion. We excluded 19 full text assessed articles. Reason for exclusion of these 19 studies is listed in appendix 6. In total, five RCTs met the inclusion criteria and were included in the review (41,45,50–52).

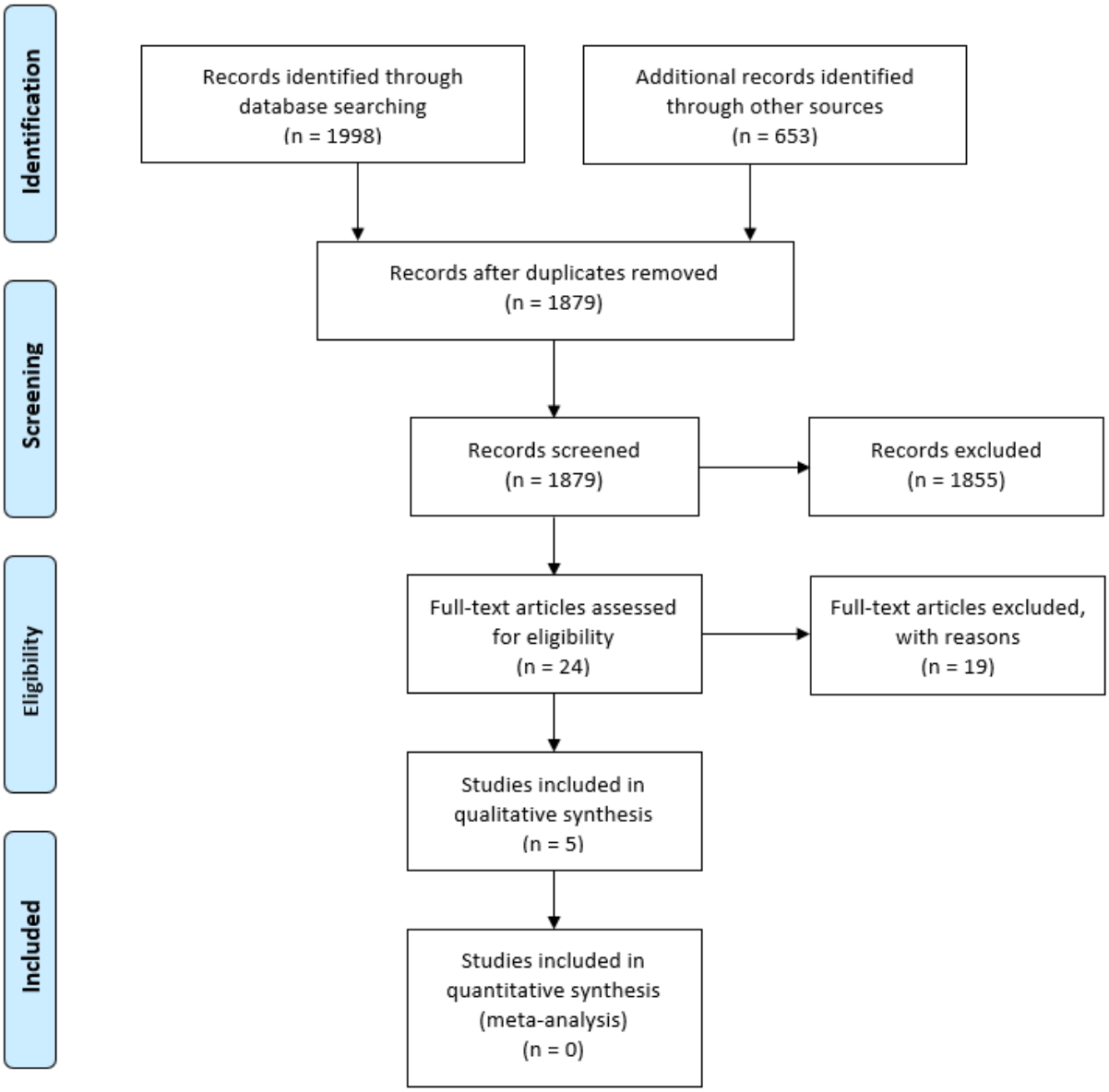

Figure 1: PRISMA flow diagram of literature review

Description of the included studies

The included studies were published between 2012 and 2017. All studies are RCTs. They included a total of 831 participants. Three RCTs were conducted in North America (41,50,52) and two RCTs in Northern Europe (45,51). A brief description of included studies is presented in table 2, and the following section gives further details of the included studies.

Table 2: Brief description of the included studies (N=5)

Author, year	Population	Intervention	Comparison	Outcome
Agboola et al., 2016	126 T2DM participants from USA	Text message intervention with daily interaction with HCP	Web portal	HbA1c and weight
Kempf et al., 2017	202 T2DM participants from Germany	Telephone based intervention. Weekly interaction with HCP	Online portal	HbA1c, weight, blood pressure and LDL
Lutes et al., 2017	200 T2DM participants from USA	Telephone based intervention. Monthly interaction with HCP	Educational material by email	HbA1c, blood pressure and weight
McMahon et al., 2012	152 T2DM participants from USA	Online care management application and telephone-based intervention. Biweekly interaction with HCP	diabetes education website	HbA1c, Blood pressure, weight, and LDL

Torbjørnsen et al., 2014	151 T2DM participants from Norway	Mobile application with health counselling. Monthly interaction with HCP	Mobile application	HbA1c

Explanation: T2DM= Type 2 Diabetes Mellitus. HCP= Healthcare personnel. LDL= Low Density Lipoprotein.

Population

All of the included studies had participants with type 2 diabetes. The population in the included studies were middle aged (ranging from 51.5 to 60.2 years), obese (BMI ranging from 31.7-37.7) with poorly regulated diabetes (mean baseline HbA1c ranging from 8.2% to 9.9%).

There was an equal gender distribution in three of the studies (45,50,51). Lutes et al. (41) had an all-female population and McMahon et al. (52) had a 95% male population. There were large discrepancies in the participants` socio economic status among the studies. Two of the studies conducted in North America had a low-income ethnic population (41,50). Further descriptions of the populations are presented in table 3.

Table 3: *Description of the population in the included studies*

Author, year	Population
Agboola et al., 2016	N=126 (64/62) T2DM participants from Boston, USA. Mean age: 51.5 (18-? years), 48.4 % male, 51.6% female. Baseline mean HbA1c 8.7%. High proportion Hispanic, low income population. Obese population, BMI unknown.
Kempf et al., 2017	N=202 (102/100) T2DM participants from Dusseldorf, Germany. Mean age: 59.5 (25-79 years). 54% male, 46% female, baseline mean HbA1c 8.3%. Mean BMI 36.1.
Lutes et al., 2017	N=200 (100/100) T2DM participants from south eastern USA. Mean age: 53.5 (19-75 years). Female 100%. Baseline mean HbA1c. 9.1%. Mean BMI 37.7. Poor African American women.
McMahon et al., 2012	N=152 (51 & 51/ 50)[1] T2DM participants from Boston, USA. Mean age: 60.2 (25-? years) 94.7% male, 5.3% female. Mean baseline HbA1c 9.9 %. Mean BMI 34.1. 90% had completed high school.
Torbjørnsen et al., 2014	N=151 (50 / 51 & 50)[2] T2DM participants from Northern and South-eastern parts of Norway. 57.9% male, 42.1% female. Mean age 57.3 (18-? years) mean baseline Hba1c 8.2%. Mean BMI 31.7.

Explanation: T2DM = Type 2 Diabetes Mellitus. [1]McMahon et al., 2012 had three study arms (two control conditions). [2]Torbjørnsen et al., 2014 had three study arms (two intervention conditions).

Intervention

All of the included studies had an intervention that required use of a telephone. Four RCTs used telephone calls as the main communication channel (41,45,51,52). Agboola et al. (50) differed from the other studies, using a text-message based communication system. In addition to the telephone call intervention, McMahon et al. (52) also had an online communication intervention.

The interventions also differed by the diabetes incentives provided. All of the included studies made use of glucometers. The participants in Agboola et al. (50), Kempf et al. (51), and Lutes et al. (41) received pedometers for daily step count measurements. The participants in Kempf et al. (51) and Lutes et al. (41) also received a weight scale. McMahon et al. (52) was the only study that gave the participants blood pressure monitors.

In the four telephone call interventions (41,45,51,52) and in the SMS intervention (50), healthcare personnel had some educational or informative purpose with the telephone contact. However, the topics in each intervention varied. All telephone calls included a review of monitored data from different diabetes incentives and diabetes related information.

Type of healthcare personnel and their diabetes related experience varied in the included studies. Four of the studies (45,50–52) had licensed healthcare personnel while Lutes et al. (41) had community workers who received training from the study team. In Kempf et al. (51) the HCP was trained diabetes coaches, however their occupational background is not mentioned in the study. Torbjørnsen et al. (45) used a specialist diabetes nurse, while McMahon et al. (52) used a nurse or pharmacist. In Agboola et al. (50) premade text messages were made by an interdisciplinary team with nurses, physicians, behavioural

psychologist, social workers, health educators, and coaches.

The length of the intervention (dose) varied from 3 months in Kempf et al. (51) to 12 months in Lutes et al. (41) and McMahon (52). Torbjørnsen et al. (45) and Agboola et al. (50) had 4 months and 6 months intervention length, respectively. The frequency of the communication between healthcare personnel and participants varied from twice a day in Agboola et.al (50) to once a month for Torbjørnsen et al. (45). Kempf et al. (51) had weekly calls, McMahon et al. (52) biweekly calls and Lutes et al. (41) had 16 phone calls during a 12-month period. A full description of the interventions is presented in table 4.

Table 4: Description of the intervention in the included studies

Author, year	Content	Frequency	Delivery
Agboola et al., 2016	Tailored text messages. Included information about physical activity goal, education, motivation/self-efficacy, support and health assessment. Participants provided daily step counts captured by pedometer.	Twice a day for 6 months	Premade text messages made by an interdisciplinary team

Kempf et al., 2017	Care calls. Included information about type 2 diabetes, medications, healthy diets, physical activity and lifestyle changes. The participants` measured data were discussed.	Weekly calls. Daily glucose, step and weight monitoring for 3 months	Trained diabetes coaches
Lutes et al., 2017	Educational telephone calls about self-management and lifestyle behaviour and reviewing monitored behaviour given by pedometer, weight scale and glucose meter.	16 phone calls for 12 months	Trained community healthcare workers
McMahon et al., 2012	1: Telephone based care management, monitoring glucose and blood pressure and lifestyle modification coaching. 2. Online care management application with glucose and blood pressure data. Secure	Biweekly communication with healthcare personnel for 12 months	Practice nurse or pharmacist

	message system allowed communication with HCP.		
Torbjørnsen et al., 2014	FTA diary with telephone coaching. The FTA includes: blood glucose data, food habits, physical activity, personal goal setting and general diabetes look-up system.	Daily blood glucose measurements and monthly telephone coaching for 4 months	special diabetes nurse

Explanation: HCP= Healthcare personnel FTA = Few Touch Application.

Comparison

Three of the studies had educational interventions for the control group. The medium used to deliver these interventions varied. McMahon et al. (52) used a website with possibilities for peer support to deliver diabetes education and Lutes et al. (41) sent education material by email. Torbjørnsen et al. (45) provided diabetes information through a mobile application. Agboola et al. (50) and Kempf et al. (51) used a web portal for the control group where the participants could upload measurement data from the diabetes measurement devices. The purpose was to monitor progression. In addition, Kempf et al. (51) also received a self-management guide on how to use the diabetes incentives. All the included studies used some sort of diabetes incentives. An unknown number of participants in the control group in Lutes et al. (41) received pedometers. This information was obtained via email communication with the study author. The study authors did not address how this might have affected the study

outcomes. A detailed description of the comparisons is presented in table 5.

Table 5: Description of the comparison in the included studies

Author, year	Content	Frequency
Agboola et al., 2016	Pedometer data is uploaded to a web portal.	At least every third day for 6 months
Kempf et al., 2017	Personalized online portal where step counts and weight scale results were automatically uploaded.	Daily measurements for 3 months
Lutes et al., 2017	Educational material was emailed, and pedometers to track physical activity were given to an unknown number of controls.	16 emails were sent during 12 months
McMahon et al., 2012	Diabetes educational website with possibilities for peer support.	Number of website encounters were collected every three months during a 12 months period
Torbjørnsen et al., 2014	1. FTA diary. The app includes: blood glucose data, food habits, physical activity, personal goal setting and general diabetes look-up system.	FTA: Daily blood glucose measurements for 4 months

	2. Usual care only.	

Explanation: FTA = Few Touch Application.

Outcomes

Length of intervention from baseline to end of the intervention (closeout), varied from three to twelve months among the included studies. All studies did a within group comparison from baseline to closeout reporting a mean difference change score with standard deviation. All studies did a between group comparison for the primary outcome (HbA1c), however not all of the included studies did between group measurements for the secondary outcomes (weight, blood pressure and LDL). The studies that reported between-group measurements reported difference in change by a mean difference score and a p-value, without reporting standard deviation. The included studies reported confidence intervals (CI) in various degree. Full description of each outcome is presented in table 6-9.

All five included studies had HbA1c measurements at baseline and closeout, measuring HbA1c in %. All studies did a between group comparison for HbA1c. A complete description of the HbA1c outcome is presented in table 6.

Four studies reported on weight (41,50–52). Two studies reported on weight in kilograms, and two studies reported on weight in pounds (lb). We converted lb into kilograms using

statistical software online. Three of the studies reported a between group difference in weight change. A complete description of weight outcome is presented in table 7.

Three studies reported on diastolic and systolic blood pressure in mmHg (41,51,52). Two studies did a between group comparison reporting mean difference in change score and p-value, for diastolic and systolic separately. A complete description of the blood pressure outcome is presented in table 8.

Two studies reported on low density lipoprotein in mg/dL (51,52). None of the studies did a between group comparison on LDL. A complete description of the LDL outcome is presented in table 9.

Risk of bias in the included studies

We did a risk of bias assessment for the included RCTs using the Cochrane risk of bias tool (46). Bias for each domain was assessed as high, low or unclear. The risk of bias summary of the included studies is presented in figure 2. A detailed description of risk of bias for each study is presented in appendix 7.

Sequence generation (selection bias)

All studies had an adequate random sequence generation. Agboola et al. (50), Lutes et al. (41) and Torbjørnsen et al. (45) used computer generated block randomisation, while Kempf et al. (51) and McMahon et al. (52) used an electronically generated random number list.

Allocation concealment (selection bias)

In two of the studies, the allocation sequence was adequately concealed from the person allocating participants to groups. In Kempf et al. (51) each participant was assigned a closed envelope with group assignment through their study identification number, while Agboola et al. (50) used a third-party person not involved in the study to allocate treatment assignment. Lutes et al. (41), McMahon et al. (52) and Torbjørnsen et al. (45) did not provide information about allocation concealment, thus the risk of bias is unclear.

Blinding of participants and personnel (performance bias)

Four of the studies (41,45,50,52) had no blinding of participants and personnel. In Kempf et al. (51) the risk of bias is unclear due to insufficient information about blinding. However, due to the objective outcome measurements, we believe that lack of blinding does not impose high risk of performance bias in the included studies.

Blinding of outcome assessor (detection bias)

Two of the studies had low risk of detection bias. In Kempf et al. (51) and Lutes et al.(41) the outcome assessor was blinded to participant assignment to the treatment arms. The general practitioner who collected the outcome data in Agboola et al. (50) and Torbjørnsen et al. (45) was not blinded to the outcome assessment, while in McMahon et al. (52) the risk of detection bias is unclear due to insufficient information about the outcome assessment. However, due to the objective nature of the outcome measurement, we believe that lack of blinding of the outcome assessor does not impose high risk of detection bias in the included studies.

Incomplete outcome data (attrition bias)

Three studies had low risk of attrition bias. There was similar attrition between the treatment groups with less than 20% in Lutes et al.(41), McMahon et al. (52) and Torbjørnsen et al. (45). However, we note that McMahon et al. (52) did not provide a description of characteristics about dropouts and if they were different from those who completed the study. Two studies had a high risk of attrition bias. Agboola et al. (50) had 46.8% attrition, which the authors state resulted in too small sample size to detect an anticipated effect. Kempf et al. (51) had a significantly lower dropout rate in the intervention group compared to the control group with 9% and 26% attrition, respectively. The overall feedback from the dropouts was that they did not perceive any benefit in glucose control, and therefore dropped out. All studies did an intent to treat analysis, where the participants were analysed in the treatment group to which they were allocated.

Selective reporting (reporting bias)

In four studies (41,45,50,51) both primary and secondary outcomes were analysed according to the pre-specified plan and reported in the result section. McMahon et al. (52) did not report HbA1c outcome measurements every third month, as pre-specified. This outcome was only reported at baseline and at the 12-month closeout and we consider the risk of reporting bias to be high.

Other biases

We found no risk of "other biases" in the included studies. For example, there were no extreme baseline imbalances between groups, and we consider there were no risk of researcher bias.

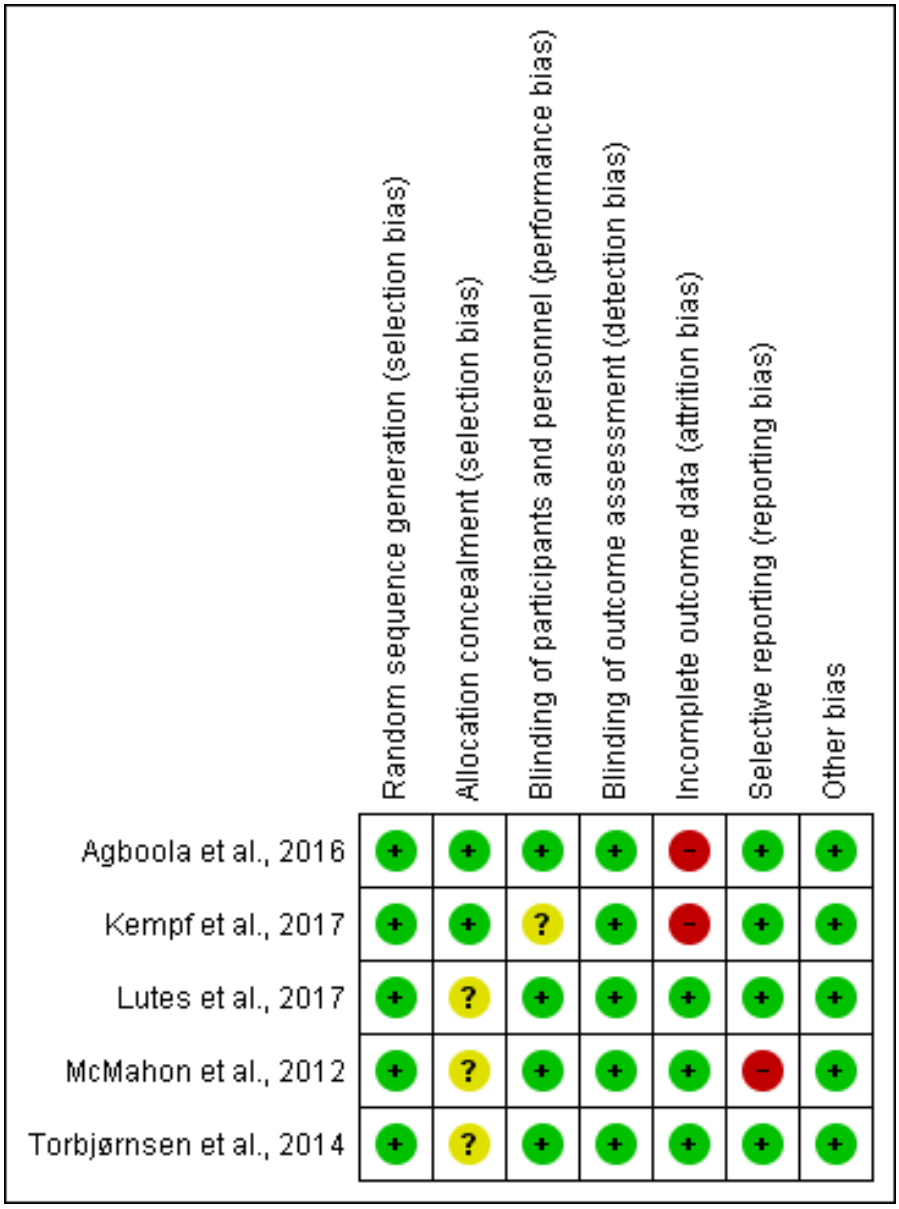

Figure 2: The risk of bias summary

Data analysis

The aim of our systematic review was to investigate if there was added health benefits when e-health intervention with HCP was compared to e-health without HCP. After assessing the studies' similarities in PICO, we made forest plots in Review manager 5.3 to check I^2 as an indication of heterogeneity for HbA1c. There is a strong heterogeneity where I^2 =72%. Based

on the heterogeneity in PICO and high I^2 we chose not to perform any meta-analyses. We cannot be certain that the observed effect in the included studies gives a true pooled effect estimate.

All studies did an intent to treat analysis, participants were analysed in the treatment group to which they were allocated. All studies have continuous outcome variables reporting mean difference. All studies except from Torbjørnsen et al. (45) reported standard deviation. Therefore, we contacted the study author and received the requested SPSS output by email. There was inconsistent reporting of statistical output among studies. Only two studies (50,51) provided confidence interval and none reported SD in the between group comparison. A p-value in Torbjørnsen et al. (45) was not obtainable between the Few Touch Application (FTA) groups with or without telephone consulting. This because they combined the p-value for the intervention group and both control conditions together.

Results

HbA1c

Kempf et al. (51) was the only study that managed to find a significant between-group change in HbA1c when HCP was involved in e-health interventions, with a difference of 0.8% in the adjusted model, $p<0.001$ (95% CI -1.1, -0.5). All of the intervention groups showed within-group improvement in HbA1c from baseline to closeout. Lutes et al. (41) was the only study where the comparison group had a higher HbA1c at closeout compared to the intervention group, without making a significant difference, $p=0.789$. A detailed description of the results for primary outcome in each study is presented in table 6.

Table 6: Description of HbA1c in the included studies

Author, year	Outcome	Intervention (%) MD, (SD)	Comparison (%) MD, (SD)	Difference in change MD, (SD) [95% CI]
Agboola et al., 2016	Change in HbA1c at 6 months.	Baseline: 9.02 (1.63) Closeout: 8.59 (1.60) Change score: - 0.43	Baseline: 8.38 (1.37) Closeout: 8.17 (1.60) Change score: -0.21	0.22 [-0.19, 0.64] p=0.29
Kempf et al., 2017	Change in HbA1c at 3 months.	Baseline: 8.4 (1.3) Closeout: 7.3 (1.1) Change score: - 1.1 (1.2) ****	Baseline: 8.2 (1.2) Closeout: 8.0 (1.3) Change score: - 0.2 (0.8)	0.9 [No CI] Adjusted model: 0.8 [-1.1, -0.5] ****

Lutes et al., 2017	Change in HbA1c at 12 months.	Baseline: 9.13 (1.79) Closeout: 8.84 (1.98) Change score: -0.29 (1.84) [8.61, 9.28]	Baseline: 9.05 (1.88) Closeout: 9.10 (2.24) Change score: +0.05 (1.61) [8.67, 9.36]	0.34 [No CI] p=0.789

McMahon et al., 2012	Change in HbA1c at 12 months.	Online care group Baseline: 9.6 (1.0) Closeout: 8.3 (1.1) Change score: -1.3 (1.4) **** Telephone care group Baseline: 9.9 (1.2) Closeout: 8.5 (1.6) Change score: -1.5 (1.6) ****	Baseline: 10.1 (1.4) Closeout: 8.4 (1.7) Change score: -1.7 (1.8) ****	Online group vs control group 0.4 [No CI] p= 0.12 Telephone group vs control group 0.2 [No CI] p=0.35

Torbjørnsen et al., 2014	Change in HbA1c at 4 months.	Baseline: 8.2 (1.1) [7.9, 8.5] Closeout: 7.8 [7.4, 8.2] Change score: -0.41 [-0.71, -0.11]	Baseline: 8.1 (1.1) [7.8, 8.4] Closeout: 7.8 [7.5, 8.0] Change score: -0.23 [-0.47, 0.01]	0.22 [No CI] p= 0.65

Explanation: ****= p< 0.0001.CI = Confidence Interval. MD = Mean Difference. SD = Standard Deviation.

Figure 3 shows that three of the studies favours e-health with HCP and one study is inconclusive. Agboola et al. (50) is the only study that favours e-health alone. The forest plot illustrates wide CI that crosses the line of no difference. Thus, the studies with no statistically significant result could possibly favour both treatments.

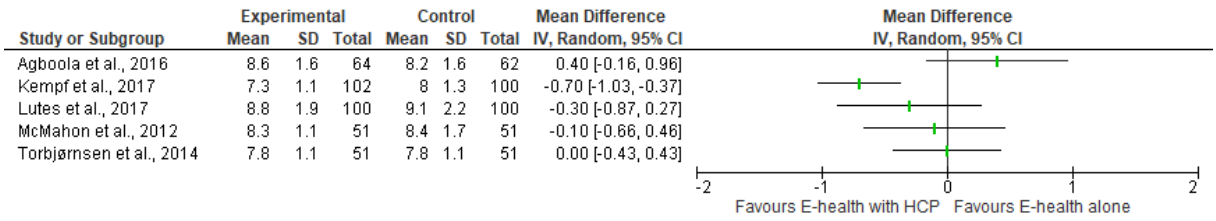

Figure 3 Forest plot, HbA1c

Weight

Four of the studies reported on weight. Two of the studies showed significant reduction in weight when HCP was involved. In Kempf et al. (51), the intervention had a significant weight reduction when compared to the control group, p=0.0001. While Lutes et al. (41) had a small, but significant greater weight loss in the intervention group, p=0.046. The two remaining studies did not detect a significant change in weight (50,52). A detailed description of the result for weight in each study is presented in table 7.

Table 7: Description of weight in the included studies

Author, year	Outcome	Intervention (Kg) MD, (SD)	Control (Kg) MD, (SD)	Difference in change MD, (SD) [95% CI]
Agboola et al., 2016	Change in weight at 6 months.	Baseline: 97.5 (25.8) Closeout: 96.2 (24.4) Change score: -1.3	Baseline: 94.4 (21.3) Closeout: 94.8 (22) Change score: +0.4	1.4 [-11.1, 8.3] p = 0.77

Kempf et al., 2017	Change in weight at 3 months.	Baseline: 104.3 (19.4) Closeout: 98.1 (19.1) **** Change score: -6.2 (4.6)	Baseline: 110.8 (21.1) Closeout: 109.8 (20.7) Change score: -1 (3.4)	5.2 [No CI] p= 0.0001
Lutes et al., 2017	Change in weight at 12 months.	Baseline: 98.1 (21.2) Closeout: 96.74 (22.1) Change score: - 1.35 (6.22)	Baseline: 104.20 (25.4) Closeout: 103.8 (25.7) Change score: -0.39 (4.6)	0.96 [No CI] p= 0.046

McMahon et al., 2012	Change in weight at 12 months.	Online care group Baseline: 105.6 (21.0) Closeout: 106.3 (21.8) Change score: +0.7 (2.8) Telephone care group Baseline: 106.7 (25.1) Closeout: 108.5 (25.3) Change score: +1.8 (6.7)	Baseline: 106.9 (23.7) Closeout: 107.7 (22.1) Change score: +0.3 (6.8)	No between group comparison
Torbjørnsen et al., 2014	Change in weight at 4 months.	N/A	N/A	N/A

Explanation: Kg = Kilogram. CI = Confidence Interval. MD = Mean Difference. SD = Standard Deviation. **** p= 0.0001. N/A = Not Applicable.

Figure 4 shows that two of the studies favours e-health with HCP involvement (41,51). Both Agboola et al. (50) and McMahon et al. (52) are inconclusive and could possibly favour both treatments.

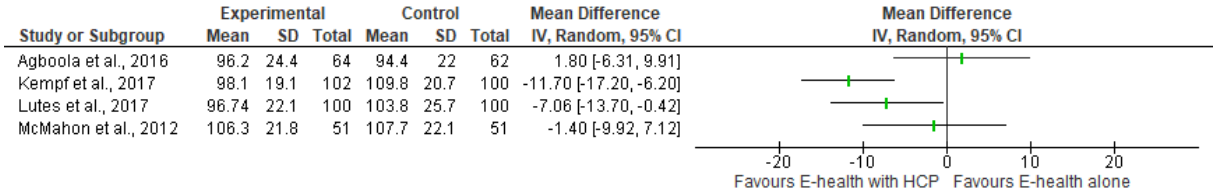

Figure 4: Forest plot, weight

Blood pressure

Three studies reported on blood pressure. Two studies had a significant within-group change in the intervention (51,52). Kempf et al. (51) was the only study that had a significant between-group change in systolic (p=0.0006) and diastolic blood pressure (p=0.02) in the adjusted model. A detailed description of the result for blood pressure in each study is presented in table 8.

Table 8: Description of blood pressure in the included studies

Author, year	Outcome	Intervention Systolic/Diastolic (mmHg) MD, (SD)	Comparison Systolic/Diastolic (mmHg) MD, (SD)	Difference in change MD, (SD) [95% CI]

Agboola et al., 2016	Change in blood pressure at 6 months.	N/A	N/A	N/A
Kempf et al., 2017	Change in blood pressure at 3 months.	Baseline: 139/93 (16/10) Closeout: 133/80 (15*/9) Change score: -6/ -13	Baseline: 134/81 (13/9) Closeout: 135/80 (12/10) Change score: +1/-1	Adjusted model: Systolic 5.7 (15.3) p=0.0006 Diastolic 3.4 (9.5) p=0.02
Lutes et al., 2017	Change in blood pressure at 12 months.	Baseline: 134.71/85.41 (22.01/13.03) Closeout: 134.93/82.54 (22.5/13.52) Change score: +0.22/-2.87 (25.33/1.52)	Baseline: 137.75/84.74 (20.02/11.83) Closeout: 136.73/85.4 (21.10/10.84) Change score: -1.01/+0.66 (20.46/13.24)	Systolic: 0.79 p=0.100 Diastolic: 2.21 p= 0.224

McMahon et al., 2012	Change in blood pressure at 12 months.	Online care group Baseline: 135.6/75.7 (17.4/11.8) Closeout: 135.2/73.2 (19.2/10.7) Change score: -0.3/2.5 (16.9/12.9) Telephone care group Baseline: 139.9/80.8 (17.4/13.1) Closeout: 133.2/74.6 (17.1/10.7) Change score: -6.7/-6.3 **	Baseline: 139.8/83.1 (19.1/15.8) Closeout: 136.7/77.3 (19.3/11.5) Change score: -3.1/-5.8 (20.4/15.5) ***	No between group comparison

Torbjørnsen et al., 2014	Change in blood pressure at 4 months.	N/A	N/A	N/A

Explanation: CI = Confidence Interval. MD = Mean Difference. SD = Standard Deviation. *= p< 0.05. **=p=0.006/0.001. ***= p=0.012. N/A = Not Applicable. mmHg = millimetres of mercury.

Figure 5 illustrates the systolic blood pressure in the included studies. The forest plot shows no statistically significant result. However, we do not have the numbers from the adjusted model in Kempf et al. (51), where the e-health intervention with HCP had a significant improvement compared to the control.

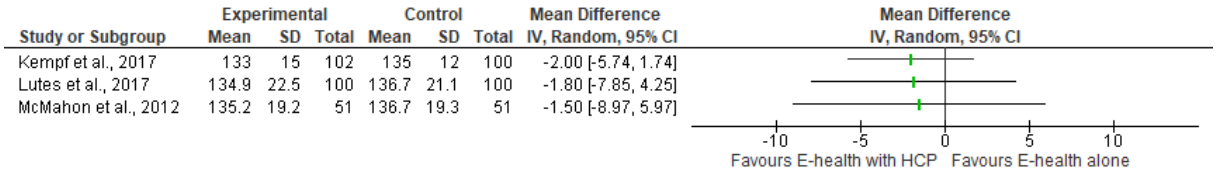

Figure 5: Forest plot, blood pressure

Low density lipoprotein

Both RCTs reporting on LDL made a within-group comparison (51,52). All the intervention and control groups showed a non-significant LDL reduction from baseline to closeout. A detailed description of the result for LDL in each study is presented in table 9.

Table 9: Description of low density lipoprotein in the included studies

Author, year	Outcome	Intervention (mg/dL) MD, (SD)	Comparison (mg/dL) MD, (SD)	Difference in change MD, (SD) [95% CI]
Agboola et al., 2016	Change in LDL at 6 months.	N/A	N/A	N/A
Kempf et al., 2017	Change in LDL at 3 months.	Baseline: 115 (40) Closeout: 112 (36) Change score: -3 (17.6)	Baseline: 117 (36) Closeout: 116 (37) Change score: -0.9 (14.0)	No between group comparison
Lutes et al., 2017	Change in LDL at 12 months.	N/A	N/A	N/A

McMahon et al., 2012	Change in LDL at 12 months.	Online care group Baseline: 95.1 (29.4) Closeout: 92.4 (27.4) Change score: -4.0 (25.8) Telephone care group Baseline: 91.7 (37.8) Closeout: 85.9 (27.1) Change score: -5.5 (24.1)	Baseline: 92.5 (32.3) Closeout: 86.3 (29.4) Change score: -5.8 (24.6)	No between group comparison
Torbjørnsen et al., 2014	Change in LDL at 4 months.	N/A	N/A	N/A

Explanation: LDL= Low Density Lipoprotein. N/A= Not Applicable. mg/dL= milligrams per decilitre. CI = Confidence Interval. MD = Mean Difference. SD = Standard Deviation.

Figure 6 illustrates that both studies have wide CI that crosses the line of no difference. Thus, the studies are inconclusive and could possibly favour both treatments.

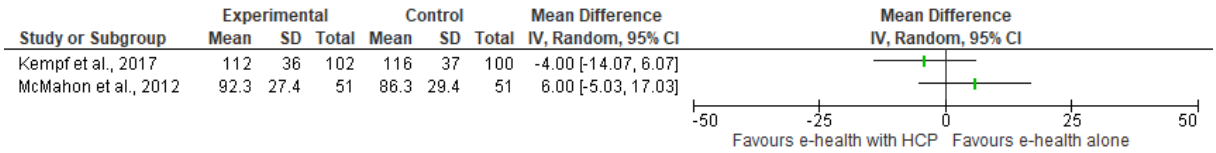

Figure 6: Forest plot, LDL

Certainty of the evidence

We graded the documentation for all four continuous outcomes regarding added benefit when healthcare personnel are involved in e-health interventions. After assessing the certainty of all outcomes, we judged that there is moderate certainty in the effect estimates for HbA1c, weight and blood pressure, and low certainty for LDL. The assessment of certainty of evidence is presented in table 10. Since we only have RCTs we started off with high certainty in the effect estimates. However, we downgraded all outcomes from high to moderate because of inconsistency. Participants, interventions and comparison had a large diversity, thus there is a probability that the variation is higher than what is expected by chance. LDL was further judged as low quality because of imprecision. The sample size is under 400 participants thus contradicting the rule of thumb of at least 400 participants to reach statistical power (49).

Table 10: GRADE

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with [comparison]	**Risk with [intervention]**			
HbA1c (%) Scale from: 6.5-12% Follow up: range 3-12 months	The mean hbA1c ranged from **7.8-9.1** HbA1c%	The mean hbA1c ranged from **7.3- 8.5** HbA1c%	No possible estimate	831 (5 RCTs)	⨁⨁⨁◯ MODERATE [a]
Weight (kg) Scale from: 80-160kg Follow up: range 3-12 months	The mean weight ranged from **94.8-109.8 kg**	The mean weight ranged from **96.2-108.5 kg**	No possible estimate	680 (4 RCTs)	⨁⨁⨁◯ MODERATE [a]
Blood pressure, Systolic/ Diastolic	The mean blood pressure, Systolic/Diastolic ranged from	The mean blood pressure, Systolic/Diastolic ranged from	No possible estimate	554 (3 RCTs)	⨁⨁⨁◯ MODERATE [a]

Scale from: 70/40 - 190/100 mmHg Follow up: range 3-12 months	**135/80 mmHg- 136.7/85.4. mmHg**	**133.2/74.6 mmHg- 135.2/73.2 mmHg**			
Low density lipoprotein Scale from: 70 -190 mg/dL Follow up: range 3-12 months	The mean low density lipoprotein ranged from **86.3-116**	The mean low density lipoprotein ranged from **85.9-112**	No possible estimate	354 (2 RCTs)	⊕⊕◯◯ LOW [a b,]

Explanations

a. Very different population, intervention and comparison in the included studies. High heterogeneity.

b. Small study sample.

Discussion

Aim of the review

This systematic review summarizes the results of five RCTs covering the effect of HCP in e-health interventions for adults with type 2 diabetes. The results can contribute to frame future healthcare services and research.

Main findings

Effects of intervention

The results showed that there was no convincing evidence of added HbA1c benefits when HCP was involved in e-health interventions. Only one study had significant change in HbA1c, and the other studies showed no evidence of clinically relevant effect. There seems to be a small but beneficial effect in weight reduction when HCP was involved. One study showed a significant improvement in blood pressure. Thus, the results are promising but conclusions must be made with caution. Additionally, there was no added benefit in LDL improvement when HCP was involved. Tailored feedback provided by HCP does not seem to have added health benefit when the control group also receives e-health interventions.

The five RCTs all had low risk of bias. Some studies were unclear on allocation concealment and had incomplete outcome data (see, figure 2). Due to blinding of outcome assessment with an objective outcome measurement and appropriate statistical analysis the risk was overall considered to be low. However, after grading all outcomes the documentation was assessed to be of moderate or low quality. Our certainty in the effect estimates are compromised by the

high heterogeneity among the included studies. The true effect is likely to be close to our result, but there is a possibility that the effect could be substantially different.

Current evidence

To our knowledge, this is the first systematic review to investigate the impact of HCP in e-health interventions for adults with type 2 diabetes, when the control group also receives e-health. Several systematic reviews have investigated the effect of e-health with HCP compared to usual care and found evidence of significant but modest effect in HbA1c (53). The greatest effect are seen in telephone delivered interventions (2) and there is evidence that health professional feedback further enhances the change in HbA1c (54). Few trials have attempted to compare some type of e-health with another type of e-health, and this with various degrees of methodological quality (e.g. lacking information about blinding, confidence intervals, standard deviation and confounding factors).

Implication for research

Population

The participants in this review were from Europe and the U.S, and were comparable in age and disease duration. However, they differed in gender distribution, ethnicity, BMI and socioeconomic status such as education and income. The studies from the U.S had participants with high ethnic diversity, lower education and lower income than the European studies. They also had slightly higher HbA1c and BMI indicating that there could be cultural differences involved. Thus, there seems to be variation in characteristics for the participants included. It is possible that a population with more similar characteristics would result in

greater consistency in the findings, and the results would be more conclusive.

All of the participants displayed poor glycaemic control. Patients with poor glycaemic control are more likely to experience a greater reduction in HbA1c when exposed to e-health (54). It is therefore not likely that patients with better glycaemic control would have experienced greater reduction in HbA1c when exposed to e-health than what is found in our review.

There is evidence that disease duration might affect the patient's response to e-health interventions. Patients with a disease duration of five years or less appears to have better effect of e-health interventions in regards to disease management and reaching HbA1c treatment target, compared to those with longer disease duration. This because many newly diagnosed patients with diabetes have little or no knowledge on how to manage their disease, and therefore respond well to a more frequent follow-up through e-health than what is offered in usual care (55). Research shows that newly diagnosed patients with diabetes has a greater potential for improvement in glycaemic control when provided with necessary information and skill-set through e-health (56). The participants in our review all had a disease duration of 10 years or more. It is therefore possible that the duration of disease could have affected our findings. A study with newly diagnosed patients might show different results from e-health interventions than what is found in our review.

Several of our included studies required access to a telephone or a computer with internet access, and the capability of handling complex software. This is a possible restrain for many patients and might have hindered some of the oldest and poorest patients with diabetes from participating in the included studies (57). Using e-health requires a minimum of technical skill set in addition to health literacy, which is the individual's ability to obtain, process and

appropriately act on health information (58). If not taken into consideration at planning and execution stage, implementation of e-health solutions is at risk of undermining the potential benefits for those who need it the most (59).

Socioeconomic status has been identified to have a large impact on technology adoption and usage. There seems to be a connection between technology adoption and level of education and income. Those with lower socioeconomic status has poorer technology adoption compared to individuals with higher socioeconomic status (5). In our review, including studies from the U.S. where the participants had low socioeconomic status could explain why we did not see greater differences between the groups in those studies. Due to differences in socioeconomic status there could be a difference in the ability to utilize e-health with HCP among the participants in our review. We cannot disregard the possibility that poorer technology adoption could have undermined the potential benefits of HCP in the e-health interventions.

Intervention

Kempf et al. (51), as the only study with a significant change in HbA1c, had the most comprehensive intervention consisting of more than glucose measurement and phone calls. Kempf et al. (51) had a five-part intervention including dietary supplements and dietary restrictions. Dietary change has from previous research shown to improve HbA1c (60), raising the question whether this have impacted the results found in the study. Due to the variety of e-health solutions available, it is necessary to identify what an e-health solution must include as a minimum in order to provide health benefits for patients with diabetes. Kempf et al. (51) argues that one of the reasons the intervention was effective was due to the comprehensiveness of the intervention. It is therefore reasonable to question if it was one or

more of the other components of the intervention, rather than tailored HCP feedback provided to the participants that was the reason for the effect.

Kempf et al. (51) had the most telephone calls between participants and HCP, compared to the other studies that had biweekly or monthly contact. Previous research has shown that more than six calls a year does not add any benefits when participants have HbA1c level above 7.5% (61). This contradicts the significant results seen in Kempf et al. (51), who had weekly HCP contact. However, it could be the many components in the intervention rather than the weekly HCP contact in Kempf et al. (51) that contributed to the significant change seen in HbA1c. We need more trials to further investigate the frequency of HCP contact on HbA1c to be certain that we utilize HCP in the most beneficial way when it comes to resources used and patient satisfaction in e-health.

We question whether the intervention in Kempf et al. (51) could be carried out into a real-life context, or if it is too extensive for diabetic patients to incorporate it into everyday life. Implementing interventions focusing on multiple lifestyle changes simultaneously might be overwhelming for many patients and become difficult to manage over time.

The interventions in our review had a duration from three to twelve months. The significant results seen in the three months intervention in Kempf et al. (51) demonstrates that we may not need long-term interventions to achieve significant reductions in HbA1c. Similar systematic reviews have also shown significant HbA1c change at three months when compared to usual care (53). However, there is a tendency that the impact of e-health intervention decreases over time (62). A reason for this decline is that participant engagement wanes (63). Perhaps HCP could counterbalance the decrease in effect of e-health

interventions seen over time, by increasing patient commitment to e-health when patient engagement starts to diminish?

Due to the chronic nature of diabetes, it has been suggested that we need long term interventions intensified over time. This with positive motivation and personalized content adapted to each individual user (63). None of our included studies lasted longer than 12 months or followed the participants after study end. Therefore, we do not have any knowledge about the long-term effect of HCP involvement in e-health for diabetic patients in our review. This must be further addressed in future research.

Previous research has shown that including some sort of educational component in e-health interventions has provided health benefits for patients with type 2 diabetes (34). Diabetes education was one of the main components in many of the interventions and control conditions in our review. The education was delivered by different methods such as telephone, online portal, web page, email or a mobile application. All of the groups experienced a change in HbA1c. It could be that education itself is the important element in e-health interventions regardless of the method for delivery. Our review findings further indicate that it does not seem to differ if education is delivered by HCP or without HCP, because the change in HbA1c is similar across all groups. The role of diabetes education and increasing diabetes awareness must be addressed further in order to understand the effect of education in e-health interventions without HCP. This because our findings seem to indicate that participants using e-health is able to benefit from diabetes education through use of e-health without HCP.

Tailored feedback from HCP did not give any significant reduction in HbA1c when the control group also received e-health. The results showed that there appears to be no dose-response relationship between increasing personalized feedback by HCP through e-health delivery and reduction in HbA1c. The difference in frequency of HCP contact in the included studies did not reduce the level of HbA1c differently among the groups. Thus, increasing frequent HCP contact might not further improve HbA1c.

Previous studies comparing e-health with HCP to usual care have reported that participants experience the HCP contact as particularly appealing. They felt more closely monitored and encouraged to play a more active role in self-management (30). In our review, even though adding HCP did not result in a significant change in health benefits, the participants in the studies reporting on treatment satisfaction reported satisfaction with having the opportunity to communicate with HCP during the intervention period.

In our review, the HCP consisted mainly of trained diabetes nurses. None of our included studies mentions how the educational background of HCP might affect the results in the studies. Previous research has shown that the HbA1c decreases independently of educational background of the HCP. This is important for policy makers to consider if HCP were to be applied in future e-health solutions. This because the lack of difference between healthcare professions e.g. a physician versus a nurse, could significantly decrease the staffing cost (62).

Comparison

The control groups received different diabetes incentives and some additionally received some sort of educational material. Providing the control groups in our review with both diabetes incentives and education material made the difference between what the control

groups and intervention groups received less. We cannot disregard the possibility that the similarity between the groups reduced the effect of including HCP in the e-health interventions. The control group in Kempf et al. (51) was offered the least of diabetes incentives of all groups, and was the study with the greatest difference in HbA1c between the intervention and control condition. This difference between what the control group and intervention group received, might explain why the change in HbA1c only became significant between the groups in Kempf et al. (51).

In this review the included studies did not require the participants to stop their usual care regimen during the intervention period. Therefore, we cannot rule out the possibility that there has been contact between participants in the control group and HCP due to routine follow ups. This might have increased the benefits the control groups experienced and reduced the effect of HCP contact in the intervention groups.

Several authors of the included studies acknowledge the possibility of the Hawthorne effect. The Hawthorne effect refers to the situation where people will modify their behaviour simply because they are being observed and not because of any experimental effect. They will often work harder and perform better when they know they are participating in an experiment (64). The effect will however subside when the experiment ends. Agboola et al. (50) emphasizes that giving pedometers to both groups may have blunted the effect of the intervention as a response of being observed. Due to the lack of follow-up time beyond 12 months in the included studies it is uncertain to what extent the participants are affected by the Hawthorne effect. Future research needs to include longer follow up time to show any possibility for such an effect.

Outcome

We selected HbA1c as the primary outcome since it is considered the gold standard for detecting change in disease stage for individuals with type 2 diabetes (65). However, it is reasonable to question what outcome measures could be used to better judge the effectiveness of including HCP in e-health interventions. This could be reduction in oral medication usage, diabetes treatment satisfaction or first cardiovascular event. Even though we did not find a significant reduction in HbA1c, we cannot disregard the possibility that use of e-health with HCP could have a beneficial effect in other outcomes when the control condition also receives e-health. For instance, the possibility for support by HCP might show a more beneficial effect if the measurements were more qualitative, self-reported outcomes. Such potential outcomes could be diabetes distress, depressive symptoms or confidence in disease management and self-care.

We included other biometric and physiological measurements to see if HCP in e-health interventions could reduce the risk of developing cardiovascular disease for participants with type 2 diabetes. The lack of clinically relevant impact on LDL and blood pressure should be interpreted with caution. Since we have few studies with small sample sizes there is a chance that new research might alter the results. The two studies that assessed the effect on weight, demonstrated a tendency of weight reduction when HCP was involved in e-health. This might indicate that e-health with HCP could be a contributor in reducing the risk of diabetes related complications by decreasing obesity. However, these outcomes should be further explored in future trials in order to obtain more conclusive evidence on how e-health with HCP might reduce the risk of cardiovascular disease.

High attrition is a known problem in many e-health interventions, especially for the control group (30). Many participants tend to drop out when they do not experience any effect of their participation or experience usability issues, which is likely to affect the true results of e-health interventions. An intent to treat analysis was conducted in all included studies as a way to handle the difference in completion. This could have underestimated the effect of the intervention compared to the control condition, by replacing the missing values with estimates closer to the mean. In our review, there seems to be a connection between attrition rate and what the control groups received. There was higher attrition rate when the control participants received a bare minimum of elements. Such as only uploading biometric and physiological measurements automatically, with no additional components in the control group. Kempf et al. (51) argues that the high drop-out rate in the control group in this study, might have led to an underestimation of the effect. Thus, the significant effect of HCP in the intervention group could have been even greater in the study.

Future research

In previous research on diabetes, few studies have attempted to compare HCP in e-health interventions with a control group that also receives e-health. We need more primary research in order to increase our understanding in this particular field, both for short- and long-term effects. In our review, we found no studies that measured how HbA1c changes over time when HCP are involved in e-health, since the longest intervention lasted twelve months. If future research unveils a long-term effect of HCP it is important to investigate the frequency of HCP contact needed. There is a need to investigate the number of weeks or months that HCP should be involved in such interventions before the effect declines. This to maximize the potential health benefits from adding HCP in e-health interventions for the patients.

Drop in adherence over time is a common occurrence in technology-based studies (50). We need more research on how to make participants continue to use e-health solutions over time. Use of email or SMS reminders has been found to be a sufficient method for reinforcing web-based interventions and smartphone applications delivering periodic prompts or nudges to reinforce adherence (14,66). We need to investigate if tailored feedback and reminders from HCP could be a way to increase adherence. It is central for developers to include patients' personal experiences, so that users can influence what services is offered to them. The intent is to offer more user-friendly services that will strengthen the patient's utilization of the intervention and to improve adherence (67).

In this review we are not able to establish if adding HCP exceeds the benefit of implementing e-health without HCP regarding resources used. A health technology assessment is necessary to evaluate this. Can decrease in medication usage, decrease in comorbidity or increased quality of life over time surpass the additional cost of including HCP in e-health?

Implications for clinical practice

The primary target audience for this systematic review are health policy makers, healthcare personnel, patients and other stakeholders, who will benefit from the implications of HCP involvement in e-health interventions for patients with type 2 diabetes. This systematic review may also prove beneficial to developers and organizations that invest resources into implementation and development of e-health solutions. This because our review indicates that tailored feedback from HCP might not be necessary in future e-health development.

The development of national guidelines for implementing e-health solutions and assessing the quality and security of these are still in its initial phase (33,37). It is therefore a need to provide health policy makers with evidence-based knowledge and equip them with national guidelines. This in order to make informed investments on e-health interventions, so it can be designed to maximize the health benefits for patients within each countries financial and resource constraints.

Today, there is no implementation of e-health usage in the education of healthcare professionals in Norway. However, the Norwegian government aims to implement basic e-health knowledge into the education of healthcare professionals within year 2022 (68). HCP must obtain sufficient knowledge and information about e-health solutions to be able to guide patients and to make recommendations for the use of e-health. This in order to ensure the quality of the delivery and the safety of the patients (67).

This review has small study samples (831 participants), geographical and cultural differences, in addition to large variation in intervention content delivered to the participants. Due to this, it is difficult to determine the implications of the findings for those allocating resources. It may seem that adding HCP in e-health does not give added health benefits when participants with type 2 diabetes already receives e-health.

Ethical considerations

In order to handle the cost and resources spent on diabetes, we need a new way to handle diabetes and diabetes related problems. By using e-health we can deliver health services by distance, better follow up of patients with type 2 diabetes, and increase self-management and

personal autonomy (68). However, e-health presents several ethical and legal challenges, which if not addressed could undermine the effect of e-health and possibly harm the patient.

The medical industry is transforming the healthcare system, making it more digital and susceptible to e-health solutions and data delivery. We need to have proper guidelines on how to handle personal medical data, otherwise we could risk having personal medical data at astray. Today, it is normal to outsource e-health solutions. Mainly non-governmental organizations or companies are involved in delivering e-health solutions. This without necessarily meeting governmental regulations and security settings for each country, which can impose a threat to the security of patients' privacy. In addition, e-health is known to have some usability issues such as poorly designed interfaces and unreliable technology (5). This might lead to the patient not adopting the technology in the way it is intended to or having patients lose their medical data.

Overall completeness and applicability of evidence

All of the studies had similar inclusion and exclusion criteria, by excluding those with severe mental or physical illnesses. However, some e-health interventions require diabetes incentives at inclusion. Two of the included studies demanded access to a telephone and/or a computer with internet access. We cannot disregard the possibility that some poor or elderly participants might have been excluded from those studies due to the requirement of technological devices. These are people at higher risk of diabetes complications with poorer glycaemic control (57). Thus, this is a group that could largely benefit from e-health interventions and excluding these participants might have undermined the results in our review.

In our review, the participants in the included studies had poorly regulated HbA1c, were obese, middle-aged, ethnic diverse and represented both genders. Additionally, two of the studies were conducted in Europe, including Norway. Torbjørnsen et al. (45) focused mainly on self-management through mobile applications in the Norwegian population. This coincides with the development in Northern Europe, where e-health solutions are focusing on empowering patients by increasing self-management skills through use of mobile applications and web portals (59). We therefore believe that the findings in our review could be applicable to a Norwegian context. Furthermore, the results from this systematic review might be generalizable to other chronic illnesses that could benefit from e-health intervention targeting lifestyle modification and disease monitoring. E.g. patients with hypertension, chronic obstructive pulmonary disease or thyroid disease.

Timestamp

With a 4-month period from literature search until submission of this systematic review it is not likely that a sufficient number of new studies have been published that could alter the results. We have identified one study about to be published (43), however we do not think that this study with 101 participants is likely to alter our findings.

Potential biases in the review process

There are many systematic reviews covering the topic of e-health with HCP. This is the first systematic review to investigate the effect of e-health with HCP compared to e-health without HCP for patients with diabetes.

A strength in this systematic review is that the review authors screened, extracted data and assessed risk of bias independently from each other. This in accordance to the Cochrane Handbook for Systematic Reviews of Interventions (38). This systematic review is based on a systematic literature search in international databases with the use of a specific search strategy. This was designed and performed by the authors. The authors were not experienced in systematic literature search, but a specialist librarian overlooked the process assuring quality in the search. We have done an extensive search to minimize the risk of missing relevant studies. This includes searching relevant reference lists and grey literature in Google Scholar. MeSH terms used in the field of e-health are still new and unstandardized. Researchers often use different terms for the same intervention. We used a large variation of MeSH terms, and therefore lowered the risk of not identifying relevant titles.

There are some limitations present in this review. A possible limitation is the strict inclusion criteria. Lowering the frequency of HCP feedback to every second month or less and allowing for algorithm-based feedback made by HCP could have resulted in a greater number of trials in our review. We only included published trials written in English. There is a possibility that relevant studies in other languages were not considered in this review. Additionally, the heterogeneous characteristics of participants, intervention and control conditions together with small sample size excluded the possibility of conducting any meta-analyses.

Agreement and disagreement with other studies or reviews

In our review, the interventions included devices for biometric and physiological measurements and use of a telephone. The studies differed in how HCP and patients communicated with each other. The interventions used either text messages, educational calls, coaching- or care calls. Our review shows that even though the technological development

has improved the last decades, we still use telephone calls as the main e-health method for providing tailored HCP feedback to participants with type 2 diabetes. This is supported by the findings in a comprehensive systematic review from 2018 (14) establishing the important role of telephone calls in patient-HCP communication still present**.**

Previous e-health research has found that participants with a HbA1c level of 8% or higher had the greatest improvement in glycaemic control in e-health interventions when the control condition received usual care (2). In our review the HbA1c level was above 8% at inclusion, however the effect of the intervention was limited when the control group also received e-health. Although the participants experienced a reduction in the HbA1c level, none of the groups that received e-health, neither with or without HCP were close to reaching treatment target of HbA1c less than 7%.

Even though we did not find convincing evidence for added health benefits when HCP was involved, other systematic reviews have found HCP involvement to significantly reduce HbA1c when compared to usual care (66). This indicates that e-health both with and without HCP have a significant effect when compared to usual care. However, when the comparison groups also receive e-health the effect seems to diminish.

Conclusion

This systematic review shows that providing e-health with tailored HCP feedback to patients with type 2 diabetes, does not have added health benefits when the control group also receives e-health. While all of the included studies had some reduction in HbA1c levels, none of the study groups reach treatment target of HbA1c, less than 7%. Furthermore, there was no clinically relevant impact on blood pressure, low density lipoprotein or weight. The review studies were highly heterogeneous, with different characteristics of participants, interventions and control conditions. There is a need for additional high quality RCTs and subsequently systematic reviews in order to draw firm conclusions about the effect of including HCP in e-health interventions. For policy makers to assess the overall effectiveness of HCP involvement in e-health interventions, future reviews must also address other types of diabetes related outcomes. Furthermore, future primary studies must address the long-term effects of HCP involvement in e-health when it comes to cost-effectiveness and patient utilization.

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Appendix

Appendix 1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Front page, 9
ABSTRACT			
Structured summary	2	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.	III-IV
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	7-8
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	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.	9
Eligibility criteria	6	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.	10-11
Information sources	7	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.	9
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	81-85
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	12
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	12-13
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	13
Risk of bias in individual studies	12	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.	13-14

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	14-15
Synthesis of results	14	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.	14-15

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	13-14
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	15
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.	17
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.	18-19
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).	31,146
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.	32-46
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	28-31
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	46
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).	49, 59-60
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).	62-63
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	65
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.	9

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000

Appendix 2: Search strategies

OVID Medline 1946 – present

Date of search: 17.01.2019

487 references

1. exp Diabetes Mellitus, Type 2/
2. Adult-onset diabetes mellitus.ti,ab,kw.
3. Noninsulin-dependent diabetes mellitus.ti,ab,kw.
4. Type 2 diabetes.ti,kw.
5. Type 2 diabetes mellitus.ti,kw.
6. 1 or 2 or 3 or 4 or 5
7. exp telemedicine/ or exp telerehabilitation/
8. (mobile adj health).ti,ab,kw.
9. mhealth.ti,ab,kw.
10. m-health.ti,ab,kw.
11. telehealth.ti,ab,kw.
12. ehealth.ti,ab,kw.
13. e-health.ti,ab,kw.
14. telecare.ti,ab,kw.
15. Remote consultation.ti,ab,kw.
16. teleconsultation*.ti,ab,kw.
17. videoconsult*.ti,ab,kw.
18. exp Mobile Applications/
19. (mobile adj3 app).ti,ab,kw.
20. (software adj3 app).ti,ab,kw.

21. telecommunication*.ti,ab,kw.

22. (electronic adj mail).ti,ab,kw.

23. email.ti,ab,kw.

24. telemetry.ti,ab,kw.

25. videoconferenc*.ti,ab,kw.

26. exp telephone/ or exp cell phone/

27. (mobile adj phone).ti,ab,kw.

28. (Text adj messaging).ti,ab,kw.

29. sms.ti,ab,kw.

30. Patient portal*.ti,ab,kw.

31. (internet adj based).ti,ab,kw.

32. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31

33. 6 and 32

34. limit 33 to (English language and humans and yr="2012 -Current")

EMBASE Classic + EMBASE (1974 to present).

Date of search: 21.01.2019

1066 references

1. exp non insulin dependent diabetes mellitus/

2. exp telemedicine/ or exp telerehabilitation/

3. (mobile adj health).ti,ab,kw.

4. mhealth.ti,ab,kw.

5. m-health.ti,ab,kw.

6. telehealth.ti,ab,kw.

7. ehealth.ti,ab,kw.

8. e-health.ti,ab,kw.

9. telecare.ti,ab,kw.

10. Remote consultation.ti,ab,kw.

11. telecommunication*.ti,ab,kw.

12. videoconsult*.ti,ab,kw.

13. exp mobile application/

14. (mobile adj3 app).ti,ab,kw.

15. (software adj3 app).ti,ab,kw.

16. telecommunication*.ti,ab,kw.

17. (electronic adj mail).ti,ab,kw.

18. email.ti,ab,kw.

19. telemetry.ti,ab,kw.

20. videoconferenc*.ti,ab,kw.

21. exp telephone/

22. (mobile adj phone).ti,ab,kw.

23. (cell adj phone).ti,ab,kw.

24. (Text adj messaging).ti,ab,kw.

25. Patient portal*.ti,ab,kw.

26. (internet adj based).ti,ab,kw.

27. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26

28. 1 and 27

29. limit 28 to (human and English language and yr="2012 -Current")

EBSCOhost CINAHL Plus with Full Text

Date of search: 29.01.2019

445 references.

1. (MH "Diabetes Mellitus, Type 2") OR "diabetes mellitus type 2"

2. "adult onset diabetes"

3. "non insulin dependent diabetes mellitus"

4. "type 2 diabetes"

5. 1 OR 2 OR 3 OR 4

6. (MH "Telemedicine+") OR (MH "Telerehabilitation")

7. "mobile health"

8. "mhealth"

9. "m-health"

10. "telehealth"

11. "ehealth"

12. "e-health"

13. "telecare"

14. "remote consultation"

15. "teleconsultation"

16. "video consultations"

17. (MH "Mobile Applications") OR "mobile applications"

18. "mobile app*"

19. ""software app*""

20. "telecommunication*"

21. "electronic mail"

22. "email"

23. "telemetry"

24.(MH "Telephone+") OR (MH "Cellular Phone+") ‘

25. "mobile phone"

26. "text messag*"

27. "patient portal"

28. ""internet based""

29. "videoconferencing"

30. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29

31.limit 30 to (English language and yr="2012 -Current")

4. Advanced search in Google Scholar.

12.02.2019

1065 references.

ehealth OR mhealth OR "mobile health" OR telemedicine OR "mobile application" AND "type 2 diabetes" AND HbA1c AND "randomized trial"

Appendix 3: Article selection form

Title:_____

Author:_____

Year:_____

Study design:_____

Selection level:

Title___ Abstract___ Text____

Selection criteria:

Population

Does >75% of the participants have type 2 diabetes? Yes/No

Are participants 18 years of age or older included? Yes/No

Intervention

Did the intervention group receive e-health? Yes/No

Did the intervention include healthcare personnel? Yes/No

Was there personalized/tailored feedback? Yes/No

Was there feedback at least once a month? Yes/No

Did the intervention last for three months or more? Yes/No

Control

Did the control group receive e-health? Yes/No

If participants were provided with feedback, was it automated? Yes/No

Outcome

Is HbA1c or fasting glucose reported? Yes/No

Action only if the answers to ALL the question is "yes".

Include_____Exclude_____Unclear_____

Appendix 4: Data extraction form

	Descriptions as stated in report/paper	Location in text or source
Study characteristics		
Study title		
Author		
Year of publication		
Country of study		
Study setting (location)		
Years of data collection		
Study design and unit of allocation		

Aim of the study		
Study methods		
Inclusion criteria		
Exclusion criteria		
Withdrawals and exclusions		
Baseline imbalances		
Notes		
Participants		
Population description (from which study participants are drawn)		
Total number randomised (total population)		
Year since type 2 diabetes diagnosis		

Age + mean age		
Sex		
Ethnicity		
Mean level HbA1c at inclusion		
Other relevant sociodemographic		
Notes		
Intervention		
No. randomised to group		
Description of intervention		
Duration of intervention		
Frequency of intervention		
Healthcare providers		

Description of interaction between HCP and participants.		
Delivery/medium (phone, app, email, tools)		
Co intervention if applicable		
Compliance		
Notes:		
Control group		
No. randomised to group		
Description of intervention		
Duration of intervention		
Frequency of intervention		

Description of interaction between HCP and participants.		
Delivery/medium (phone, app, email, tools)		
Co intervention if applicable		
Compliance		
Notes		
Outcome		
Unit of measurement		
Time points measured (specify whether from start or end of intervention)		
Mean HbA1c / FG		
Change in HbA1c/ FG		

Person measuring/reporting		
Imputation of missing data (E.g. assumptions made for ITT analysis)		
Sample size calculations		
Notes		
Secondary outcomes: (weight, blood pressure, low density lipoprotein)		
Other		
Study funding source		
Possible conflict of interest		
Notes		

Appendix 5: Data extraction of included studies

Agboola et al., 2016

	Descriptions as stated in report/paper	Location in text or source
<u>Study characteristics</u>		
Study title	Text to Move: A randomized Control Trial of a Text-Messaging program to improve physical activity behaviours in patients with Type 2 Diabetes Mellitus.	p.1
Author	S, Agboola,. K, Jethwani,. L, Lopez,. M, Searl,. S, O'keefe., & J, Kvadar,.	p.1
Year of publication	2016	p.1
Country of study	United States	p.1
Study setting (location)	City, Boston	p.1
Years of data collection	12 months (July 2012 to October 2013)	
Study design and unit of allocation	Randomized Controlled Trial	p.1
Aim of the study	Test the hypothesis that T2DM patients assigned to a PA monitoring and text-message program will be more active and attain better clinical outcomes compared to a control group of patients not receiving text messages.	p.2

Study methods		
Inclusion criteria	- English or Spanish speaking patients - Age 18 years and older - Diabetes type 2 diagnosis - Most recent HbA1c of 7.0 % and above - Need to have a computer with internet access - Be willing to attend 2 in-person study visits and receive a minimum of 60 text messages per month for 6 months	p.2
Exclusion criteria	Patients with significant cognitive deficits, physical disabilities and medical/surgical conditions excluding participation in moderate physical activity.	p.2
Withdrawals and exclusions	Voluntary withdraw: 11 Investigator terminated: 6 Loss to follow up: 12 Withdrawn for ineligibility	p. 5
Baseline imbalances	There is 15% more female in the control group compared to the intervention group. 44 % had completed grade 12 in the intervention group compared with 22 % in the control group. The two groups were not statistically different at baseline.	p.6 P. 5
Notes		

Participants		
Population description (from which study participants are drawn)	Participants was drawn from four health centers in Boston. Highly diverse population.	p.2
Total number randomised (total population)	126	p.5
Year since type 2 diabetes diagnosis	Not mentioned	
Age + mean age	Intervention group: 50.3, mean SD 10.5 Control group: 52.6, mean SD 12.6.	p.6
Sex	Intervention group: 28 females, 36 males Control group: 37 females, 25 males	p.6
Ethnicity	High proportion of ethnic minorities Intervention group: 61% White 23 % Hispanic 8 % African Americans 5% Pacific islander Control group: 61% White 26 % Hispanic 11 % African Americans 0 % Pacific islander	p.2

Mean level HbA1c at inclusion	Baseline HbA1c: Intervention 9.08 (SD 1.63) Control: 8.38 (SD 1.37)	p.2
Other relevant sociodemographic	High proportion of low income participants: Employment full time intervention: 52% control:52% Employment part time intervention: 13% control:10% Unemployed intervention: 14% control: 19% Retired intervention: 5% control: 11% Disabled, student, others: intervention: 11% control: 3%	p.3 p.7
Notes		
Intervention		
No. randomised to group	64	p.5

Description of intervention	The participants received at least two automated text messages per day, one in the morning and one in the evening. The messages were at 160 characters length, and provided daily step counts (captures by the pedometer), physical activity goal, education, motivation/self-efficacy, support and health assessment. At the baseline visit it was collected baseline characteristics and behavioural information from the participants. State of behaviour change was also assessed. This was entered into to the text message system to tailor the messages to the participants. To optimize engagement some of the messages were interactive, two-way response messages. The text messages were in English and Spanish.	p.3-4
Duration of intervention	Six months	p.3
Frequency of intervention	At least two personalized automated text messages per day. Twice a week there was a two-way response message.	p.3
Healthcare providers	Nurses, physicians, behavioural psychologist, social workers, health educators and coaches.	p.3

Description of interaction between HCP and participants.	The text messages were premade by nurses, physicians, behavioural psychologist, social workers, health educators and coaches. In all more than 1000 messages was design by the multidisciplinary team. All study data, including outgoing and incoming text messages were displayed on the study dashboard, this was monitored weekly by study staff.	p.3
Delivery/medium (phone, app, email, tools)	Phone and pedometer	p.3
Co intervention if applicable	N/A	
Compliance	33 of 64 participants discontinued the TTM intervention for various reasons. 67% of intervention participants had pedometer data at the end of the study.	p.10
Notes		
Control group		
No. randomised to group	62	p.5
Description of intervention	The control group got a pedometer (actpedi+) with Bluetooth wireless technology. The pedometer served only to capture and track data.	p.3

	The pedometer data was uploaded to the device web-portal. Participants could view their physical activity data and modify their physical activity goals.	
Duration of intervention	Six months	
Frequency of intervention	The participants uploaded the data from the pedometer at least every third day.	p.3
Description of interaction between HCP and participants.	The pedometer did not deliver any form of personalized feedback to the participants.	p.3
Delivery/medium (phone, app, email, tools)	Pedometer and a web portal.	p.3
Co intervention if applicable	N/A	
Compliance	26 of 62 participants discontinued the control intervention for various reasons. 55% of the control participants had pedometer data at the end of the study.	p.10
Notes		
Outcome		
Unit of measurement	HbA1c	

Time points measured (specify whether from start or end of intervention)	HbA1c measured at baseline and at the end of the six months study period.	p.8
Mean HbA1c/FG	HbA1c at baseline: TTM group: 9.02%, SD 1.63 Control group: 8.38%, SD 1.37 Mean difference: 0.64 Change scores: -0.43 HbA1c at closeout (six months): TTM group: 8.59%, SD 1.60 Control group: 8.17%, SD 1.60 Mean difference: 0.42 Change scores: -0.21	p. 8
Change in HbA1c/FG	After adjusting for baseline differences, HbA1c decreased by 0.07% in the TTM group compared with the control group. Within groups, HbA1c decreased significantly from baseline in the TTM group by -0.43% (95% CI -0.75 to -0.12, p=.01), but non significantly in the control group by -0.21% (95% CI -0.49 to 0.06, p=.13)	p. 7 and p.1
Person measuring/reporting	HbA1c test results collected at enrolment and closeout visits at their study site.	p.4
Imputation of missing data (e.g. assumptions made for ITT analysis)	Intent to treat principle was used, and participants were analysed in the treatment group to which they were allocated. The last observation carried forward method was used for missing data from drop out and lost to follow-up.	p.4

Sample size calculations	"We calculated a sample size of 120 (60 participants per group) would be sufficient to detect a true difference of 1500 in mean step count between the control and intervention arms with 80% power and a 2-sided .05 significance level. This was based on the assumption that the standard deviation of the response variable was 2600 step counts in both groups and was adjusted for a dropout rate of 20%."	p.4
Notes	In the TTM group, engaged participants (those responding to at least one text message per week for all six months) on average had 1122 more daily step counts (95% CI 84 - 2160, p=.04), and also had a greater reduction in HbA1c levels (mean difference -0.78%, 95% CI -1.64 to 0.09, p=0.8) compared with the unengaged participants in the TTM group.	p. 8
Secondary outcomes: (weight, blood pressure, low density lipoprotein)	Weight: Follow-up weight not significant different between groups. TTM group: mean 211.99, SD 53.93 lb Control group: mean 208.89, SD 48.59 lb. Mean difference 3.10 lb (95% CI -24.50 to 18.30, p=.77).	p.8
Other		
Study funding source	Funded by the McKesson Foundation.	p.11

Possible conflict of interest	Non declared	
Notes		

Kempf et al., 2017

	Descriptions as stated in report/paper	Location in text or source
Study characteristics		
Study title	Efficacy of the telemedical lifestyle intervention program TeLiPro in advanced stages of Type 2 diabetes: A Randomized Controlled Trial	
Author	Kempf,K,. Altpeter,B,. Berger,J,. Reub, O,. Fuchs, M,. Schneider,M,. Gartner, B,. Niedermeier, K,. Martin, S,.	
Year of publication	2017	
Country of study	Germany	
Study setting (location)	Düsseldorf	p.2
Years of data collection	February 2014 to December 2015	p.2
Study design and unit of allocation	Randomized controlled trial	

Aim of the study	"Evaluate the efficacy of the telemedical Lifestyle intervention Program (TeLiPro) in improving metabolic control in advanced-stage type 2 diabetes."	p.1
Study methods		
Inclusion criteria	- Between 25 and 79 years - HbA1c > 7.5% - BMI > 27 kg/m^2 - Were treated with more than two antidiabetic drugs	p.2
Exclusion criteria	• Acute infections • Chronic conditions other than type 2 diabetes and hypertension (e.g. cancer, dementia, asthma etc.) • Smoking cessation for less than three months or planned smoking cessation during the study period • Weight-influencing medication • Pregnant or breastfeeding women • Known intolerance for any of the ingredients in the protein-rich meal replacement (PRMR) • Acute chemotherapy • Chronic cortisol treatment	p.2
Withdrawals and exclusions	No information about exclusions provided. Majority of the dropouts in the control group, dropped out because they did not notice any beneficial glucose metabolic effect.	p.7
Baseline imbalances	No baseline imbalances. Additionally, there were no significant difference between participants who	

	completed the intervention phase and those who dropped out.	
Notes	This study is missing a flowchart.	
Participants		
Population description (from which study participants are drawn)	Overweight patients with poorly controlled diabetes type 2 in Germany, recruited via attending physicians or newspaper articles.	p.2
Total number randomised (total population)	202 participants were randomized	p.3
Duration of diabetes type 2 diagnosis.	TeLiPro group: 11 years (SD 7) Control group: 11 years (SD 8)	p.4
Age + mean age	TeLiPro group: 59 (SD 9) Control group: 60 (SD 8)	p.4
Sex	TeLiPro group: males 55, females 42 Control group: males 53, females 47	p.4
Ethnicity	Not mentioned.	
Mean level HbA1c at inclusion	At baseline TeLiPro group: 8.4 (SD 1.3) Control group: 8.2 (SD 1.4)	p.4
Medication use	The participants were on at least two different antidiabetic drugs.	p.2
Other relevant sociodemographic		

Notes		
Intervention		
No. randomised to group	102	
Description of intervention	All of participants received a self-management guide, a weighing scale and a step counter. The intervention group additionally received a blood glucose meter. The TeLiPro received a dietary intervention (in the form of a protein-rich meal replacement to achieve an initial weight reduction) and weekly 20 minutes care calls from trained diabetic coaches. Care calls included information about: Type 2 diabetes, medications, healthy diets, physical activity and subjective possibilities for lifestyle changes. Additionally, the participants measured data (daily glucose, step counts and weight) were discussed during these care calls.	p.2
Duration of intervention	12 weeks	
Frequency of intervention	Weekly care calls and daily measurements.	p.2
Healthcare providers	Trained diabetes coaches.	p.2

Description of interaction between HCP and participants.	Trained diabetes coaches called the participants with educational and tailored information.	p.2
Delivery/medium (phone, app, email, tools)	Telephone, glucose meter, pedometer and weight scale.	p.2
Co intervention if applicable	N/A	
Compliance	93 (91%) of the participants completed the intervention. 26 week follow up data was available for 82 participants 52 week follow up data was available for 77 participants	p.3
Notes		
Control group		
No. randomised to group	100	
Description of intervention	Controls received a self-management guide, a weighing scale and a step counter. They were advised to measure steps and weight daily. The devices automatically collected, reported and transferred the measured data into a personalized	p.2

	online portal, so that the participants could monitor their own progression.	
Duration of intervention	12 weeks	p.3
Frequency of intervention	Daily measurements	p.2
Delivery/medium (phone, app, email, tools)	Pedometer, weight scale and online portal	p.2
Co intervention if applicable	N/A	
Compliance	74 participants completed the intervention. 26 weeks follow up data was available for 66 participants. 52 weeks follow up data was available for 56 participants.	p.3
Notes	Drop-out rates were significantly higher in the control group (p=0.001). The overall feedback of the dropouts in the control group was that they did not perceive any benefit in glucose metabolic control during the study and therefore they dropped out.	p.3 p.7
Outcome		

Unit of measurement	HbA1c	
Time points measured (specify whether from start or end of intervention)	At baseline At 12 weeks of intervention At 26 weeks of follow up At 52 weeks of follow up	p.2
Mean HbA1c / FG	At baseline TeLiPro group: 8.4 (SD 1.3) Control group: 8.2 (SD 1.4) At 12 weeks TeLiPro group: 7.3 (SD 1.1) Control group: 8.0 (SD 1.3) At 26 weeks of follow up TeLiPro group: 7.5 (SD 1.3) Control group: 8.1 (SD 1.2) At 52 weeks of follow up TeLiPro group: 7.6 (SD 1.2) Control group: 8.2 (SD 1.3)	p.4
Change in HbA1c/ FG	After 12 weeks TeLiPro group: HbA1c decreased with 1.1 (SD 1.2, p=0.0001) Control group: HbA1c decreased with 0.2 (SD 0.8, no significance) After 26 weeks TeLiPro group: HbA1c decreased with 0.9 (SD 1.3, p=0.0001)	p.7

	Control group: HbA1c decreased with 0.2 (SD 0.8, no significance) After 52 weeks TeLiPro group: HbA1c decreased with 0.7 (SD 1.3, p=0.001) Control group: HbA1c decreased with 0.1 (SD 0.9 no significance)	
Person measuring/reporting	Attending physician measured health parameters at baseline, after 12 weeks and at 26 and 52 weeks follow up. This includes HbA1c, fasting blood glucose, cholesterol, triglycerides, weight, BMI and blood pressure.	p.2
Imputation of missing data (e.g. assumptions made for ITT analysis)	Single missing values of participants who completed the study were imputed using a last-observation-carried-forward (LOCF) approach. Intent to treat analysis with missing values due to drop out or loss to follow up were imputed with the following method. “1) Missing values simulated based on the mean of each group at each time point, and 2) The lower limit at the 95% CI for the control group versus upper limit for the TeLiPro group”.	p.3
Sample size calculation	Not mentioned	
Notes	Estimated treatment difference between the TeLiPro and control group is -0.7 (CI 1.1-0.5,	p.8

	p=0.0001) Medication demand for antidiabetic drugs was significantly reduced (p=0.0001) in the intervention group.	 p.3
Secondary outcomes: (weight, blood pressure, low density lipoprotein)	**Weight at baseline** TeLiPro group: 104.3 kg (SD 19.4) Control group: 110.8 kg (SD 21.1) Weight change after 12 weeks TeLiPro group: -6.1(SD 4.6) (p=0.0001) Control group: -1.0 (SD 3.4) Weight change after 26 weeks TeLiPro group: -6.7 (SD 6.1) (p=0.0001) Control group: -1.1 (SD 4.2) Weight change after 52 weeks TeLiPro group: -6.5 (SD 6.8) (p=0.0001) Control group:-1.4 (SD 5.0) **Blood pressure, baseline** TeLiPro group: 139/93 (SD 16/SD 10) Control group:134/81 (SD 13/SD 9) Blood pressure change after 12 weeks: <u>TeLiPro group:</u> systolic -5.7 (SD 15.3, p=0.001) diastolic -3.4 (SD 9.5, p=0.05) <u>Control group:</u> systolic +1.6 (SD 13.8) diastolic -0.4 (SD 7.6) Blood pressure change after 26 weeks:	p 4 p.7 p.4 p.7

	TeLiPro group: Systolic -6.5 (SD 16) (P=0.001) Diastolic -3.5 (SD 9.6) Control group: systolic +0.1 (SD 15.9) diastolic -1.4 (SD 9.1) Blood pressure change after 52 weeks: TeLiPro group: systolic -3.5 (SD 18.4) diastolic -2.9 (11.5) Control group: systolic -0.5 (SD 12.8) diastolic -1.7 (SD 9.3) **Low density lipoprotein Baseline:** TeLiPro group: 115 (SD 40) Control group: 117 (SD 36) Low density lipoprotein 12 weeks: TeLiPro group: -3.0 (SD 17.6) Control group: -0.9 (SD 14.0) Low density lipoprotein 26 weeks: TeLiPro group: -0.9 (SD 22.7) Control group: -2.0 (SD 16.4) Low density lipoprotein 52 weeks: TeLiPro group: +1.7 (SD 30.4) Control group: -3.3 (SD 17.6)	p.4 p.7
Other		
Study funding source	The study was funded by Boehringer Ingelheim International GmbH and by Gesellschaft von	p.8

	freunden und fôrderen der Heinrich-heine-universitât	
Possible conflict of interest	No possible conflict of interest.	p.8
Notes	“The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript”.	p.8

Lutes et al., 2017

	Descriptions as stated in report/paper	Location in text or source
Study characteristics		
Study title	A community health worker delivered intervention to African American women with type 2 diabetes.	p.1329
Author	Lutes, L,. Cummings, D,. Littlewood, K,. Dinatale, E,. Hambidge, B,.	p.1329
Year of publication	2017	p.1329
Country of study	USA	p.1329
Study setting (location)		
Years of data collection	From July 2012 to July 2013	p.1330

Study design and unit of allocation	Pragmatic randomized trial	p.1329
Aim of the study	To empower rural African American women and examine the impact of the small change lifestyle treatment approach delivered by community healthcare workers (CHW), primary by phone, compared to an email-based group.	p. 1330
Study methods		
Inclusion criteria	- Rural adult (19-75 years old) - African American women - Diagnosed with type 2 diabetes - HbA1c >7.0% - Competency to provide consent - English communication skills	p.1330
Exclusion criteria	- Diagnosis of advanced disease (e.g. end-stage renal disease, advanced heart failure, blindness, metastatic cancer) - Alcoholism - Major psychiatric disease - Participation in another diabetes weight loss program	p.1330
Withdrawals and exclusions	Within 12 months: Dropped out: 30 Missed appointments: 43 Died: 2	p. 1331
Baseline imbalances	A difference of p=0.06 between the weight in the treatment arms. Due to this, weight was included as a covariate in the analysis.	p.1332

	"There were no significant differences between the two groups at baseline in demographic, clinical or psychosocial characteristics."	
Notes		
Participants		
Population description (from which study participants are drawn)	Rural and impoverished African American women, with class 2 obesity and uncontrolled type 2 diabetes. The population had reduced medication adherence and self-care behaviours.	p.1333
Total number randomised (total population)	200	p.1333
Year since diabetes type 2 diagnosis	Total population: 10.83 years (SD 8.44) Intervention group: 10.57 years (SD 7.04) Control group: 11.08 years (SD 9.46)	p.1332
Age + mean age	Total population: 53.45 years (SD 10.24) Intervention group: 52.70 years (SD 10.62) Control group: 54.20 years (SD 9.84)	p.1332
Sex	Only women were included	
Ethnicity	African American	

Mean level HbA1c at inclusion	Total population: 9.09% (SD 1.83) Intervention group: 9.13% (SD 1.79) Control group: 9.05 % (SD 1.88)	p.1332
Medication use	Total population using insulin: 60% Intervention group using insulin: 56% Control group using insulin: 65%	p.1332
Other relevant sociodemographic	Average income under 30 000 a year: Total population: 79% Intervention group: 75% Control group: 82%	p.1332
Notes	Low income population. Additionally, an obese population with a total population mean BMI of 37.67 (SD 8.02).	p.1332
Intervention		
No. randomised to group	100	p.1333
Description of intervention	Small change intervention group. The intervention group was provided with a 16 week empower treatment manual, recording forms, weight scale, a glucose monitor and a pedometer. Each session after baseline visit started with the CHW reviewing monitored behaviours, success,	

	challenges and barriers to treatment. Next the CHW covered the session material in one of the following topics: “self-monitor, goal setting, nutrition, physical activity, skill power vs will power, diabetes 101, planning and time management, communication, mindfulness and awareness, breaking negative thought chains, dealing with challenges, stress and problem solving.” The session ended with the CHW setting a small changes-consistent goal for the upcoming weeks. The participant would then set their own goal for achieving the small change goal. E.g. reduction of sugar beverages, the participant would then set her own quantity goal.	
Duration of intervention	12 months	
Frequency of intervention	16 telephone sessions lasting for 20-30 min each.	p. 1329 and p.1332
Healthcare providers	Community health care workers (CHW), who had residence in the target area for >5 years. Received 50 hours of training by the investigator. Each CHW was given a detailed treatment manual and outline for each session, additionally they were given a template for completing progress notes.	p.1331
Description of interaction between HCP and participants.	CHW called the participant and reviewed the participants monitored data and delivered educational sessions on specific themes.	p.1331 - p.1332

Delivery/medium (phone, app, email, tools)	Telephone, glucose meter, pedometer, weigh scale	p. 1332
Co intervention if applicable	N/A	
Compliance	Participants completed 9.6/16 phone calls across the 12 months period, they received in average 60% of the planned dose of treatment across the year. Attrition rate was 23%.	p.1333
Notes	Participants received approximately 60% of the planned dose of treatment across the year (9.6/16 calls).	p.1333
Control group		
No. randomised to group	100	p.1333
Description of intervention	Email based group: Participants received education material from the academy of nutrition and diabetes regarding diet selection, management of education, healthy snacking, monitoring blood glucose and engagement in physical activity. An unknown proportion of the participants received pedometers.	p.1332
Duration of intervention	12 months	
Frequency of intervention	16 emails were sent during the 12 months period.	

Description of interaction between HCP and participants.	No interaction	
Delivery/medium (phone, app, email, tools)	Email. Additionally, an unknown number of the controls received pedometers from the healthcare worker. (This information was obtained from email correspondence between the author of the article and us).	p.1332
Co intervention if applicable	N/A	
Compliance	Attrition rate 15%.	p.1333
Notes		
Outcome		
Unit of measurement	HbA1c	
Time points measured (specify whether from start or end of intervention)	- At Baseline - At 6 months of intervention - At 12 months of intervention	p.1333
Mean HbA1c / FG	At baseline: Intervention group: 9.13 (SD 1.79) Control group: 9.05 (SD 1.88) At 6 months: Intervention group: 8.87 (SD 1.92)	p.1333

	Control group: 8.89 (SD 2.11) At 12 months: Intervention group: 8.84 (SD 1.98) Control group: 9.10 (SD 2.24)	
Change in HbA1c/ FG	Total change: Intervention group: -0.29% (SD 1.84) (95% CI= 8.61-9.28) Control group: +0.05% (SD 1.61) (95% CI=8.67-9.36) There is no significant difference between the change in both groups, p=0.789.	p.1333
Person measuring/reporting	"Biological and psychosocial data is collected from patients at baseline, six months, and 12 months using paper-based data collection forms in community-based settings" (47). No additional information about person measuring/reporting is given in the study.	
Sample size calculation	"Using a power of 80%, an alpha = 0.05, and an anticipated difference between groups of 0.5 ± 1.2,	

	gives a sample size needed of approximately 90 women in each group" (47).	
Imputation of missing data (e.g. assumptions made for ITT analysis)	Using an intent to treat analysis. Missing data at follow up was addressed by using multiple imputations to replace missing values. All variables with less than 20% of randomly missing data were kept and imputed.	p.1332
Secondary outcomes: (weight, blood pressure, low density lipoprotein)	<u>Weight at baseline</u> Intervention group: 98.09 (SD 21.21) Control group:104.20 (SD 25.36) Weight at 6 months Intervention group: 97.72 (SD 21.08) Control group: 104.42 (SD 25.35) Weight at 12 months Intervention group: 96.74 (SD 22.13) (CI 92.03-101.06) Control group: 103.81 (SD 25.74) (CI 98.49-107.71) Weight total change Intervention group: -1.35 (SD 6.22) Control group: -0.39 (SD 4.57)	p.1333

	statistical significant change, p= 0.046 Blood pressure at baseline Intervention group: 134.71/85.41 (SD 22.01/SD 13.03) Control group: 137.75/84.74 (SD 25.36/SD 20.02) Blood pressure at 6 months Intervention group: 138.16/85.73 (SD 19.43/SD 12.23) Control group:145.22/88.50 (SD 22.14/SD 12.02) Blood pressure at 12 months Intervention group:134.93/82.54 (SD 22.5/SD 13.52) Control group:136.73/85.4 (SD 21.10/SD 10.84) Total change Intervention group: systolic +0.22 (SD 25.33) diastolic -2.87 (SD 1.52) Control group: systolic - 1.01 (SD 20.46) diastolic	

	+ 0.66 (SD 13.24) (p= 0.224)	
Notes		
Other		
Study funding source	Bristol-Myers Squibb Foundation Together on Diabetes Initiative	p.1329
Possible conflict of interest	No possible conflict of interest	p.1329
Notes		

McMahon et al., 2012

	Descriptions as stated in report/paper	Location in text or source
<u>Study characteristics</u>		
Study title	A Randomized comparison of online and telephone-based care management with internet	p.1060

	training alone in adult patients with poorly controlled type 2 diabetes.	
Author	McMahon, G, T,. Fonda, S, J,. Gomes, H, E,. Alexis, G, Paul, R, Conlin.	p.1060
Year of publication	2012	p.1060
Country of study	USA	p.1060
Study setting (location)	Boston, Massachusetts	p.1060
Years of data collection	?	
Study design and unit of allocation	Randomised controlled trial	
Aim of the study	Investigate whether telephone or online care management improves diabetes outcomes over time compared with web training.	p.1060
Study methods		
Inclusion criteria	- Over 25 years - >8.5% - Ability to understand English - Access to a telephone - Willingness to use the devices for the intervention	p.1061

	- “Participants were required to have a VA-based physician at one of four hospital-based clinics or 20 community-based outpatient clinics”.	
Exclusion criteria	Not mentioned	
Withdrawals and exclusions	Two withdrawals caused by death during follow-up and 1 excluded from analysis due to A1c value out of range.	p.1062
Baseline imbalances	No baseline imbalances	p.1063
Notes	Regardless of intervention or control group all participants continued to receiving usual care from their primary care provider	p.1062
Participants		
Population description (from which study participants are drawn)	Mostly male patients (>90%) over 25 years with poorly regulated diabetes living in Boston area. Participants were screened for eligibility by laboratory hospital data, and then received a letter with the study details.	p.1061
Total number randomised (total population)	152	p.1062

Years since type 2 diabetes diagnosis	Total: <1 year (2,1%) 1-5 years (19%) 6-10 years (29,6%) >10 years (49,5%) Web training: <1 year (2.3%) 1-5 years (25%) 6-10 years (27,3%) >10 years (45.5%) Telephone care:<1 year (2.1%), 1-5 years (16.7%), 6-10 years (27.1%) >10 years (54.2%) Online care: <1 year (2.0%), 1-5 years (16.0%), 6-10 years (34.0%) >10 years (48.0%)	p.1063
Age + mean age	Total: 60.2 years (SD 10.8) Web training: 58.9 years (SD 10.2) Telephone care: 58.5 (SD 11.5) Online care: 63.0 years (SD 10.5)	p.1063
Sex	Total: males 94.7% Web training: males 95.9% Telephone care: males 98.0% Online care: males 90.2%	p.1063
Ethnicity	Total: non-Hispanic whites(74.2%), non-Hispanic black(12.6%), Hispanic (9.3%), other (2.7%), no response (1.3%)	p.1063

	Web training: non-Hispanic whites (69.4%), non-Hispanic black (12.2%), Hispanic (12.2%), other (4.1%), no response (2.0%) Telephone care: non-Hispanic whites (74.5%), non-Hispanic black (11.8%), Hispanic (9.8%), others (2.0%), no response (2.0%) Online care: non-Hispanic whites (78.4%), non-Hispanic black (13.7%), Hispanic (5.9%), others (2.0%),no response (0.0%)	
Mean level HbA1c at inclusion	Online care: 9.6 (SD 1.0) Telephone care: 9.9 (SD 1.2) Web training: Baseline 10.1 (SD 1.4)	p.1064
Medication use	Not mentioned	
Other relevant sociodemographic	Fairly high education level. 90% of participants had completed high school education. 25.6% of the participants had completed college.	p.1063 p.1065

Notes	90% of the participants were males, this does not reflect the real world, and may affect the generalizability of the results.	
Intervention		
No. randomised to group	Online care management: 51 Telephone care management: 51	p.1062
Description of intervention	Telephone based care management: Patients got a glucose monitor and blood pressure device. Care managers used a software to log and track results on glucose and blood pressure. Telephone calls regarded reviewing progress, reinforce nutritional and lifestyle modifications and make medication changes that was affirmed by the participants primary care provider.	p.1061
Duration of intervention	12 months	
Frequency of intervention	- Blood pressure monitoring three times a week - Individual recommendations for frequency of glucose monitoring - Follow up visits every 3 months	p.1061

	- Telephone based group: telephone calls occurred biweekly - Online care management group: log in to patient portal biweekly	
Healthcare providers	Practice nurse or clinical pharmacist who were qualified diabetes educators. They had 30 years of experience with care management.	p.1061
Description of interaction between HCP and participants.	A trained nurse or pharmacist reviewed the participants data and called the participants biweekly in the telephone-based intervention group. In the online-care healthcare personnel communicated via the secure message system in the online application.	p.1062
Delivery/medium (phone, app, email, tools)	Phone or online application plus, glucose monitor and blood pressure measurement.	p.1062
Co intervention if applicable	Online care management group: Participants received a notebook computer and internet access. They also received the same blood glucose and blood pressure monitors as the telephone-based group. Data was uploaded to the care management application.	p.1061

	The patient portal care manager application also had a provider portal that allowed care managers to review a participant panel, and for the care manager to give personalized advices (on nutrition, exercise, medication), review blood glucose and blood pressure data. Providers could use a secure message system to communicate with participants.	
Compliance	Online care: 47 participants completed the trial (92.1%) Telephone care: 44 participants completed the trial (86.3%)	p.1063
Notes		
Control group		
No. randomised to group	50	p.1062
Description of intervention	Web training group. Participants were provided with a laptop computer with internet access.	p.1062

	The internet browser was set to a diabetes education site, designed for this study. The website contains links to several websites with content related to self-management and sites that facilitated peer-sharing and mutual support.	
Duration of intervention	12 months	
Frequency of intervention	Follow up visits every three months. Frequency of website use is not stated in the article. “Data on process measures (including number of Web site interactions, number of encounters, and time spent by the care managers per patient encounter) were collected every three months and analysed as possible explanations for interindividual differences in change over time in the primary outcomes”.	p.1062
Description of interaction between HCP and participants.	N/A	
Delivery/medium (phone, app, email, tools)	Laptop computer with internet access	p.1061
Co intervention if applicable	N/A	

Compliance	41 participants completed the trial (82%).	p.1063
Notes	Utilization of the web-based resources was at the private discretion of the patient.	p.1062
Outcome		
Unit of measurement	HbA1c	
Time points measured (specify whether from start or end of intervention)	Outcome measurement were collected at baseline 3, 6, 9 and 12 months after randomization. However, only measurements for baseline and 12 months were stated in the tables in the article.	p.1064
Mean HbA1c/FG	Online care: Baseline 9.6 (SD 1.0) 12 months 8.3 (SD 1.1) Telephone care: Baseline 9.9 (SD 1.2) 12 months 8.5 (SD 1.6) Web training: Baseline 10.1 (SD 1.4) 12 months 8.4 (SD 1.7)	p.1064
Change in HbA1c/FG	Online care, change from baseline to 12 months:	p. 1064

	-1.3 (SD 1.4, p<0.0001) Telephone care change from baseline to 12 months: 1.5 (SD 1.6, p<0.0001) Web training change from baseline to 12 months: 1.7 (p<0.0001)	
Person measuring/reporting	Not specified. Measurements were collected every three months for a year.	
Sample size calculation	Not mentioned	
Imputation of missing data (e.g. assumptions made for ITT analysis)	"All analysis was intent to treat analysis". The study carried forward the last or most recent observation to the participants who missed study visits or did not respond to all questions. For participants who were missing data at baseline, observations were not carried forward. "Missing data was also reduced with using medical records for patients who missed follow up but had lab test within the required time period".	p.1063

Secondary outcomes: (weight, blood pressure, low density lipoprotein)	Blood pressure at baseline:: Online care: 135.6 /75.7 (SD 17.4/SD 11.8) Telephone care: 139.9/80.8 (SD 17.4/SD 13.1) Web training: 139.8/83.1 (SD 19.1/SD 15.8) Blood pressure change after 12 months: Online care: systolic 0.3 (SD 16.9, p=0.891) diastolic -2.5 (SD 12.9, p=0.178) Telephone care: systolic -6.7 (SD 16.7) p=0.006 diastolic -6.3 (SD 11.5, p=0.001) Web training: systolic -3.1 (SD 20.4, p=0.297) diastolic -5.8 (SD 15.5, p=0.012) LDL at baseline: Online care: 95.1 (SD 29.4) Telephone care: 91.7 (SD 37.8) Web training: 92.5 (SD 32.3) LDL change after 12 months: Online care: -4.9 (SD 25.8, p =0.290) Telephone care: -5.5 (SD 24.1, p= 0.122) Web training: +5.8 (SD 24.6, p=0.118) Weight at baseline in pounds:	p.1064

	Online care: 232.9 (SD 46.2) Telephone care: 235.2 (SD 55.3) Web training: 235.6 (SD 52.2) Weight change after 12 months: Online care: +1.4 (SD 13.5, p=0.458) Telephone care: +4 (SD 14.8, p=0.062) Web training: +0.7 (SD 15.1, p=0.747)	
Notes	This study showed that tailored telephone or online care management offered no additional benefits for diabetic outcomes compared with using self-management resources at the web-based group. "Providing access to online resources to patients with poorly controlled diabetes improves outcomes to the same degree as active care management".	p.1065
Other		
Study funding source	The study was supported by grants from VA health services research and development.	p.1066
Possible conflict of interest	Not mentioned	
Notes		

Torbjørnsen et al., 2014

	Descriptions as stated in report/paper	Location in text or source
Study characteristics		
Study title	A low-intensity mobile health intervention with and without health counselling for persons with type 2 diabetes, part 1: Baseline and short-term results from a randomized controlled trial in the Norwegian part of RENEWING HEALTH	p.1
Author	Torbjørnsen, A,. Jenum, A,K,. Småstuen, M, C,. Årsand, E,. Holmen, H,. Whal, K, A,. Ribu, L,.	p.1
Year of publication	2014	p.1
Country of study	Norway	p.1
Study setting (location)	Northern and South-Eastern part of Norway.	p.3
Years of data collection	Short Time follow-up was conducted from august 2011 to January 2013.	p.3
Study design and unit of allocation	Randomized controlled trial	p.1

Aim of the study	"The aim was to evaluate whether the introduction of technology-support self-management using the Few Touch Application (FTA) diabetes diary with or without health counselling improved glycated haemoglobin (HbA1c) levels, self-management, behaviour change, and health-related quality of life, and to describe the sociodemographic. Clinical, and lifestyle characteristics of the participants after four months"	p.1
Study methods		
Inclusion criteria	"> 18 years, diagnosed with type 2 diabetes minimum of 3 months before inclusion, HbA1c >7.1%, able to use the FTA system, and able to understand and complete questionnaires. "	p.3
Exclusion criteria	"Mental or physical conditions that interfered the protocol"	p.3
Withdrawals and exclusions	Drop out: Technical difficulties: 4 Too much work: 5 Unknown: 2 Did not answer request: 6	p.7

	Died: 2 Controls who preferred Intervention:1 Serious disease: 2 Total drop out: 20, + 2 died.	
Baseline imbalances	No significant differences between the groups except from comorbidity in the FTA only intervention.	p.7-8.
Notes		
Participants		
Population description (from which study participants are drawn)	Adult Norwegian population	
Total number randomised (total population)	164 participants (of which 13 was excluded)	s.7
Year since diabetes type 2 diagnosis	The patients in the study had a mean diabetes duration of 10 years.	p.12
Age + mean age	FTA health counselling: 57.4 years (SD 12.1) FTA: 58.6 (SD 11.8)	p.8

Sex	FTA health counselling: females 50%, males 50% FTA: females 33%, males 67%	p.8
Ethnicity	N/A	
Mean level HbA1c at inclusion	Baseline mean HbA1c: FTA health counselling: 8.2 % (SD 1.1) FTA: 8.1 (SD 1.1)	p.8
Medication use	0nly 9 of 131 participants (6.9%) did not receive glucose-lowering medication.	p.7
Other relevant sociodemographic	Education background <12 years FTA health consulting: 52% FTA: 51%	p.8
Notes	60% of the participants were obese	p.12
Intervention		
No. randomised to group	50	p.8
Description of intervention	In addition to usual care the participants received the Few Touch Application (FTA) diary and health counselling. Participants were given smartphones with the FTA diary app and blood glucose meter. These were	p.3

	linked using Bluetooth wireless communication so that the blood glucose levels was automatically transferred to the FTA diary app. The FTA included five different management systems: blood glucose data, food habits, physical activity, personal goal setting and general diabetes look-up system. In addition to this the participants in FTA with health counselling was offered health counselling with a specialist nurse for four months. The nurse supported the participants in the use of the FTA. The participants received five telephone calls (with an average of 20 minutes). Additionally, the participants could contact the nurse via a secure text messaging system.	
Duration of intervention	Four months	p.4
Frequency of intervention	Daily blood glucose monitoring, and manual implementation of nutrition and physical activity data. Telephone calls approximately once a month.	p.3-4
Healthcare providers	Specialist diabetes nurse.	p.3

Description of interaction between HCP and participants.	Specialist diabetes nurse, answered text messages twice a week and had five telephone calls during four months.	p.3
Delivery/medium (phone, app, email, tools)	Mobile phone with an app, and blood glucose meter.	p.3
Co intervention if applicable	N/A	
Compliance	43 participants completed the 4-months follow-up. However only 38 participants (76%) completed the whole program (all five health consulting modules).	p.7 p.4
Notes		
Control group		
No. randomised to group	Intervention group FTA: 51 Usual care group: 50	p.8
Description of intervention	FTA group: Identical to intervention above, just without health counselling.	p.3
Duration of intervention	Four months	

Frequency of intervention	Intervention group FTA: Daily blood glucose monitoring, and manual implementation of nutrition and physical activity data.	p.4
Description of interaction between HCP and participants.	N/A	
Delivery / medium (phone, app, email, tools)	FTA group: Mobile phone with an app, and blood glucose meter.	p.3
Co intervention if applicable	Control group with 50 participants receiving only usual care and no intervention.	p.3
Compliance	FTA group: 42 participants completed the 4-month follow-up.	p.7
Notes	Both the FTA and the FTA health counselling group were trained to use the mobile phone-base system at the start up meetings.	p.4
Outcome		
Outcome name	HbA1c	

Time points measured (specify whether from start or end of intervention)	Baseline and four months.	
Mean HbA1c/FG	Baseline: FTA health counselling: 8.2% (SD 1.1) (CI 7.9-8.5) FTA: 8.1 (SD 1.1) (CI 7.8-8.4) Four months: FTA health counselling: 7.8 (CI 7.4-8.2) FTA: 7.8% (CI 7.5-8.0)	p.9
Change in HbA1c/FG	FTA health consulting: -0.41 (CI -0.71- 0.11) FTA: -0.23 (CI -0.47- -0.01)	p.9
Person measuring/reporting	After four months, all the participants were asked to visit their general practitioner for measurement of their HbA1c levels and collection of data from their medical record.	p.3
Sample size calculation	The sample size was estimated to be 34 individuals in each group, with decrease in HbA1c level of 0.35%, a significance level of 5%, a standard deviation in the outcome variable of 0.5, statistical	p.3

	power of 80%. To compensate for dropout the sample size was set to 50 in all groups.	
Imputation of missing data (e.g. assumptions made for ITT analysis)	"Data that were not available were considered missing and the results were based on the intention-to-treat approach".	p.6
secondary outcomes:		
Notes	In total 118/151 (78.2%) participants provided HbA1c data at four months. There were no statistically significant differences in HbA1c level changes from baseline between the groups. HbA1c level decreased in all groups, thus the FTA with health counselling group may not be sufficient effective.	p.9
Other		
Study funding source	The project was funded by the EU through the ICT Policy Support Programme.	p.13

	The project is also funded by Norwegian Research Council, Health Authorities of Northern Norway, Norwegian Centre of Integrated Care and Telemedicine at the University Hospital of North-Norway, the Oslo and Akershus University College, the Akershus University Hospital and the Norwegian Diabetes Association.,	
Possible conflict of interest	None declared	p.13
Notes		

Appendix 6: Reason for exclusion

Excluded studies that we screened in full text.

Author, **reference number ()**	**Exclusion reason**
Anzaldo-Campos et al. (69)	Comparison does not receive e-health
Becker et al. (70)	Comparison does not receive e-health
Bender et al. (71)	Intervention does not include tailored feedback
Bollyky et al. (72)	Comparison received feedback from HCP
Chamany et al. (40)	Comparison does not receive e-health
Devkota et al. (73)	Study design not RCT
Egede et al. (74)	Comparison does not receive e-health
Fang et al. (75)	Comparison does not receive e-health
Kumar et al. (76)	Comparison does not receive e-health
O'Neill et al. (77)	Comparison does not receive e-health
Pacaud et al. (78)	Comparison received feedback from HCP
Parsons et al. (42)	Comparison does not receive e-health
Peimani et al. (79)	Intervention does not include HCP
Prato et al. (80)	Comparison does not receive e-health
Ramallo-Farina et al. (81)	Comparison received feedback from HCP
Sakane et al. (82)	Prevention of type 2 diabetes

Tang et al. (83)	Comparison received feedback from HCP
Wongrochananan et al. (44)	Did not contain the necessary information to decide upon inclusion
Zolfaghari et al. (84)	Article has been retrieved

Appendix 7: Risk of bias assessment

Study: Agboola et al., 2016		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligible participants were randomly assigned to receive the TTM intervention or to the control group with a 1:1 allocation ratio using a computer-generated permuted block randomization schedule.
Allocation concealment (selection bias)	Low risk	A third party, not involved with the study, randomly picked blocks and treatment assignment then concealed them in numbered opaque envelopes. The allocation sequence was concealed

		until participants opened the envelope at the enrolment visit.
Blinding of participants and personnel (performance bias)	Low risk	Research assistants and study participants were not blinded to treatment assignment. However due to the nature of the intervention, this is not likely to affect the outcome.
Blinding of outcome assessment (detection bias)	Low risk	The research assistants who conducted the follow up HbA1c test were not blinded at the 6 months follow-up. Additional information about the outcome blinding is not provided. However due to the objectiveness of the measurement, this is not likely to affect the outcome.
Incomplete outcome data (attrition bias)	High risk	"The lost to follow-up and attrition between the groups were similar". However due to the high attrition rate of 46.8%, the sample size is not

		large enough to detect an anticipated difference.
Selective reporting (reporting bias)	Low risk	Both primary and secondary outcomes are analysed according to the pre-specified plan and reported in the results section.
Other bias	Low risk	No risk of other bias was found.

Study: Kempf et al., 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were randomized in a 1:1 ratio using an electronically generated random list (created by trial statistician) into two parallel groups (assigned by the study nurse).
Allocation concealment (selection bias)	Low risk	"The allocation sequence was concealed from the participants, study nurse and outcome assessor." "Each participant was assigned to a serial study identification number. For each

		identification number, there was a closed envelope with the group assignment". No use of opaque envelopes.
Blinding of participants and personnel (performance bias)	Unclear	Insufficient information provided to make judgement.
Blinding of outcome assessment (detection bias)	Low risk	"The data analyst was blinded after assignment to the intervention". The outcome measurement is objective (HbA1c). Attending physician from the independent clinicians ensures blinding of the outcome.
Incomplete outcome data (attrition bias)	High risk	The dropout rates in the intervention group was significantly lower (9%) than the dropout rate in the control (26%). This may lead to a deviation from the true difference between the control and the intervention group. "The overall feedback of participants who dropped out in the control group was that they did not perceive any benefit for glucose metabolic control during the study and therefor dropped out".
Selective reporting (reporting bias)	Low risk	Both primary and secondary outcomes are analysed according to the pre-specified plan and reported in the results section.
Other bias	Low risk	No risk of other bias was found

Study: Lutes et al., 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization involved a blocked randomization sequence to assure similar numbers of participants in each group" (47).
Allocation concealment (selection bias)	Unclear	Insufficient information provided to make judgement.
Blinding of participants and personnel (performance bias)	Low risk	The study was not blinded. The outcome measurement is objective. Thus, the risk of bias is low.
Blinding of outcome assessment (detection bias)	Low risk	"Primary care providers were informed of patient participation but were blind to random assignment of participants to treatment arms."
Incomplete outcome data (attrition bias)	Low risk	"There were no differences in attrition between the Small Changes group (23%) and the email-based education group (15%). p= 0.093."
Selective reporting (reporting bias)	Low risk	Both primary and secondary outcomes are analysed according to the pre-specified plan and reported in the results section.
Other bias	Low risk	No risk of other bias was found.

Study: McMahon et al., 2012		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Participants were randomly assigned to one of three groups using a random number generator and a series of sealed envelopes". No use of opaque envelopes.
Allocation concealment (selection bias)	Unclear	Insufficient information provided to make judgement.
Blinding of participants and personnel (performance bias)	Low risk	The study was not blinded. The outcome measurement is objective thus the risk of bias is low.
Blinding of outcome assessment (detection bias)	Low risk	Insufficient information is provided about the outcome assessor. However due to the objectiveness of the measurement, this is not likely to affect the outcome.
Incomplete outcome data (attrition bias)	Low risk	Similar attrition rate between the groups. Attrition rate is under 20 %. However, no characteristics about the dropouts is provided, we don't know if they differ significantly from those who completed the study**.**

Selective reporting (reporting bias)	High risk	Did not report HbA1c outcome measurements every third month, as pre-specified. Outcome was only reported at baseline and at the 12 months closeout.
Other bias	Low risk	No risk of other bias was found.

Study: Torbjørnsen et al., 2014		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computer-generated block randomization system was used. “It was developed and administered by the Unit of Applied Clinical Research, Institute of Cancer Research and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway to ensure a good balance between the numbers and confounding factors in each of the 3 groups”.
Allocation concealment (selection bias)	Unclear risk	According to the study protocol participants are randomized into one of the three groups in the start-up meeting. No further details regarding allocation concealment is provided.

Blinding of participants and personnel (performance bias)	Low risk	No blinding of either the general practitioners or participants in this study, according to the study protocol**.** “Participants are immediately after randomization told which group they have been placed”. “The general practitioners were not blinded because the participants were encouraged to discuss the progression of their glucose measurements, diet records and activity logs with them”.
Blinding of outcome assessment (detection bias)	Low risk	The participants were asked to visit their general practitioner for measurement of their HbA1c levels. The physician was not blinded to the outcome assessment. However due to the objectiveness of the measurement, this is not likely to affect the outcome.
Incomplete outcome data (attrition bias)	Low risk	The groups had an equal dropout rate. The attrition rate was 18 % in total. According to the power calculation the sample size was acceptable.
Selective reporting (reporting bias)	Low risk	Both primary and secondary outcomes are analysed according to the pre-specified plan and reported in the results section.
Other bias	Low risk	No risk of other bias was found.